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Continuous Flow Reactors, a Tool for the Modern Synthetic Chemist

Charlotte Wiles[a] and Paul Watts*[a]

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The competitive nature of the chemical industry means that researchers involved in product development and lead compound generation are under continued pressure to identify, and develop, promising programmes of research in order to secure vital intellectual property. The potential of a compound, however, depends not only on structural complexity, but also on the ability to prepare the compound via a scalable synthetic pathway. Consequently, micro reaction and continuous flow technologies have captured the attention of the modern synthetic chemist as they enable reactions to be performed with an unprecedented level of control, affording excellent transferability between laboratory based investigations and subsequent production scales. With these features in mind, this Microreview focuses on recent developments made in the field of micro reaction technology, highlighting the advantages associated with its use through the synthesis of a diverse array of molecules.

1.0 Introduction

The past decade has seen the synthetic chemist embrace many new technologies, the most notable being that of microwave chemistry,[1] during this time the field of micro reaction technology was extensively investigated at an academic level; however, it is only in the past five years, with the advent of commercially available systems, that the technique has entered mainstream research and development.[2]

Micro reaction technology is widely termed the continuous processing of reactions within well defined reaction channels, where dimensions are typically of the order of less than 1000 μm. On this length scale, laminar flow dominates and mixing occurs exclusively by diffusion,[3] which leads to excellent control over reaction times. In addition, the high surface to volume ratio[4] affords the ability to rapidly change reaction temperature through the application or removal of heat,[5] affording novel thermal regimes inaccessible within conventional apparatus.[6] The intrinsically low reaction volumes obtained within such systems is advantageous, not only with respect to reactor safety, but also as it enables a wide array of reaction conditions to be evaluated, affording a wealth of information from small quantities of catalyst or reagent (range from ng to μg).[7] Furthermore, the ability to automate such devices[8] has the potential to afford intelligent reaction systems capable of op-

[a] Department of Chemistry, The University of Hull, Cottingham Road, Hull, HU6 7RX, UK

Dr Charlotte Wiles obtained her PhD, entitled 'Organic synthesis in micro reactors', in 2003 from The University of Hull (UK) under the tutelage of Professor Stephen J. Haswell. Her postdoctoral research, supervised by Dr Paul Watts, currently focuses on improving the efficiency of common synthetic transformations through coupling reaction miniaturisation with the use of solid-supported reagents/catalysts and has led to the publication of more than 30 scientific papers in the field.

Dr Paul Watts obtained a PhD in bio-organic natural product chemistry under the supervision of Professors Tom Simpson FRS and Chris Willis. His PhD focussed on the synthesis of isotopically labelled compounds, for use in determination of biosynthetic pathways to polyketide derived natural products. Paul subsequently worked as a postdoctoral research associate at The University of Hull, where he investigated organic synthesis in micro reactors. In 2002, he was appointed as an academic at The University of Hull, where he now leads the micro reactor group, which consists of 3 postdoctoral researchers and 7 PhD students. He is interested in organic chemistry, biocatalysis and electrosynthesis within micro reactors and has published more than 50 papers in the area.

erating unaided, 24 h a day, leading to increases in the throughput of such processes.

A particularly attractive feature of continuous-flow synthesis is the ease with which reaction conditions can be transferred between reactors and production sites, without the need for re-optimisation. This feature therefore enables reactions optimised within a laboratory to be scaled through the operation of multiple systems in parallel, a process termed numbering-up or scale-out.[9] Compared to conventional scale-up, i.e. laboratory→pilot plant→production-scale, this approach is advantageous as it removes the financial risks associated with failing to scale a process; due to changes that occur in the thermal and mass transportation properties of a reactor, or the inability to safely conduct the reaction at the desired scale. Other benefits of reaction miniaturisation include reduced exposure to hazardous chemicals, through the use of sealed reactor units, increased atom efficiency as a result of precise reaction control and the ability to incorporate in-line analytics to monitor processes more closely.

To illustrate the attractive features associated with conducting reactions under continuous flow, the remainder of the Microreview aims to provide practical examples of the technology, highlighting the advantages that the technology brings through an array of synthetic transformations.

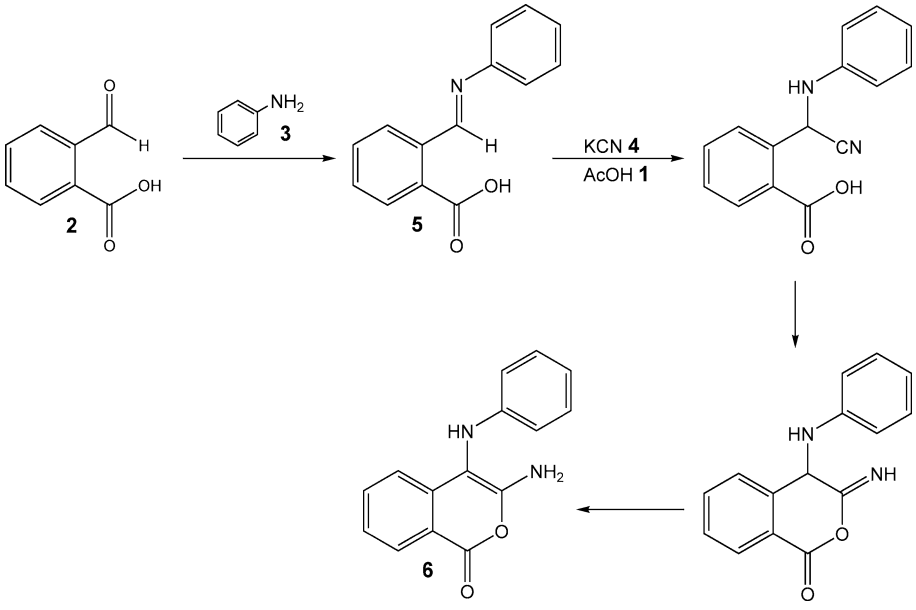
2.0 Single-Phase Micro Reactions

One of the earliest examples of a liquid-phase micro reaction was reported in 1997 by Harrison and co-workers[10] who demonstrated the synthesis of an azo dye, within a Pyrex micro reactor, achieving controlled reagent manipulation under electroosmotic flow (EOF). Since this pioneering work, many groups have focussed on exploring the practical advantages associated with conducting reactions under continuous flow. With this in mind, the following section details some of the more recent examples of liquid phase reactions investigated within micro fluidic devices.

Employing a stacked plate micro reactor (channel dimensions: 100 μm, total volume: 2 mL), Stevens and Acke[11] reported the continuous-flow synthesis of a series of pharmaceutically interesting chromones via a multi-component route that consisted of a sequential Strecker reaction-intramolecular nucleophilic addition and tautomerisation (Scheme 1).

To perform a reaction, methanolic solutions of acetic acid **1** (2 equiv.)/2-formylbenzoic acid **2** (1 equiv.) and aniline **3** (2 equiv.)/potassium cyanide **4** (1.2 equiv. in MeOH) were introduced into the reactor from separate inlets, thus ensuring the formation of HCN and the imine **5** occurred within the confines of the micro reactor. In order to prevent precipitation of the reaction products within the residence time extension unit, and at the reactor outlet, a maximum concentration of 0.15 M was selected for 2-formylbenzoic acid **2**. Employing a residence time of 40 min, the authors reported a maximum isocoumarin **6** yield of 66% (1.80 g h^{-1}); however, decomposition products were observed when the product was stored in solution; this was readily circumvented by isolation and storage of the respective product as the solid substrate. To demonstrate the flexibility of the system an array of amines were also employed, affording yields in the range of 6–75% (Table 1).

Although only moderate yields were obtained within the micro reactor, in the case of Entry 3 the authors report a 9.0% increase over conventional batch techniques. Further investigations focussed on the use of a biphasic system comprising of fluorinated/alcoholic solvents and although the authors comment on reduced precipitation, the increased residence time required to obtain comparable yields to those reported in the previous set-up, led to a reduction in the overall system throughput.

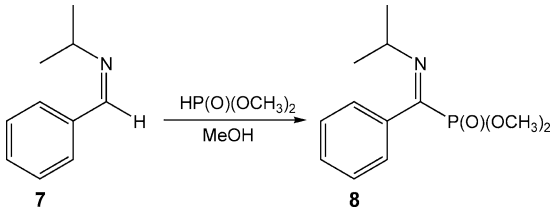


Scheme 1. Reaction sequence employed in the continuous-flow synthesis of a 3-diamino-1*H*-isochromen-1-one **6**.

Table 1. A selection of the results obtained for the synthesis of chromones under continuous flow.

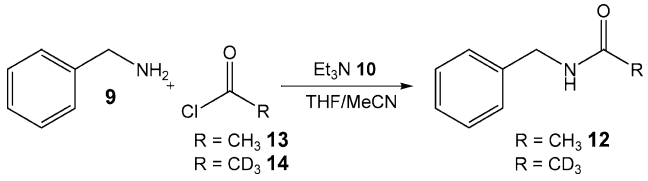
Entry	Amine	% Yield	Throughput [h^{-1}]
1	aniline **3**	66	1.80
2	3-methoxyaniline	75	2.28
3	3-methylaniline	69	1.98
4	*N*-methylaniline	49	1.41
5	allylamine	6.0	0.14

The authors also demonstrated the synthesis of numerous α-aminophosphonates of pharmaceutical interest, via the Kabachnick–Fields reaction (Scheme 2).[12] Using a metal flow-reactor maintained at 50 °C, it was found that a residence time of 78 min (0.6 mL min^{-1}) was required in order to obtain quantitative conversion of an aldimine **7** to the respective α-aminophosphonate **8**. After subjecting the reaction products to an off-line acid-base extraction, isolated yields of 94% were obtained, equating to a throughput of 10.3 g h^{-1}. Using the optimised reaction conditions a further four compounds were synthesised, affording isolated yields in the range of 68–91%. Compared to conventional batch methodology where catalysts such as $LiClO_4$ or $InCl_3$ are employed, the advantage of the continuous flow technique was the fact that the reaction could be performed in the absence of a catalyst and without the need for lengthy reaction times at reflux.



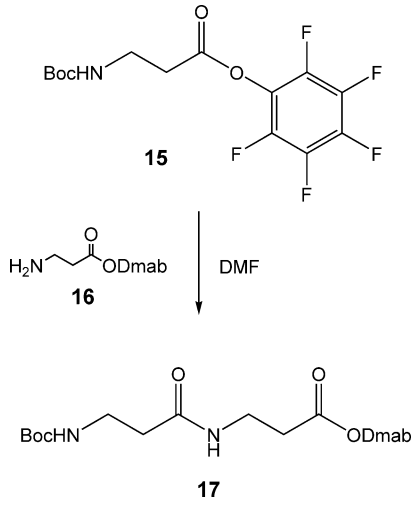
Scheme 2. An α-aminophosphonate synthesised under continuous flow.

In a recent example reported by Hooper et al.,[13] the atom efficiency of reactions conducted within micro-fluidic systems was demonstrated via the incorporation of deuterium labels into an array of small organic compounds. Employing the base-mediated acylation of primary amines as a model reaction (Scheme 3), the authors demonstrated the ease by which reactions could firstly be conducted using unlabelled precursors and once optimised, substitution with the labelled reagent enabled the efficient synthesis of the deuterated analogue. To perform a reaction, two borosilicate glass micro reactors were employed in series [Reactor 1 = 201 μm (wide) × 75 μm (deep) × 2.0 cm (long) and Reactor 2 = 158 μm (wide) × 60 μm (deep) × 1.5 cm (long)] and reagents manipulated using pressure-driven flow. To ensure long-term operation of the reactor set-up, the authors found it necessary to employ a mixed solvent system in order to obtain a balance between by-product solubility (Et_3N·HCl) and degradation of the acylating reagent. To perform a reaction, solutions of benzylamine **9** and triethylamine **10** in MeCN (0.1 M respectively) were introduced into the reactor from separate inlets where they mixed prior to the addition of the acyl halide (0.05 M) as a solution in THF. Employing a total flow rate of 40 μL min^{-1} and a residence time of 2.6 s, the authors obtained *N*-benzamide **12** in an optimised conversion of 95.3%. The ease of method transfer was subsequently demonstrated via substitution of acetyl chloride **13** with acetyl [D_3]chloride **14** and operating the reactor under the previously optimised reaction conditions, the authors obtained comparable results (98.2% conversion). This is an important result in the field of isotope labelling as it means that reactions can be optimised using cheap and readily available precursors, which can then be substituted with the labelled analogue, not only reducing development costs but also affording a rapid and efficient means of preparing labelled compounds.

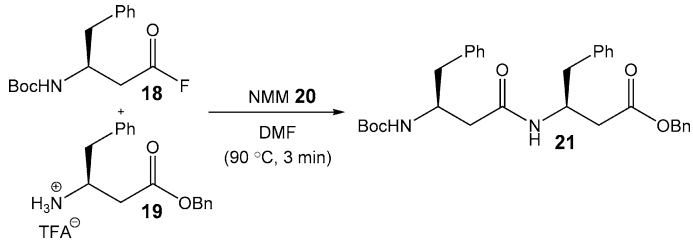


Scheme 3. Efficient technique for the incorporation of deuterium labels into small organic compounds.

In 2002, Watts and co-workers[14] reported the successful synthesis of an array of dipeptides in a borosilicate glass micro reactor. As Scheme 4 illustrates a typical reaction investigated was the coupling of an activated ester **15** (0.1 M) and Boc-β-alanine **16** (0.1 M) to afford Boc-β-alanine-β-alanine-ODmab **17** (0.05 M). Employing DMF as the reaction solvent and manipulating the reagents via EOF, the authors were able to obtain quantitative conversion of the amine **16** to the desired dipeptide **17**, as confirmed by off-line HPLC analysis. In addition, a series of carbodiimide coupling reactions were also performed, with the investigation culminating in the synthesis of the tripeptide Fmoc-β-alanine-β-alanine-β-alanine-ODmab.[15] Although this approach afforded a rapid route to the formation of peptide bonds, the resulting reaction products remained contaminated with



Scheme 4. Synthesis of a dipeptide **17** via a pentafluorophenyl ester **15**.

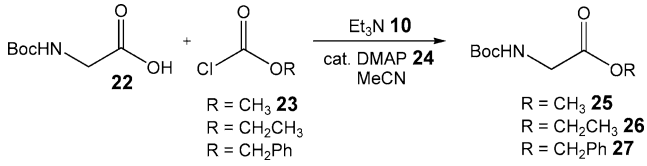


Scheme 5. Synthesis of a β-dipeptide **21** under continuous flow.

protecting group residues and coupling reagents. This problem was subsequently addressed by the continuous electrophoretic separations reported by George et al.,[16] affording an elegant approach to peptide purification.

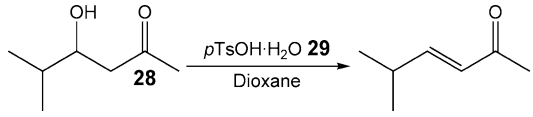
Following these initial investigations, Seeberger and co-workers[17] recently reported the preparation of numerous β-amino acids within a heated silicon micro reactor (Scheme 5). To perform a reaction, the authors introduced DMF solutions of acyl fluoride **18** (0.48 M), TFA salt **19** (0.24 M) and *N*-methylmorpholine (NMM) **20** (2.40 M) from separate inlets, under pressure-driven flow. The reagents then mixed in a micro channel (total volume: 9.5 μL), passed into the reaction loop (total volume: 68.8 μL), where they reacted, prior to in-line quenching with TFA in DMF (0.72 M) and subsequent analysis by LC-MS. Maintaining the reactor at 90 °C, by immersion in an oil bath, the authors found that a residence time of only 3 min afforded the desired dipeptide **21**, after column chromatography, in 92% yield. Using this approach further studies were conducted into the synthesis of tri- and tetrapeptides, at 90 °C and 120 °C, respectively, affording excellent isolated yields and purities following fluorous solid-phase extraction. Compared to the previous EOF-based examples reported by Watts and co-workers, the use of a heated silicon micro reactor enables the rapid synthesis of peptides with throughputs capable of affording several grams of the target molecule day^{-1} $reactor^{-1}$.

Although many techniques are reported within the literature for the synthesis of esters, due to the extremes of pH and elevated reaction temperatures, few are mild enough to be performed on acid sensitive compounds. With this in mind, Haswell and co-workers[18] investigated the preparation of esters via the catalytic conversion of a series of in-situ generated mixed anhydrides (Scheme 6). Employing a borosilicate glass micro reactor [channel dimensions: 350 μm (wide) × 52 μm (deep) × 2.5 cm (long)] with reagents manipulated under EOF, solutions of Et_3N **10** (1.0 M), pre-mixed Boc-glycine **22**/methyl chloroformate **23** (1.0 M respectively) and 4-dimethylaminopyridine (DMAP) **24** (0.5 M) were introduced into the reactor from separate inlets. The reaction products were collected at the outlet in MeCN and analysed off-line by GC-MS in order to determine the conversion of carboxylic acid **22** to ester **25**. Employing optimised conditions of 385, 417 and 364 $V\,cm^{-1}$, the authors reported quantitative conversion of Boc-glycine **22** to Boc-glycine methyl ester **25**, detecting no residual anhydride or deprotection products. The generality of the technique was subsequently evaluated, demonstrating the quantitative synthesis of the ethyl **26** and benzyl **27** esters, along with the esterification of numerous aromatic carboxylic acids, affording conversions ranging from 91% to quantitative.



Scheme 6. Preparation of Boc-glycine esters **25**–**27** in an EOF-based micro reactor.

Fukase et al.[19] recently demonstrated the use of an IMM micro mixer for the efficient dehydration of β-hydroxy ketones to the respective unsaturated product. As Scheme 7 illustrates, a typical protocol involved the introduction of 4-hydroxy-5-methylhexan-2-one **28** (1×10^{-2} in dioxane) and *p*TsOH·H_2O **29** (1×10^{-2} M in dioxane) into the mixer from separate inlets and the resulting solution quenched with aq. NaOH (1.0 M). Using this approach, the authors found the optimal reaction conditions to be a flow rate of 200 $\mu L\,min^{-1}$, equivalent to a residence time of 47 s, and a reaction temperature of 110 °C. Compared to reactions performed in batch, the use of a continuous protocol enabled the authors to obtain reaction products with increased purity (100%) due to the suppression of side reactions, which were found to lead to the formation of by-products on the macro-scale (71% yield). Using this approach, the authors extended the methodology to the preparation of key reaction intermediate in the synthesis of pristane **30** (see Section 8.2).



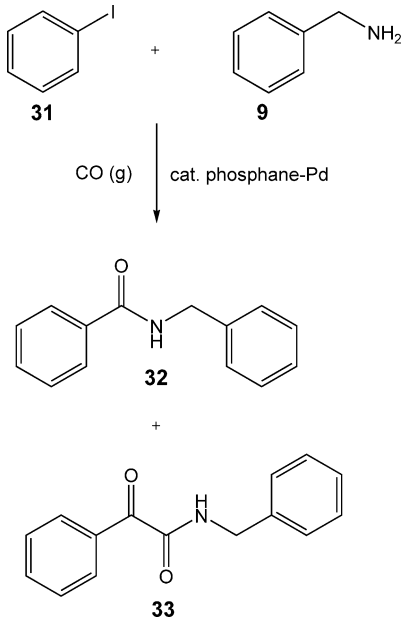
Scheme 7. Continuous dehydration of β-hydroxy ketones via an acid-catalysed elimination reaction.

3.0 Biphasic Micro Reactions

3.1 Gas-Liquid Phase

Due to the corrosive, and often toxic, nature of gases employed in synthetic transformations, biphasic reactions

are frequently over-looked when it comes to process chemistry; however, through careful design micro fluidic systems enable the controlled addition and manipulation of gaseous and liquid streams. With this in mind, a number of transformations have been successfully conducted within such systems, including chlorinations[20] and fluorinations[21] (also see Section 9.0). More recently de Mello and co-workers[22] reported a continuous flow system that enabled the efficient synthesis of amides via a carbonylative coupling reaction (Scheme 8).



Scheme 8. Carbonylative coupling reaction conducted in a glass micro reactor.

Conducting the reaction in a glass device, with channel dimensions of 200 μm (wide) × 75 μm (deep) × 5 m (long), the authors employed a biphasic reaction mixture comprising of gaseous carbon monoxide and a solution of iodobenzene **31**, benzylamine **9** and phosphane-palladium catalyst. Under a constant flow of gas (2 sccm) the authors investigated the effect of liquid flow rate (5.0–20 μL min^{-1}), in all cases, annular flow dominated (where liquid is forced to the outer surface and gas flows through the middle); however, the most stable flow regime was observed at 5.0 μL min^{-1}. Conducting the reactions under the aforementioned conditions 46% conversion to the desired amide **32** was obtained, along with 9.0% α-ketoamide **33**. The authors therefore propose that with further optimisation, this represents an interesting route to the synthesis of α-ketoamides.

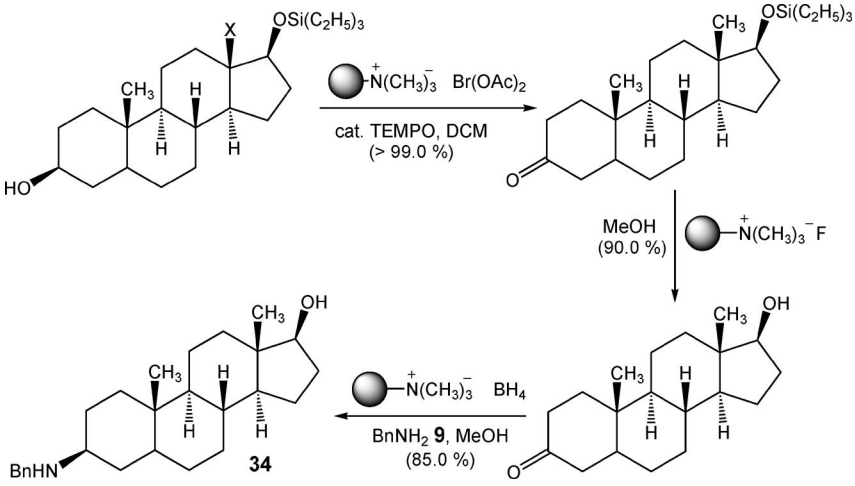
Another area to benefit from being conducted under continuous flow is that of direct fluorinations. Owing to the highly exothermic nature of the conversion of a C–H bond to a C–F bond, using fluorine gas, the transformation has long been considered too dangerous to carry out on a large scale. The technique is, however, of significant synthetic value; and as such a great deal of research has been undertaken into conducting direct fluorinations under continuous flow. In a thin-film nickel reactor Chambers and co-workers[23] demonstrated the biphasic fluorination of a range of 1,3-dicarbonyl compounds, such as ethyl acetoacetate. Employing 10% elemental fluorine in nitrogen, the authors demonstrated a facile route to the selective synthesis of ethyl 2-fluoro-3-oxobutyrate, with only small quantities of the product undergoing further fluorination to afford ethyl 2,2-difluoro-3-oxobutyrate as the by-product. In addition, the group reported the fluorination of compounds such as toluene and ethyl 2-chloroacetate,[24] again demonstrating excellent control over conversion and selectivity to the mono-fluorinated compound.

3.2 Liquid-Solid Phase

Although there are clearly many advantages associated with the use of micro reactors, the purification of reaction products prepared under continuous flow remains challenging, with many groups still favouring to perform off-line, batch-wise purifications. One successful approach, however, has been the incorporation of polymer-supported reagents, catalysts and scavengers into packed-beds, thus enabling the synthesis and purification of reaction products generated under continuous flow (see Section 6.0 for additional techniques).

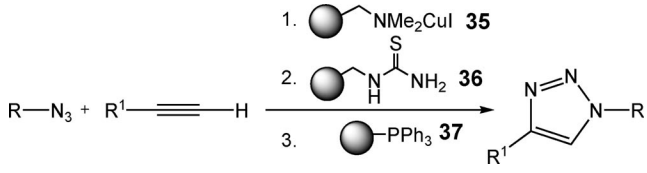
Polymer/silica-assisted flow reactions: Using a series of PASSflow reactors [5 mm (i.d.) × 10 cm (long)] Kirschning and co-workers[25] demonstrated the ability to combine immobilised reagents to perform a series of synthetically useful transformations. In one example, the group demonstrated this serial approach enabling an oxidation, silyl deprotection and reductive amination to be performed, affording a derivatised steroid **34** in excellent purity (Scheme 9).

Haswell and co-workers later demonstrated the use of a glass flow reactor [3.0 mm (i.d.) × 3.0 cm (long)], containing silica-supported piperazine, in which a series of Knoevenagel condensations were performed. Employing EOF as the pumping mechanism, the authors reported the synthesis of numerous pharmaceutically interesting α,β-unsaturated compounds in excellent yield and purity. The reaction methodology was further extended to the multi-step synthesis of α,β-unsaurated compounds from a series of dimethyl acetals. In this case the first step of the reaction involved the acid-catalysed deprotection of the dimethyl acetal to afford the respective aldehyde, followed by base-catalysed condensation with ethyl cyanoacetate. Using this approach, the authors reported the ability to generate the desired ethyl 3-(4-bromophenyl)-2-cyanoacrylate in excellent purity, with a throughput of 0.93 g h^{-1}. Additional transformations performed by the group include the chemoselective oxidation of primary alcohols to aldehydes or carboxylic acids (product defined by residence time),[26] the continuous-flow synthesis of dimethyl acetals[27] and the chemoselective protection of carbonyl moieties as their 1,3-dithiane or 1,3-dithiolane (controlled as a function of reagent residence time).[28]



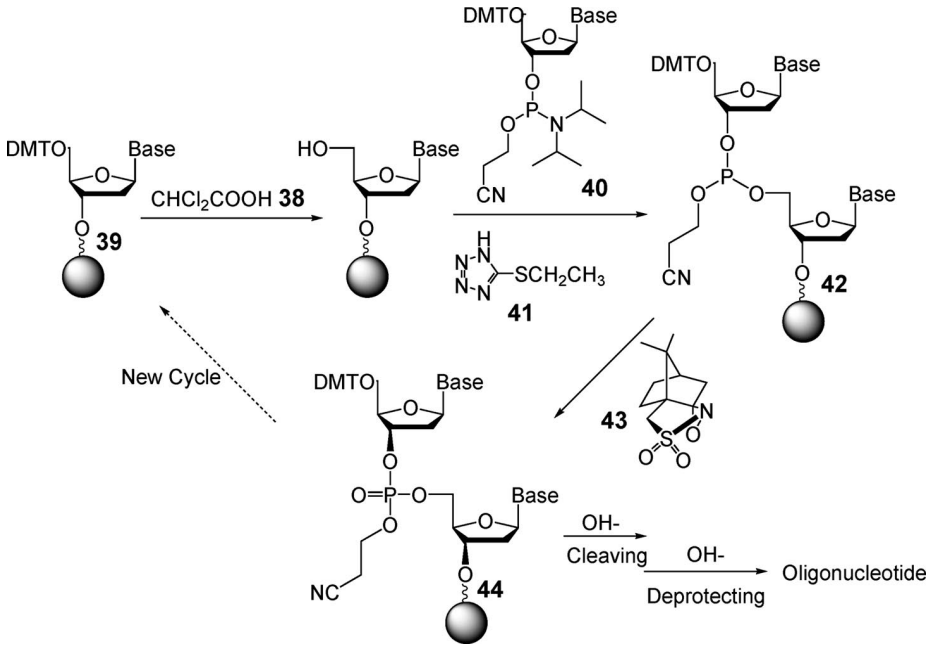
Scheme 9. Polymer-assisted derivatisation of a steroid under continuous flow.

In another example employing multiple supported catalysts and reagents, Ley and co-workers[29] presented a modular flow reactor in which fourteen 1,4-disubstituted-1,2,3-triazoles were synthesised. Coupling an immobilised copper(I) iodide species **35** with two scavenger modules (QuadraPure TU **36** and phosphane resin **37**), the authors reported the [3+2] cycloaddition of an array of azides and terminal acetylenes (30 μL min^{-1}) to afford the desired 1,4-disubstituted 1,2,3-triazoles (Scheme 10) in moderate to excellent isolated yield (70 to 93%). In analytical mode, the reactor was optimised to afford between 20 and 200 mg of product; however, in the case of propargylic alcohol (R^1 = CH_2OH) and benzyl azide (R = CH_2Ph), the reactor was operated continuously for 3 h, to afford 1.50 g of the desired product; representing 85% yield and at least 95% purity. Additional examples reported by the group include the synthesis of amides and guanidines, whereby purification was facilitated by the use of tagged phosphane reagents.[30]



Scheme 10. Illustration of the [3+2] cycloadditions performed using a modular flow reactor.

In an alternative approach, Huang and co-workers[31] reported the fabrication of a DNA oligonucleotide synthesizer from the chemically resistant elastomer perfluoropoly-

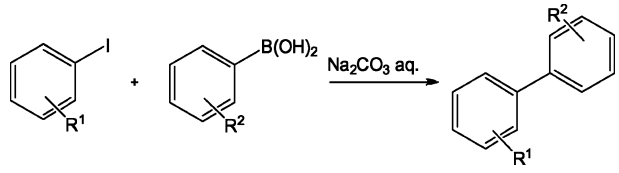


Scheme 11. Procedure employed for the continuous-flow synthesis of oligonucleotides.

ether (PFPE), demonstrating its use for the synthesis of 20-*mer* oligonucleotides. As illustrated in Scheme 11, the reaction sequence employed involved the acid catalysed (dichloroacetic acid **38**) deprotection of an immobilised nucleoside **39**, which was coupled to phosphoramidite **40** in the presence of 5-ethylthio-1*H*-tetrazole **41**, the resulting nucleoside **42** was subsequently oxidised using (1*S*)-(+)-(10-camphorsulfonyl)oxaziridine **43** to afford **44**. These steps were repeated numerous times, dependant on the size of the desired oligomer, followed by a final dimethoxytrityl (DMT) deprotection and cleavage of the product from the silica support, using ammonium hydroxide. The resulting reaction products were subsequently analysed off-line by LC-MS to confirm product formation and purity. Using this approach, the authors report that the reactor is capable of synthesising 60 pmol of DNA oligonucleotides whilst consuming only 500 nl of phosphoramidite **40** (0.1 M) in each cycle. Through the integration of micro valves, the authors have successfully automated a complex synthetic procedure, enabling reaction conditions to be optimised with ease.

Membrane reactors: In addition to packed and wall-coated systems,[32] numerous researchers have investigated the fabrication of membranes, within micro channel systems, in which catalytic material can be incorporated. Employing a protocol developed by Whitesides and co-workers,[33] Uozumi et al.[34] deposited a poly(acrylamide)-triarylphosphane-palladium membrane (PA-TAP-Pd) (1.3 μm wide, 0.37 mmol g^{-1} Pd) within a glass micro channel of dimensions 100 μm (wide) × 40 μm (deep) × 1.4 cm (long). Once formed, the membrane was used to catalyse a series of Suzuki–Miyaura C–C bond forming reactions. To perform a reaction, the authors employed two reactant solutions, the first containing the aryl iodide (6.3×10^{-3} M) in EtOAc/2-PrOH (1:2.5) and the second the aryl boronic acid (9.4×10^{-3} M) in aqueous Na_2CO_3 (1.8×10^{-2} M).

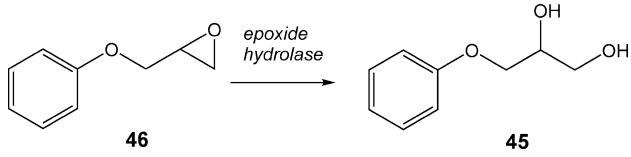
Table 2. Summary of the Suzuki–Miyaura coupling reactions conducted in a membrane reactor.



R^1	R^2	% Yield
H **31**	4-MeO	99
H **31**	3-Me	96
H **31**	2-Me	99
3-$EtCO_2$	4-Me	99
3-Cl	4-MeO	88
4-CF_3	4-MeO	99

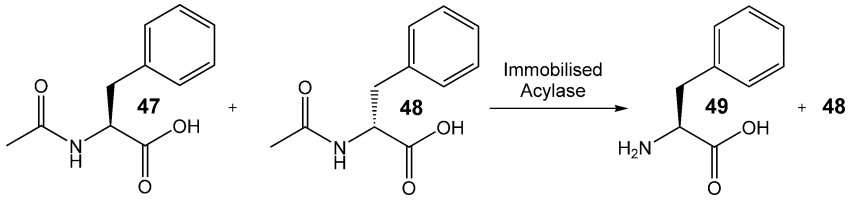
The reagents were infused through the heated reactor (50 °C) at a flow rate of 2.5 μL min^{-1}, which afforded a residence time of 4 s, the biphasic reaction products were subsequently collected, analysed off-line by GC and ^{1}H NMR spectroscopy. As Table 2 illustrates, in all cases excellent yields were obtained, ranging from 88–99%, demonstrating the high catalytic activity of the PA-TAP-Pd membrane. Importantly, the authors report that no coupling products were obtained when the reaction was performed in the absence of the catalytic membrane.

Immobilised enzyme reactors: In addition to the array of chemically catalysed reaction systems reported, the past two years has seen a rapid increase in the number of enzyme-catalysed systems being developed.[35] Of these, possibly the most noteworthy is the fused-silica micro-fluidic device reported by Belder and Reetz,[36] which enabled synthesis, separation and detection steps to be integrated within a single micro-fluidic device. As Scheme 12 illustrates, the enantioselective synthesis of 3-phenoxypropane-1,2-diol **45** was selected as a model reaction. The first step of the process involved hydrolysis of 2-phenoxymethyloxirane **46** in the presence of an epoxide hydrolase, this was followed by electrophoretic separation of the reaction mixture (90 s) and detection of the respective enantiomers by fluorescence, using a deep-UV laser (Nd:YAG, 266 nm). Using this approach, three mutants of epoxide hydrolase (*Aspergillus niger*) were evaluated in rapid succession and conversions in the range of 22–43% (*ee* values of 49 to 95%) were obtained.



Scheme 12. Continuous flow, enantioselective hydrolysis of 2-phenoxymethyloxirane **46**.

In 2006, Maeda and Miyazaki et al.[37] reported an integrated micro fluidic system, consisting of an enzymatic micro reactor and an in-line liquid-liquid extraction device, capable of achieving the optical resolution of racemic amino acids under continuous flow. As Scheme 13 illustrates, the first step in the optical resolution is an enzyme catalysed, enantioselective hydrolysis of a racemic mixture of acetyl-D,L-phenylalanine **47** and **48** to afford L-phenylalanine **49** (99.2–99.9% *ee*) and acetyl-D-phenylalanine **48**.



Scheme 13. Reaction employed to demonstrate the efficient resolution of racemic amino acids under continuous flow.

Acidification of the reaction products, prior to the addition of ethyl acetate, enabled efficient continuous extraction of L-phenylalanine **49** into the aqueous stream and acetyl-D-phenylalanine **48** (84–92% efficiency) into the organic phase. Employing the optimal reaction conditions of 0.5 μL min^{-1} for the enzymatic reaction and 2.0 μL min^{-1} for the in-line separation, the authors were able to resolve 240 nmol h^{-1} of racemate.

Employing a multi-channel PDMS micro reactor [350 μm (wide) × 250 μm (deep) × 0.64 cm (long)] in which the thermophilic enzyme β-glycosidase was immobilised, Nidetzky and co-workers[38] evaluated the hydrolysis of 2-nitrophenyl-β-D-galactopyranoside. Heating the reactor to 80 °C, the authors were able to continuously hydrolyse 2-nitrophenyl-β-D-galactopyranoside, monitoring the reaction efficiency via the generation of 2-nitrophenol. Unlike the previous example, only 20% conversion was obtained, an observation that the authors attributed to the reversible absorption of 2-nitrophenol by the PDMS. To overcome this, the reactors performance was evaluated using the polar disaccharide lactose, whereby hydrolysis afforded glucose and galactose in 60% yield, showing stability over extended periods of operation (100 h).

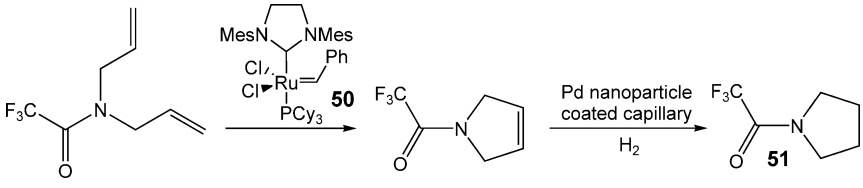
Due to their cost, instability and limited longevity, enzymes are not readily employed in production scale syntheses; however, through their incorporation into flow reactors, biocatalytic material can be employed for the continuous preparation of synthetically valuable compounds.

4.0 Tri-phasic Micro Reactions

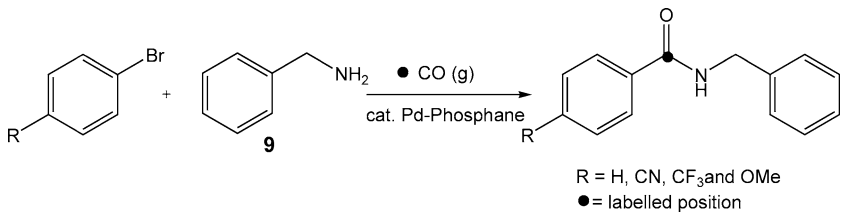
Employing a series of catalyst coated capillaries coupled to separation columns, Trapp and co-workers[39] were able to combine the steps of synthesis, separation and analysis to afford a system that was capable of extracting reaction kinetics from an array of multi-phase reactions. With this in mind, the authors firstly evaluated the chemoselective hydrogenation of a range of substrates, employing a Pd nanoparticle coated capillary reactor and H_2 as the carrier gas. In order to extract kinetic data, incomplete conversions of starting material to product were desired and as a result, a reactor length of only 2 cm was selected, affording residence times in the range of 20 ms to 1 s, the authors note, however, that for synthetic applications longer columns promote quantitative conversion (throughputs: about 0.02 mg h^{-1}). Using flame ionisation detection (FID) for quantification and MS for compound identification, a substrate library of 22 unsaturated compounds, ranging from alkenes to aromatic hydrocarbons, was evaluated affording a throughput of 147 reactions h^{-1}. In addition, other examples of continuous flow hydrogenations have been reported within the open literature and include chemoselective reductive aminations[40] and debenzylations.[41]

As an extension to this technique, the authors subsequently investigated the fabrication of a system capable of probing the reaction kinetics of numerous ring closing metathesis (RCM) reactions. In this case, the on-column reactor consisted of a capillary coated with Grubbs 2nd generation catalyst **50** (1.6 μg m^{-1}), 10 m in length and employed an inert carrier gas of He to transport substrates through the reactor and separation columns. Using this approach, an array of alkenic substrates were investigated, affording kinetic profiles at a rate of 36 h^{-1}. Further to these single step investigations, it was found that by coupling the RCM column (80 cm) with a Pd-nanoparticle coated column, followed by a separation column, the authors were able to perform a two-step cascade reaction to afford 2,2,2-trifluoro-1-(pyrrolidin-1-yl)ethanone **51** in an overall yield of 49% (Scheme 14).

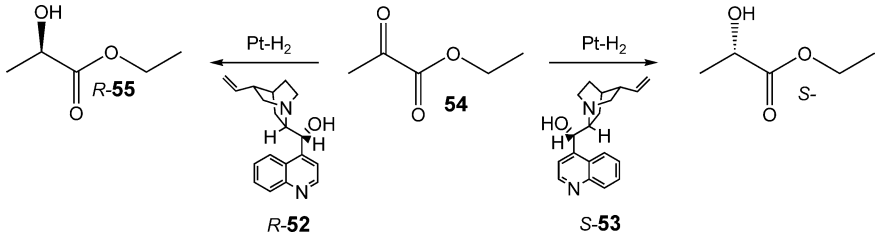
In an extension to their earlier biphasic system (Scheme 8), de Mello and co-workers[42] extended the synthetic utility of their reaction set-up through the incorporation of silica-supported palladium phosphane derivative which enabled recycling of the catalyst (18 times with no loss of activity). Using this approach, the efficient carbonylation of six aryl halides with benzylamine **9** was investigated, affording the desired amides in yields ranging from 26–99%. To further demonstrate the application of such a system, the authors evaluated the incorporation of ^{11}CO into four amides, as can be seen from Scheme 15, whereby



Scheme 14. Schematic illustrating a two-step cascade reaction conducted in coated micro capillaries.



Scheme 15. ^{11}CO carbonylative cross-coupling reactions conducted in a tri-phasic system, under continuous flow.



Scheme 16. Enantioselective hydrogenation of ethyl pyruvate **54** in a packed-bed reactor.

good radiochemical yields (> 33%) and purities (> 70%) were obtained.

Using a Pt-alumina catalyst, Bartok et al.[43] reported an efficient technique for the enantioselective hydrogenation of α-keto esters in a packed-bed reactor, investigating the effect of flow rate, H_2 pressure, solvent system and modifier **52**, **53** on the hydrogenation of ethyl pyruvate **54** (Scheme 16). Over the course of the study, the authors found the optimal conditions to be a reaction temperature of 289 K, H_2 pressure of 60 bar, chiral modifier **52** and a mixed solvent system of toluene and acetic acid **1**; which afforded (*R*)-ethyl lactate **55** in 65% conversion and an *ee* of 90%. Using the aforementioned conditions in conjunction with a substrate concentration of 0.18 M afforded a production rate of 0.19 mmol g^{-1}catalyst h^{-1} (89% *ee*) and a TOF of 275 h^{-1}.

As an extension to earlier work, Ryu and co-workers[44,45] reported a low-pressure multi-phase system capable of performing carbonylative Sonogashira coupling and amidation reactions. The authors found that by conducting the multi-phase reactions in a series of stainless steel micro mixers (1000 μm i.d. and 400 μm i.d.), superior selectivities and yields could be obtained compared to those reactions conducted under conventional batch methodology. In addition, the use of an ionic liquid ([BMim]PF_6 **56**) as reaction solvent afforded efficient isolation of the Pd-catalyst $PdCl_2(PPh_3)_2$ **57** from the reaction products and facilitated catalyst recycle.

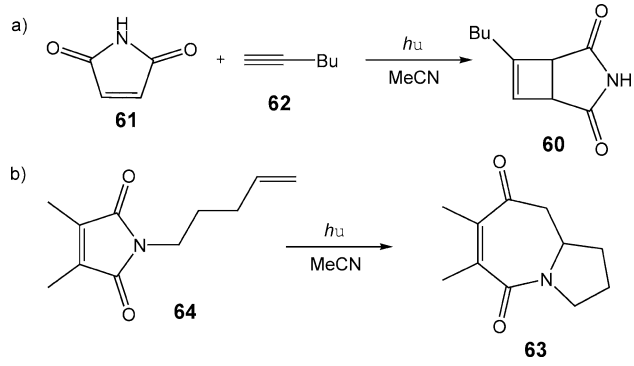
Kawanami and Ikushima[46] and co-workers more recently demonstrated the ability to perform a series of copper-free Sonogashira C–C couplings in water, using a technique inaccessible through conventional reaction methodology. Employing a flow process consisting of rapid collision mixing between a substrate and water (to afford particle dispersion) followed by rapid heating (to induce reaction) and cooling to afford a binary phase (consisting of the reaction products and water) the authors were able to obtain excellent yields and selectivities compared to the use of organic solvents. Employing palladium(II) chloride **58** (2 mol-%) as the catalyst, sodium hydroxide (2.0 M) as the base and a reaction temperature of 250 °C (at 16 MPa), near quantitative conversion of iodobenzene **31** to diphenylacetylene **59** was obtained with reaction times in the range of 0.1–4.0 s. Upon collection, the reaction product floated on the surface of the water and the catalyst precipitated as Pd^0, the reaction product was therefore isolated by filtration and phase separation. In addition to the rate acceleration observed, the technique of rapid mixing and heating afforded an unprecedented turnover frequency of 4.3×10^6 h^{-1}. This technique therefore has great potential as it removes the need for organic solvents enabling these reactions to be performed in an environmentally benign solvent system.

5.0 Continuous-Flow Photochemistry and Electrochemistry

In addition to improving reactions that are frequently employed in lead compound generation and subsequently translated to a process environment, areas such as electrochemistry and photochemistry have also benefited greatly from coupling reactor miniaturisation and continuous flow.

5.1 Photochemistry

Although photochemical transformations provide an attractive, atom efficient approach to the synthesis of complex molecules, the ability to scale-up such reactions is hampered by the difficulties associated with the scaling of light sources; consequently, its use in the development of drug candidates and fine chemicals is limited. The synthetic utility of photochemical transformations has, however, more recently been harnessed through the use of continuous flow reactors, enabling large volumes of material to be synthesised using commercially available, bench top light sources. One such reactor was recently reported by Booker-Milburn et al.[47] whereby a series of photocycloadditions were performed using a standard, water cooled immersion well wrapped in FEP tubing (700 μm i.d.). In the first instance, the authors demonstrated the synthesis of 6-butyl-3-aza-



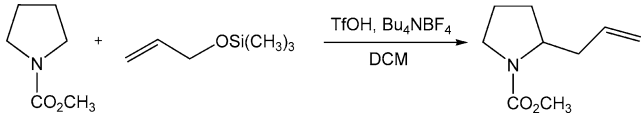
Scheme 17. (a) [2+2] Photocycloaddition of maleimide **61** and 1-hexyne **62** and (b) intramolecular [5+2] photocycloaddition of 3,4-dimethyl-1-pent-4-enylpyrrole-2,5-dione **64**.

bicyclo[3.2.0]hept-6-ene-2,4-dione **60** (Scheme 17, a), which was achieved by pumping a solution of maleimide **61** (0.10 M) and 1-hexyne **62** (0.15 M), in MeCN, through the reactor at 2.0 mL min^{-1}; affording 95% conversion to the desired product **60** at a throughput of 2.1 g h^{-1}. Additional photochemical transformations performed by the group included the synthesis of 7,8-dimethyl-1,2,3,9a-tetrahydropyrrolo[1,2-*a*]azepine-6,9-dione **63** (Scheme 17, b) which was achieved in 80% yield and a throughput of 7.4 g h^{-1}.

In addition to the photocycloadditions discussed, Mizuno and co-workers[48] reported enhanced regioselectivity as a result of conducting reactions under flow, Ehrich et al.[49] described the efficient chlorination of toluene-2,4-diisocyanate whereby space time yields of 410.0 mol^{-1} h^{-1} were obtained compared to 1.3 mol l^{-1} h^{-1} in a conventional batch reactor and Ryu et al.[50] performed the Barton reaction to afford a key intermediate in the synthesis of an endothelin receptor antagonist.

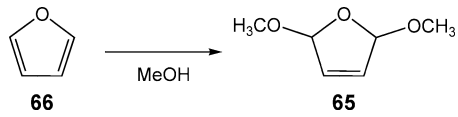
5.2 Electrochemistry

As observed with photochemical transformations, electrochemical reactions are rarely employed for the large-scale production of chemicals, due to inhomogeneities that arise within the electric field when reactors are increased in size. With this in mind, several authors have reported the use of miniaturised flow cells in order to achieve the desired reaction throughput without the need to increase the overall size of the reactor. This approach therefore has the potential to enable well characterised electrochemical systems to be employed for the manufacture of novel chemical agents. One such example is illustrated in Scheme 18 where Yoshida and co-workers,[51] reported a series of reactions based on 'cation flow' methodology. Employing a diaphragm flow cell, reactants were introduced in rapid sequence into a carrier stream whereby highly reactive carbocations, such as *N*-acyliminium ions, were generated and converted into the respective product. Using this approach, the authors were able to readily screen their electrochemical process, in a serial manner, to afford an array of interesting compounds derived from the coupling of carbamates and allylsilanes.



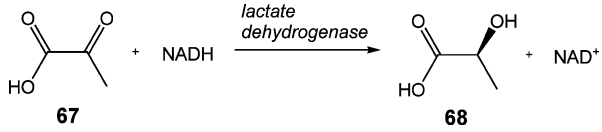
Scheme 18. An example of an electrochemical reaction conducted under 'cation flow' conditions.

In an electrochemical thin-layer flow cell, comprising of a Pt cathode and glassy carbon anode in parallel (with an inter-electrode distance of 80 μm), Atobe and co-workers[52] subsequently reported the synthesis of 2,5-dimethoxy-2,5-dihydrofuran **65** via the reduction of the methanolic solvent stream (Scheme 19). Employing a flow rate of 10–100 μL min^{-1}, and a current density of 3 mA cm^{-2}, the authors were able to obtain the target molecule **65** in 98% chemical yield and excellent purity without the need for an intentionally added electrolyte or subsequent purification of the reaction stream.



Scheme 19. Electrochemical oxidation of furan **66** to afford 2,5-dimethoxy-2,5-dihydrofuran **65**.

Although the use of enzymes as catalysts, has the potential to revolutionise synthetic chemistry, their cost and the difficulties associated with the efficiently recycling them, and any co-factors, has led to limited industrial uptake of the technology (see Section 3.2 for examples describing immobilised enzyme reactors). With this in mind, Kenis et al.[53] reported a PDMS micro fluidic system [channel dimensions: 250 μm (wide) × 3 cm (long)] capable of electrochemically regenerating nicotinamide co-factors. The authors found that by employing multi-stream laminar flow, comprising of a buffer stream and a reagent stream, regeneration of the co-factor could be achieved at the surface of a gold electrode. Using the conversion of achiral pyruvate **67** to L-lactate **68** in the presence of the enzyme lactate dehydrogenase (Scheme 20), the authors were able to demonstrate efficient enzyme/co-factor regeneration, equivalent to a turnover number of 75.6 h^{-1}.

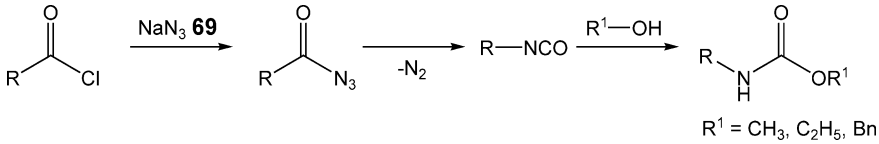


Scheme 20. Enzymatic synthesis of L-lactate **68**, employing electrochemical co-factor regeneration.

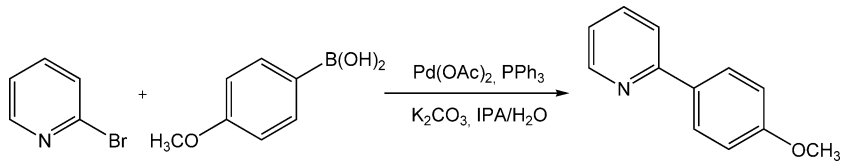
In addition to the reactions discussed, numerous electrochemical transformations have been investigated under continuous flow conditions, including C–C bond formations (achieved in the absence of electrolytes),[54] oxidative methoxylations[55] and cathodic reductions of allylic halides.[56]

6.0 Continuous Liquid-Liquid Extractions

Although the use of solid-supported reagents, catalysts and scavengers provides an important route to the continuous-flow synthesis of compounds of excellent purity, the technique does not suit all reaction types and consequently there remains a need to perform aqueous-organic extractions. In the field of micro fluidics, this problem has been tackled to some extent by the fabrication of reaction modules that enable liquid-liquid extractions to be performed within a continuous flow environment. In 2000, Kitamori and co-workers[57,58] observed an order of magnitude increase in extraction efficiency as a result of conducting separations within a miniaturised, pressure-driven system compared with a traditional separating funnel and mechanical shaker set-up.



Scheme 21. Multi-step reaction used to illustrate the ability to perform in-line separations and multiple reaction steps under continuous flow.



Scheme 22. Model reaction used to demonstrate the efficient removal of trace metals from continuous reaction streams.

An extension to this was later reported by Jensen and co-workers[59] who demonstrated a micro fluidic set-up capable of performing three synthetic steps and two in-line separations.[60] To illustrate the potential of the technique, the authors selected the synthesis of carbamates as a model reaction (Scheme 21). Employing an integrated silicon micro reactor, the first step was a phase transfer reaction between the aqueous sodium azide **69** (0.4 M in aq. NaOH) and the benzoyl chloride (0.36 M in toluene), affording the respective organic azide in 98% conversion. This was followed by a liquid-liquid extraction of the organic and aqueous phases, using a micro separator, based on a differential wettability of a fluoropolymer membrane. Decomposition of benzoyl azide to phenyl isocyanate was subsequently achieved in a second heated silicon reactor (105 °C) whereby 99% conversion was obtained. Unlike analogous batch reactions, where gentle heating (50 to 80 °C) is employed in order to prevent uncontrollable energy release, this represents an ability to significantly increase the operating temperature. After complete decomposition of the azide, toluene was removed in a gas-liquid separator and followed by the final reaction step, a biphasic reaction between the isocyanate and an alcohol. This system therefore provides an excellent solution to the problem faced with multi-step transformations, i.e. the need to perform a separation/purification or solvent exchange between reaction steps.

6.1 Trace Metal Removal

Within the pharmaceutical industry in particular, another form of purification that is required is the removal of heavy metals (to an acceptable level) from catalysed reaction mixtures and is often achieved through the use of solid-supported scavengers. As previously discussed, when operating reactions under continuous flow it is desirable to also perform subsequent purification steps continuously. With this in mind Pitts et al.[61] developed a reactor that enabled the removal trace metals, such as Pd, Cu, Co and Hg, from continuously flowing product mixtures. Using the Pd-catalysed Suzuki reaction illustrated in Scheme 22, the authors investigated a series of scavengers ranging from silica gel and carbon, to various QuadraPure resins (TU, IDA and AMPA) as a means of reducing the Pd content of the resulting product under continuous flow. Using this approach, they identified the thiourea-derived QuadraPure (TU) to be the most effective, removing at least 99.9% Pd from the reaction mixture in a single pass, to afford less than 1 ppm of residual Pd. The technique therefore represents a facile technique for the removal of trace metals from pharmaceutical agents prepared under flow conditions.

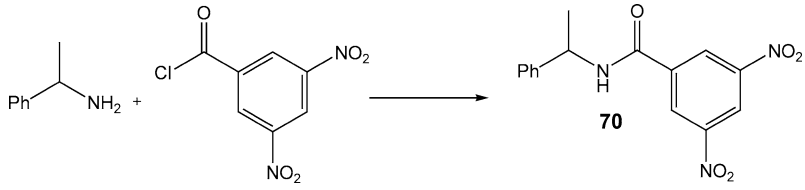
7.0 Screening of Substrates, Catalysts and Reaction Conditions

From the examples summarised herein, it can be seen that flow reactor methodology lends itself well to the rapid generation of synthetically diverse compounds via the serial introduction of reactants. Although this technique has the ability to be automated, many systems are still operated manually making the technique time-consuming and laborious.

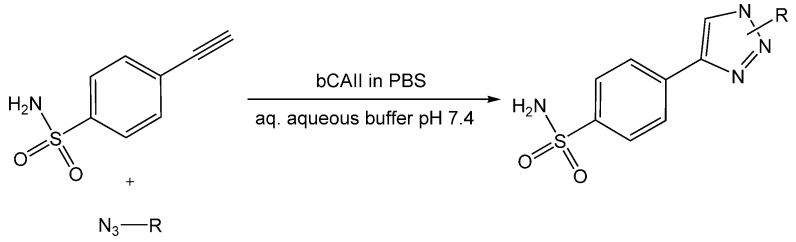
7.1 Continuous-Flow Parallel Synthesis

In addition to the synthesis of multiple reaction products using a serial approach, the following Section details the initial steps that have been taken towards developing continuous-flow parallel syntheses. The first example of such a system was reported by Kikutani and Kitamori,[62] who employed phase transfer amide formation as a model reaction to demonstrate the synthesis of a 2×2 parallel array. Pumping pairs of reactant solutions (A, B and C, D) through the four-channel device, the authors were able to generate 4 products, AC, AD, BC and BD, in at least 80% yield; with Scheme 23 illustrating an example of the reactions performed, affording 3,5-dinitro-*N*-(1-phenylethyl)-benzamide **70**.

More recently, however, Tseng and co-workers[63] described the fabrication and evaluation of a PDMS reactor, capable of performing 32 click reactions in parallel



Scheme 23. Synthesis of 3,5-dinitro-*N*-(1-phenylethyl)benzamide **70** in a parallel micro reactor.



Scheme 24. Illustration of the click reactions conducted in a parallel screening reactor.

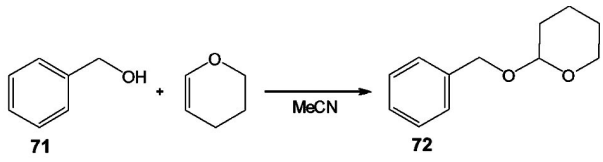
(Scheme 24). Employing a single planar sample loop, the authors were able to meter discrete aliquots of reactants (57 s reaction^{-1}), serially depositing them into addressable wells and enabling multiple reactions to be performed in parallel. As Table 3 illustrates, compared to a typical batch protocol, the micro-fluidic platform demonstrates between a 2- and 12-fold decrease in reagent consumption. Analysing the reactions by LC-MS, the authors obtained analogous results to those generated in a 96-well system, reporting the identification of the same 9 hits out of 20 compounds.

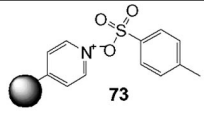
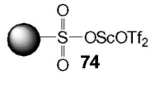
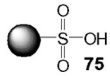
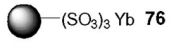
Table 3. Comparison of reagent consumption for the screening of a click chemistry library in batch and a micro-fluidic system.

	bCAII [μg]	Acetylene [nmol]	Azide [nmol]	Total volume [μL]
Batch	94	6.0	40.0	100.0
Micro-fluidic	19	2.4	3.6	4.0

In comparison, having previously demonstrated the successful incorporation of solid-supported reagents and catalysts into a series of EOF-based capillary-flow reactors, Haswell and co-workers[64] developed a micro reactor capable of performing parallel screening of 4 catalysts or supported reagents [channel dimensions: 280 μm (wide) × 90 μm (deep) × 2.0 cm (long)]. Employing the protection of benzyl alcohol **71** as its respective THP ether **72**, the authors evaluated a series of solid-supported Lewis acid catalysts **73**–**76** (1 mg channel^{-1}), the results of which are summarised in Table 4. In addition, the authors demonstrated the protection of a further 14 alcohols, affording isolated yields in excess of 99.4% and the quantitative deprotection of THP ethers when a methanolic solvent system was employed. Using this approach, catalytic turnover numbers in excess of 2760 were obtained, with no sign of degradation to date.

Table 4. Summary of the results obtained for the synthesis of 2-(benzyloxy)tetrahydropyran **72**, employing an array of solid-supported catalysts.



Channel number	Supported Lewis acid	Loading [mmol g^{-1}]	Flow rate [μl min^{-1}]	% Conversion
1	 **73**	3.50	1.10	100.0 (0.0)[a]
2	 **74**	0.60	1.60	99.9 (3.5×10^{-4})
3	 **75**	4.20	1.80	100.0 (0.0)
4	 **76**	2.00	1.50	99.9 (2.6×10^{-4})

[a] The numbers in parentheses represent the % RSD value, where $n = 15$.

7.2 Increasing Throughput by Multiplexing

The past decade has provided overwhelming evidence that micro-reaction technology is a powerful tool with respect to reaction optimisation; unfortunately, however, it is the analysis of the samples generated by such systems that can cause a bottleneck, leading to reduced efficiency of the overall system. This is illustrated by the fact that conservatively, a single micro reactor can generate enough sample to analyse chromatographically every five minutes, therefore

should the analytical methodology take longer than this, a list builds-up immediately. Consequently, sampling rates are frequently reduced and data from these information rich systems is lost. With this in mind, Trapp[65] recently communicated a methodology that enables the on-line analysis of up to 453 samples h^{-1} using a single chromatographic column. The technique is based on the fact that the majority of analysis time is spent recording detector noise therefore by increasing the duty cycle of a system, the amount of information can be maximised, whilst minimising analysis time. To enable the rapid, reproducible injection of multiple samples, the authors constructed a six-channel continuous flow split/splitless multiplexing injector, mounted onto a standard split injector of a GC, samples are then continuously evaporated in the sample ports and injected by short pressure pulses. A multiplexed chromatogram results, which is then deconvoluted to afford an overview of the chromatogram detailing the number of analytes, retention times and peak widths. Such a technique clearly has advantages for the field of reaction miniaturisation as it would reduce/remove the lag time currently experienced between sample generation and analysis.

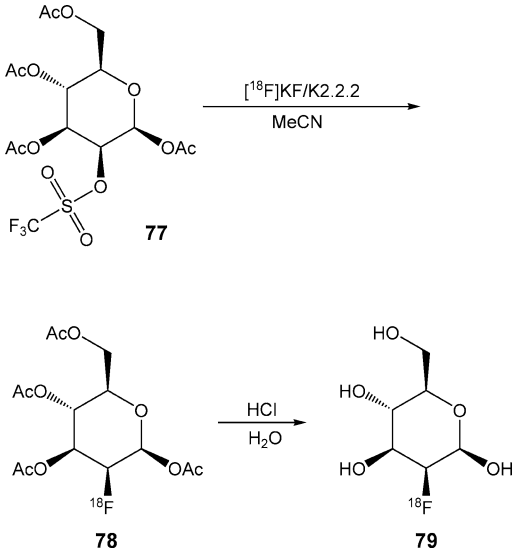
8.0 Examples of Molecules of Interest Synthesised in Micro Reactors

8.1 Synthesis of 2-[^{18}F]-FDG, a Radio-Labelled Imaging Probe

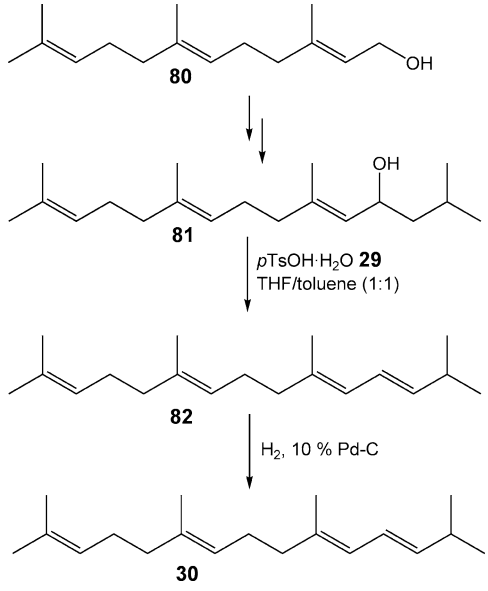
Cheng-Lee and co-workers[66] recently demonstrated the multi-step synthesis of a radio-labelled imaging probe in a PDMS micro reactor, consisting of a complex array of reaction channels with typical dimensions of 200 μm (wide) × 45 μm (deep). Employing a sequence of five steps, comprising of (i) [^{18}F]fluoride concentration (500 μCi), (ii) solvent exchange from H_2O to MeCN, (iii) [^{18}F]fluoride substitution of the D-mannose triflate **77** (324 ng), to afford the labelled probe **78** (100 °C for 30 s and 120 °C for 50 s), (iv) solvent exchange from MeCN to H_2O and finally (v) acid hydrolysis of **78** (60 °C), the authors demonstrated the synthesis of 2-[^{18}F]-FDG **79** (Scheme 25). Using this approach, 2-[^{18}F]-FDG **79** was obtained in 38% radiochemical yield, with a purity of 97.6%, determined by radioTLC. In addition, miniaturisation of the technique enabled the entire sequence to be performed in 14 min, compared to 50 min for the existing automated protocol. Most importantly, however, the authors not only found the synthesis to be reproducible between runs but also between reactors and propose that by increasing the size of the reaction chamber, the technique could be used to synthesise sufficient quantities of material suitable for human PET imaging (10 mCi $patient^{-1}$).

8.2 Synthesis of the Natural Product Pristane

In an extension to their earlier work (Scheme 7), Fukase and co-workers[17] employed the continuous flow dehydration of alkanols as a key reaction step in the synthesis of the immunoactivating natural product pristane (2,6,10,14-tetramethylpentadecane) **30** (Scheme 26). Since 2002, the availability of pristane **30** has been limited due to the listing of the basking shark *Cetorhinus maximus* as an endangered species; with this in mind, the authors evaluated a microfluidic approach to the large-scale synthesis of the hydrocarbon **30**. The first step of the reaction involved the treatment of farnesol **80** with MnO_2 to afford the respective aldehyde, which subsequently underwent reaction with isobutylmagnesium chloride to afford the allylic alcohol derivative **81**. The alcohol **81** (1.0 M in THF) was subsequently dehydrated within a micro mixer (Comet X-01) using



Scheme 25. Synthesis of the radiolabel 2-[^{18}F]-fluorodeoxyglucose (2-[^{18}F]-FDG) **79**.

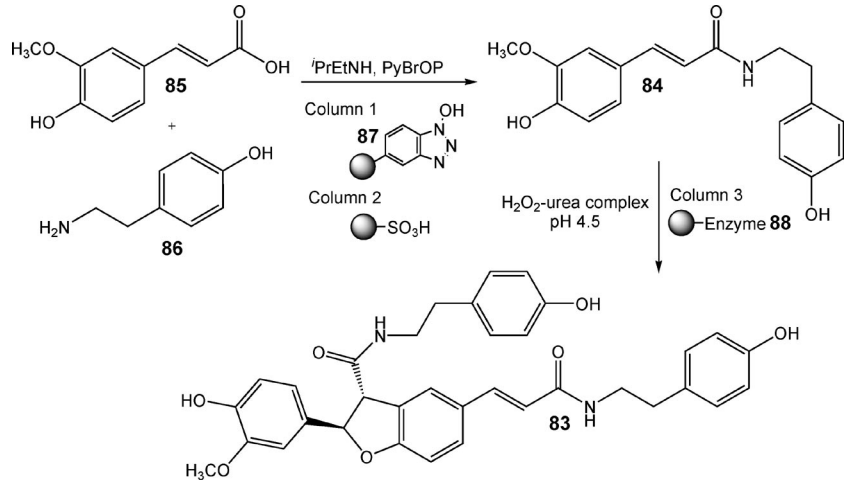


Scheme 26. Synthesis of the natural product pristane **30** via a continuous flow dehydration step.

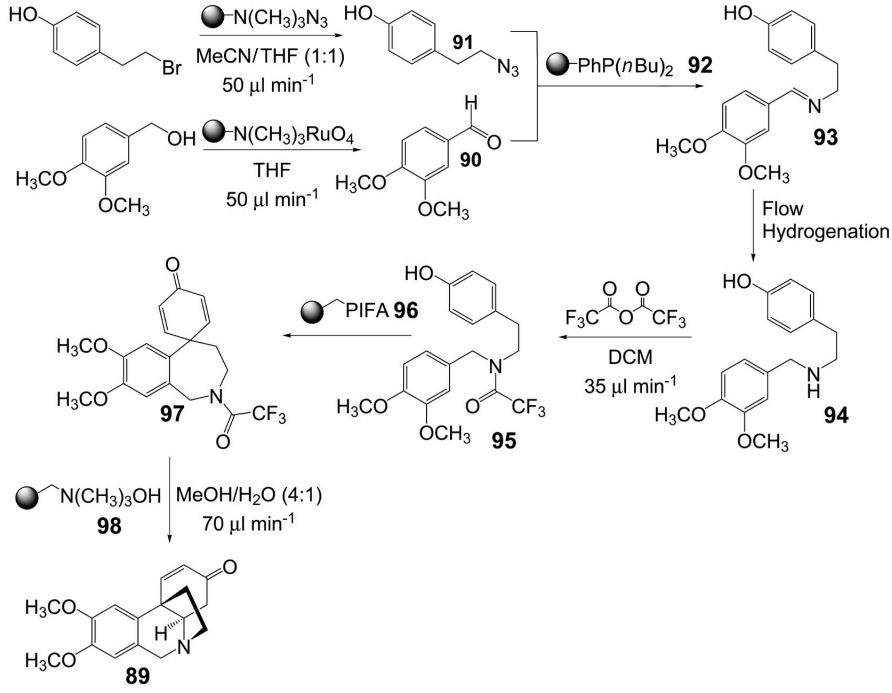
*p*TsOH·H_2O **29** in THF/toluene (0.2 to 1.0 M), a total flow rate of 600 μL min^{-1}, a reaction temperature of 90 °C followed by catalytic hydrogenation of alkene **82**. Using this approach, the authors were pleased to report the synthesis of pristane **30** in 80% yield from farnesol **80**. Compared to conventional batch techniques, this synthetic route proved advantageous as it only requires a simple purification to be conducted unlike the multiple distillations previously employed. The route presents significant advancements over traditional techniques, enabling an efficient route to the multi-kilogram synthesis of pristane **30**, which is in-line with the current demand of ca. 5 kg per week.

8.3 Enantioselective Synthesis of Grossamide

Ley and co-workers[67] recently described the first enantioselective synthesis of 2-aryl-2,3-dihydro-3-benzofurancarboxyamide neolignan (grossamide) **83** conducted under continuous flow conditions. As Scheme 27 illustrates, the first step of the reaction involved the synthesis of amide **84**, which was achieved via the coupling of ferulic acid **85** and tyramine **86**, in the presence of polymer-supported HOBt **87** (column 1), with the reaction progress monitored by LC-MS. Using this approach, an optimal conversion of 90% amide **84** was obtained, consequently prior to conducting



Scheme 27. Synthetic strategy employed for the continuous-flow synthesis of the natural product grossamide **83**.



Scheme 28. Synthesis of the natural alkaloid (±)-oxomaritidine **89** under continuous flow conditions.

the second step, it was imperative to remove any residual tyramine **86**; this was achieved using a scavenging resin. The purified amide **84** was then pre-mixed with a H_2O_2–urea complex and passed through a third column which contained silica-supported peroxidise **88**, affording the desired product, grossamide **83**, in excellent purity.

8.4 Continuous-Flow Synthesis of (±)-Oxomaritidine

The group subsequently reported the use of a series of packed columns, containing immobilised reagents, catalysts and scavengers, in conjunction with a glass micro reactor for the continuous-flow synthesis of the alkaloid natural product (±)-oxomaritidine **89**.[68] As Scheme 28 illustrates, the first step of the process involves the parallel synthesis of an azide **90** and an aldehyde **91**, which when combined react in the presence of a polymer-supported phosphane **92** to afford the desired imine **93**. Continuous flow hydrogenation afforded the respective 2° amine **94** which subsequently underwent near quantitative trifluoroacetylation in a glass micro reactor (at 80 °C, 35.0 μL min^{-1}) to afford amide **95**, followed by oxidative phenolic coupling in the presence of polymer-supported (ditrifluoroacetoxyiodo)benzene **96** to afford a seven-membered tricyclic derivative **97**. Base (**98**) promoted 1,4-conjugate addition followed to afford (±)-oxomaritidine **89** in an overall yield of 40%.

9.0 The Role of Flow Reactors in Chemical Production

Production technology, at present, relies on the scale-up of laboratory optimised reaction, firstly to a pilot plant and finally to a production plant that is capable of generating the desired volume of material. This technique is, however, flawed as at each stage of the scale-up, reactor modifications lead to changes in the thermal and mass transportation properties of the reaction. Consequently, reactions may need to be re-optimised at each stage of the process or in some cases, may fail to be scaled-up. This can lead to severe delays once a target has been identified, making the route from the laboratory to production both costly and time consuming. Micro reaction technology aims to address this by employing reactor configurations at the stage of lead development that can simply be replicated in order to meet the production criteria, either by internal numbering-up or be operating multiple reactors in parallel. Using this approach ensures that the reaction conditions employed at a research level are those that are subsequently used on a production-scale, reducing the risk and costs associated with reaction transfer. The technique also removes operator dependency from the system, ensuring that once optimised, a reaction can be performed by anyone that follows the standard operating procedure. Furthermore, the use of continuous-flow technology enables changes in production volume to be met with ease, reducing the costs associated with the manufacture and storage of unsold products and removing the need to reconfigure batch reactors.

As an extension to their earlier work conducted in single channel reactors, Chambers and co-workers[69] recently published a manuscript detailing the successful scale-out of their reactor whereby 30 reaction channels were operated in parallel. Employing this approach enabled the efficient heat exchange and gas/liquid mixing obtained in the single channel reactor to be maintained whilst providing an increased throughput without resorting to the use of a hazardous batch-scale fluorination. In order to demonstrate the scalability of the technique, the authors again used the fluorination of ethylacetoacetate as a model, whereby a throughput of 0.2 g channel^{-1} h^{-1} was obtained which translates to 150.0 g d^{-1}.

Although the use of micro reaction technology is well documented within academia, few papers appear in the open literature describing their industrial use.[70] In 2004 Zhang and co-workers,[71] from Johnson and Johnson Pharmaceuticals, reported the use of a stainless steel flow reactor to perform a series of reactions using unstable intermediates and high reaction temperatures, for the controlled synthesis of kilogram scale quantities of product. One such example was the synthesis of *N*-methoxycarbonyl-L-*tert*-leucine via the addition of methyl chloroformate **23** to L-*tert*-leucine in the presence of aq. NaOH. Conducting the flow reactions at –40 °C afforded the desired product, with a throughput of 83.0 g h^{-1}.

10.0 Conclusions and Outlook

Through providing a brief overview of the field of micro reaction technology, it is hoped that newcomers to the area will have gained an insight into the advantages associated with this up and coming technique and for those researching within the area, a summary of the recent advancements made has been provided.

Compared to conventional batch techniques, it can be seen that continuous flow reactors, in particular micro reactors, can lead to significant improvements in the quality of product synthesised and possibly most importantly, the ease with which transformations can be taken from a laboratory setting to a production environment through the process of scale-out. It is at this point that we would like to draw the readers attention to the fact that clearly not all reactions are suitable for conducting in such continuous flow systems, with one of the main limitations being the relative insolubility of reactants and the formation of precipitates over the course of a reaction, which could preclude the use of such micro channels.[72] As a result, part of the optimisation process associated with the use of such reactors is to perform exhaustive solvent studies in order to evaluate the feasibility associated with the transfer of a particular reaction from batch to flow. With this in mind, a present drawback of the technique is the rate at which reactions can be optimised, with limitations resting largely on the throughput of commercially available analytical instrumentation. Consequently for the technique to be adopted by mainstream synthetic chemists, further advances in the use of on-line ana-

lytics is required. Whether or not micro reactors will replace round bottomed flasks remains to be seen; however, the current uptake of the technology appears promising.

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