Recent advances in synthetic micro reaction technology

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Although in its infancy, the field of micro reaction technology is growing rapidly, with many research groups investigating the practical advantages associated with reaction miniaturisation. With this in mind, the following *Feature Article* aims to provide an overview of the progress made in the past decade, paying particular attention to the field of synthetic organic chemistry.

Introduction

At present, the majority of synthetic reactions are performed using techniques and apparatus that have been in place for decades. A major problem observed with conventional process technology however, is the failure to scale-up successful laboratory reactions in order to achieve mass production. Micro reaction technology has the potential to bypass this step, attaining large volume production through the replication of unit processes, enabling the direct transfer of laboratory optimised conditions to production scale. Reaction miniaturisation is therefore of particular interest to the pharmaceutical industry where long-term objectives include the desire to perform multiple functions such as synthesis, screening, detection and biological evaluation on a single integrated device, resulting in an overall reduction in the time taken to discover new lead compounds and transfer them to production.

With this in mind, the theoretical advantages associated with micro reaction technology are briefly discussed herein, along with a series of practical examples, which aim to illustrate the intrinsic advantages associated with reaction miniaturisation.

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Paul Watts graduated from the University of Bristol in 1995 with a first class BSc in chemistry. He continued his studies at Bristol, obtaining a PhD in bio-organic natural product chemistry under the supervision of Professor Tom Simpson FRS and Professor Chris Willis. His PhD focused 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 February 2002, he was appointed as an academic at The University of Hull where he now leads the micro reactor group, which consists of 3 post doctoral researchers and 7 PhD students. He is interested in organic chemistry, catalysis, biocatalysis and electrosynthesis in micro reactors and has published more than 50 papers in the area.

Charlotte Wiles studied at The University of Hull where she obtained her PhD in 2003, entitled 'Organic Synthesis in Micro Reactors', under the guidance of Professor S. J. Haswell. Her post-doctoral research currently focuses on improving reaction efficiency as a function of incorporating solid-supported reagents and catalysts into micro-fabricated reactors.

1.0 Basic concepts of micro reaction technology

In the context of this article, a micro reactor is defined as a device that contains micro structured features, with a sub-millimetre dimension, in which chemical reactions are performed in a continuous manner.

1.1 Fabrication of micro reactors

To date, micro structured reactors have been fabricated from a variety of substrates including silicon,[1] quartz,[2] metals,[3] polymers,[4] ceramics[5] and glass,[6] with the choice of substrate being largely governed by the end use of the reactor and the fabrication technique employed. Consequently, when 'designing' a micro reactor, the substrate must be evaluated for chemical compatibility, thermal/pressure resistance and ease of fabrication. Depending on the substrate selected and the degree of complexity required, a range of micro fabrication techniques are available, including LIGA (LIthographie Galvanoformung Abformung, translating to lithography, electroforming and moulding), DRIE (Deep Reactive Ion Etching), laser ablation, photolithography, hot embossing, injection moulding, powder blasting and microlamination.[7] Due to the exceptional surface quality, definition and reproducibility afforded by techniques such as laser ablation and DRIE, they have featured widely within the literature. The costs associated with precision engineering and the serial nature of the technique however, makes mass production *via* this route undesirable. Conversely, techniques such as hot embossing and injection moulding have proved advantageous as they enable rapid device replication through the use of a master/template, providing a relatively inexpensive approach to high quality, mass-produced reactors. The technique is principally used for the fabrication of ceramic, polymeric and metallic based devices; with photolithographic wet-etching or powder blasting techniques employed for the rapid fabrication of low aspect ratio features in glass.

1.2 Manipulation of fluids within micro fluidic systems

In order to achieve the overall goal of performing multiple functions, such as product synthesis, purification and biological assessment with an integrated micro fabricated device,

accurate pumping mechanisms are required. In conjunction with the field of μTAS (micro total analysis systems), a diverse array of pumps have been developed and for simplicity they have been loosely categorised as either mechanical or non-mechanical.[8]

1.2.1 Mechanical pumping. Most mechanical or reciprocating micro pumps are based on the movement of a membrane resulting in the delivery of fluids or gases in discrete aliquots. Due to the wide array of primary sources, actuation of a membrane can be achieved using a variety of techniques including piezoelectric,[9] thermo-pneumatic[10] and shape memory alloys.[11] As the pumping mechanism is independent of the device material, any fluid can be mobilised, the disadvantage of the technique is that flow is often pulsed (although exceptions have been demonstrated[12]). Alternatively, external displacement pumps (such as syringe pumps) have found widespread use at a research level, due to their ability to deliver stable bi-directional flow. The main challenges associated with this approach are obtaining low dead volume, leak-free connections between the pump and device,[13] along with the uniform control of multiple reagent inlets.[14]

1.2.2 Non-mechanical pumping. In contrast, non-mechanical pumping mechanisms are often termed continuous flow as they are based on the direct transfer of energy, which results in a steady, pulse-free flow throughout the device. Many non-mechanical pumps are available including, electrochemical displacement (bubble formation),[15] thermal expansion,[16] microsphere deformation,[17] electrohydrodynamic[18] and those employing capillary[19] or evaporation[20] forces. Compared to mechanical micro pumps, the use of non-mechanical pumping mechanisms is advantageous as the techniques are inherently simple, contain no moving parts and enable pulse-free, low flow rates to be achieved. The main disadvantage however is that in some cases, the performance of the pump is directly linked to the properties of the liquid; an example of this is electrokinetic flow.

Manz and co-workers[21] first described the use of electrokinetic flow in a miniaturised flow injection system, a concept that Dasgupta and Lui[22] further developed. Harrison and co-workers[23] later applied the technique to the mobilisation of fluorescein labelled amino acids in a glass reaction manifold, where the valve-less control of fluids was demonstrated at a T-shaped intersection (Fig. 1). In comparison to mechanical pumps, field induced flow is advantageous as it acts as a valve and a pump, enabling both the direction and magnitude of flow to be controlled.[24]

1.2.2.1 Electrokinetic flow. Electrokinetic flow comprises of two physical effects, electroosmotic flow (EOF), which is responsible for the velocity of the fluidic system as a whole, and electrophoretic flow (EPF), which is an additional velocity effect experienced by charged species within the bulk system. As Fig. 2 illustrates, when an ionisable surface such as glass, quartz or Teflon comes in contact with a suitable solvent system, the surface is neutralised with a diffuse layer of positive ions from the bulk.[25] A proportion of the counterions are adsorbed onto the surface, resulting in the formation of an

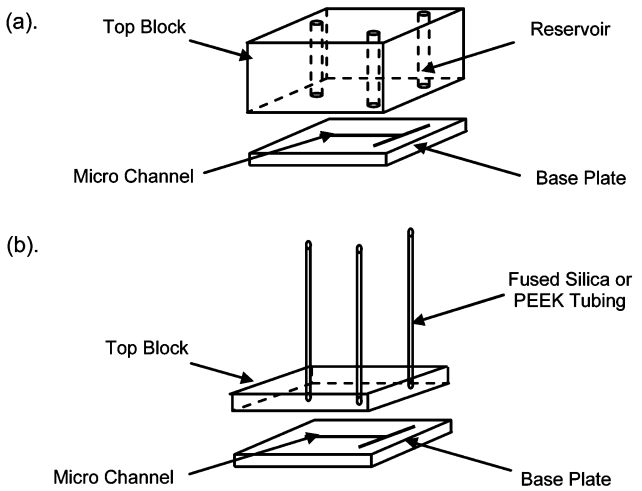


Fig. 1 Schematic illustrating the basic components of glass micro reactors fabricated for (a) electroosmotic and (b) pressure-driven applications.

immobile layer, and the remaining positive ions form a transient double layer. Application of an electric field causes the double layer to move towards, in the case of glass, the most negative electrode; inducing bulk flow within the micro channel.

While EOF has largely been associated with the manipulation of aqueous systems, with respect to analytical applications, more recently the technique has been employed for the manipulation of organic solvents such as methanol (MeOH), acetonitrile (MeCN) and *N,N*-dimethylformamide (DMF).[26] As eqn (1) illustrates, the electroosmotic flow velocity is largely determined by the dielectric constant, polarity and viscosity of the solvent system. Consequently, the technique is restricted to the use of solvents such as alcohols, tetrahydrofuran (THF), DMF, MeCN and aqueous systems (pH 2 to 14).

$$v_{\mathrm{eof}} = -\frac{E\varepsilon\varepsilon_0\zeta}{\eta} \quad (1)$$

In eqn (1) the determination of electroosmotic flow velocity (v_{eof}) is dependent on E = applied field, ε = relative dielectric constant of the fluid, ε_0 = the permittivity of free space, ζ = zeta potential and η = viscosity.[27]

1.3 Control of reaction conditions

The regulation of temperature and concentration is crucial in maintaining control over a process, not only to

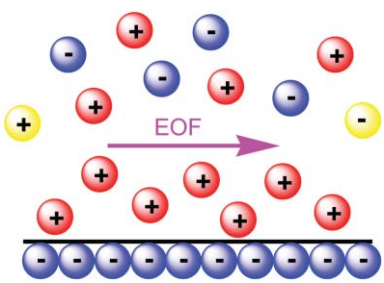


Fig. 2 Schematic illustrating the principle of EOF in a glass micro channel.

ensure selective product formation, but also from a safety perspective.[28,29]

1.3.1 Mixing on the micro-scale. On a macro-scale, mixing is achieved using mechanical or magnetic stirrers whereby large eddies (circular motion) are generated, allowing bulk diffusion to dominate.[30] On the micro-scale however, due to high viscous forces, turbulence is not induced (eqn (2)) and mixing is dominated by molecular diffusion (eqn (3)). Consequently, a facile technique used to increase the rate of diffusive mixing is to employ narrow, high aspect ratio reaction channels, hence increasing the interfacial surface area.[31] Whitesides and co-workers[32] exploited this interfacial diffusion, as a means of preparing silver electrodes within a sealed micro channel. Although this example demonstrated the advantages associated with a laminar flow environment, with respect to performing synthetic reactions, rapid mixing is desirable and is often achieved by the incorporation of a micro mixer.

$$Re = \frac{D_e v \rho}{\eta} \quad (2)$$

In eqn (2) the determination of a systems Reynolds number (Re) is dependent on v the velocity, ρ the density of the liquid, η the viscosity of the liquid and D_e the effective channel diameter.

$$t_d = \frac{L^2}{D} \quad (3)$$

Eqn (3) shows the approximation for molecular diffusion within a micro channel,[33] where t_d is the diffusion time, L is the distance over which the diffusion must occur and D is the diffusion coefficient.

To date, the micro mixers developed fall into two categories, those that impose control over of reagent flow through the use of moving parts or varying pressure gradients (active) and those that require no energy input other than that used to mobilise fluid within the device (passive).[34] Although many different types of micro mixer have been reported within the literature, one of the most popular approaches involves increasing the contact area between reagent streams by lamination. An example of this described by Manz and co-workers[35] involved splitting two reagent streams into thin 'laminae' and subsequently bringing them back together to allow a greater degree of diffusive mixing at the point of confluence (n laminae = n^2 faster mixing); affording complete mixing in 15 ms. Consequently, with the ability to efficiently mix reagent streams, reactions performed in such miniaturised systems are simply limited by the inherent reaction kinetics.

1.3.2 Temperature control. In traditional large-scale reactor vessels, fluctuations in reaction temperature are difficult to correct as any alterations made take time to have an effect on the system as a whole. In comparison, changes are observed almost immediately on the micron-scale. As the flow regime obtained within micro fluidic devices is laminar, the time taken to enable thermal mixing across a micro channel can be approximated by diffusion theory. Along with increasing the rate of thermal mixing, decreasing the channel diameter results in an inherently high surface-to-volume ratio (Fig. 3), which enables the rapid dissipation of heat generated over the course of a reaction (silicon channels = 41 000 W m^{-2} K^{-1} and glass = 740 W m^{-2} K^{-1}).

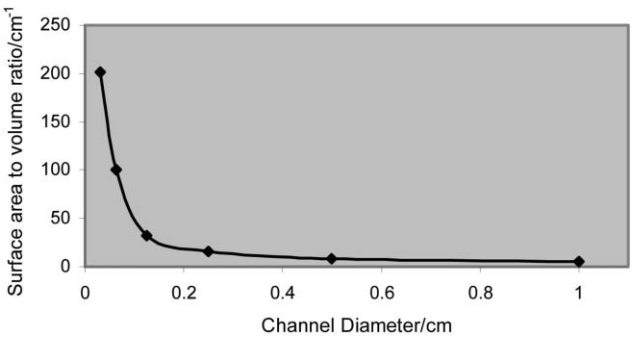


Fig. 3 Graph illustrating the effect of channel diameter on the surface-to-volume ratio.

Until recently, the majority of temperature control applied to micro reaction systems was based on the removal of heat in order to prevent hot-spot formation and thermal runaway in highly exothermic reactions.[36] More recently however, research has centred on techniques that enable micro reactors to be heated; this is not a trivial task however as micro reactors are renowned for their ability to efficiently dissipate heat (See Section 2.1.1.1 for examples).

1.4 Process intensification

Although many theoretical advantages of reaction miniaturisation have been presented, a perceived disadvantage of the technique is the fact that only small quantities of material can be synthesised, this can however be addressed through a process known as scale-out or numbering-up.

Whereas current production technology is based on the scale-up of bench-optimised processes, firstly by construction of a pilot plant, followed by a final increase in scale to achieve mass production, micro reaction technology is based on the replication of successful reaction units. This approach not only removes the problems associated with any changes in surface-to-volume ratio (and hence the thermal and mass transportation properties of the reaction) that are experienced as a reactor is scaled-up, but also enables process flexibility (as reactors are no longer configured for a single operation).[37]

It has therefore been proposed that through the application of micro reaction technology, processes would initially be optimised on a single device and in order to increase the production capacity, more devices would simply be employed. In addition to the obvious time and cost savings, the approach of scale-out is advantageous as the laboratory-optimised conditions are retained on a production scale. This is a particularly attractive feature, as it enables the use of previously unscalable reactions for the production of fine chemicals and pharmaceuticals.

As illustrated in Section 3.0, with the ability to mass produce micro reactors becoming a reality, the gap between research based applications and their use as tools for chemical production has begun to be bridged.

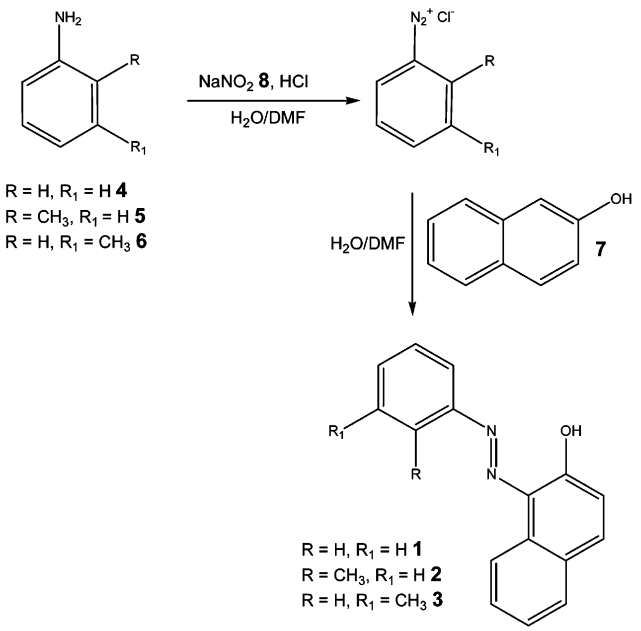
2.0 Synthetic micro reactions

Having provided a brief overview of the theoretical advantages associated with reaction miniaturisation, the remainder of the article details the application of micro reaction technology to an array of reaction types ranging from liquid-phase (Section 2.1) and multi-phase (Section 2.2), to the recent advances in multi-step syntheses (Section 2.6) and process intensification (Section 3.0).

2.1 Liquid-phase reactions

Based on the many practical advantages demonstrated by the gas-phase community,[38] research into liquid-phase micro reactions began in the late 1990's, focussing on the miniaturisation of successful batch reactions. As the following section highlights, an array of reactions have been conducted within miniaturised systems, with the most apparent advantages being reduced reaction times and increased reaction selectivity compared to batch.

An early example of a liquid-phase micro reaction was reported by Harrison and co-workers[39] who demonstrated the EOF-based synthesis of an azo dye in a Pyrex micro reactor (channel dimensions = 90 μm (deep) × 190 μm (wide)). This example not only served to illustrate the feasibility of performing liquid-phase micro reactions, but also the use of field induced flow as a means of controlling organic reagents and products within micro channel networks. Based on this preliminary investigation, many research groups have subsequently demonstrated the synthesis of azo dyes. One such example was reported by de Mello and co-workers[40] whereby a pressure-driven glass reactor (channel dimensions = 150 μm (wide) × 50 μm (deep) × 8 cm (length)) was employed for the synthesis of three azo dyes **1**, **2** and **3** (Scheme 1) derived from the coupling of aniline **4**, 2-toluidine **5** and 3-toluidine **6** with β-naphthol **7**.



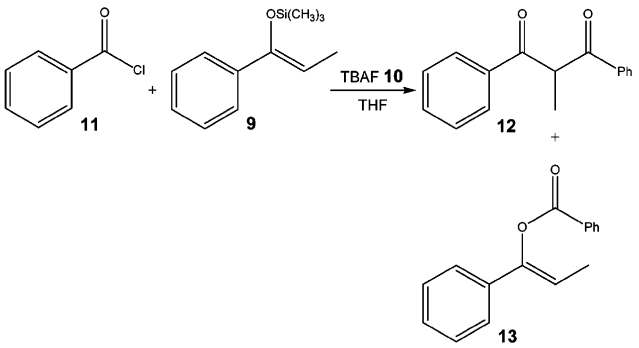
Scheme 1 Diazonium chemistry performed within a pressure-driven micro reactor.

In comparison to the previous example, de Mello *et al.* described both the synthesis and subsequent *in situ* reaction of the diazonium salt, demonstrating the ability to prepare and handle reactive intermediates within micro fabricated reactors. Furthermore, the authors highlighted the potential of micro reaction technology for the large-scale production of highly unstable reaction intermediates (Section 3.0). To perform a reaction, an acidified solution of aryl amine and a solution of sodium nitrite **8**, in aqueous DMF, were introduced from two separate inlets (at 3.5 μl min^{-1}). The reagents diffused over a channel length of 4.0 cm to afford the diazonium salt, prior to the addition of a basic solution of β-naphthol **7** from a third inlet (at 7.0 μl min^{-1}). Product formation was subsequently inferred *via* a persistent red colouration of the latter 4.0 cm of micro channel, which was confirmed off-line by spectral analysis. Using this approach, the authors reported conversions of 52.0%, 23.0% and 9.0% for the synthesis of Sudan I **1**, 1-(2-methylphenylazo)-2-naphthol **2** and 1-(3-methylphenyl)-2-naphthol **3**, respectively.

In addition, Wille and co-workers[41] recently reported the industrial application of micro reaction technology, employing a CPC stainless steel/glass micro reactor for the pilot-scale synthesis of a red and a yellow pigment. Utilising standard diazotisation chemistry, the authors focussed their investigations on the colouristic properties of the pigments produced within the micro reactor compared to those obtained from standard batch produced pigments. Upon scale-up of the undisclosed reactions from a lab-scale to pilot-scale, the authors noted a dramatic reduction in pigment quality, an observation that can be attributed to a reduction in mixing efficiency as a function of increasing reactor volume (Section 1.3). In comparison, through numbering-up of the micro reactor set-up, to achieve a greater throughput, comparable pigment qualities were obtained on both a lab-scale and pilot-scale. In all cases, dyes of a higher purity, brightness and glossiness were prepared using the micro reactors than obtained in a conventional stirred batch reactor, due to the enhanced reaction control obtained. Using this approach, the authors report a pilot-stage micro reactor output of 30.0 l h^{-1}, demonstrating the feasible transfer of traditional synthetic processes from lab-scale micro reaction set-ups, to those capable of operating on a production scale.

As part of an ongoing investigation into the use of micro reactors as tools for organic synthesis, Wiles *et al.*[42] demonstrated the regioselective synthesis of an array of 1,3-diketones in a borosilicate glass micro reactor (channel dimensions = 100 μm (wide) × 50 μm (deep) × 3.0 cm (length)), under electroosmotic flow conditions.

As Scheme 2 illustrates, a typical reaction involved the *in situ* regeneration of an ammonium enolate, by treatment of a silyl enol ether **9** with 'anhydrous' tetrabutylammonium fluoride (TBAF) **10**, followed by acylation with benzoyl chloride **11** to afford the respective 1,3-diketone **12**. In order to perform a micro reaction, solutions of 'anhydrous' TBAF **10** (0.10 M), benzoyl chloride **11** (1.00 M) and trimethyl(1-phenylpropenyloxy)silane **9** (1.00 M) in anhydrous THF were introduced into the micro reaction channel from three separate inlets *via* the application of 375, 455 and 405 V cm^{-1} respectively. Reactions were performed for 20 min, the reaction products collected at

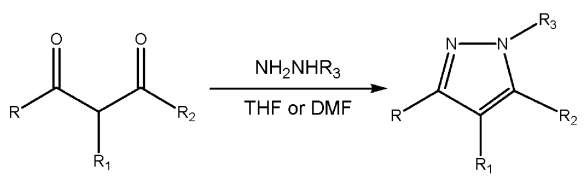


Scheme 2 Synthesis of 2-methyl-1,3-diphenylpropane-1,3-dione **12**.

the outlet (0 V cm^{-1}) and analysed off-line by GC-MS; whereby chromatograms of the reaction products were compared to a synthetic standard. Using the aforementioned methodology, quantitative conversion of trimethyl(1-phenylpropenyloxy)silane **9** to 2-methyl-1,3-diphenyl-1,3-dione **12** was reported, with no sign of the *O*-acylated product **13** formation. The authors subsequently reported additional examples of enolate chemistry performed within EOF-based micro reactors, including the aldol reaction and a series of Michael additions.[43]

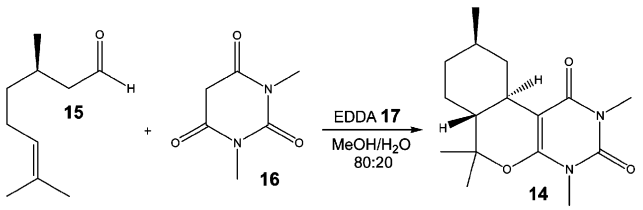
As an extension to the aforementioned selective synthesis of 1,3-diketones (Scheme 2), the group subsequently demonstrated the use of a borosilicate glass micro reactor (channel dimensions = 350 μm (wide) × 52 μm (deep) × 2.5 cm (length)) for the synthesis of an array of 1,2-azoles (Table 1).[44] To conduct a micro reaction, solutions of 1,3-diketone (1.00 M) and hydrazine derivative (1.00 M) in anhydrous THF were introduced into the micro reactor from separate inlets, by application of a positive voltage and the reaction products collected at the common ground; typical flow rates of 1.5 μl min^{-1} were employed. Reactions were performed over a period of 20 min and the reaction mixture analysed off-line by GC-MS in order to determine the percentage conversion of 1,3-diketone to the respective 1,2-azole. As Table 1 illustrates, the reactions of 1,3-diketones and hydrazine monohydrate (Entries 1–5) afforded excellent conversions, however when employing benzyl hydrazine hydrochloride (318, 318 and

Table 1 Summary of the results obtained for the synthesis of an array of 1,2-azoles in an EOF-based micro reactor



Entry	R	R_1	R_2	R_3	Applied field/V cm^{-1}	Conversion (%)
1	CH_3	H	CH_3	H	292, 318 and 0	100.0
2	Ph	H	CH_3	H	364, 341 and 0	100.0
3	$-(CH_2)_4-$		Ph	H	260, 303 and 0	100.0
4	Ph	H	Ph	H	386, 364 and 0	100.0
5	Ph	CH_3	CH_3	H	292, 318 and 0	98.0
6	Ph	H	CH_3	CH_2Ph	318, 318 and 0	42.0 (100.0)[a]

[a] Micro reaction performed using a stopped flow regime.



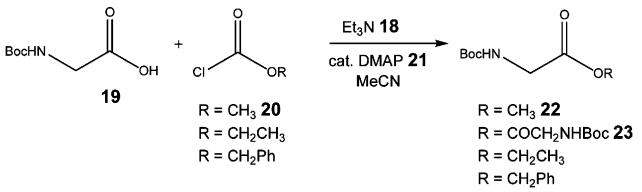
Scheme 3 Schematic illustrating a Domino reaction performed in a micro reactor.

0 V cm^{-1}) (Entry 6) only 42.0% conversion to the substituted 1,2-azole was obtained. This was later optimised, by the use of a stopped flow technique (resulting in an increased reagent residence time), to afford quantitative conversion. Furthermore, substitution of hydroxylamine hydrochloride (1.00 M) for hydrazine monohydrate enabled the synthesis of 5-methyl-3-phenylisoxazole in 98.0% conversion (292, 318 and 0 V cm^{-1}), representing a reactor throughput of 0.339 g day^{-1} (therefore, operating 1000 devices in parallel would enable the synthesis of 339.0 g day^{-1}).

Using pressure-driven flow, Fernandez-Suarez and co-workers[45] investigated a series of Domino reactions in a soda-lime glass micro reactor, with reaction channel dimensions of 74 μm (wide). As Scheme 3 illustrates, the reactions involved a base catalysed Knoevenagel condensation followed by an intra-molecular hetero-Diels–Alder reaction. In order to synthesise cycloadduct **14** within a micro reactor, a solution of *rac*-citronellal **15** (0.10 M) and a pre-mixed solution of barbituric acid **16** (0.12 M) and ethylenediamine acetate (EDDA) **17** (0.01 M), in MeOH–H_2O (80 : 20), were introduced into the reaction channel from inlets A and B respectively. Reagents were mobilised within the reactor using a series of computer controlled peristaltic pumps and micro reactions performed for 30 min, prior to off-line analysis of the reaction products by LC-MS. Employing an initial reagent residence time of 2 min, the authors reported 59.5% conversion to cycloadduct **14**, which was further increased to 68.0% conversion by extending the reagent residence time to 6 min.

Another commonly employed synthetic transformation investigated within EOF-based micro reactors is the esterification of carboxylic acids. Although many techniques are reported within the literature, due to the extremes of pH and elevated reaction temperatures often employed, few are mild enough to be performed in electrokinetic systems or on acid sensitive compounds. With this in mind, Haswell *et al.*[46] investigated the catalytic conversion of a series of *in situ* generated mixed anhydrides to esters in an EOF-based, borosilicate glass micro reactor (channel dimensions = 350 μm (wide) × 52 μm (deep) × 2.5 cm (length)).

To perform a micro reaction, solutions of triethylamine (Et_3N) **18** (1.00 M), pre-mixed Boc-glycine **19** and methylchloroformate **20** (1.00 M) and 4-dimethylaminopyridine (DMAP) **21** (0.50 M) in anhydrous MeCN were mobilised through the micro reactor (385, 417 and 364 V cm^{-1}) for a period of 20 min and the reaction products collected at the common ground in MeCN. Analysis of the resulting reaction mixture, off-line, by GC-MS confirmed quantitative conversion of Boc-glycine **19** to the respective methyl ester **22**, with

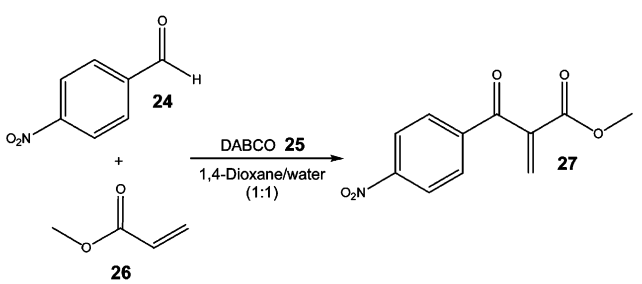


Scheme 4 Esterification of boc-glycine in an EOF-based micro reactor.

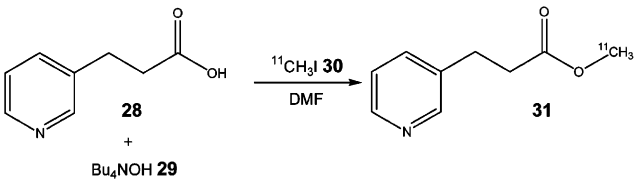
no sign of the competing anhydride formation **23**. To demonstrate the generality of the technique, the ethyl and benzyl esters of Boc-glycine were also synthesised (Scheme 4), along with the esterification of an array of substituted aromatic carboxylic acids, in all cases, excellent conversions, ranging from 91.0 to 100.0%, were obtained.

Stevens and co-workers[47] recently reported dramatic reductions in reaction times when performing the Baylis–Hillman reaction in a CYTOS micro reaction system (Scheme 5). In order to perform a reaction, the authors employed a mixed solvent system comprising of 1,4-dioxane and water (1 : 1) and introduced the reactants into the micro reactor (channel dimensions = 100 μm wide) as a pre-mixed solution of 4-nitrobenzaldehyde **24** and 1,4-diazabicyclo[2.2.2]octane (DABCO) **25** (0.20 M respectively) followed by a solution of methyl acrylate **26** (0.60 M). Employing a residence time of 1 h 58 min (flow rate = 1.4 ml min^{-1}), the authors obtained 2-(4-nitrobenzoyl)acrylic acid methyl ester **27** in 82.0% yield. This was subsequently increased to 95.0% when a stopped flow regime was employed, affording a residence time of 9 h 50 min. In comparison to an analogous batch reaction, the use of a flow reactor led to a 30.0% reduction in reaction time.

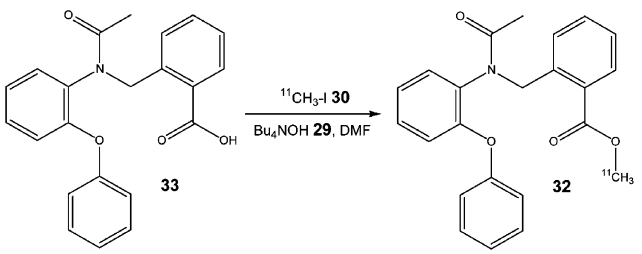
Possibly the most application driven area of liquid-phase reaction miniaturisation is that of radiosynthetic chemistry, where time constraints govern the techniques used for the preparation of labelled compounds. With this in mind, Lu and co-workers[48] recently demonstrated the use of a borosilicate glass micro reactor (channel dimensions = 220 μm (wide) × 60 μm (deep) × 1.4 cm (length)) for the rapid synthesis of a series of radiolabelled compounds (Schemes 6 and 7). Using pressure-driven flow, a pre-mixed solution of 3-pyridin-3-yl-propionic acid **28** (0.01 M) and tetra-*n*-butylammonium hydroxide **29** (0.01 M in DMF) was introduced from inlet A, a solution of $^{11}CH_3I$ **30** (0.01 M in DMF) from inlet B and the reaction products quenched upon collection, in MeCN, prior to off-line analysis and purification by HPLC. Operating the



Scheme 5 The Baylis–Hillman reaction investigated in a CYTOS micro reactor.



Scheme 6 Methylation of 3-pyridin-3-yl-propionic acid **28**, in a pressure-driven micro reactor, to afford the ^{11}C-labelled ester **31**.

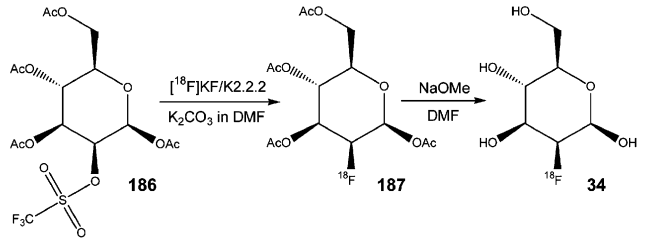


Scheme 7 Synthesis of ^{11}C-labelled peripheral benzodiazepine ligand **32**.

micro reactor at 1.0 μl min^{-1} (residence time = 12 sec) afforded the respective labelled ester **31** (Scheme 6) with a radiochemical yield (RCY) of 88.0% (n = 2). This provided an overall processing time of 10 min, which is comparable to those reaction times currently employed in PET tracer synthesis. Among other examples, the authors also demonstrated the synthesis of a peripheral benzodiazepine receptor (PBR) ligand **32** *via* the ^{11}C-methylation of carboxylic acid **33** (Scheme 7), employing an optimised flow rate of 1.0 μl min^{-1} the desired PBR ligand **32** was obtained with a RCY of 65.0% (n = 2).

The principle was further developed by Gillies and co-workers,[49] whereby a soda-lime glass micro reactor was employed for the incorporation of radiolabels into Annexin-V and 2-fluorodeoxyglucose **34**. In order to perform a micro reaction, reagents were introduced into a cylindrical reaction chamber at a rate of 250.0 μl min^{-1} (10 mm × 100 μm, reaction volume = 16.0 μl), where they mixed and reacted to afford the desired radiolabelled product. Incorporation of the radiolabel was subsequently determined by radioTLC of the crude micro reaction products. Radioiodination of Annexin-V was achieved by the introduction of Annexin-V (10 μl in 200 μl PBS at pH 7.0), ^{124}I (5 μl (20 M Bq) in 200 μl PBS at pH 7.0) and iodogen (40 μg in 200 μl MeCN) into the micro reactor from inlets A, B and C respectively. Employing a reagent residence time of 2 min, the authors reported 40.0% radiolabel incorporation into Annexin-V, comparing favourably with standard batch techniques. As a further example, the micro reactor was also used to synthesise [^{18}F]fluorodeoxyglucose (2-[^{18}F]FDG) **34** (Scheme 8) whereby 50.0% incorporation of the radiolabel was achieved, with a residence time of just 4 s. Owing to the importance of this PET tracer **34**, Cheng-Lee and co-workers[50] more recently demonstrated the fabrication of an integrated micro fluidic system capable of performing the multi-step synthesis of 2-[^{18}F]FDG **34**. See Section 2.6 for a detailed discussion of the process.

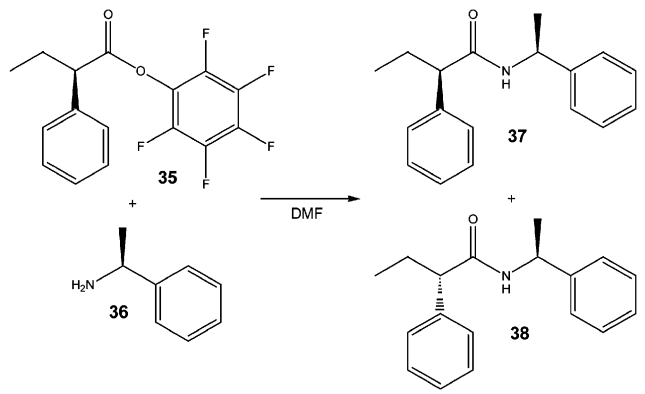
Along with the ability to increase a reactions yield and purity, the increased reaction control brought about by the use



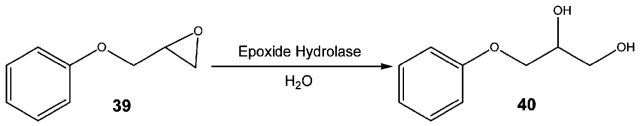
Scheme 8 Synthesis of the radiolabel 2-[^{18}F]fluorodeoxyglucose (2-[^{18}F]FDG) **34**.

of micro reaction technology has also led to increased product selectivity, an observation first reported by Haswell and co-workers.[51] As an extension to their early work on the solution phase synthesis of β-dipeptides within EOF-based micro reactors,[52] the authors subsequently investigated the degree of racemisation obtained when coupling α-amino acids in a micro fluidic reactor (Scheme 9). Employing a borosilicate glass micro reactor, with channel dimensions of 100 μm (wide) × 50 μm (deep) × 3 cm (length), the authors investigated the coupling of an (*R*)-2-phenylbutyric acid derivative **35** and (*S*)-α-methylbenzylamine **36** to afford amide **37**, comparing the degree of racemisation with that obtained in batch (6.2% amide **38**). To perform a reaction, a solution of the pentafluorophenyl ester of *R*-2-phenyl butyric acid **35** (0.10 M in DMF) was placed in reservoir A and a solution of *S*-α-methylbenzylamine **36** (0.10 M in DMF) placed in reservoir B. The reagents were manipulated through the device using an applied field of 333 V cm^{-1} and the reaction products collected in reservoir C, at the common ground, prior to off-line analysis by GC-MS. Using this approach, the authors reported quantitative conversion of the pentafluorophenyl ester **35** and 4.2% racemisation. The authors attributed the observed reduction in racemisation to the decreased reaction times employed in micro fluidic systems (min) compared with traditional batch reactions (h).

Using a range of epoxide hydrolase mutants, Belder and Reetz[53] more recently demonstrated the ability to hydrolyse glycidyl phenyl ether **39**, to the respective diol (±) **40** (Scheme 10), separate the enantiomers and detect them in a single, miniaturised glass device. To achieve this, the authors introduced an aqueous solution of epoxide hydrolase from one



Scheme 9 Coupling of α-amino acids to afford diastereomers **37** and **38**.



Scheme 10 Enantioselective hydrolysis of 2-phenoxymethyloxirane **39** to 3-phenoxypropane-1,2-diol **40** using epoxide hydrolase mutants.

inlet and a solution of glycidyl phenyl ether **39** from a second inlet; the reagents subsequently mixed and reacted in a meandering channel, followed by chiral electrophoretic separation and determination of the enantiomeric excess *via* on-chip fluorescence detection. Using this approach, the authors were able to investigate the enantioselectivity of three epoxide hydrolase mutants, obtaining conversions in the range of 22.0 to 43.0% and ee's of between 49.0 and 95.0%.

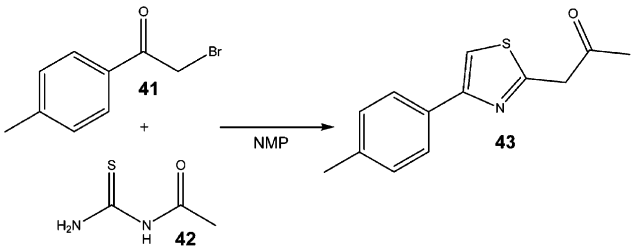
An important facet of this investigation was the ability to integrate synthesis, separation and detection within a single planar device, an advantage that will undoubtedly assist technology transfer to the mainstream.

2.1.1 Temperature control in liquid-phase micro reactions. Up to now, the discussion has focused on room temperature, liquid-phase micro reactions and their associated advantages, the following section therefore aims to highlight some of the challenges associated with performing micro reactions at elevated and reduced temperatures, along with the advantages with respect to exothermic reactions.

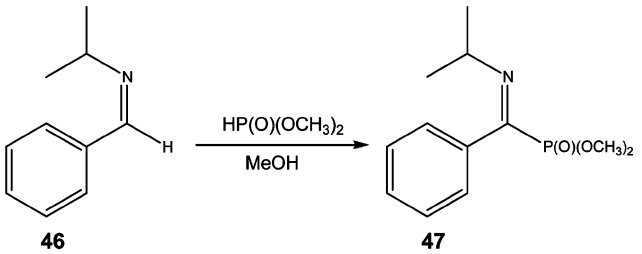
2.1.1.1 Elevated reaction temperatures in the liquid-phase. As discussed in Section 1.3, an inherent advantage associated with the miniaturisation of reactor vessels is their ability to dissipate heat, consequently the task of heating micro fluidic systems is not trivial.

An early example of a heated micro reactor was reported by Garcia-Egido and co-workers,[54] whereby a T-shaped Peltier heater, located under the reaction channel, enabled the synthesis of substituted 2-aminothiazoles within an EOF-based system. Employing a borosilicate glass micro reactor (channel dimensions = 300 μm (wide) × 115 μm (deep) and 3 cm (length)) maintained at 70 °C, standard solutions of 2-bromo-4′-methylacetophenone **41** (1.4×10^{-2} M) and 1-acetyl-2-thiourea **42** (2.2×10^{-2} M) in *N*-methylpyrrolidone (NMP) were manipulated within the reactor using an applied field of 133 V cm^{-1}. Conducting the micro reactions at these optimised conditions afforded 1-(4-*p*-tolylthiazol-2-yl) propan-2-one **43** (Scheme 11) in 72.0% conversion. Further examples reported included the synthesis of the pharmacological agent Fanetizole, whereby the target molecule was obtained in 99.0% conversion.

As an alternative approach, Iles and co-workers[55] incorporated thin film resistive elements into a soda lime glass micro reactor, as a means of heating micro fluidic channels (dimensions = 150 μm (wide) × 50 μm (deep) × 14 cm (long)). By incorporating thermochromic liquid crystals (TLC's) into the reactor, the authors were able to monitor (by reflectance spectroscopy) temperature distribution across the device, reporting a temperature gradient of ±0.2 °C, over an operational range of 60 to 70 °C. As Scheme 12 illustrates,



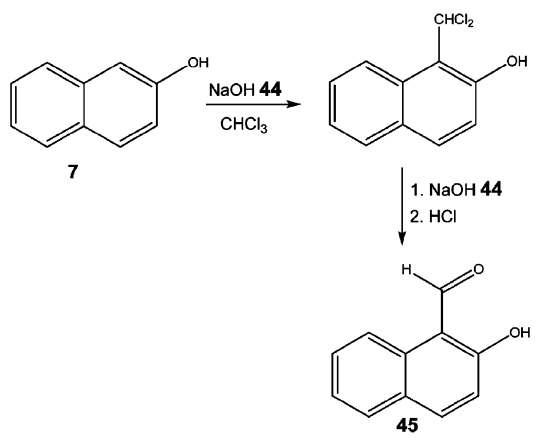
Scheme 11 Preparation of 2-aminothiazoles *via* the Hantzch synthesis in a heated, EOF-based, micro reactor.



Scheme 13 Synthesis of α-aminophosphonates in a micro reactor.

the reactor was subsequently investigated for the biphasic Reimer–Tiemann formylation. Employing solutions of 2-naphthol **7** in $CHCl_3$ and aqueous NaOH **44**, the authors investigated the effect of reaction temperature (51 to 75 °C) and flow rate (5.00 to 20.00 μl min^{-1}) on the formation of 2-hydroxynaphthalene-1-carbaldehyde **45** (reaction products were quenched in dilute HCl prior to off-line analysis by GC). Using this approach, optimal reaction conditions comprised of a reactor temperature of 65 °C and a flow rate of 5.0 μl min^{-1}, afforded 10.0% of the formylated product **45**; proving comparable to standard batch techniques whereby yields of 10.0 to 20.0% are frequently obtained.

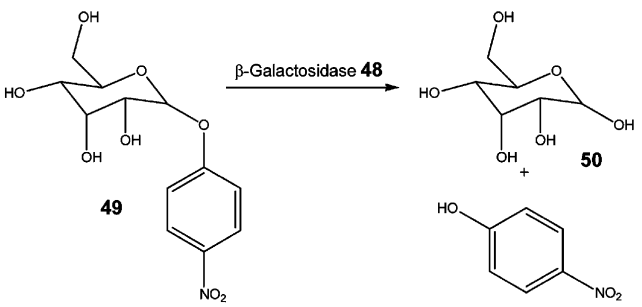
More recently, Stevens and co-workers[56] described the use of a CPC college system for the continuous flow synthesis of an array of pharmaceutically important α-aminophosphonates (Scheme 13) *via* the Kabachnik–Fields reaction. The authors found that by maintaining the micro reactor at 50 °C and operating at a flow rate of 600.0 μl min^{-1} (residence time = 78 min), quantitative conversion of an aldimine **46** to the respective α-aminophosphonate **47** could be obtained. After subjecting the reaction products to an off-line acid–base extraction, yields of 94.0% were obtained; equating to a throughput of 10.3 g h^{-1}. Using these optimised reaction conditions, the authors reported the synthesis of a further four α-aminophosphonates whereby isolated yields ranged from 68.0 to 91.0%, proving advantageous compared to standard batch techniques where catalysts are frequently required.



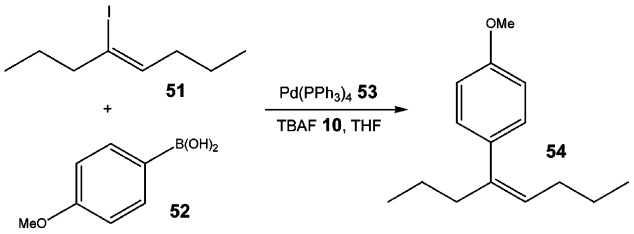
Scheme 12 Synthesis of β-naphthol **7** *via* the Reimer–Tiemann formylation.

Using the enzyme β-galactosidase **48**, isolated from *E. coli*, Kanno and co-workers[57] reported quantitative hydrolysis of *p*-nitrophenyl-β-D-galactopyranoside **49** to D-galactose **50** (Scheme 14) within a PMMA micro reactor (channel dimensions = 200 μm (wide) × 200 μm (deep) × 40 cm (length)). The authors observed that by maintaining the micro reactor at 37 °C, achieved by submerging the reactor in a heated bath, the reaction proceeded five times faster than in an analogous batch reaction. This enhancement was attributed to the efficient diffusive mixing obtained within the micro channel compared to a traditional batch set-up. Further to this, the authors demonstrated the enzymatic transgalactosylation of **49** and *p*-nitrophenyl-2-acetamide-2-deoxy-β-D-glucopyranoside, to afford galactosylated *p*-nitrophenyl-2-acetamide-2-deoxy-β-D-glucopyranoside in excellent yield.

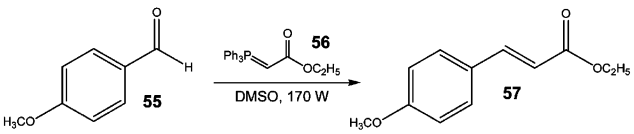
Organ and co-workers[58,59] recently demonstrated the use of microwave (MW) irradiation as an alternative heating source for glass capillary reactors (ranging from 200 to 1150 μm (i.d.)). To perform a reaction, the authors introduced reactants into the flow reactor through a stainless steel mixing chamber and collected the reaction products outside the MW chamber *via* a length of Teflon tubing. Employing pressure-driven flow, the Suzuki–Miyaura coupling (Scheme 15) of 4-iodooct-4-ene **51** (0.20 M) and 4-methoxyboronic acid **52** (0.24 M) in THF was investigated in the presence of palladium tetrakis(triphenylphosphine) **53** and TBAF **10** (0.60 M). Conducting the reaction in a 200 μm capillary (100 W), the authors obtained 100.0% conversion to 1-methoxy-4-(1-propylpent-1-enyl)benzene **54** when a flow rate of 2.0 μl min^{-1} was employed (residence time of ~28 min). With this in mind, the reaction was subsequently repeated using an array of aryl halides and substituted boronic acids, affording the desired products in 37.0 to 100.0% conversion. Compared to conventional batch techniques, these results illustrate dramatic improvements in



Scheme 14 Biocatalytic hydrolysis of *p*-nitrophenyl-β-D-galactopyranoside **49** using β-galactosidase **48**.



Scheme 15 Synthesis of 1-methoxy-4-(1-propylpent-1-enyl)benzene **54** *via* the Suzuki–Miyaura coupling, in a microwave-assisted capillary reactor.

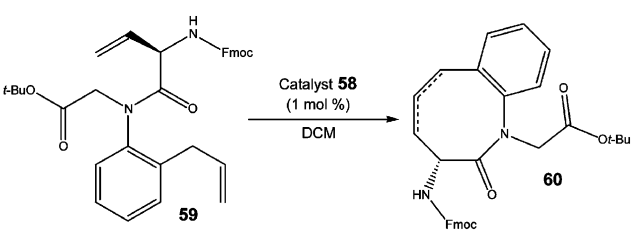


Scheme 16 Continuous flow synthesis of 3-(4-methoxyphenyl)acrylic acid ethyl ester **57** in a microwave-assisted capillary reactor.

conversion, the suppression of side reactions and a marked reduction in reaction time.

Based on these encouraging results, the authors subsequently investigated a series of non-organometallic reactions, including the Wittig olefination.[59] As Scheme 16 illustrates, the reaction of 4-methoxybenzaldehyde **55** and ethyl(triphenylphosphoranylidene)acetate **56**, to afford 3-(4-methoxy-phenyl) acrylic acid ethyl ester **57**, was conducted in the capillary (1150 μm (i.d.)) based flow reactor. To perform a reaction, a premixed solution of aldehyde **55** (0.27 M) and phosphorane **56** (0.30 M) in DMSO was irradiated at 170 W. By varying the flow rate of the reaction mixture from 30.0 to 10.0 μl min^{-1} (residence time = 4 to 11 min), the conversion to 3-(4-methoxyphenyl)acrylic acid ethyl ester **57** was observed to increase from 73.0 to 89.0%. Again, the use of a flow reactor resulted in enhanced conversions compared to an analogous static MW assisted reaction, whereby only 54.0% conversion to 3-(4-methoxyphenyl)acrylic acid ethyl ester **57** was observed.

In addition, the authors investigated a MW-assisted ring closing metathesis (RCM), in a continuous flow reactor, using Grubb's II catalyst **58** (Scheme 17). Employing a premixed solution of Grubb's II catalyst **58** (1 mol%) and diene **59** (0.15 M) in DCM, the capillary reactor was operated at a flow rate of 40.0 μl min^{-1} and 100 W, affording the RCM product **60** in 100.0% conversion. In comparison, to a standard MW assisted reaction performed in a vial, conducting the reaction in a flow reactor resulted in a reduction in both power consumption (50.0%) and reaction time (3.8 min *cf.* 30 min).



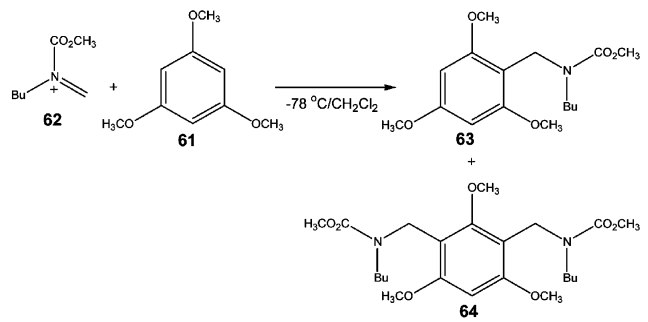
Scheme 17 Ring-closing metathesis using a continuous flow micro reactor.

Although the introduction of heat into micro fabricated systems proves challenging, from the examples presented it is evident that it is possible to heat micro reactions, increasing the scope of reactions that can be performed using this technology.

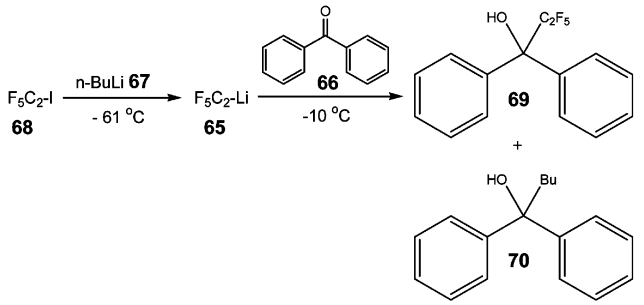
2.1.1.2 Reduced reaction temperatures in the liquid-phase. Along with the obvious requirement to provide heat to reaction systems, there are also cases where reduced temperatures are required; such scenarios include the generation of highly unstable intermediates along with the control of product distribution. With this in mind, several research groups have investigated the ability to conduct micro reactions at reduced temperatures, ranging from 0 to −100 °C.

Yoshida *et al.*[60] reported an early example of reduced temperature micro reactions, demonstrating the selective electrophilic substitution of 1,3,5-trimethoxybenzene **61**. As Scheme 18 illustrates, the reaction involved the selective monoalkylation of 1,3,5-trimethoxybenzene **61** with an *N*-acyliminium ion **62**, to afford butyl-(2,4,6-trimethoxybenzyl)-carbamic acid methyl ester **63**. Owing to the exothermicity of the reaction, product distribution proved difficult to control on a macro-scale, resulting in the synthesis of a large proportion of dialkylated product (54 : 46 (**63** : **64**)). On the other hand, by performing the reaction in a pressure-driven micro mixer (supplied by IMM, channel width = 25 μm) at −78 °C, a reaction selectivity of 96 : 4 (**63** : **64**) was obtained. Further to this, the authors investigated the effect of reaction temperature on product distribution, noting that as the temperature increased, from −78 to −10 °C, the yield of monoalkylated product **63** dramatically decreased from 92.0% to 30.0%, whilst the proportion of dialkylated product **64** increased (4.0 to 18%). Therefore, by performing the reaction in a micro fabricated reactor, where precise temperature control can be obtained; enhanced product selectivity was achieved compared to batch.

Schwalbe and co-workers[3] then demonstrated the *in situ* generation of C_2F_5-Li **65**, and its subsequent nucleophilic addition to benzophenone **66** (Scheme 19). Employing a two-stage CYTOS reactor, the authors were able to conduct the first step of the reaction at −61 °C and the second step at −10 °C, using a series of external thermostatted baths. To perform a reaction, solutions of *n*-BuLi **67** (0.82 M) in hexane and C_2F_5-I **68** (0.75 M) in DCM were pumped into the reactor, achieving a residence time of 4 min. A solution of benzophenone **66** (0.62 M) in DCM was then pumped into the second



Scheme 18 Selective Friedel–Crafts alkylation of 1,3,5-trimethoxybenzene **61**.

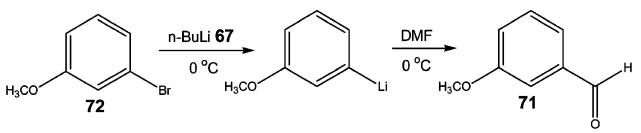


Scheme 19 *In situ* generation of a short-lived organometallic compound **65** and its nucleophilic addition to benzophenone **66**.

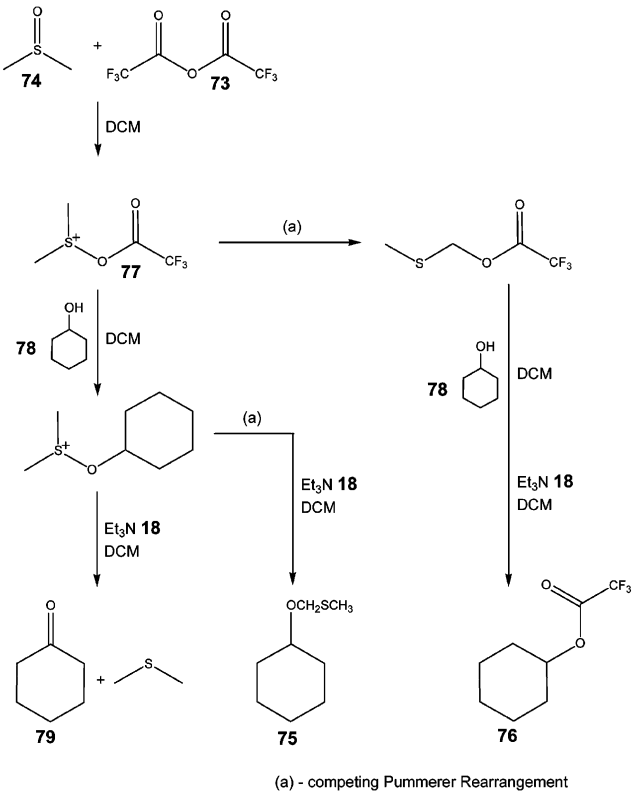
stage of the reactor (−10 °C) to afford a residence time of 17 min; the reaction products were then subjected to an off-line aqueous work-up, prior to analysis by GC. Employing the aforementioned reaction conditions resulted in 51.0% yield of the desired product **69**, compared to 14.0% in a batch system. The authors did however report the formation of a competing side product **70** (35.0%), attributed to incomplete halogen–lithium exchange in the first stage reactor. The reaction nonetheless serves to illustrate the feasibility of conducting different steps of a reaction under varying reaction conditions.

As Scheme 20 illustrates, the authors subsequently investigated the synthesis of 3-methoxybenzaldehyde **71** *via* a lithium–halide exchange and formylation with DMF. Maintaining both stages of the reactor at 0 °C, a solution of *n*-BuLi **67** (1.60 M) in hexane was introduced into the first stage reactor at a flow rate of 6.0 ml min^{-1} followed by a solution of 3-bromoanisole **72** (1.90 M) in THF at 4.7 ml min^{-1} (residence time = 0.19 min). A solution of DMF (5.00 M) in THF was subsequently pumped into the second stage reactor at a flow rate of 2.5 ml min^{-1} (residence time = 0.15 min) and the resulting reaction mixture subjected to an aqueous work-up prior to analysis by GC. Using this approach, the authors report an isolated yield of 88.0% 3-methoxybenzaldehyde **71** and a GC purity of 96.0%.

More recently, Yoshida and co-workers[61] reported a series of Moffat–Swern type oxidations (Scheme 21) performed in a micro reactor, comprising of multi-lamination micro mixers and stainless steel tube reactors. As Scheme 21 illustrates when employing trifluoroacetic anhydride **73** as the activating agent for DMSO **74**, the Pummerer rearrangement is an inevitable side reaction, which leads to the undesirable formation of by-products **75** and **76**. In order to suppress these side reactions, batch reactions are typically performed at reduced temperatures, for example at −70 °C only 10.0% **75** and 5.0% **76** were obtained, compared with 2.0% **75** and 70.0% **76** when the reaction was performed at −20 °C. The authors proposed that by conducting the reaction in a micro reactor, where rapid



Scheme 20 Synthesis of 3-methoxybenzaldehyde **Q2c** in a micro reactor, at 0 °C.



Scheme 21 An example of the Moffat–Swern oxidation performed in a reduced temperature micro reactor.

mixing and precise temperature control are attained, increased reaction temperatures could be employed whilst maintaining reaction selectivity. With this in mind, the micro reactor set-up was submerged in a cooling bath, the reagents supplied to the reactor using a series of syringe pumps and reaction products analysed off-line by GC. To perform a reaction, solutions of DMSO **74** (4.00 M) and trifluoroacetic anhydride **73** (2.40 M) in DCM were introduced into the micro mixer from two separate inlets, the reagents subsequently reacted to afford the intermediate **77**, prior to the addition of cyclohexanol **78** (1.00 M) in DCM. The reagents again mixed and reacted in a second tube reactor prior to the addition of Et_3N **18** (1.45 M) in DCM, a third tube reactor followed, prior to the collection of the reaction products at 30 °C. Using this approach, the authors investigated the effect of reaction temperature (−20 to 20 °C) and reagent residence time (0.01 to 2.4 s) on the synthesis of cyclohexanone **79**, comparing the results obtained to a standard batch reaction (−20 °C). As Table 2 illustrates, the authors obtained comparable conversions and selectivities to batch, even when the micro reactions were performed at room temperature; an observation that is attributed to the short residence time employed for the generation of the reactive intermediate **77**.

2.1.1.3 Exothermic reaction control. In addition to maintaining a reactions' temperature, an additional advantage of micro reaction technology is the ability to rapidly dissipate heat formed over the course of a reaction. With this in mind, numerous research groups have been interested in performing

Table 2 Effect of reaction temperature on the oxidation of cyclohexanol **78**

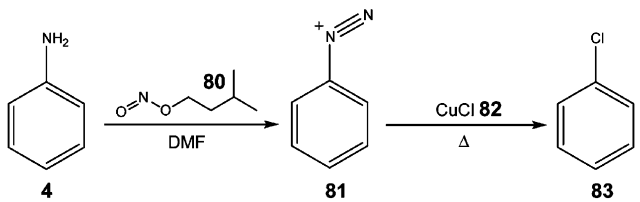
	Batch reactor	Micro reactor		
Residence time/s	N/A	2.4	0.01	0.01
Temperature/°C	−20	−20	0	20
Total Conversion (%)	86.0	88.0	90.0	81.0
Cyclohexanone **79** (%)	19.0	88.0	89.0	88.0
By-product **75** (%)	2.0	6.0	7.0	5.0
By-product **76** (%)	70.0	5.0	1.0	2.0

hazardous, exothermic reactions in microfabricated systems as a means of obtaining enhanced process control.

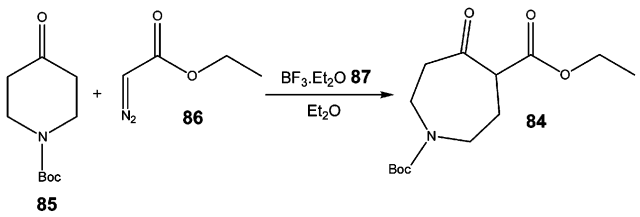
A particularly problematic area of synthetic chemistry is that of diazonium chemistry, where hazards include light, heat and shock sensitivity, which can all lead to uncontrollable decomposition of the diazonium salts formed, with the risk of explosion. Owing to the fact that the technique provides a synthetically useful route to an array of compounds such as, azo dyes (Scheme 1), hydroxyarenes and chloroarenes (Scheme 22), rigorous operational conditions are required for the large-scale application of diazonium salts. These hazards are however amplified when amyl nitrite **80** is used in the preparation of the diazonium salts, as it is prone to decomposition even when refrigerated, limiting its use on an industrial scale.

de Mello and co-workers[62] recently addressed these issues by investigating the synthesis of chloroarenes in a pressure-driven, glass micro reactor (channel dimensions = 150 μm (wide) × 50 μm (deep) × 3.6 cm (length)). As Scheme 22 illustrates, the first step of the reaction involved treatment of the amine, aniline **4**, with isoamyl nitrite **80** (2.4 equiv.), at room temperature, to afford the diazonium salt **81**, followed by halogen abstraction, from copper chloride **82** (1.3 equiv.), at 65 °C, to afford the respective chloroarene **83**. Conducting the micro reaction in DMF, the authors found the reaction proceeded in up to 71.0% conversion, remarking that the halogen abstraction was extremely efficient compared to traditional batch approaches (where typical conversions of 40.0 to 49.0% are reported).

The use of hazardous reagents was also demonstrated by Zhang *et al.*[63] for the synthesis of *N*-*tert*-butoxycarbonyl-5-ethoxycarbonyl-4-perhydro-azepinone **84** *via* a ring expansion reaction. As Scheme 23 illustrates reaction of *N*-Boc-4-piperidone **85** with ethyl diazoacetate **86**, in the presence of boron trifluoride etherate **87**, affords the desired product **84**. Employing a residence time of 1.8 min within the CYTOS micro reactor, the authors report an isolated yield of in 89.0% and a throughput of 91.0 g h^{-1}; clearly representing a safe



Scheme 22 Synthesis and reaction of diazonium salts in a micro reactor.

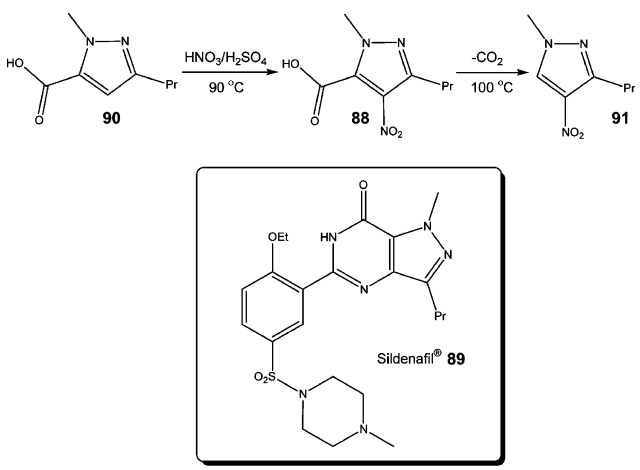


Scheme 23 Synthesis of *N*-*tert*-butoxycarbonyl-5-ethoxycarbonyl-4-perhydroazepinone **84** using the CYTOS micro reactor system.

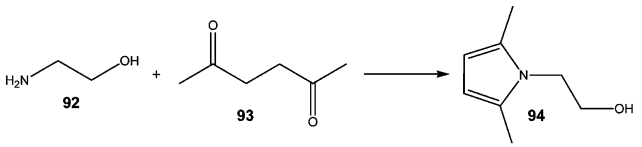
synthetic route, suitable for the large-scale preparation of such derivatives.

Taghavi-Moghadam *et al.*[64] also demonstrated enhanced reaction control with respect to the temperature sensitive synthesis of 2-methyl-4-nitro-5-propyl-2*H*-pyrazole-3-carboxylic **88**, a key intermediate in the preparation of the lifestyle drug Sildenafil® **89** (Scheme 24). When performing the nitration of 2-methyl-5-propyl-2*H*-pyrazole-3-carboxylic acid **90** under adiabatic conditions (with a dilution of 6.0 l kg^{-1}), Dunn *et al.*[65] observed a temperature rise from 50 °C to 92 °C upon addition of the nitrating solution. As Scheme 24 illustrates, this proved problematic as at 100 °C decomposition of the product **88** was observed to afford the decarboxylated pyrazole **91**. In order to reduce the undesired decarboxylation and increase process safety, the authors investigated the addition of the nitrating solution in three portions, resulting in a reduced reaction temperature of 71 °C. Although this led to increased reaction control and chemoselective nitration, the reaction time was increased from 8 h to 10 h as a result of adding the nitrating solution in three aliquots.

Conversely, by conducting the nitration in a micro reactor, where the heat of reaction is rapidly dissipated, Taghavi-Moghadam and co-workers were able to maintain the reaction temperature at 90 °C even though the nitrating solution was added continuously. Employing a reagent residence time of just 35 min, the authors reported a throughput of 5.5 g h^{-1}, obtaining an overall yield of 73.0% **88**. In addition to the reduced reaction time and increased reaction safety, this approach is advantageous as the authors were able to ensure



Scheme 24 Chemoselective synthesis of 2-methyl-4-nitro-5-propyl-2*H*-pyrazole-3-carboxylic acid **88**, a key intermediate of Sildenafil® **89**.



Scheme 25 Paal–Knorr synthesis performed in a micro fabricated reactor.

the chemoselective synthesis of 2-methyl-4-nitro-5-propyl-2*H*-pyrazole-3-carboxylic acid **88**.

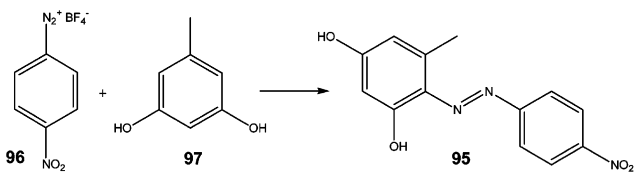
A further example of reduced reaction times as a function of increased temperature control was the Paal–Knorr synthesis performed by Schwalbe *et al.*[66] (Scheme 25). Due to the exothermic nature of the reaction, when adding ethanolamine **92** to acetonylacetone **93** in batch, it was necessary to add the reagents over an extended period of time, consequently even though the reaction itself was rapid, the dropwise addition of reagents increased the reaction time considerably. Conversely, by performing the synthesis of 2-(2,5-dimethylpyrrol-1yl)ethanol **94** in a CYTOS reactor, the authors were able to employ neat reagents, resulting in a residence time of 5.2 min, affording pyrrole **94** in 91.0% yield (260.0 g h^{-1}).

2.2 Multi-phase reactions

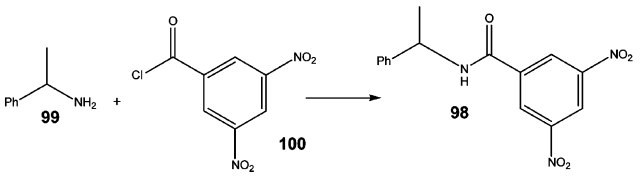
Although the versatility of micro reaction technology has been clearly demonstrated within the previous sections, the reactions described concentrate on the use of a single phase *i.e.* gas or liquid. With this in mind, the following section discusses the use of multiple phases in the micro domain, with examples ranging from liquid–liquid to those involving solids, liquids and gases.

2.2.1 Liquid–liquid micro reactions. When employing two immiscible liquids in a batch reactor, vigorous stirring is often required in order to increase the interfacial area between both phases, along with extended reaction times. With this in mind, phase transfer reactions, in particular, have benefited from reaction miniaturisation where a large longitudinal interface is created between two co-flowing liquids, across which diffusion occurs. As interfacial areas of 5000 to 50 000 m^2 m^{-3} are typical within such systems, reactions proceed rapidly and efficiently, compared to analogous stirred reactions.[67] The technique can also be employed as a means of performing continuous purifications, by means of a liquid–liquid extraction, as illustrated in the synthesis of 5-methyl-4-(4-nitrophenylazo)benzene-1,3-diol **95** (Scheme 26).

An alternative approach to parallel flow is the use of slug flow, a technique that enables the interfacial surface area to be



Scheme 26 Phase transfer synthesis of 5-methyl-4-(4-nitrophenylazo)benzene-1,3-diol **95** in a micro reactor.



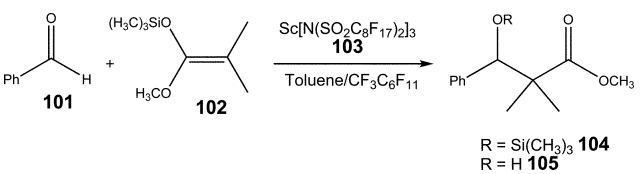
Scheme 27 Synthesis of 3,5-dinitro-*N*-(1-phenylethyl)benzamide **98** in a biphasic, parallel micro reactor.

further increased, by the formation of liquid (or gas) slugs in an immiscible continuous phase. This technique has been used to great effect by many research groups, including that of Burns and Ramshaw,[68] where the intensification of reagent transfer was demonstrated through the visual assessment of acid–base titrations and by McQuade and co-workers[69] as a means of preventing precipitation within micro channels.

In addition to the numerous examples of diazo coupling reactions reported by Kitamori *et al.*,[70] the authors also demonstrated the first phase transfer reaction to be conducted within a pressure-driven, glass micro reactor. Introduction of the diazonium salt **96** in the aqueous phase and 5-methylresorcinol **97** in the organic phase enabled the formation of a longitudinal interface over which, 5-methyl-4-(4-nitrophenylazo)benzene-1,3-diol **95** was synthesised in quantitative conversion (Scheme 26). Due to the biphasic nature of the reaction, the reaction products were collected in the organic layer and any inorganic residues generated over the course of the reaction remained in the aqueous layer.

The group subsequently demonstrated the use of a glass micro reactor coupled to a series of displacement pumps in order to perform a 2 × 2 parallel synthesis.[71] Using phase transfer amide formation the following products could be prepared AC, AD, BC and BD, by flowing reagent pairs through the device *i.e.* A, B and C, D. Although problems were encountered with obtaining equal flow at all junctions, yields of >80.0% were reported and no cross-flow contamination was reported. Scheme 27 provides an example of the synthesis performed within the parallel reactor, illustrating the synthesis of 3,5-dinitro-*N*-(1-phenylethyl)benzamide **98** *via* the reaction of 1-phenylethylamine **99** and 3,5-dinitrobenzoyl chloride **100**.

Mikami *et al.*[72] further demonstrated the advantages associated with the use of micro reactors to perform biphasic reactions. Employing a borosilicate glass micro reactor (channel dimensions = 60 μm (wide) × 30 μm (deep) × 1, 2 or 3 cm (length)), the authors investigated the application of a fluorous biphasic nanoflow system to the Mukaiyama aldol reaction (Scheme 28). Under pressure-driven flow, a solution of benzaldehyde **101** (0.10 M) and 1-methoxy-2-methyl-propenyloxy)trimethylsilane **102** (0.20 M) in toluene and a solution of $Sc[N(SO_2C_8F_{17})_2]_3$ **103** in perfluoromethylcyclohexane



Scheme 28 Mukaiyama aldol reaction performed in a micro reactor.

(6.25×10^{-5} M, 0.625 mol%) were introduced into the heated micro reactor (55 °C) where they formed a biphasic reaction stream. Since the catalyst **103** is virtually insoluble in hydrocarbon solvents, the catalyst remained in the perfluoromethylcyclohexane whilst the reaction products separated into the toluene layer. Consequently, by collecting the micro reaction products in a vial, the organic layer could be sampled and analysed by GC, enabling the percentage conversion of benzaldehyde **101** to silylated product **104**, and de-silylated product **105**, to be determined.

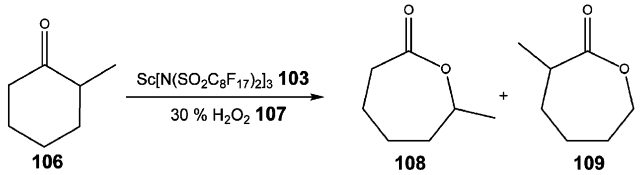
Employing a range of flow rates (20.0 to 200.0 nl min^{-1}), channel lengths (1.0 to 3.0 cm) and widths (30 and 60 μm), the authors found the optimal reaction conditions to be a flow rate of 50.0 nl min^{-1}, coupled with a reaction length of 1.0 cm and a channel width of 30 μm. Using the aforementioned reaction conditions, a reagent residence time of 10.8 sec was achieved, resulting in 92.0% conversion of benzaldehyde **101**, with a product distribution of 2.2 : 1 (**104** : **105**). In contrast, when the reaction was performed in a traditional batch reactor, under vigorous stirring, only 11.0% yield was obtained after a reaction time of 2 h. The acceleration observed due to conducting the reaction in a micro reactor was attributed to the high interfacial surface area and short diffusional distance compared to that obtained in a stirred batch reactor.

More recently, Mikami and co-workers[73] reported enhanced regiocontrol when performing a series of Baeyer–Villiger oxidations within the aforementioned fluorous nanoflow system. As Scheme 29 illustrates a typical reaction involved the insertion of an oxygen atom into a carbon–carbon bond, to afford a lactone. Again, under pressure-driven flow a biphasic reagent stream was obtained by introducing a solution of $Sc[N(SO_2C_8F_{17})_2]_3$ **103** (5.00×10^{-5} M) and 2-methylcyclohexanone **106** (0.10 M) in benzotrifluoride from one inlet and 30.0% aqueous hydrogen peroxide **107** from a second inlet. The reaction products were subsequently collected in a vial and the organic layer analysed by GC in order to determine the percentage conversion and reaction regioselectivity.

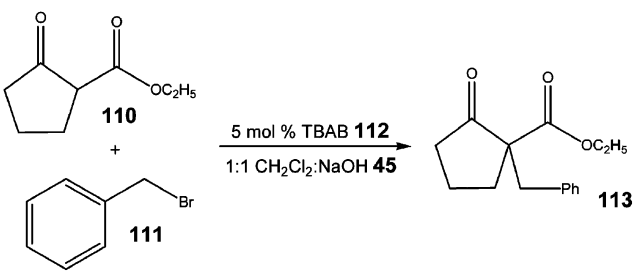
Employing a residence time of 8.1 s (reactor dimensions = 30 μm (wide) × 30 μm (deep) × 3 cm (length), flow rate = 100 nl min^{-1}), the authors report 91.0% conversion of 2-methylcyclohexanone **106** to lactone **108** with 100.0% regioselectivity. When conducting the comparable reaction in a stirred batch reactor, the authors reported 28.0% conversion of 2-methylcyclohexanone **106** with a product distribution of 69 : 31 (**108** : **109**), an observation that the authors attribute to the inhomogeneity obtained in a stirred reactor.

Kobayashi and co-workers[74] also demonstrated the potential of biphasic reactions within micro fabricated reactors. As Scheme 30 illustrates, the model reaction selected involved the alkylation of ethyl-2-oxocyclopentanecarboxylate **110** with benzyl bromide **111** in the presence of a phase transfer catalyst, tetrabutylammonium bromide (TBAB) **112**. Employing a micro reactor with the following dimensions, 100 μm (wide) × 100 μm (deep) × 45 cm (length), the authors investigated the effect of residence time on the yield of the reaction. To perform a reaction, a solution of substrate **110** and benzyl bromide **111** (0.30 and 0.45 M respectively) in DCM was added from one inlet and an aqueous solution of sodium hydroxide **45** (0.50 M) and TBAB **112** (1.5×10^{-2} M) from a second inlet. Maintaining the reactor at room temperature, the authors investigated the effect of reagent residence time on the conversion to product **113**, collecting the reaction products in aqueous ammonium chloride, prior to analysis by HPLC. Operating the reactor at a flow rate of 5.9 μl min^{-1}, obtaining a residence time of 2 min, the authors reported 75.0% yield of the desired product **113**; in comparison to a stirred batch reactor, this represented an increase of 26.0% over the same reaction time. By reducing the flow rate to 1.2 μl min^{-1}, and hence increasing the reagents residence time to 10 min, an increase in yield was observed, affording 1-benzyl-2-oxo-cyclopentanecarboxylic acid ethyl ester **113** in 96.0% yield.

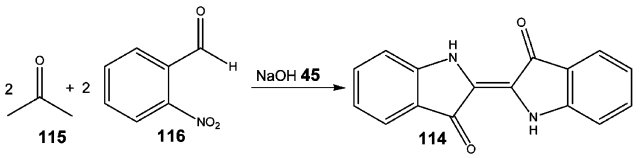
One of the reasons researchers remain reticent to embrace new technologies, such as the use of micro reactors, is the belief that precipitation within the micro channels can lead to disruptive blockage formation. To date, numerous techniques, such as periodic purging of the channels,[75] or the exchange of reagents for more soluble equivalents, have been routine techniques employed in order to reduce the problems associated with precipitation over the course of a reaction. In order to address this problem, McQuade and co-workers[69] recently reported a technique suitable for the manipulation of precipitates within continuous flow systems. By performing reactions within monodisperse droplets, the authors report the ability to conduct reactions that readily produce solids upon reaction, without 'clogging' of the reactor channel. Using the synthesis of indigo **114** as a model reaction (Scheme 31), the authors formed a monodisperse droplet flow in which the reaction occurred. Operating a carrier phase of mineral oil, at a flow rate of 3.0 ml min^{-1} ensured that reagent droplets containing acetone **115** and 2-nitrobenzaldehyde **116** were held within the centre of the channel (160 μm i.d.), preventing precipitation of the product **114** and contact with the poly(vinyl chloride) channel walls. The versatility of the technique was further demonstrated using the synthesis of



Scheme 29 Regiocontrol of the Baeyer–Villiger oxidation in a micro reactor.



Scheme 30 Phase transfer alkylation of ethyl-2-oxocyclopentanecarboxylate **113**.

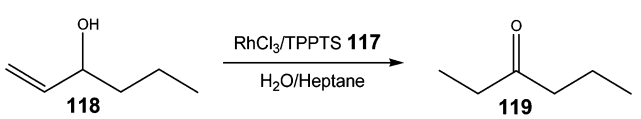


Scheme 31 Synthesis of indigo **114** within a mondisperse droplet system.

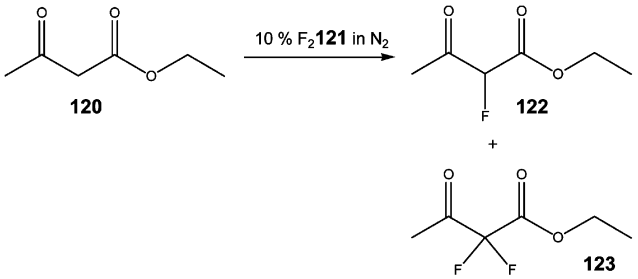
N,N-dicyclohexylethylendiimine (97.0% yield) and 4-chloro-*N*-methylbenzamide (87.6% yield), employing carrier phases of hexane and toluene respectively.

de Bellefon *et al.*[76] also demonstrated a technique for the high-throughput screening of homogeneously catalysed reactions employing a multi-phase micro reaction system. Employing an array of transition metal precursors and sulfonated phosphane or diphosphane ligands, the authors investigated the isomerisation of allylic alcohols using an interdigital micro mixer (15 × 25 μm (wide) micro channels) and a stainless steel, tubular reactor (400 μm (i.d.) × 80 cm (length)). As Scheme 32 illustrates, one such reaction was the $RhCl_3$/tris(*m*-sulfophenyl)phosphorane (TPPTS) **117** catalysed isomerisation of 1-hexen-3-ol **118** to hexan-3-one **119**. In order to perform a reaction, a carrier phase comprising of water and heptane was continuously pumped through the reactor while the allylic alcohol **118** and catalyst were periodically injected into the carrier stream. Using this approach, mixing occurred in $<10^{-2}$ s, resulting in the formation of a continuously flowing emulsified segment in which the reaction took place. Upon collection from the reactor outlet, the reaction products were analysed by GC and the percentage conversion of 1-hexen-3-ol **118** to hexane-3-one **119** was found to be 53.0% with respect to residual 1-hexen-3-ol **118**. Using the same reaction set-up, the authors evaluated a further five catalysts for the isomerisation of 1-hexen-3-ol **118** obtaining conversions in the range of 1.0 to 61.0%.

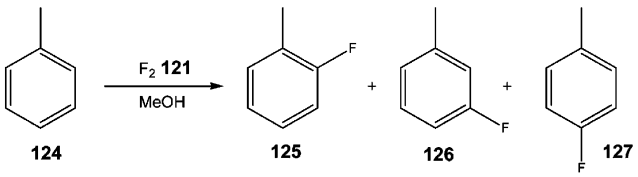
2.2.2 Gas–liquid micro reactions. Chambers *et al.*[77] demonstrated an early example of a biphasic micro reactor for the selective fluorination of a range of 1,3-dicarbonyl compounds, such as ethylacetoacetate **120**. Employing a thin film nickel reactor and 10.0% elemental fluorine **121** in nitrogen, the authors demonstrated a facile route to the preparation of the monofluorinated diketone, 2-fluoro-3-oxo-butyric acid ethyl ester **122**, with only small quantities of the product undergoing further fluorination to afford 2,2-difluoro-3-oxo-butyric acid ethyl ester **123** (Scheme 33). The group have subsequently reported the fluorination of compounds such as nitrotoluene and ethyl-2-chloroacetoacetate, again demonstrating excellent conversion, product selectivity and reaction control.[78] In comparison to standard batch-scale fluorinations, performing such reactions in miniaturised flow reactors proves



Scheme 32 Synthesis of 1-hexan-3-one **119** *via* the isomerisation of 1-hexen-3-ol **118**.



Scheme 33 Selective fluorination of ethylacetoacetate **120**.



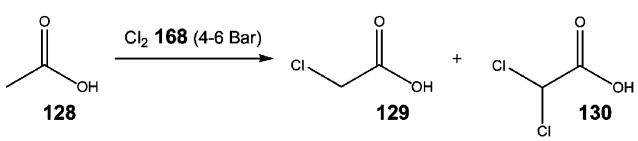
Scheme 34 Monofluorination of toluene in nickel coated micro channels.

advantageous as the enhanced temperature control leads to unprecedented reaction control and hence process safety.

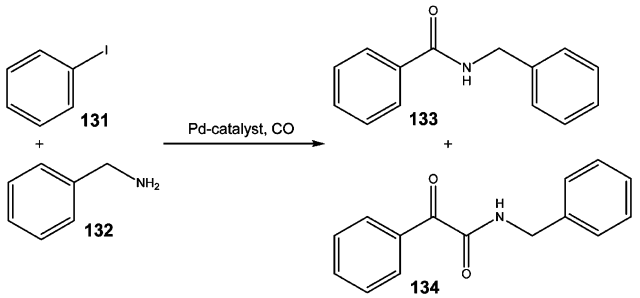
Jensen *et al.*[79] further demonstrated the direct fluorination of aromatic compounds within a silicon/Pyrex micro reactor, with nickel coated micro channels. As Scheme 34 illustrates, the fluorination of toluene **124** was selected as a model reaction, enabling monofluorinated toluene to be obtained in 96.0% conversion. Analysis of the reaction mixture, by GC, confirmed the substitution pattern to be 3 : 2 : 1 *ortho*- **125**, *meta*- **126** and *para*- **127** fluorinated toluene.

An industrial application of a gas–liquid micro reactor was described recently in a patent,[80] whereby a falling film reactor was used to investigate the selective chlorination of acetic acid **128** to afford chloroacetic acid **129** (Scheme 35). Employing a series of micro structured plates (channel dimensions = 1000 μm (wide) × 300 μm (deep)) maintained at 170–190 °C, the authors observed that the optimised gas–liquid contacting achieved enabled acetic acid **128** to be efficiently converted to the mono-chlorinated product **129**. Operating at a flow rate of 50.0 g min^{-1}, a yield of 90.0% chloroacetic acid **129** was obtained, contaminated with 0.01% dichlorinated by-product **130**. Compared to conventional processing techniques (the use of a bubble column), this represents a reduction of ~3.5%, removing the need for the additional purification steps that are commonly required.

More recently, de Mello *et al.*[81] demonstrated the continuous synthesis of a series of secondary amides *via* a carbonylative coupling reaction within a glass micro reactor (channel dimensions = 200 μm (wide) × 75 μm (deep) × 5 m



Scheme 35 Selective chlorination of acetic acid **128** to afford chloroacetic acid **129**.



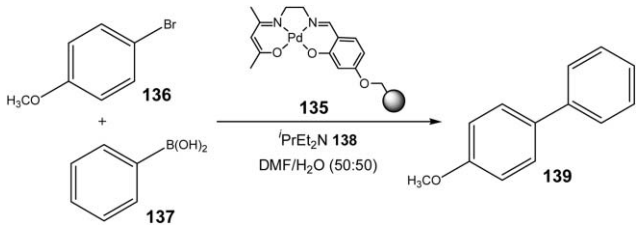
Scheme 36 Micro-scale carbonylative synthesis of *N*-benzylbenzamide **133** and α-ketoamide **134**.

(length)). Employing a biphasic reaction system, comprising of gaseous carbon monoxide and a solution of iodobenzene **131**, benzylamine **132** and a palladium–phosphine catalyst, the effect of liquid flow rate under a constant gas flow (2 sccm) was investigated. Using the synthesis of *N*-benzylbenzamide **133** as a model reaction (Scheme 36), the authors found that annular flow dominated (whereby liquid is forced to the surface of the micro channel and gas flows through the centre) when flow rates of 5.0 to 20.0 μl min^{-1} were employed. Conducting the micro reactions for 10 min, and analysing the reaction products by GC, the authors reported an increase in conversion as a function of increased reagent residence time, an observation that the authors attribute to the formation of a stable flow regime within the reactor. Using the optimal flow rate of 5.0 μl min^{-1}, 46.0% conversion to the respective amide **133** was achieved along with 9.0% α-ketoamide **134**. In contrast, a comparable reaction performed in batch afforded only 25.0% amide **133** and 0.0% α-ketoamide **134**. Although the example presented represents a simple route to the synthesis of α-ketoamides, further reaction optimisation is clearly required.

As these examples illustrate, the enhanced mass transport obtained in miniaturised reaction systems leads to increased product yield, selectivity and most importantly reaction control, affording enhanced space time yields compared to traditional reaction set-ups.

2.2.3 Solid–liquid micro reactions. In addition to the many homogeneously catalysed micro reactions performed to date, numerous groups have investigated the advantages associated with the incorporation of heterogeneous catalysts into micro fabricated reactors. With this in mind, an array of techniques have been reported for their implementation, including the formation of packed beds, channel wall derivatisation and the preparation of functionalised monoliths.

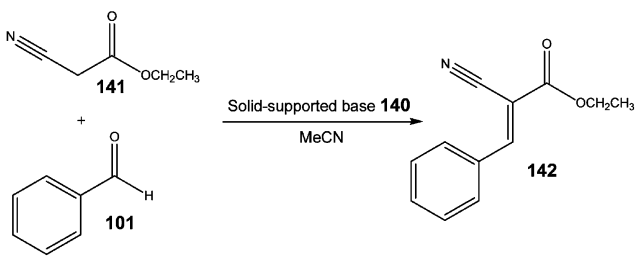
An example of a packed-bed was recently reported by Styring and co-workers[82] who performed a series of Suzuki–Miyaura reactions (Scheme 37) utilising a polymer-supported palladium(II) salen type complex **135** in a pressure driven, glass reactor (3 mm (i.d.) × 2.5 cm (length). Employing a pre-mixed solution of 4-bromoanisole **136** (0.10 M), phenylboronic acid **137** (0.15 M) and *N,N*-diisopropylethylamine ($^{i}PrEt_2N$) **138** (0.30 M) in aqueous DMF (50 : 50), the effect of residence time within the packed-bed was evaluated. Operating the reactor at flow rates >25.0 μl min^{-1} resulted in somewhat low



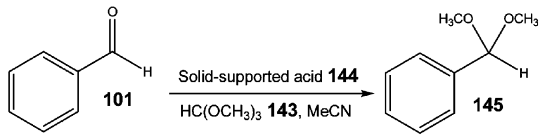
Scheme 37 Synthesis of 4-methoxybiphenyl **S3c** *via* the Suzuki–Miyaura reaction.

conversions to the desired 4-methoxybiphenyl **139** (22.0%), however reducing the flow rate to 3.0 μl min^{-1} (21 min) resulted in an increase to 52.0% conversion. Applying a stopped flow regime, hence increasing the residence time further, led to an optimal conversion of 86.0%. Compared to an analogous batch reaction, the authors report a 20-fold increase in the rate of reaction, attributed to the increased reagent/catalyst contact, as a result reaction times can be reduced from 24 h to 10.5 min.

A further example of miniaturised packed-beds was reported by Wiles and co-workers,[83] who investigated the use of commercially available supported bases as catalysts for the generation of enolates. Using this approach, the authors proposed that compounds of analytical purity could be synthesised within continuous flow reactors, through careful reaction optimisation. In order to evaluate this hypothesis, silica-supported piperazine **140** (5.0×10^{-3} g, 1.70 mmol g^{-1}) was packed into a borosilicate glass capillary reactor (500 μm (i.d.) × 3.0 cm (length)) and held in place by two micro porous silica frits. To perform a reaction, a pre-mixed solution of ethyl cyanoacetate **141** and benzaldehyde **101** (1.00 M in MeCN) was mobilised through the packed-bed, where condensation occurred, to afford 2-cyano-3-phenylacrylic acid ethyl ester **142** in 99.1% conversion (% RSD = 0.65, $n = 15$) (Scheme 38). Using these optimised reaction conditions, the reactor was operated continuously for a period of 4 h, enabling the synthesis of 28 mg of 2-cyano-3-phenylacrylic acid ethyl ester **142** in excellent yield (98.9%) and purity, without the need for additional product purification. Furthermore, the authors investigated the synthesis of 2-cyano-3-phenylacrylic acid ethyl ester **142** using an array of silica and polymer-supported bases[84] whereby conversions of 99.1 to 100.0% were obtained, demonstrating the generality of the technique. Compared to traditional stirred or shaken reactors, the use of a continuous flow system proved advantageous as it lead to reduced



Scheme 38 The use of solid-supported bases for the continuous flow synthesis of 2-cyano-3-phenylacrylic acid ethyl ester **142**, under electroosmotic flow.



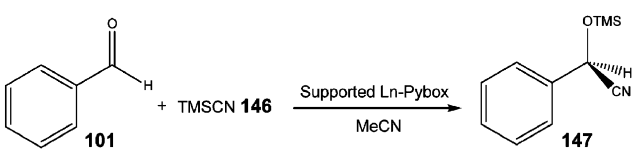
Scheme 39 Synthesis of dimethyl acetals using solid-supported acid catalysts.

degradation of the support material, leading to enhanced reagent lifetimes and run to run reproducibility.

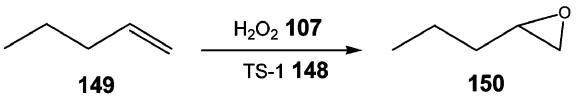
Additionally, the authors investigated the use of solid-supported acid catalysts, using the synthesis of dimethyl acetals as a model reaction.[85] As illustrated in Scheme 39, the reaction involved passing a pre-mixed solution of benzaldehyde **101** and trimethylorthoformate **143** (1.00 M and 2.50 M in MeCN respectively) over a packed bed, containing Amberlyst-15 **144** (5.0×10^{-3} g, 4.20 mmol g^{-1})) using electroosmotic flow. Off-line chromatographic analysis of the reaction products enabled the percentage conversion of aldehyde **101** to dimethoxymethyl benzene **145** to be determined. Using this approach, 99.8% (% RSD = 0.13, n = 15) conversion to the desired dimethyl acetal **145** was obtained, affording 2.5×10^{-2} g (96.6% yield) of the desired product in 2.5 h. The authors subsequently investigated the synthesis of a further 14 dimethyl acetals, all of which were obtained in excellent yield (>95.4%) and purity without off-line purification. In addition to the advantages highlighted in the previous example, the use of solid-supported acid catalysts also enable acid-catalysed reactions to be performed in EOF-based systems; which are clearly not feasible in solution (Section 1.2.2.1).

Further to these synthetic transformations, Moberg *et al.*[86] demonstrated an example of asymmetric catalysis in a micro fabricated reactor. As Scheme 40 illustrates the model reaction selected involved the enantioselective addition of trimethyl cyanide (TMSCN) **146** to benzaldehyde **101**. To perform a reaction, a pre-mixed solution of benzaldehyde **101** and TMSCN **146** was pumped through the packed-bed, containing the polymer-supported Lanthanide-pybox catalyst, and the reaction products analysed off-line. Compared to standard batch techniques, this approach proved advantageous as it enabled the enantioselective synthesis of cyanohydrin **147**, without the need for additional extraction steps to enable the recovery and reuse of the lanthanide catalyst.

In addition to the array of examples employing catalytic packed-beds, numerous examples feature within the literature whereby catalysts are deposited on the micro channel surface. In one example, Gavriilidis and co-workers[87] report coating a silicon micro channel (500 μm or 1000 μm (wide) and 250 μm (deep)) with a TS-1 zeolite layer **148** (3 μm) and its subsequent application in the synthesis of epoxides (Scheme 41). Employing a 1000 μm coated micro channel, the oxidation



Scheme 40 Enantioselective addition in a micro reactor.



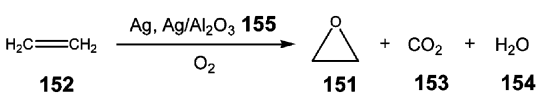
Scheme 41 Epoxidation of 1-pentene **149** using TS-1 **148** in a micro reactor.

of l-pentene **149** was investigated in the presence of hydrogen peroxide **107**, to afford epoxypentane **150** in 4.0% yield. In order to increase product conversion, the authors subsequently investigated reducing the channel width to 500 μm, hence increasing the surface-to-volume ratio, resulting in an increase to 10.0% conversion. A problem associated with the reactor however was the unexplained deactivation of the TS-1 **148** that occurred after operating for >100 h; consequently, techniques to prevent this are currently under investigation.

2.2.4 Gas-solid micro reactions. Owing to the extreme reaction conditions frequently employed in gas–solid chemistry, it remains one of the most investigated areas of micro reaction technology. To date, an array of reactions have been reported in the literature, including oxidations,[88] dehydrations,[89] dehydrogenations[90] and hydrogenations,[91] with many benchmarked against conventional reaction methodology.[92] Consequently, in order to demonstrate the practical advantages associated with the miniaturisation of gas–solid reactions, two industrially relevant examples are discussed herein.

In 2002, Schuth and co-workers[93] investigated the synthesis of ethylene oxide **151** in a micro structured reactor, benchmarking it against an existing industrial process. When conducted on a large-scale, the oxidation of ethylene **152**, to ethylene oxide **151**, is particularly problematic as the formation of hot-spots can lead to the total oxidation of ethylene **152**, affording carbon dioxide **153** and water **154**, resulting in an inefficient process. To address this, the authors investigated the incorporation of a silver catalyst **155** within a PMMA–nickel micro reactor to enable the controlled partial oxidation of ethylene **152** (Scheme 42). Owing to the enhanced heat transfer obtained in such micro fabricated reactors, the authors adeptly demonstrated the advantages associated with conducting high temperature, gas–solid reactions within micro fabricated systems. Employing a reagent stream of 15.0% ethylene **152** in oxygen, a reactor temperature of 290 °C and a system pressure of 5 bar, 65.0% conversion to ethylene oxide **151** was obtained, in the absence of a promoter, such as 1,2-dichloroethane (DCE); however when DCE was employed, the selectivity increased by 15.0%.

Further to this example, Jensen and co-workers[94] reported a micro fluidic system capable of the on-site synthesis of phosgene. Using a silicon micro packed-bed reactor, the authors described quantitative conversion of chlorine to phosgene, when employing a 1 : 1 feedstock and operating the micro reactor at 8 std.cm^3 min^{-1}. Under the aforementioned reaction conditions, the authors calculated that a ten-channel reactor would be



Scheme 42 Synthesis of ethylene oxide **151** in a micro reactor.

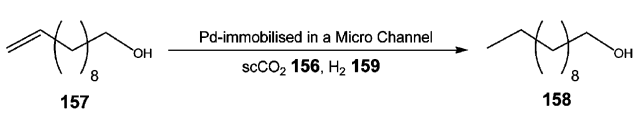
capable of preparing 100.0 kg per year of phosgene. In addition, the authors also reported the ability to extract kinetic data from the lab-based reactor set-up enabling the reactions activation energy to be determined.

Compared to conventional methodology, this approach is advantageous as it not only reduces the risks associated with the synthesis of phosgene, but also enables the compound to be synthesised at the point of use, reducing the hazards associated with its transportation and storage. The approach of synthesis on demand, particularly with respect to the preparation of hazardous materials, is an attractive feature for chemical manufacturers. In addition to the added benefits of enhanced yield and product selectivity, the inherent process safety associated with the manipulation of small quantities of hazardous material, in sealed reactor units, is of great interest, particularly with respect to the extreme reaction conditions encountered in gas–solid reactions.

2.3 Tri-phasic micro reactions

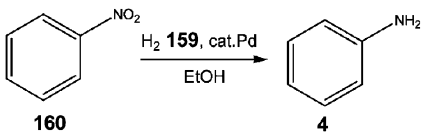
More recently, Kobayashi *et al.*[95] demonstrated the efficient palladium catalysed hydrogenation of an array of alkenes and alkynes using supercritical carbon dioxide ($scCO_2$) **156** within a micro fabricated reactor. In order to perform hydrogenation reactions within the glass micro reactor, the authors firstly coated the micro channel (200 μm (wide) × 100 μm (deep) × 40 cm (length)) with microencapsulated palladium. Once coated, the micro reactor was connected to a high-pressure cell, through which reagents were added and the $scCO_2$ formed; in order to maintain and control pressure within the system, a back-pressure regulator was placed at the end of the micro channel. To perform a reaction, 0.20 mmol of 10-undecen-1-ol **157** was placed in a high-pressure cell at 50 °C, whilst $scCO_2$ containing dissolved H_2 was formed in an adjacent autoclave. The $scCO_2$ **156** was subsequently passed through the cell, containing 10-undecen-1-ol **157**, and the resulting reaction mixture transferred to the micro reactor where the hydrogenation occurred; employing a residence time of <1 s, 10-undecen-1-ol **157** was quantitatively reduced, affording **158** (Scheme 43). The authors attribute the impressive rate of reaction to the high surface-to-volume ratio obtained in the micro fabricated system enabling efficient interaction of the substrate **157** with the catalyst and H_2 (no Pd leaching was detected). In addition to the efficient reduction of alkenes, the selective reduction of an alkyne in the presence of a benzyloxy group (91.0% yield) was also demonstrated within the reactor. Using this approach, the authors demonstrate enhanced productivity (0.1 mmol h^{-1}) compared to an earlier tri-phasic micro reaction system where a throughput of 0.01 mmol h^{-1} was obtained, an observation that is credited to the enhanced solubility of hydrogen **159** within the $scCO_2$ **156**.[96]

Gavriilidis and co-workers[97] also demonstrated the use of a falling film reactor for the exothermic (545 kJ mol^{-1}) hydrogenation of nitrobenzene **160** (Scheme 44). Employing palladium coated micro channels (300 μm (wide) × 100 μm (deep) × 7.8 cm (long)), 1–4 bar H_2 **159** and an ethanolic solution of nitrobenzene **160**, the authors describe the synthesis of aniline **4**. Conducting the reactions at 60 °C, and employing a reagent residence time of 17 s, a maximum conversion to aniline **4** of 82.0% was reported. In batch, side reactions often led to the formation of by-products such as cyclohexanol **78**, *N*-ethylaniline, toluidine, cyclohexyl amine and diaminobenzene; however in the falling film reactor, side reactions were minimised due to the excellent thermal and mass transportation properties obtained.



157 158

Scheme 43 Reaction scheme illustrating the hydrogenation of 10-undecen-1-ol **157** in a micro fabricated reactor.



160 4

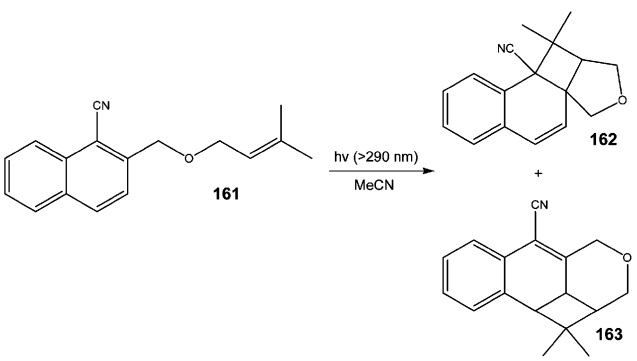
Scheme 44 Palladium catalysed hydrogenation of nitrobenzene **160**, in a falling-film reactor, to afford aniline **5**.

These examples of tri-phasic (gas–liquid–solid) reactions serve to demonstrate the system flexibility associated with micro reaction technology, particularly with respect to the future of heterogeneous catalysis.

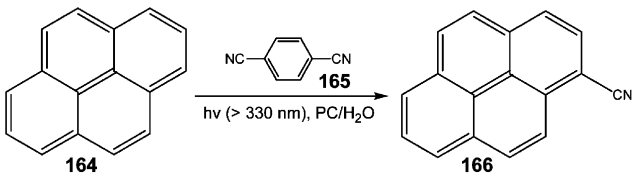
2.4 Miniaturised photochemistry

Photochemistry provides an attractive, environmentally friendly approach to the synthesis of complex molecules; however, the ability to scale-up such reactions is marred with problems that are largely associated with the scale-up of light sources.

Mizuno and co-workers,[98] reported an enhancement in reaction efficiency, and regioselectivity, by conducting the photocycloaddition of a naphthalene derivative **161** (Scheme 45) in a PDMS micro reactor. The authors found that in batch, irradiation of a 1-cyanonaphthalene derivative **161**, using a filtered Xenon lamp ($\lambda > 290$ nm), afforded photocycloadducts **162** and **163** in 56.0% and 17.0% yield respectively. In comparison, when conducting the reaction in a micro reactor, employing flow rates of 0.50 μl min^{-1} and an irradiation time of 3.4 min, afforded in 59.0% **162** and 9.0% **163**. In addition, employing a stoichiometric quantity of (tris[3-heptafluoropropylhydroxymethylene)-+-camphorato])europium ($Eu(hfc)_3$) resulted in the regioselective synthesis of photocycloadduct **162** with a low enantiomeric excess of 2.0 ± 0.3%. Compared



Scheme 45 Photocycloaddition of naphthalene derivative **161**.



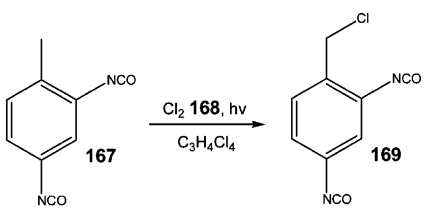
Scheme 46 Photocyanation of pyrene **164** to afford 1-cyanopyrene **166**, across an oil–water interface.

to the batch study where an irradiation time of 3 h was employed, this approach clearly demonstrates the enhanced reaction efficiency attainable in micro fluidic systems.

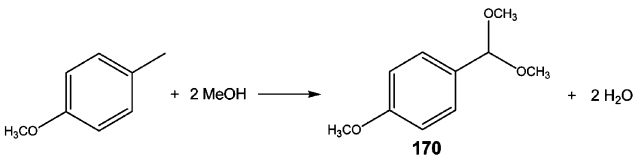
Similarly, Kitamura and co-workers,[99] demonstrated the photocyanation of pyrene **164** (Scheme 46) across an oil–water interface within a polystyrol, dual-Y-shaped micro channel (dimensions = 100 μm wide × 20 μm deep × 3.5 cm length). To perform a reaction, an aqueous solution of sodium cyanide (1.00 M) and a solution of pyrene **164** (2.00×10^{-3} M) and 1,4-dicyanobenzene **165** (4.00×10^{-3} M) in propylene carbonate (PC) were introduced from separate inlets at a flow rate of 0.2 μl min^{-1} (residence time = 3.5 min) and the whole reactor irradiated using a high-pressure Hg lamp (~330 nm). Upon exiting the micro reactor, the oil and water phases were separated using a second Y-shaped micro channel, prior to analysis of the oil phase by GC. Using this approach, the authors reported 28.0% conversion of pyrene **164** to 1-cyanopyrene **166**, which was subsequently increased to 73.0% conversion by employing a three-layer reaction stream comprising of water–oil–water.

Another interesting photochemical transformation conducted in a micro fabricated reactor, was the photochemical chlorination of toluene-2,4-diisocyanate **167** (Scheme 47) reported by Ehrich and co-workers.[100] Employing a falling film micro reactor (channel dimensions = 600 μm (wide) × 300 μm (deep) × 6.6 cm (length)) consisting of 32 parallel micro channels, the authors investigated the irradiation of gaseous chlorine **168**, through a quartz window, generating chlorine radicals in the presence of toluene-2,4-diisocyanate **167** in tetrachloroethane. Using this approach, the authors investigated the effect of varying the flow rate of chlorine **168** (14.0 to 56.0 ml min^{-1}) and toluene-2,4-diisocyanate **167** (0.1 to 0.6 ml min^{-1}) on the proportion of benzyl chloride-2,4-diisocyanate **169** produced. Maintaining the reactor at 130 °C, the authors identified the optimal residence time to be 9 s, affording benzyl chloride-2,4-diisocyanate **169** in 81.0% conversion and space–time yields of 401.0 mol l^{-1} h^{-1} compared with only 1.3 mol l^{-1} h^{-1} in a conventional reactor.

From the examples presented it can be seen that the miniaturisation of photochemical reactions has many advantages



Scheme 47 Photochemical chlorination of toluene-2,4-diisocyanate **167**.



Scheme 48 Anodic methoxylation in the absence of supporting electrolytes.

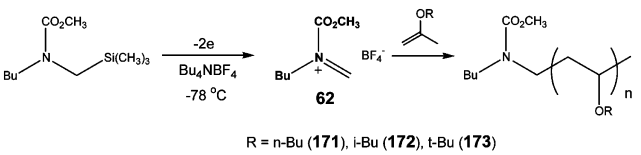
compared to standard techniques, the most apparent being the ability to prepare large quantities of material, *via* scale-out, using commercially available light sources.

2.5 Electrochemical synthesis in micro fluidic systems

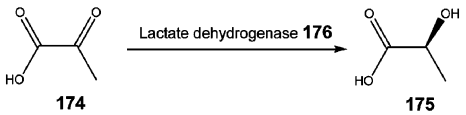
Yoshida and co-workers[101] recently demonstrated the ability to perform electrochemical syntheses within a micro fluidic system without the need for intentionally added supporting electrolytes (Scheme 48). The reactor consisted of two carbon fibre electrodes that are separated by a porous, PTFE membrane spacer (75 μm); to conduct a reaction reagents flow into the reactor through the anodic chamber, cross a membrane and flow out of the cathodic chamber. Using this cross flow approach, where the liquid flow and electric current are parallel, the authors obtained 1-dimethoxymethyl-4-methoxybenzene **170** in 90.0% yield when employing a constant current of 11 mA and a flow rate of 50.0 μl min^{-1}.

The same group also demonstrated the use of a cation-pool technique for the generation of highly reactive cations, such as *N*-acyliminium ions **62**, demonstrating their application for the selective alkylation of aromatic compounds[102,103] and, as described herein, the initiation of living cationic polymerisations (Scheme 49).[104] The authors found that by combining the principles of a cation-pool with those of micromixing, they were able to obtain rapid and controlled polymerisation, affording polymeric products with narrow molecular weight distributions (typically M_w/M_n = 1.14 (**171**), 1.12 (**172**) and 1.5 (**173**)) compared to those obtained in batch reactions (M_w/M_n = 2.56). Further examples illustrating the advantages associated with coupling microfluidics and the electrochemical generation of reactive intermediates can be found in a recent review by Yoshida *et al.*[105]

Although the use of enzymes, as catalysts, has the potential to revolutionise synthetic chemistry, their cost and the inability to efficiently recycle them (and any related co-factors) has lead to limited industrial uptake. With this in mind, Kenis and co-workers[106] recently demonstrated an efficient technique for the electrochemical regeneration of nicotinamide co-factors in a Y-shaped PDMS micro reactor (channel dimensions = 250 μm (wide) × 3 cm (length)). The authors found that by employing multi-stream laminar flow, comprising of a buffer stream and



Scheme 49 Synthesis of an *N*-acyliminium cation-pool **AB** and its use as a polymerisation initiator.



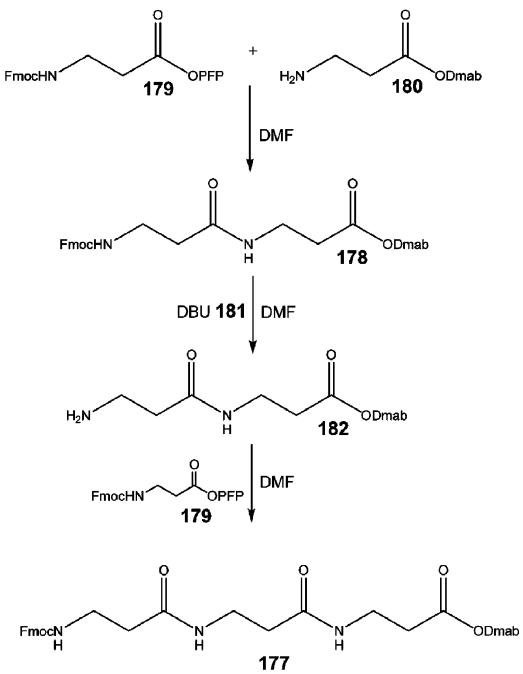
Scheme 50 Biocatalytic synthesis of L-lactate **175** in a micro reactor.

a reagent stream, efficient regeneration of the co-factor NADH could be achieved at the surface of a gold electrode. Using this approach, enzyme/co-factor regeneration was demonstrated for the conversion of achiral pyruvate **174** to L-lactate **175** in the presence of lactate dehydrogenase **176** (Scheme 50); whereby yields of 41.0% L-lactate **175** were achieved (turnover number = 75.6 h^{-1}). This result clearly illustrates enhancements over conventional approaches, providing a feasible, cost effective route to the biocatalytic synthesis of large quantities of chiral material.

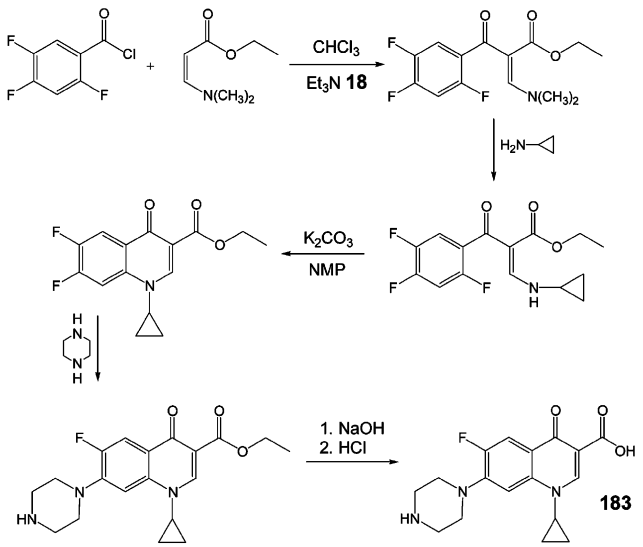
2.6 Multi-step micro reactions

Over the past decade, many research groups have contributed to the development of a 'toolbox' of single-step reactions, performed in an array of micro fabricated reactors. With this in mind, the next step for many researchers has been to investigate increasing the reaction complexity to incorporate multiple reaction steps.

In 2002, Watts *et al.*[107] demonstrated the multi-step synthesis of a tripeptide **177** by combining many previously reported single-step peptide coupling reactions. As Scheme 51 illustrates, a dipeptide **178** was firstly prepared by coupling a pentafluorophenyl (PFP) ester **179** with an amine **180**. Fmoc deprotection of the resulting dipeptide **178** was achieved by treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene **181** (DBU) to afford amine **182**. A second equivalent of PFP ester **179** was subsequently introduced into the micro reactor where it was



Scheme 51 Multi-step synthesis of tripeptide **177** within an EOF-based micro reactor.



Scheme 52 Synthesis of Ciprofloxacin™ **183** in a micro reactor.

reacted with amine **182** to afford the desired tripeptide **177**, in an overall yield of 30.0%; demonstrating the first multi-step reaction to be performed using a field induced pumping mechanism.

Schwalbe *et al.*[108] similarly performed the multi-step synthesis of Ciprofloxacin™ **183** within a CYTOS micro reactor, demonstrating one of the most complex micro fluidic reactions investigated to date (Scheme 52).

Having successfully demonstrated the incorporation of both polymeric and silica-supported catalysts into an EOF-based continuous flow reactor (Schemes 38 and 39), Wiles *et al.*[109] evaluated the feasibility of performing multi-step syntheses using supported reagents. As Scheme 53 illustrates, the first step of the reaction consisted of an acetal **145** deprotection, using an acid catalyst, Amberlyst-15 **144**, to afford the respective aldehyde **101**, followed by a base-catalysed (silica-supported piperazine **140**) condensation of the aldehyde **101** with malononitrile **184**, to afford 2-benzylidene malononitrile **185**.

To perform a reaction, a pre-mixed solution of malononitrile **184** and dimethoxymethyl benzene **145** (1.00 M in MeCN), was mobilised through the spatially resolved catalysts using EOF (167 V cm^{-1}); the reaction products were subsequently analysed off-line using GC-MS. Using the aforementioned methodology, 100.0% conversion of the starting materials to product, was obtained at a flow rate of 0.53 μl min^{-1}. Operating the reactor for 2.5 h enabled the

Scheme 53 Multi-step synthesis of an α,β-unsaturated compound **185**.

synthesis of 1.2×10^{-2} g of product **185** that upon solvent removal was found to be analytically pure by NMR spectroscopy and elemental analysis. In addition, the authors investigated the diversity of the technique illustrating the reaction of a further 14 dimethyl acetals with malononitrile **184** and ethylcyanoacetate **141**, obtaining excellent conversions in all cases (>99.9%).

Cheng-Lee, Sui and Elizarov[110] recently demonstrated the multi-step synthesis of a radiolabelled imaging probe, in a PDMS micro fluidic reactor (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 **186** (324 ng), to afford the labelled probe **187**, (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 **187** (60 °C), the authors demonstrated the synthesis of 2-[^{18}F]FDG **34** (Scheme 8). Using this approach, 2-[^{18}F]FDG **34** was obtained with a radiochemical yield of 38.0% and a purity of 97.6% (by radioTLC) demonstrating a significantly shorter synthesis time (14 min) than that observed for conventional automated techniques (50 min); most importantly, the authors found the synthesis to be reproducible between both runs and devices. The purified, sterilised probe **34**, was subsequently used for microPET (positron emission tomography) molecular imaging of two mouse models of cancer, and reported that by increasing the size of the reaction chamber greater quantities of imaging probe could be generated, suitable for multiple human PET scans; where typical requirements are 10 mCi per patient.

2.7 On-line purification

Having established the ability to conduct complex synthetic transformations within micro fabricated reactors, one of the remaining challenges associated with micro-scale synthesis is the purification of compounds produced in a continuous manner. On the macro-scale, product purification is typically achieved *via* an aqueous work-up (to remove inorganic material), column chromatography (to remove any by-products or unreacted starting materials) and finally recrystallisation.[111] In its traditional form however, this approach is not amenable to the micro-scale environment as it means collecting the effluent from multiple micro reaction channels and essentially performing a batch-type work-up, therefore removing some of the advantages associated with micro-scale synthesis, such as speed and automation. While techniques such as capillary electrophoresis (CE) have found widespread application in μ-TAS (micro total analysis systems),[112] the technique is not widely applicable for the isolation of reaction products in continuous reagent streams; although examples of this have been reported.[113] That said, techniques that have made the successful transition from the macro domain to the micro, include μ-dialysis,[114] μ-filtration[115] and as previously discussed, liquid–liquid extractions,[116] with the latter showing the most promise with respect to universal applicability.

Kitamori and co-workers[117] observed that by conducting extractions within a miniaturised pressure-driven system, extraction efficiencies were at least one order of magnitude greater that those obtained when using a traditional separating funnel and a mechanical shaker. This was illustrated by the extraction of an iron complex from an aqueous solution into chloroform, conducting the extraction in a 250 μm glass channel, the complex was extracted in 45 sec, compared to the use of a separating funnel where the mixture took ~20 min to simply equilibrate. As the miniaturised systems operate under stable two-phase flow, a high degree of phase separation results, along with efficient analyte extraction due to the short diffusion lengths and the high interfacial surface area obtained.

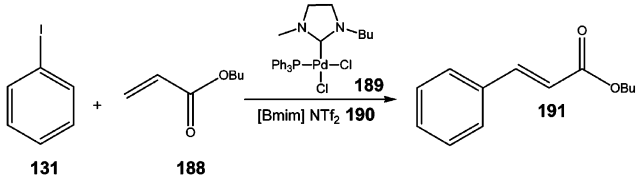
Another frequently encountered problem in solution phase chemistry is the ability to recover, and recycle, homogeneous catalysts from resulting reaction mixtures, this is particularly problematic on the small reaction volumes obtained in miniaturised systems. To address this problem, and prevent precipitation within the micro reactor, Ryu and co-workers[118] investigated the use of ionic liquids within a CYTOS micro reaction system. Employing pressure-driven flow, a solution containing iodobenzene **131**, butyl acrylate **188** and tripropylamine was introduced into the reactor from one inlet and a solution of Pd catalyst **189** in 1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide ([Bmim]NTf_2) **190** (5 mol%) was introduced from a second inlet. The ammonium salts were washed from the resulting reaction mixture in an automated micro extraction unit, enabling the Pd-catalyst **189** to remain in the ionic liquid and be readily recycled. Employing a reaction temperature of 130 °C and a flow rate of 500.0 μl min^{-1} (residence time of 17 min), the authors report the synthesis of butyl cinnamate **191** in 97.0% yield (Scheme 54). Using the aforementioned reaction conditions, the authors operated the reactor continuously over a period of 11.5 h, affording 144.8 g (0.71 mol) of butyl cinnamate **191**, whilst demonstrating the ability to efficiently recycle both the homogeneous Pd-catalyst **189** and the ionic liquid **190**.

As illustrated in Schemes 38, 39 and 53, an alternative approach is to incorporate supported reagents, catalysts and scavengers into such miniaturised devices as a means of synthesising analytically pure compounds in a continuous manner; consequently no off-line or in-line purification steps are required, simply evaporation of the solvent system.

To ensure the transfer of micro reaction technology from the current lab/pilot plant based operations to widespread industrial application, generic techniques that enable continuous purification to be performed are required.

3.0 Examples of process intensification (scale-out)

Having presented an array of examples illustrating the advantages associated with the miniaturisation of synthetic procedures, there remains one perceived 'disadvantage' of



Scheme 54 Synthesis of butyl cinnamate **F1a** in a micro reactor, *via* the Mizoroki–Heck reaction.

micro reaction technology, the synthesis of small quantities of material. As mentioned in Section 1.4, this can be addressed through the scale-out or numbering-up of an optimised reaction set-up, which enables the advantages of single reactors to be carried through to the preparation of large quantities of material. Although the concept of scale-out has featured widely in the literature over the past decade, until recently few groups had put the technique into practise.

As part of an on-going investigation into the fluorination of small organic compounds within biphasic micro reactors (Scheme 33), Chambers and co-workers[118] recently published a manuscript detailing the successful scale-out of their reactor, enabling 30 reaction channels to be operated in parallel. Adopting this approach, enabled the efficient heat exchange and gas–liquid mixing obtained in the single channel reactor to be maintained and provided a safe alternative to traditional batch-wise fluorinations.

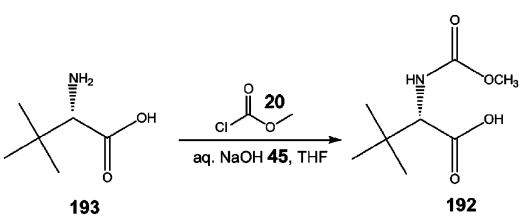
In order to demonstrate the scalability of this technique, the authors again selected the fluorination of ethyl acetoacetate **120** (Scheme 33) as a model reaction, performing the reaction in a 9, 18 and 30-channel reactor. In all cases, employing 1.4 : 1 F_2 **121** to ethyl acetoacetate **120** afforded 2-fluoro-3-oxobutyric acid ethyl ester **122** as the major product (>66.0%) with minimal by-products observed. All results obtained for the multi-channel reactors were within experimental error, demonstrating the ease with which micro reactions can be scaled-out. Using this approach, the throughput of the reactor was calculated to be in the range of 0.2 g h^{-1} $channel^{-1}$, feasibly enabling the synthesis of 150.0 g day^{-1}. The authors also comment that the reactors have been in use within their laboratories for many months, synthesising in excess of 700.0 g of **122**, with no sign of reactor degradation. From this technique alone, it can be seen that reactor scale-out provides a safe and flexible alternative to the construction of conventional pilot and production plants.

Another example of scale-out performed at a research level was reported by Kitamori and co-workers,[119] who demonstrated the fabrication of a 'pile-up' reactor. The Pyrex glass device consisted of ten-layers, each containing an etched channel network (reaction channel dimensions = 360 μm (wide) × 120 μm (deep) × 47 cm (length)), fluidic control was achieved through the use of a syringe pump and reagents delivered/collected through a single inlet/outlet. For comparative purposes, the authors again investigated the synthesis of 3,5-dinitro-*N*-(1-phenylethyl)benzamide **98** (Scheme 27), previously reported in a single channel reactor. Employing 0.01 M solutions of 1-phenylethylamine **99** in 0.10 M aqueous sodium hydroxide **45** and 3,5-dinitrobenzoyl chloride **100** in ethyl acetate, the authors investigated the effect of flow rate on the percentage yield of 3,5-dinitro-*N*-(1-phenylethyl)benzamide **98**, in a single channel reactor. Operating a total flow rate of 2.5 ml min^{-1}, the authors obtained 82.0% yield of product **98** (3.2×10^{-3} g min^{-1}), it was however observed that by reducing the flow rate to 1.0 ml min^{-1}, no further increase in yield was obtained (82.0%), leading to a reduced throughput of 1.3×10^{-3} g min^{-1}. The optimised reaction conditions were subsequently transferred to the pile-up reactor, where a total flow rate of 25 ml min^{-1} supplied reagents to all ten reaction channels (2.5 ml min^{-1} $channel^{-1}$) affording a throughput of 3.3×10^{-2} g min^{-1}. The authors concluded that through the continuous operation of such a device, amides could be synthesised at a rate of 1/60 Ton per year.

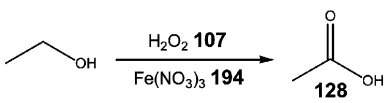
Zhang *et al.*[120] demonstrated the use of a CYTOS system for the synthesis of gram to kilogram quantities of drug substances for early clinical studies. In particular, the authors demonstrated the ability to perform a series of exothermic reactions, reporting enhanced reaction control compared to standard batch techniques. One such example was the synthesis of *N*-methoxycarbonyl-L-*tert*-leucine **192** (Scheme 55) *via* the addition of methyl chloroformate **20** to L-*tert*-leucine **193** in the presence of aqueous NaOH. Conducting the reaction in a flow reactor, at −40 °C, resulted in the synthesis of *N*-methoxycarbonyl-L-*tert*-leucine **192** in 91.0% yield affording a throughput of 83.0 g h^{-1}.

Kraut and co-workers[121] subsequently demonstrated the use of a modular micro reactor, comprising of micro mixers and reaction channels (150 μm × 300 μm × 6.0 cm), for the oxidation of ethanol. As Scheme 56 illustrates, ethanol was oxidised using hydrogen peroxide **107** in the presence of a catalytic quantity of ferric nitrate **194**. Employing aqueous solutions of ferric nitrate **194** (1.00 M), acetic acid **128** (1.00 M) and hydrogen peroxide **107** (35.0%), the oxidation of ethanol was investigated over a range of flow rates (0.2 to 0.9 kg h^{-1}) and temperatures (70–115 °C). In order to prevent boiling of the reaction mixture, the micro reactions were conducted under pressure (3 to 5 bar) affording conversions of >99.0%, with an optimised residence time of 3 s. Compared to the irreproducible, 30.0 to 95.0%, conversion obtained in a continuous stirred tank reactor (residence time ~29 min), this use of a modular micro reactor represents a 250-fold increase in the space-time yield. With this in mind, the micro reaction set-up afforded product selectivities in excess of 99.0% and a throughput of 4.3 l h^{-1}.

In addition to academic interest in scale-out, the technique has also been investigated from an industrial perspective. In 2000, Krummradt and co-workers[122] reported a multi-stage process for the production of an undisclosed fine chemical, based on the exothermic reaction of a carbonyl compound and an organometallic reagent. Using a pilot micro fluidic plant, consisting of five parallel reactors, increased yields were obtained compared to conventional batch reactions, performed on a 0.5 l lab-scale and a 6000 l technical-scale. As a



Scheme 55 Continuous flow synthesis of carbamates.



Scheme 56 Catalytic oxidation of ethanol to afford acetic acid **128**.

result of these findings, the micro reactor plant has been in continuous operation since August 1998, in place of the conventional batch system.

Based on the examples provided, it can be seen that micro reaction technology has the potential to revolutionise all aspects of modern synthetic chemistry, ranging from the rapid synthesis of target compounds for use in drug screening, to the large volume production of fine chemicals and pharmaceuticals.

4.0 Other applications of micro reactors

In addition to the synthesis of small organic molecules, the unique reaction conditions attained in miniaturised reaction systems have more recently found application for the controlled synthesis of polymers, nanoparticles and emulsions.

4.1 Controlled polymerisation

When performing polymerisations in batch, the removal of heat as a reaction progresses is often the limiting factor, being largely responsible for the wide molecular weight distributions obtained. Consequently, by performing such reactions in micro fluidic systems, where the high surface-to-volume ratio ensures rapid dissipation of heat, polymers with a narrow molecular weight distribution should be attainable.

Yoshida and Iwasaki[123] recently reported the controlled polymerisation of butyl acrylate, an industrially relevant transformation, in a stainless steel capillary reactor (dimensions = 500 μm (i.d.) × 1.0 m (length)) consisting of a micro mixer followed by a heated channel (80 to 100 °C) and a cooled (0 °C) section. Using pressure-driven flow, the authors introduced a solution of azobisisobutyronitrile (AIBN) (0.03 to 0.05 M) in toluene from inlet A and neat butyl acrylate from inlet B and reaction products were analysed off-line by GPC. Employing a reagent residence time of 3 min afforded yields of 86.5% and a polydispersity index (PDI) of 3.14; performing a comparable reaction in a traditional batch reactor, afforded 50.0% yield and a PDI of 212. It was therefore concluded that the reduction in PDI obtained when employing a micro reaction system was simply due to efficient heat removal. With respect to mass production, the authors importantly demonstrated the ability to operate the reactor, on a laboratory scale, for hours with no sign of fouling or pressure build-up (due to material adhesion).

A further illustration of controlled polymerisation was published by Beers and co-workers,[124] demonstrating molecular weight control as a function of reactor residence time. Using a glass–thiolene–glass hybrid reactor (channel dimensions = 500 μm × 600 μm, total reaction volume of 200.0 μl), the authors investigated the atom transfer radical polymerisation (ATRP) of 2-hydroxypropylmethacrylate (HPMA). Using pressure-driven flow, an aqueous methanolic (50 : 50) monomer and catalyst solution was introduced into the reactor (25 °C) from one inlet and a solution of the initiator from a second inlet; the reaction products were evaluated, off-line, using size exclusion chromatography. Operating the reactor at a range of flow rates (0.8 to 8.0 μl min^{-1}) the authors investigated the effect of reagent residence time on both the molecular weight and polydispersity of poly(2-hydroxypropyl methacrylate). Using the aforementioned reaction set-up, a direct correlation between molecular weight and flow rate was observed, for example at 8.0 μl min^{-1}, low molecular weights in the region of 1650.0 g mol^{-1} were obtained (17.0% conversion, 1.32 PDI) compared with 6240.0 g mol^{-1} (92.0% conversion, 1.21 PDI) when a flow rate of 1.7 μl min^{-1} was employed. Owing to the predictable nature of this technology, the authors proposed that such micro fluidic devices could enable the rapid generation of polymer libraries.

Along with the ability to prepare polymers of narrow molecular weight distribution, the preparation of polymeric beads has been demonstrated within microfabricated systems. Recently, Zourob and co-workers[125] used a spiral microflow reactor, consisting of a polycarbonate reaction channel (channel dimensions = 200 μm (wide) × 200 μm (deep) × 2.0 cm (length)) and an acetate cover sheet, for the preparation of molecularly imprinted polymers (MIP). To prepare an MIP, an argon purged solution of (*R,S*)-propranolol (1.0 mmol), methacrylic acid (10.0 mmol), trimethylolpropane trimethylacrylate (3.0 mmol) and 2,2-dimethoxy-2-phenylacetophenone (1.5×10^{-2} g) in MeCN (3.0 ml) was introduced into a mineral oil carrier stream and polymerisation initiated using UV-light (60 to 80 mW cm^{-2}). The (*R,S*)-propranolol template was subsequently removed from the polymeric beads by shaking in MeOH–acetic acid **128** (1 : 1) for 24 h, followed by washing with MeOH and MeCN. The aforementioned polymerisation methodology was subsequently repeated using a perfluoro-(1,3-dimethylcyclohexane) carrier stream, and the resulting beads washed with chloroform and acetone.

Using this approach, near-monodisperse polymeric beads were obtained in all cases, affording a coefficient of variation (CV) of <2.0%, compared to analogous batch reactions whereby a CV of 67.0% was attained for beads prepared using mineral oil and 17.0% for those prepared in perfluoro-(1,3-dimethylcyclohexane). Importantly, although the technique provides a simple means of preparing monodisperse polymeric beads, the technique did not affect the internal morphology of the beads, affording pore sizes and specific surface areas comparable to those obtained by conventional polymerisation techniques. In addition, by altering the flow rate of the pre-polymerisation mixture the authors found the particle size ranged from 10 to 120 μm, again affording near-monodisperse beads.

4.2 Formation of nanoparticles

As observed for polymerisations, controlled and reproducible techniques are required for the fabrication of nanoparticles as any changes in the temperature or concentration across a reactor vessel can lead to variations in particle size. In addition, to ensure that a narrow size distribution of particles is achieved, it is essential that the reagents mix thoroughly on a timescale that is shorter than the reaction itself. To this end, reaction miniaturisation provides the desired reaction control, coupled with the ability to achieve production scale quantities *via* process intensification. In 2002, de Mello and co-workers[126] reported the first example of nanoparticle production in micro fluidic devices, describing the synthesis of cadmium sulfide nanoparticles. Under pressure-driven flow (10.0 and 300.0 μl min^{-1}), an aqueous solution of cadmium nitrate and sodium polyphosphate (4.0×10^{-4} M) was mixed with an

aqueous solution of disodium sulfite (4.0×10^{-4} M) in a glass–silicon–glass micro mixer (internal volume of 600.0 nl).[35] To monitor the physical properties of the nanoparticles produced, the outlet of the micro mixer was coupled to a quartz cell (10 mm path length) through which UV-Vis spectra were obtained. Using this approach, the authors reported controlled initiation of nucleation followed by growth, affording CdS nanoparticles with a size distribution unparalleled by macro-scale investigations. In addition, a direct link between residence time and particle size was reported, confirming that crystallite monodispersity could be increased by reducing residence time and hence reducing the risk of coalescence.

Following this initial example, Maeda and co-workers[127] demonstrated the preparation of composite nanoparticles comprising of a cadmium selenide (CdSe) core and a zinc sulfide (ZnS) shell. To prepare the composite nanoparticles within a micro fluidic system, three steps were required, firstly CdSe synthesis (300 °C), followed by the introduction of the ZnS raw materials and finally the ZnS coating step (220 °C). To enable a series of steps to be performed at different reaction temperatures, the micro fluidic system comprised of a 10.0 cm length of micro capillary (200 μm i.d.), connected to a ceramic micro mixer (85.0 cm) followed by 20.0 cm of micro capillary. Using this approach, the first portion of micro capillary could be maintained at 300 °C, and the second at 220 °C. Employing a flow rate of 100.0 μl min^{-1} enabled a residence time of 2 s to be achieved for the CdSe synthesis, 8 s for mixing with ZnS followed by 2 s for ZnS coating.

Further to the fabrication of inorganic nanoparticles, Wagner and co-workers[128] reported the preparation of metallic nanoparticles, using a seed-mediated approach, in a Pyrex–silicon micro reactor (channel volume = 25.0 μl). The 12 nm gold seed particles were prepared off-chip and filtered through 0.2 μm filter, in order to remove any aggregates. Prior to investigating the preparation of larger Au nanoparticles within the micro reactor, the 12 nm Au seeds were passed through the reactor at a flow rate of 50.0 μl min^{-1} and analysed by UV-Vis spectroscopy. Using this approach, the authors reported no change in both the concentration and electronic properties of the 12 nm Au seeds, confirming that the particles remain unaffected by the micro reactor surface. The fabrication of larger Au nanoparticles was subsequently investigated in a micro reactor, using the following methodology; aqueous solutions of 12 nm Au seeds (3.0×10^{-4} M) chloroauric acid (2.5×10^{-5} to 1.0×10^{-3} M) and ascorbic acid (2.4×10^{-3} to 6.0×10^{-2} M) were introduced into the micro reactor from three separate inlets, using pressure-driven flow, and the resulting nanoparticles analysed by UV-Vis spectroscopy. Comparison of the spectra obtained with those from the 12 nm seed particles enabled the authors to investigate the effect of flow rate and the seed/Au^{3+} ratio on the particle size of the resulting nanoparticles. Employing a seed/Au^{3+} ratio of 1 : 3, the authors observed an increase in particle size, from 15.4 to 18.7 nm, as a function of decreased flow rate (50.0 to 10.0 μl min^{-1}) whereas reducing the proportion of Au^{3+} (1 : 1.25) was found to increase nanoparticle size to 23.7 nm. Although this preliminary study confirmed the ability to manipulate colloidal suspensions, and the resulting Au nanoparticles, within micro fluidic systems without the formation of blockages, further work is required in order to realise the full potential of this technique.

4.3 Emulsions

Nisisako and co-workers[129] demonstrated a further example of micro fluidic control whereby the phenomena of droplet formation was exploited for the production of monodisperse double emulsions. These emulsions are a multiple phase dispersion in which droplets containing smaller droplets are suspended in a continuous liquid phase and find application in cosmetics, pharmaceuticals and foodstuffs. Traditional techniques for their preparation include a two-stage emulsification whereby vigorous mixing is employed in order to rupture the droplets; this approach however results in a broad size distribution of both the internal and external droplet size. Consequently, by performing the emulsification in a micro fluidic device, controlled production of these monodisperse double emulsions can be achieved.

Employing a Pyrex micro reactor comprising of hydrophilic and hydrophobic portions, the authors investigated the formation of water-in-oil-in-water (W/O/W) dispersions. Firstly, the internal aqueous phase (deionised water) was pumped into a continuously flowing oil phase (corn oil) through a hydrophobic 90° junction, forming a series of aqueous drops. These drops were subsequently pumped to a second hydrophilic 90° junction where each aqueous droplet was enclosed in an organic droplet within a continuous external aqueous phase. Using this approach, the authors were able to reproducibly prepare 22 droplets s^{-1}, whereby the internal water droplets had an average size of 52.2 μm and the outer oil droplets 83.4 μm. By altering the flow conditions employed, the authors were able to prepare organic droplets containing two aqueous drops. This did however result in a slight increase in polydispersity and occasionally led to coalescence of the internal aqueous droplets. In addition, by changing the flow conditions, both the size and number of internal droplets could be controlled, demonstrating the flexibility of the technique for the production of monodisperse emulsions.

The power of the technique was subsequently demonstrated by the controlled preparation of oil droplets containing two differently coloured aqueous drops; clearly demonstrating the ability to encapsulate multiple components within vesicles producing a system suitable for drug delivery.

5.0 Concluding remarks

Micro reaction technology is currently exhibiting great promise as a novel technique for the rapid optimisation of reaction parameters, affording a reduction in the time taken to transfer successful reactions from the laboratory to production. In addition, owing to the high degree of reaction control attainable in such micro fluidic systems, reactions are found to be more atom efficient, leading to enhanced yields and purities compared to conventional stirred reactor methodology. Consequently, the application of micro reaction technology is of great environmental importance as it has the potential to reduce the quantity of raw materials required, along with efficiently converting them into the desired product with minimal generation of side products and waste. In addition,

this approach enables stringent control of reaction conditions, such as temperature, reducing the risk associated with thermal runaway and subsequent explosion.

Although the technology is still in its early stage of development, some trends are already clear, namely its application to combinatorial chemistry where the rapid generation of a diverse array of compounds is an essential factor. Furthermore, the incorporation of separation capabilities into the micro reactor systems, enabling products to be purified in real-time, will continue to aid the development of this growing field of research. As discussed herein, other emerging areas of interest for the technology include catalyst screening, nanoparticle production and the controlled formation of emulsions.

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