The application of micro reactors for organic synthesis

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This *tutorial review* describes how micro reactors are being applied to synthetic chemistry covering a wide range of applications, from the preparation of nanograms of material for drug discovery and screening to the multi-tonne production of fine chemicals. This article explores how miniaturisation may revolutionise chemical synthesis and demonstrates that products are generated in higher yield and purity compared to the equivalent bulk reactions, in much shorter periods of time.

Introduction

In their simplest form, micro reactors consist of a network of micron-sized channels (typical dimensions are in the range 10–500 μm) etched into a solid substrate.[1] For synthetic chemistry, the channel networks are connected to a series of reservoirs containing chemical reagents (or products) to form the complete device or 'chip'. Reagents can be brought together in a specific sequence, mixed and allowed to react for a specified time in a controlled region of the channel network using various pumping techniques; including electrokinetic (electroosmotic and electrophoretic) or hydrodynamic pumping. For electrokinetically-driven systems, electrodes are placed in the appropriate reservoirs to which specific voltage sequences can be delivered under automated computer control.[2] This control offers a simple but effective method of moving and separating reactants and products within a micro reactor, without the need for moving parts. In comparison, hydrodynamic pumping uses conventional, or micro-scale pumps (notably syringe pumps) to manoeuvre solutions around the channel network, however this technique has the disadvantage of requiring either large external pumps or the complex fabrication of small moving parts within the device.

To date, research in the area has confirmed that micro reactor methodology is applicable to performing both gas and liquid phase reactions. From the work cited in this review article, the low-volume spatial and temporal control of reactants and products in a laminar flow diffusive mixing environment, in which distinctive thermal and concentration gradients exist, offers a novel method for chemical manipulation and product generation. Often, reactions performed within a micro reactor invariably generate relatively pure products in high yield, in comparison to the equivalent bulk reactions, in much shorter times and in sufficient quantities to perform full structural characterisation. One of the immediate and obvious applications is therefore in drug and process discovery, where the generation of compounds with either different reagents or under variable conditions is an essential factor. In addition, the opportunity to establish optimal chemical processes is an exciting capability of the technology,

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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 chemistry under the supervision of Professor Tom Simpson FRS and Professor Chris Willis. His PhD focussed on the synthesis of isotopically labelled compounds, for use in determination of biosynthetic pathways to polyketide-derived natural products. Paul subsequently worked as a postdoctoral research associate, with Professor Steve Haswell, at the University of Hull. During this period he investigated organic synthesis in micro reactors. In February 2002, he was appointed as a lecturer at the University of Hull. He is interested in organic chemistry and electrosynthesis in micro reactors and has published 30 papers in the area.

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Stephen Haswell is Professor of Analytical Chemistry at the University of Hull. His current research activities are in the areas of micro reactors including analytical developments, microwave enhanced reaction chemistry, trace elemental speciation and process analysis. He is author of over 120 research papers, a number of books and patents and is widely known nationally and internationally for his enthusiastic lectures. For a number of years one of the underlying principles of Professor Haswell's research has been to break down the barriers that exist in science, in particular, the integration of analytical science with main line chemistry. Many of these ideals are encompassed in his research into micro chemical reactors, the subject of this article.

which could be integrated with appropriate analytical instrumentation. An interesting twist to the chemistry reported is not just the opportunity to separate reactants and products in real time, but also the ability to manufacture and use reagents *in situ*; an important issue when using highly toxic or explosive reagents, for example. In short, micro reactors are new, safe and more atom efficient tools with which to generate molecules and to increase our knowledge of complex chemical processes. In this review, a brief description of the fabrication and operation of micro reactors is outlined, followed by a detailed description of the types of reaction that have been performed in micro reactors and the benefits observed.

Fabrication of micro reactors

A number of materials such as silicon, quartz, glass, metals and polymers have been used to construct micro reactors.[1] Depending on the material used, a range of channel microfabrication methods such as photolithography, hot embossing, powder blasting, injection moulding and laser micro forming are available.[1,3] However, the most important considerations for synthetic applications include chemical compatibility with the substrate, as well as the ease and reproducibility of fabrication. Furthermore if electrokinetic pumping is required special surface characteristics are essential as detailed below. Another issue which should be considered when *in situ* analysis is required is the compatibility of the material with the detection method to be used.

For organic chemistry glass is the most popular choice since it allows electroosmotic flow (EOF) with many common solvents, it is chemically inert, enables the use of visible light detection methods and fabrication procedures are well established. For glass micro reactors, photolithographic fabrication of channel networks is performed as shown schematically in Fig. 1.[4,5] Firstly, the channel network is designed and printed using suitable computer drawing software and a film negative of the desired final size is prepared by photoreduction to form the optical mask. Recent instrumental advances of this process also enable the direct production of the mask from computer drawings.[6] Commercially available borosilicate glass photolithographic plates (typically a few mm in thickness) coated with a thin metal layer (normally chromium) plus an upper layer of positive photoresist (0.5–2.0 μm depth) are used for channel network fabrication. The pattern of the required network of interconnecting channels is transferred from the optical mask to the photoresist layer. After light exposure, the photoresist is developed and removed, together with the chromium layer, to reveal the areas of glass to be etched. The channels are then etched using a mixture of 1% HF and 5% NH_4F in water at typically 65 °C, resulting in an etch rate of approximately 0.5 μm min^{-1}. During the etching process, it is important that the system is well agitated to ensure a consistent supply of etchant to the surface.

The base plate containing the etched channel network must next be sealed by bonding to an upper plate containing predrilled holes which act as reservoirs (or connecting conduits) for reagents and products. The most common method of bonding the two pieces of glass is thermal bonding at typically

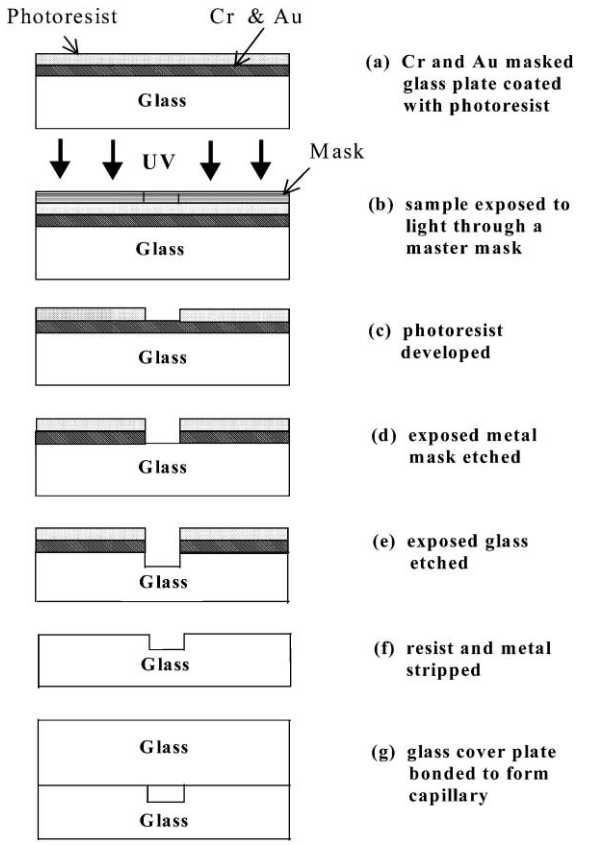


Fig. 1 Photolithographic fabrication of micro reactors.

575 °C for a few hours, using either a conventional or microwave furnace.[4,5] A photograph of an all-glass device produced by this method is shown in Fig. 2. For good thermal bonding, it is important to ensure that both glass types have the correct thermal softening and expansion properties. In addition, the surfaces to be bonded must be clean and flat. Importantly, the advantage of using thermal bonding to seal the device is that no adhesives are required, as these are not generally resistant to organic solvents and reagents.

If hydrodynamic pumping is required it is possible to thermally bond ceramic HPLC-type adaptors to the glass device (Fig. 3) or use commercially available quartz capillaries. Connecting syringe pumps to such devices is relatively easy and enables the reactor to be incorporated with a HPLC system, for example. This type of micro reactor is ideal for reaction optimisation.

Of all the fabrication media, perhaps metal is the most robust in terms of engineering requirements and more specifically, micro mixers have been constructed and applied in chemical processing. This subject is extensively reviewed in ref. 1. However in the authors' experience, chemists generally prefer to use glass reactors if possible.

Operation of micro reactors

For a newcomer to the field of micro reactor technology, the easiest way to operate a device is by hydrodynamic control, using syringe pumps to manoeuvre solutions around the channel network. However, this approach has the

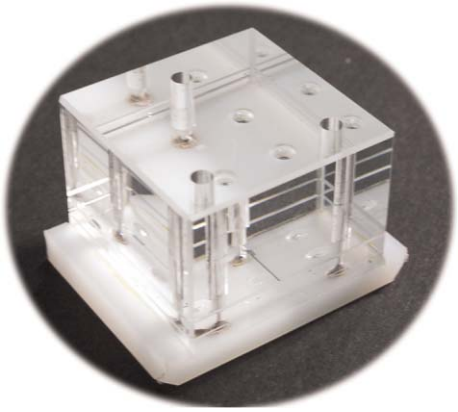


Fig. 2 A glass micro reactor suitable for electrokinetic control. The electrodes may either be placed in the reservoirs from above or may be fabricated into the base of the device.

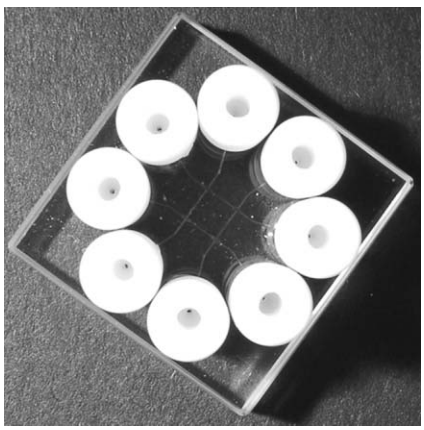


Fig. 3 A glass micro reactor fitted with ceramic HPLC adaptors.

disadvantage of requiring either large external pumps or the complex fabrication of small moving parts within the reactor itself. It should also be emphasised that although this approach is relatively easy if reacting just two solutions, it becomes far more complex to accurately control the fluidics when introducing more than three reagents into the device; in these situations much more care is required when designing the exact dimensions of the reactor channels.

A more elegant way of pumping solutions around a channel network is by electroosmotic flow (EOF),[7] using voltage sequences applied *via* electrodes placed within the reagent reservoirs. This method has several significant advantages over hydrodynamic based pumping methods,[8] as it can be easily miniaturised as no moving parts are involved and the required voltage sequences can be readily applied under automated computer control. For a glass micro reactor, the channel wall-solution interface normally has a negative charge, arising from ionisation of surface groups, which are immobile. This immobile surface charge attracts a diffuse layer (of thickness in the order of nm) of mobile, oppositely charged counterions in the solution adjacent to the channel wall (cations for a negatively-charged glass channel wall). As shown schematically in Fig. 4, application of an electric field along the channel length causes the nm thick layer of mobile cations to move towards the more negative electrode, which drags all of the intervening solution in the bulk of the channel with it. An important feature of EOF is that the liquid velocity is constant across the channel, except in the nm thick regions of the diffuse layer of counterions very close to the wall. Unlike EOF, pressure-driven flow produces a parabolic velocity profile with high velocities in the channel centre and slow velocities near to the wall, giving rise to increased blurring of reagent zones along a channel length.[8]

It should be stressed that for EOF to be achieved, polar solvent types need to be used. The EOF fluid velocity v_{eof} is given by eqn. (1)[2]

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

where E is the electric field (voltage divided by electrode separation), ε is the relative dielectric constant of the liquid, ε_0 is the permittivity of free space, ζ is the zeta potential of the channel wall–solution interface and η is the liquid viscosity. Consequently it can be deduced that solvents which possess a high dielectric constant (*i.e.* polar solvents) and low viscosity (η) will have a higher flow rate, as illustrated in Table 1 and Fig. 5.

It can be seen from Fig. 5, that the solvent flow rate is directly proportional to the field strength applied; as a result the flow rates within the channels can be easily controlled. Clearly this limitation prevents non polar solvents such as hexane and dichloromethane from being used in EOF

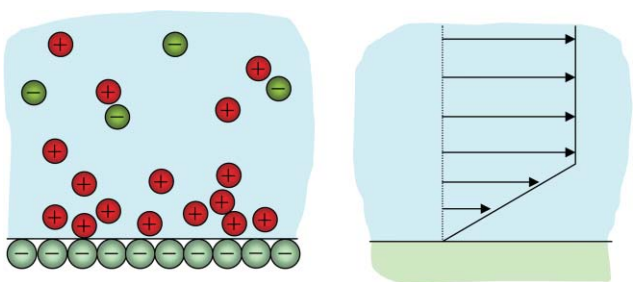


Fig. 4 Voltage-driven movement of the diffuse layer of cations adsorbed at the negatively charged channel wall (left-hand Figure) produces a flat EOF velocity profile across the channel except within the nm thick diffuse counterion layer (right-hand Figure).

Table 1 Relationship between magnitude of EOF and solvent properties

Solvent	Dielectric constant	Viscosity/cP	Polarity index/P	Flow rate/μl min^{-1}
MeCN	37.5 (20 °C)	0.38	5.8	5.30
DMF	36.7 (25 °C)	0.92	6.4	1.67
EtOH	24.6 (25 °C)	1.10	5.2	0.90
THF	7.58 (25 °C)	0.55	4.0	1.00

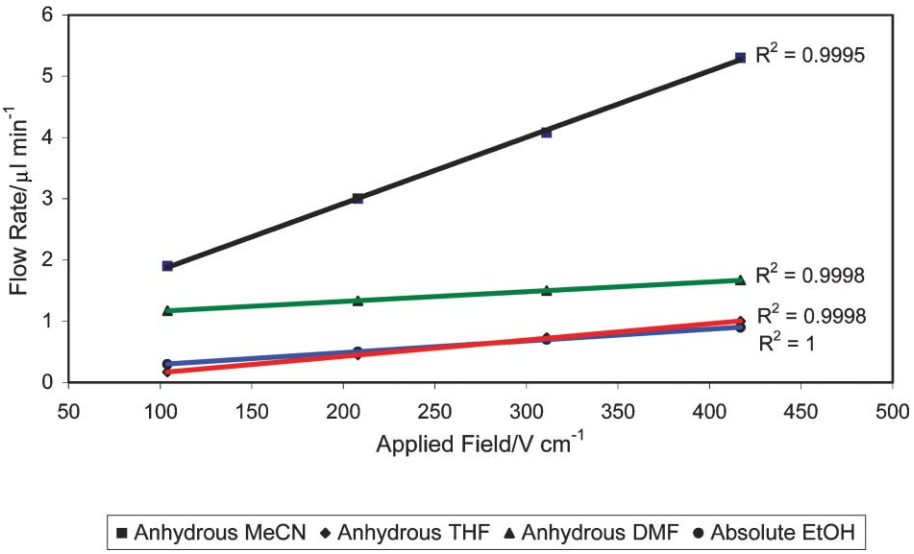


Fig. 5 Flow rates within a micro reactor for a range of common solvents.

controlled micro reactors, however research is currently underway to use combined hydrodynamic and EOF driven systems to overcome this problem.

It should however be emphasised, that under EOF control, charged solutes move with an electrophoretic velocity in addition to the electroosmotic velocity of the solvent. An elegant example of this was demonstrated by Fletcher *et al.* who reacted Ni^{2+} ions (from $Ni(NO_3)_2$) with pyridine-2-azo-*p*-dimethylaniline (PADA) within an EOF based micro reactor to produce a $[NiPADA]^{2+}$ complex.[9] The authors reacted 2mM Ni^{2+} with 2mM PADA, which in a batch reaction would produce product (assuming a 100% conversion) of 1 mM concentration; however within the micro reactor they report that the product was produced in 12 mM concentration. The explanation for this is that the positively charged Ni^{2+} ions move with a higher electrophoretic velocity than the neutral PADA molecules, hence the Ni^{2+} ions move through the PADA solution, leading to preconcentration of the product within the channel.

Reactions performed in micro reactors

The following section reviews a number of chemical reactions that have been performed within micro reactors to date. The review is divided into two sections on how micro reactor technology may be used to make small quantities of product for use in the drug discovery process and secondly how micro reactor methodology may be applied to large scale chemical manufacture.

Small scale manufacture

The success of pharmaceutical companies resides largely on the synthesis and screening of novel chemical entities representative of the universe of drug-like compounds, which may be of the order of 10^{200} compounds or about 10^{40} chemotypes; and to optimise selected leads to marketable drugs. In an industry where development costs are extraordinarily high and attrition rates from lead generation onwards are about 98%, careful lead selection and ruthless pressure to shorten optimisation cycle times are therefore critical for survival. In addition to this diligence, new technology that would enable a cost-neutral upward step-change in the number of lead candidates (and thus choice of a better lead with enhanced therapeutic effects and reduced side effects) and optimisation speed (to reduce time to market and extend patent life) would provide a distinct competitive advantage. A microchannel system also provides a potential separation column and a non-turbulent environment for partition between solvents. Integration of a micro reactor device, *via* purification to one of the many highly sensitive microchannel-based biological assay systems is not only possible, but may also address many of the industries' potential requirements. Apart from the greatly reduced reaction times demonstrated for the micro reactors, handling times to assay and chemical reagent costs are virtually eliminated. This paradigm is shown diagrammatically in Fig. 6.

In lead optimisation using conventional batch technology, validation and optimisation of reactions tends to be the rate-limiting step. Based on the model described in Fig. 6 however, it can be seen that if the biological assay was replaced by an analytical measurement and the conditions not the reagents are varied, then reaction optimisation could be easily carried out.

In a move to achieve this aim, Garcia-Egido *et al.* have recently reported the synthesis of a combinatorial library of pyrazoles within a glass micro reactor operated using hydrodynamic control.[10] A T-shaped micro reactor was used to react seven 1,3-dicarbonyl compounds **1** with three hydrazine derivatives **2** to produce a library of twenty-one pyrazoles **3** (Scheme 1). The automated system consisted of an autosampler to introduce the reagents into the chip, a HPLC pump to move the reagents through the micro reactor and a dilution system to enable a small sample to be diverted to an LC-MS instrument for analysis. Other than in a few cases most of the pyrazoles were obtained in 99% conversion, but clearly the chromatography step allowed the reaction mixtures to be purified to produce analytically pure compounds. The final step would be to couple the output of the chromatography

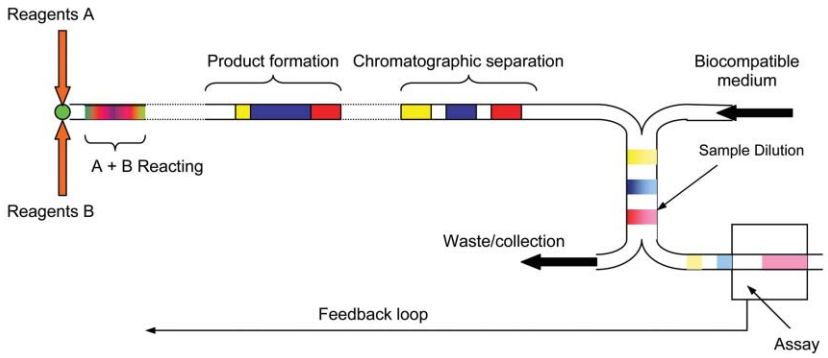
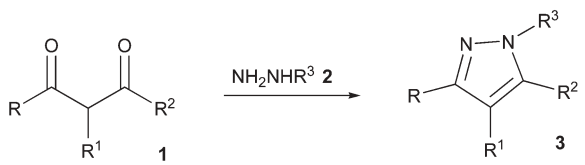


Fig. 6 Integration of a micro reactor with a biological assay system.



Scheme 1

column to a miniaturised bioassay system to enable *in situ* screening to be performed.

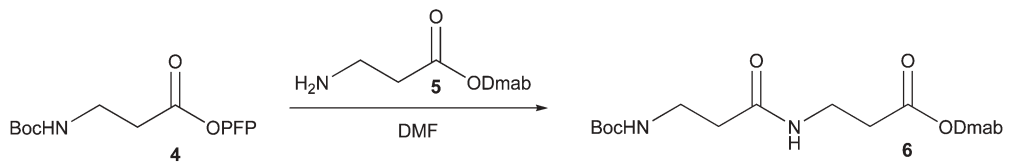
Although the above system is excellent in achieving combinatorial synthesis for the desired application, cynics argue that the overall system is hardly miniaturised; the micro reactor itself is tiny but the overall system is still composed of large bench top instrumentation. This is where EOF-based systems are potentially advantageous (as long as the solvent and/or reagents move by EOF) as external pumps are not necessary and purification could be achieved using on-chip electrophoretic separation rather than using large external instrumentation (such as the HPLC described above); it should be pointed out that the concept of miniaturisation started in analytical chemistry and separations using this technology are well established.[11]

In a move to develop an EOF based system, Watts *et al.* have demonstrated the first example of multi-step synthesis in a micro reactor where they have used the micro reactors in peptide synthesis.[12–14] The authors demonstrated that the dipeptide could be prepared from pre-activated carboxylic acids. They report that the reaction of the pentafluorophenyl (PFP) ester of Boc-β-alanine **4** with the amine **5** (Dmab is 4-[*N*-(1-(4,4-dimethyl-2,6-diococyclohexylidene)-3-methylbutyl)-amino]benzyl) gave the dipeptide **6** quantitatively in 20 min (Scheme 2). This represented a significant increase in yield compared with the traditional batch synthesis, where only a 50% yield was obtained in 24 h. The authors then used the methodology to consecutively react alternative pentafluorophenyl esters and amines to produce a library of peptides.[13]

Although the dipeptide bond forming reactions produced the dipeptide in 100% conversion based on consumption of the pentafluorophenyl ester, the product was still contaminated with residual amine as well as pentafluorophenol, the by-product of the reaction. George *et al.*[15] have reported that the dipeptide may be separated from the reaction mixture using the device in Fig. 7, where the reaction mixture is collected in the ground reservoir during the synthesis and then the peptide is purified by electrophoresis and collected in reservoir D. Hence this methodology enables the synthesis and separation to be efficiently conducted within an integrated micro reactor without the need to have large peripheral equipment attached. However, further research is still needed to investigate integration of bioassay devices to this type of system.

Having demonstrated that peptide bonds could be successfully formed using a micro reactor; the authors then extended the methodology to the preparation of longer-chain peptides. Using the micro reactor, the Dmab ester of Fmoc-β-alanine **7** was reacted with one equivalent of piperidine or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to give the free amine **5** in quantitative conversion. This is in comparison to solid phase peptide synthesis where 20% piperidine in DMF is frequently employed, which demonstrates the atom efficiency of reactions performed within the devices. The authors then reacted the amine *in situ* with the pentafluorophenyl ester **4** to give the dipeptide **6** (Scheme 3) in 96% overall conversion.[13]

Having shown that more complex peptides could be produced by removal of the *N*-protecting group, the authors then demonstrated that they could remove the Dmab ester using hydrazine. The reaction of the Dmab ester **7** with one equivalent of hydrazine resulted in quantitative deprotection, to afford the carboxylic acid **8** (Scheme 4). This is in comparison to the solid phase peptide synthesis where 2% hydrazine in DMF is generally required to effect complete



Scheme 2

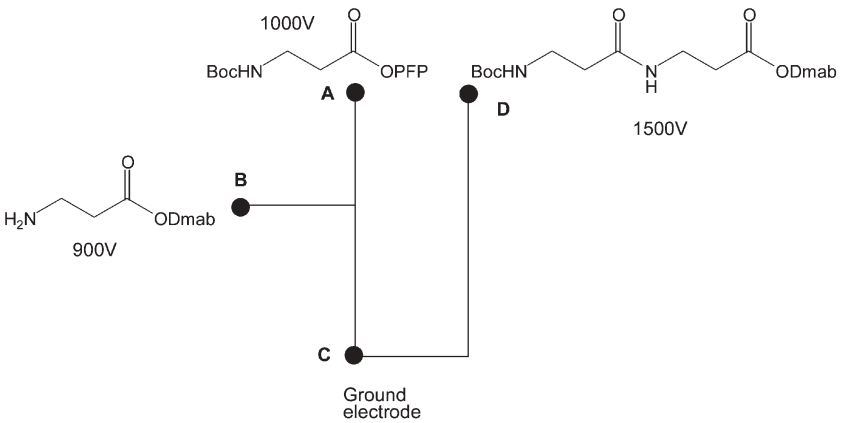
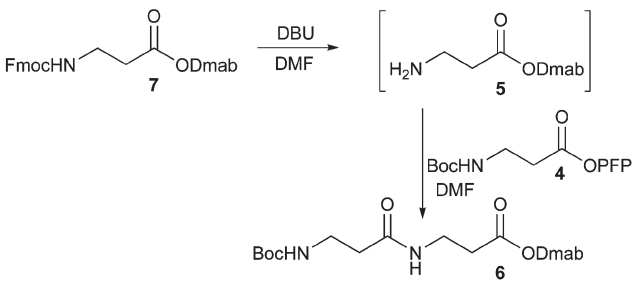
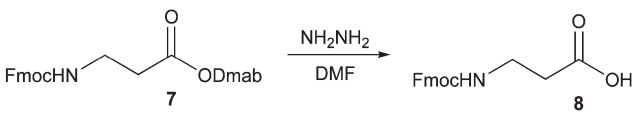


Fig. 7 Micro reactor design for simultaneous synthesis and separation of dipeptide.



Scheme 3



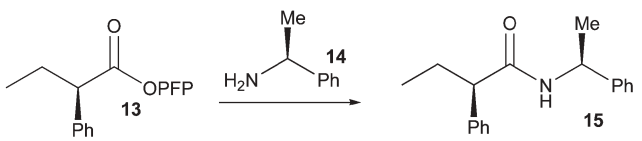
Scheme 4

deprotection.[13] From an environmental perspective the use of stoichiometric quantities of reagents in such reactions is clearly desirable, furthermore it makes the reaction mixtures easier to purify as excess reagents are eliminated.

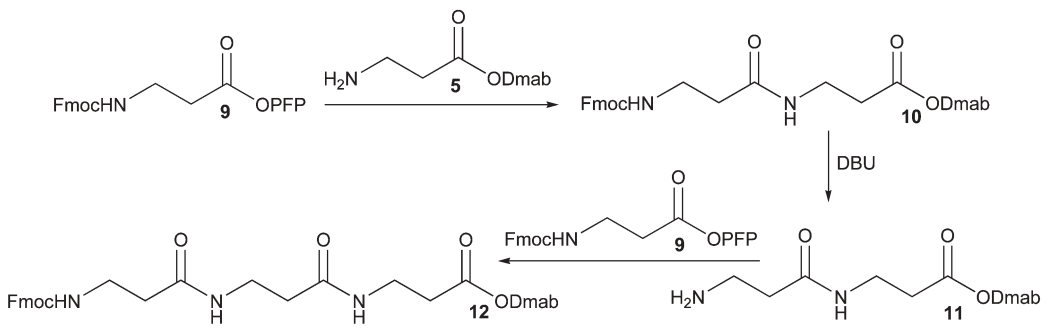
The authors have further extended the approach to the synthesis of tripeptides, such as **12**.[13] Reaction of pentafluorophenyl ester **9** with amine **5** formed dipeptide **10**, which was reacted with DBU to effect Fmoc deprotection. The amine **11** was then reacted *in situ* with another equivalent of pentafluorophenyl ester **9** to prepare tripeptide **12** in 30% overall conversion (Scheme 5). The approach clearly demonstrates that intermediates may be generated *in situ* and used in subsequent reactions. Although in the above examples the intermediates are relatively non-toxic, it is postulated that the approach may be used to generate highly toxic or explosive reagents *in situ*, that one would rather not use in organic synthesis.

Having demonstrated that peptide bonds could be successfully formed when using a micro reactor, the authors then investigated racemisation in peptide bond forming reactions derived from α-amino acids.[16] Reaction of the pentafluorophenyl ester of (*R*)-2-phenylbutyric acid **13**, at 0.1M concentration, with α-methylbenzylamine **14**, gave the product **15** in quantitative conversion with 4.2% racemisation (Scheme 6). Importantly this represented less racemisation than observed in the batch reaction at the same concentration and temperature. The reduced level of racemisation was attributed to the reduced reaction times observed within the micro reactors.

While investigating different types of reactions within micro reactors, in order to expand the range of reactions that may be



Scheme 6

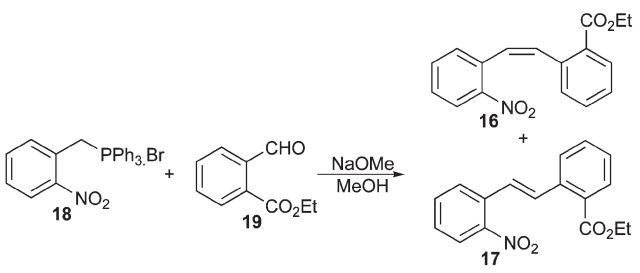


Scheme 5

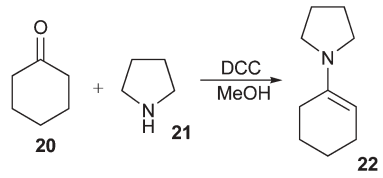
performed within such devices, various interesting results have been reported and these are discussed below.

Skelton and coworkers have reported the application of micro reactors for the Wittig reaction.[17,18] The authors used the micro reactor to prepare the *cis*- and *trans*-nitrostilbene esters **16** and **17** using the Wittig reaction (Scheme 7). A number of features such as stoichiometry and stereochemistry were investigated. When two equivalents of the aldehyde **19** to the phosphonium salt **18** were used in the reaction, a conversion of 70% was achieved. The micro reactor demonstrated an increase in reaction efficiency of 10% over the traditional batch synthesis. The reaction stoichiometry was subsequently reduced to 1 : 1, but using a continuous flow of reagents, as above, the conversion was poor (39%). The conversion was increased to 59% using an injection technique, where slugs of the phosphonium salt **18** were injected into a continuous flow of the aldehyde **19**. The research was further extended to investigate the stereochemistry of the reaction. The ratio of isomers **16** and **17** was controlled by altering the voltages applied to the reagent reservoirs, which in turn affected the EOF and electrophoretic mobility of the individual reagents, meaning that the stoichiometry of the mixture was different. The variation in the external voltage subsequently altered the relative reagent concentrations within the device, producing *cis*/*trans* ratios in the region 0.57 to 5.21. In comparison, the authors report that, when a traditional batch synthesis was performed based on the same reaction time, concentration, solvent and stoichiometry, a *cis*/*trans* ratio of approximately 3 : 1 was observed in all cases. This demonstrated that significant control was possible in a micro reactor compared with batch reactions.

Sands and coworkers[19] reported the preparation of enamines in a micro reactor. Enamines are traditionally prepared under Dean and Stark conditions, where the ketone and secondary amine are heated to reflux in toluene. These conditions remove the water from the reaction to produce the equilibrium-dependent enamine. Using the micro reactor, cyclohexanone **20** was reacted with pyrrolidine **21** to form the enamine **22** in 42% conversion at room temperature (Scheme 8). Clearly the use of methanol as solvent at room temperature, compared with the traditional Dean–Stark conditions, represents a more environmentally friendly procedure. In this case, the electrophoretic mobility of the product is thought to be greater than that of water, so enabling *in situ* separation of the by-product, which drives the equilibrium forward.



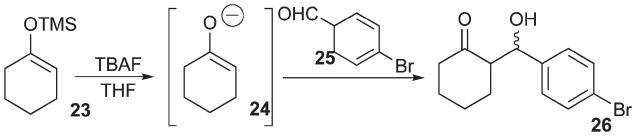
Scheme 7



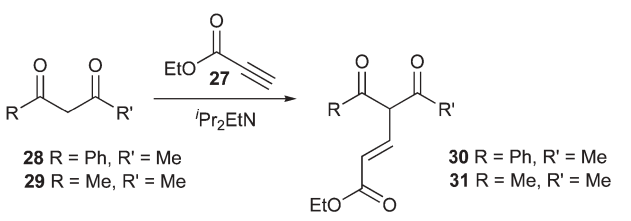
Scheme 8

Carbanion chemistry is one of the most common reactions used in organic synthesis, however large quantities of heat are frequently generated which means that careful control of the temperature, to prevent by-product formation, is required. Hence, micro reactors have a considerable attraction for these reactions because the reactor enables excellent temperature control of the reaction. Wiles *et al.*[20] have demonstrated the use of silyl enol ethers in the aldol reaction within a micro reactor. Quantitative conversion of the silyl enol ethers to β-hydroxyketones was observed in 20 min compared to traditional batch systems, where quantitative yields were only obtained when extended reaction times of up to 24 h were employed. One example involved the treatment of the TMS enol ether **23** with tetra-*n*-butylammonium fluoride (TBAF), to generate the tetra-*n*-butylammonium enolate **24** *in situ*, followed by condensation with *p*-bromobenzaldehyde **25** to give the β-hydroxyketone **26** in 100% conversion (Scheme 9). It should be emphasised that the air sensitive enolate was generated *in situ* within a sealed micro reactor and only had a lifetime of a few seconds before it was reacted with the aldehyde, consequently it was found that the reaction could be conducted on the open bench top without any problems.

Wiles *et al.*[21] have also reported the preparation of the enolates from a series of 1,3-diketones using an organic base and their subsequent reaction with a variety of Michael acceptors such as **27** to afford 1,4-addition products within a micro reactor (Scheme 10). When using a continuous flow of the reagents **27** and **28**, 15% conversion to the adduct **30** was observed, compared with 56% when the diketone **29** was reacted with **27** forming the Michael adduct **31**. The authors, however, demonstrated enhancements in conversions through the application of the stopped flow technique. This procedure involved the mobilisation of reagents through the device for a



Scheme 9

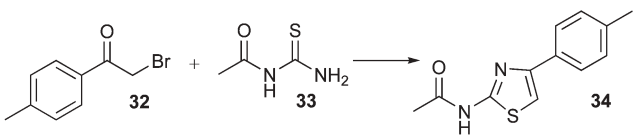


Scheme 10

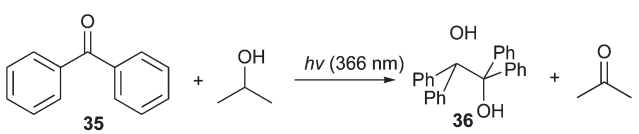
designated period of time, using an applied field, and the flow was subsequently paused by the removal of the applied field, prior to re-applying the field. Using the regime of 2.5 s on and 5 s off, the conversion to the product **30** was improved to 34%, while lengthening the stopped flow period to 10 s, resulted in a further increase to 100%. This was compared to the preparation of **31**, in which the regime of 2.5 s on and 5 s off resulted in an increase in conversion to 95%. The authors propose that the observed increase in conversion, when using the technique of stopped flow, was due to an effective increase in residence time within the device. This approach clearly shows the ease by which reactions can be optimised within micro reactors. Furthermore, in batch reactions it was found that a significant amount of by-product arose from reaction of the base with the Michael acceptor, however because the reagents were introduced sequentially within the micro reactor this was not observed.

Industrially, special equipment is required when performing large-scale reactions at elevated temperature. However, Garcia-Egido *et al.*[22] have demonstrated the synthesis of 2-aminothiazoles using a Hantzsch synthesis within a heated micro reactor. The paper represents the first example of a heated reaction using an organic solvent within a glass micro reactor under EOF conditions. During the experiments the T-shaped micro reactor was heated to 70 °C using a Peltier heater. Reaction of α-bromoketone **32** with thiourea **33**, using NMP as solvent, resulted in the preparation of aminothiazole **34** in up to 85% conversion (Scheme 11).

Jenson *et al.*[23] have reported photochemical reactions within micro reactors. The reactor was fabricated by bonding a patterned silicon wafer to a quartz wafer, the advantage of this fabrication technique being that the quartz substrate allows reaction and detection using UV light of lower wavelengths than permitted by glass substrates. The authors investigated the pinacol reaction of benzophenone **35** in propan-2-ol (Scheme 12). The reaction is known to follow a radical reaction pathway and it is reported that the longer the residence time of the reaction, the greater the conversion to benzopinacol **36**. The authors report that there was no detectable product formation for flow rates >10 μl min^{-1}. With reduced flow rates (corresponding to larger residence times) the conversion improves because the amount of light absorbed increases, and there is therefore sufficient time for the excited species to diffuse and react with the benzophenone.



Scheme 11



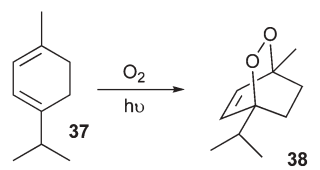
Scheme 12

The authors report conversions of up to 60% when using flow rates of 4 μl min^{-1}.

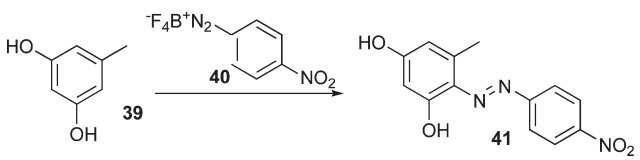
Wootton *et al.*[24] also report the ease of photochemistry to generate singlet oxygen *in situ* within a micro reactor. The technique allows the generation of singlet oxygen without the inherent dangers of forming large quantities of potentially explosive oxygenated solvents. The singlet oxygen was formed within the reactor channel by irradiation with a 20 W, 6 V tungsten lamp. The authors then used the aforementioned conditions to convert α-terpinene **37** into ascaridole **38** (Scheme 13) in greater than 80% conversion. For safety, nitrogen degassing of the product mixture was undertaken as soon as the solution was collected, hence avoiding accumulation of oxygenated solvents.

Hisamoto and coworkers[25] have described the first example of a phase transfer reaction in a micro reactor. These authors have successfully conducted a phase transfer diazo coupling reaction in which a solution of 5-methylresorcinol **39** in ethyl acetate was reacted with an aqueous solution of 4-nitrobenzenediazonium tetrafluoroborate **40** to form the azo dye **41** (Scheme 14). Syringe pumps were used to move the reagents around the reactor manifold and the authors report that the product was isolated in 100% yield and greater than 95% purity as a result of the phase transfer conditions. This example of phase transfer illustrates that the extraction of compounds into the bioassay system discussed earlier (Fig. 6) is indeed feasible.

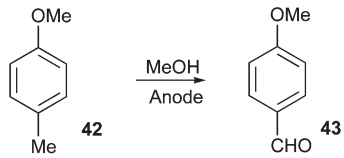
Several research groups have developed micro reactors for electrochemical synthesis. Löwe *et al.*[26] reported a micro reactor in which electrodes were fabricated within the flow channels and the system was used for the conversion of 4-methoxytoluene **42** to 4-methoxybenzaldehyde **43** (Scheme 15). By experimentally varying the voltage the selectivity was increased to 86% with a conversion of 88%.



Scheme 13



Scheme 14



Scheme 15

In contrast to the batch reaction it was possible to perform the reaction without a supporting electrolyte which makes product isolation easier.

Similarly, Suga *et al.*[27,28] have developed micro reactors for the generation of highly reactive acyliminium ions which could be reacted with nucleophiles to produce C–C bonds. The reactor was cooled to −78 °C using integrated cooling channels. For example heterocycle **44** was converted into carbocation **45** *in situ* within the reactor before being reacted with nucleophile **46** to produce alkylated product **47** (Scheme 16). The micro reactor was used to produce a library of compounds in greater than 60% yield and in higher selectivities than in batch reactions.

Greenway *et al.* have demonstrated the Suzuki reaction within a micro reactor.[29] This represented an example of heterogeneous catalysis where 1.8% palladium on silica was placed in the central channel of the device. The catalyst was immobilised between microporous silica frits. The micro reaction was optimised using flow injection analysis principles, producing a conversion of 67% of cyanobiphenyl **48** at room temperature. The flow injection method allowed the periodic injection of the aryl halide **49** into a continuous flow of the phenylboronic acid **50** (Scheme 17). Traditionally, tetrahydrofuran (THF) is used as the solvent in this reaction, however as has been found with many organic solvents THF has very low natural EOF properties and for this reason, it was mixed with water (75 : 25) for use in the reaction. The yields obtained were comparable with Suzuki reactions on a batch scale using homogeneous catalysis. Importantly, there were negligible levels of the palladium catalyst in the product, which was demonstrated using inductively coupled-mass spectrometry (ICP-MS), this illustrating that the catalyst was not leaching from the reactor.

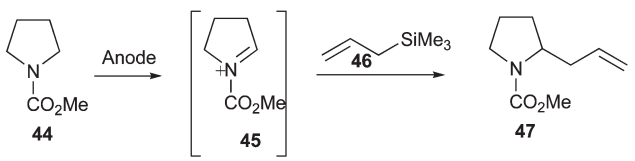
One of the interesting observations of the reaction was that, unlike conventional Suzuki reactions, an additional base was not required. Although the exact reason for this is not clear, it is postulated that the electric field may be sufficient to cause ionisation of the water at the catalyst surface. It is feasible that the hydroxide formed in this way may be sufficient to perform the function of the conventional organic or inorganic base.

As an extension to the above work, He *et al.* have reported the same Suzuki reaction in a micro reactor which was placed within a microwave cavity.[30] In this case the authors report that the conversion was increased from 67% to 99%. The authors report that in order to get effective heating of the catalyst, a 10 nm thick layer of gold was placed under the catalyst bed. The authors used the device to prepare a range of biaryls in greater than 70% conversion.

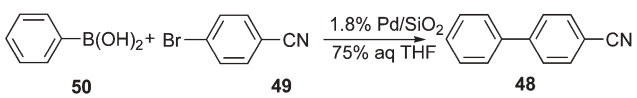
Kanno *et al.*[31] have reported the use of enzymes within micro reactors operated by hydrodynamic pumping. Hydrolysis of *p*-nitrophenyl-β-D-galactopyranoside **51** was conducted using a β-galactosidase enzyme from *E. coli* to produce sugar **52** in quantitative conversion (Scheme 18). The reactor was maintained at 37 °C using a hot plate. It was found that the hydrolysis of *p*-nitrophenyl-β-D-galactopyranoside within the micro reactor was five times faster than in a batch reactor. The paper also reports the transgalactosylation of a *p*-nitrophenyl-2-acetamide-2-deoxy-β-D-glucopyranoside using an enzymatic reaction.

Micro reactors are also showing a significant level of interest in the evaluation of catalysts. Dietzsch and coworkers[32] have reported the gas phase hydrogenation of cyclic dienes, to their corresponding monoalkenes, over a variety of catalysts. The micro reactors consisted of aluminium wafers, with mechanically-etched channels, which were activated by anodic oxidation to obtain a porous oxide layer, which was used as the catalyst support. For example, impregnation of an organic solution of palladium(II) acetylacetonate resulted in microchannels consisting of an 18 μm thick layer of 0.18% Pd catalyst. The wafers were then stacked in a stainless steel housing to form a micro reactor consisting of microchannels for a stream of reagents to pass through. The authors used the device to investigate the hydrogenation of 1,5-cyclooctadiene **53** to cyclooctene **54** (Scheme 19). The diene **53** was vaporised and mixed with hydrogen, before being passed through the micro reactor at a temperature of 150 °C. By increasing the residence time of the reaction from 35 to 115 ms the authors report that the conversion increased from 75 to 99.5%. Although the increased residence time resulted in increased quantities of cyclooctane **55** being formed, the selectivity of cyclooctene **54** decreased from 99.5 to 98% under these conditions. A microstructured mesh micro reactor has been reported by de Bellefon and co-workers for use in catalyst screening experiments.[33]

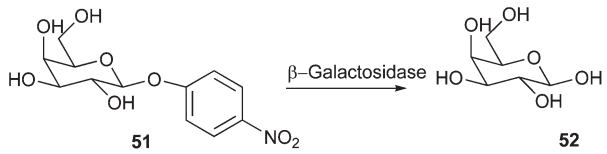
Wagner *et al.*[34] have reported the use of micro reactors in the preparation and growth of colloidal gold nanoparticles. Critically it was demonstrated that such particles could be handled in microfluidic channels without causing blockages. The authors report that the size distribution of



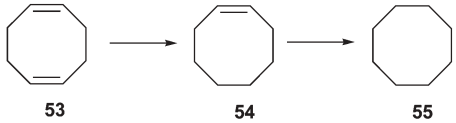
Scheme 16



Scheme 17



Scheme 18



Scheme 19

the nanoparticles may be readily controlled by simply altering the flow rates of the solutions through the channel.

Similarly Takagi *et al.*[35] have used micro reactors in the preparation of titania nanoparticles. Mixing of tetraisopropoxide and aqueous isopropanol solutions within a micro reactor enabled the preparation of mono-modal spherical particles of titania with a narrow size distribution. The authors reported that it was possible to prepare particles in the size range of 40–150 nm depending on the size of the micro reactor channels used.

Large scale manufacture

Current production technology is based on the scaling-up of successful laboratory scale reactions by firstly constructing a pilot plant, followed by a final increase in scale to enable production. This approach is however fundamentally flawed as at each stage changes are made to the overall surface to volume ratio of the reactors, which in turn affects mass and heat transfer processes. These variations in reactor conditions therefore result in changes to the process, meaning that it is necessary to evaluate the process and reoptimise it at each stage of scale up. Consequently the route from bench to large scale production is both costly and time consuming. It is therefore postulated that through the application of micro reactor technology, the transfer from laboratory to production would be both rapid and cost effective as processes would initially be optimised on a single device and in order to increase the production capacity more devices would be employed; a technique referred to as numbering up or scale out. With the number of techniques amenable to mass production increasing, the commercial availability of parallel reactors is starting to be realised. Along with the ability to reduce the transfer time between initial discovery and production, the scale out approach is also advantageous as it enables access to an array of features not commonly used in traditional scale out approaches, such as reduced reaction times and the ability to work in the explosive limit.

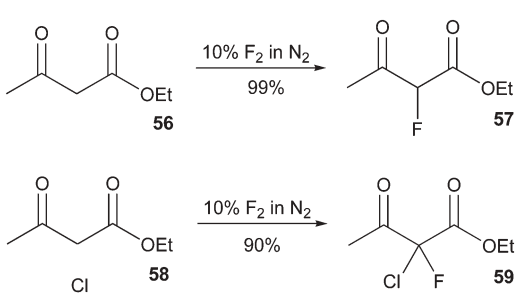
From a production perspective, the scale out approach is advantageous as it enables changes in production volume by simply increasing or decreasing the number of devices employed, therefore meeting the customer demand. Also through the use of generic reactor designs custom syntheses could be performed with relative ease. Compared to a production plant whereby reactors are configured for a single function, this flexibility is both advantageous and cost effective. In principle, all the reactions discussed in the previous section are suitable for scale out if required, but for illustrative purposes two specific examples are discussed in detail.

The diazotization of aromatic amines is an industrial process of great importance, however the dangers of diazotization are well known. The explosive nature of diazonium salts necessitates extreme care; hence the low volume associated with micro reactors affords a safe route to perform such reactions.

As a 'micro reactor' for the lab-scale diazo synthesis the standard laboratory reactor CYTOS produced by CPC, Germany was used.[36] This was constructed from stacked units comprising of mixing and reaction zones, as well as an integrated heat exchanger. To make larger quantities of product the scale-up concept of connecting three reactors in parallel was realized. The laboratory-scale reactor was used with flow rates of 20 ml min^{-1} and 80 ml min^{-1} leading to residence times of several seconds. In the case of the pilot plant the total flow rate was increased up to 500 ml min^{-1} resulting in an output of 10 t per year. Other industrial scale reactions using similar equipment have been reported in the literature.[37]

The use of elemental fluorine in organic synthesis is problematic as a result of the difficulties associated with the safe handling of gaseous fluorine. In addition, fluorination reactions are generally extremely exothermic and it is difficult to control the temperature of such reactions when performed on a large scale. Micro reactors have considerable attraction for direct fluorination processes because there is only a small amount of fluorine in the reactor at any given time. The micro reactor enables excellent temperature control of the reaction as well as an opportunity for scale up, by the simultaneous use of many such reactors.

Chambers and Spink[38,39] have reported the use of micro reactors for the fluorination and perfluorination of organic compounds using elemental fluorine. A nickel or copper micro reactor was used for the investigation and the liquid reactants and solvents were introduced into the reaction chamber *via* a syringe using a syringe-pump. Fluorine, in a nitrogen carrier gas, was introduced from a cylinder using a mass-flow controller. The liquid–gas mixing proceeded *via* cylindrical flow (sometimes called annular flow), where the liquid forms an outer cylinder coating the reactor surface with the gas flowing through the centre. This flow regime has enormous benefits in that it provides very large surface-to-volume ratios for the liquid phase, producing a very efficient reaction over a short distance. The products were trapped in a tube, which was cooled with either a salt/ice bath (0 °C) or an acetone/carbon dioxide bath (−78 °C). The fluorination of β-dicarbonyl compounds proceeded with a high efficiency using 10% fluorine in nitrogen at 5 °C and with formic acid as the solvent. Ethyl acetoacetate **56** was fluorinated in 99% conversion to give ethyl 2-fluoroacetoacetate **57** while ethyl 2-chloroacetoacetate **58** was fluorinated in 90% conversion, yielding ethyl 2-chloro-2-fluoroacetoacetate **59** (Scheme 20). Importantly, under these conditions, no perfluorination of the substrates was observed, with only the monofluorinated derivatives being isolated. The authors report that the bulk fluorination of ethyl 2-chloroacetoacetate **58** gives only a low conversion to **59**,[40] illustrating that the flow system is more



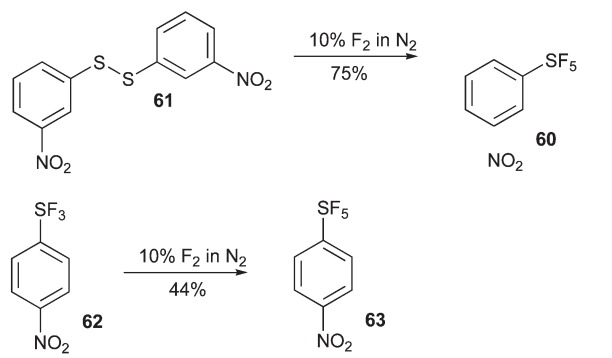
Scheme 20

efficient. This illustrates the catalytic effect of the fluorinated metal surface.

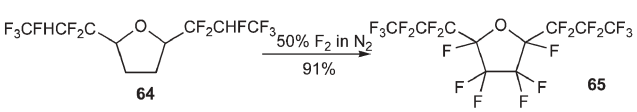
Sulfur pentafluoride derivative **60** was prepared in 75% yield by the reaction of the disulfide **61** with 10% fluorine in nitrogen, using acetonitrile as the solvent (Scheme 21). Similarly, treatment of the trifluoride **62** with fluorine gave sulfur pentafluoride derivative **63** in 44% yield.

Perfluorination reactions were found to require an additional heating stage for the reaction to go to completion. The reaction of the tetrahydrofuran derivative **64** with 50% fluorine in nitrogen at 280 °C gave the perfluorinated compound **65** in 91% yield (Scheme 22). In conventional reactions, cobalt trifluoride would be used to perfluorinate hydrocarbons.[41] Some of the reactions carried out by the authors, however, required much lower temperatures than would be expected if this compound was used.

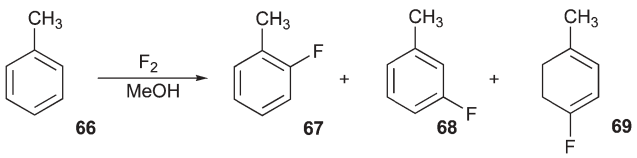
Jensen *et al.* have also demonstrated the direct fluorination of aromatic compounds in a micro reactor, a process difficult to perform on a conventional scale.[42] The reactor was fabricated from silicon and capped with Pyrex using anodic bonding. The surfaces of the reactor, which were in contact with the reagents, were coated with a nickel film using a metal deposition technique. The authors have used the micro reactor in the fluorination of toluene **66** at room temperature (Scheme 23). Using methanol as the solvent, the authors report an 80% conversion to give the monofluorinated toluenes. The substitution pattern of the *ortho*-**67**, *meta*-**68** and *para*-**69** isomers was determined to be 4:1:2 by GC.



Scheme 21



Scheme 22



Scheme 23

Conclusions

Micro reactor chemistry is currently showing great promise as a novel method on which to build new chemical technology and processes in which the reactions generally produce the desired product in higher yield and purity, in shorter periods of time, compared with traditional batch reactions. The technology is still in its early development and it would be presumptuous to expand too far on the potential applications that micro reactors will find, but some early trends are clear. One of the immediate and obvious applications is in combinatorial chemistry and drug discovery, where the generation of compounds with different reagents or under variable conditions is an essential factor. Perhaps more intriguing, is what new angles micro reactors bring to reaction chemistry and these are only now just emerging. For example, extending the heterogeneous catalyst work already described one can see how immobilised or supported reagents could be placed within a device to impart functionality to a reaction whilst maintaining spatial and temporal control.

In addition, a microchannel system also provides a potential separation column and integration of a micro reactor device to one of the many highly sensitive microchannel-based biological assay systems may therefore not only be possible, but may also address some of the pharmaceutical industries' potential requirements. Apart from the greatly reduced reaction times demonstrated for the micro reactors, handling times to assay and chemical reagent costs may be virtually eliminated. Other emerging areas for the technology include catalyst screening and nanoparticle production.

Reactions within the micro reactors are found to be more atom efficient, which is of significant environmental importance as this reduces the quantities of raw materials required and minimises waste. Furthermore, the technology allows the temperature of reactions to be controlled, enabling reactions to be conducted safely, where explosion may be observed if the reaction was conducted on a batch scale. This is where scale out to produce large volumes of products is advantageous.

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