

# But what is it good for? Applications of microreactor technology for the fine chemical industry

Andrew de Mello and Robert Wootton review developments in microreactor technology

Recent years have seen great progress in the development of microfabricated systems for use in the chemical and biological sciences. Much of this development has been driven by a need to perform analytical measurements on small sample volumes. Reducing the physical size of the measurement system naturally yields advantages such as improved efficiency with respect to sample size, response times, cost per analysis, experimental throughput and automation. However, at an even more primary level, interest in miniaturised analytical systems has been stimulated by the fact that scientists can more easily control physical processes (such as chemical reactions and molecular separations) when instrumental dimensions are reduced to the micron scale.<sup>1</sup>

It is now generally acknowledged that the application of microfabricated reaction systems (microreactors) to the field of chemical synthesis can show distinct advantages over existing technology. The high thermal- and mass-transfer rates possible in microfluidic systems allow reactions to be performed under more aggressive conditions than can be achieved with conventional reactors. This can often lead to improved reaction yields or product conversion. Furthermore, chemical processes may be rapidly interrupted in a controlled manner, leading to higher reaction selectivities and thus higher purity products. Details of research in the general area of microreaction technology can be found in excellent reviews by Klavs Jensen, Wolfgang Erhfeld and Steve Haswell.<sup>2–4</sup>

This mini-review aims to address a less explored and somewhat controversial area—the application of microfabricated reaction systems to fine chemical synthesis. Fine chemical suppliers traditionally operate equipment ranging from the twenty-litre reactor up to the

small–moderate plant scale (volume > 1000 L). A typical batch size for a catalogue company, for example, would be in the multi-hundred-gram scale. Since the primary costs in R & D are normally associated with the transfer of synthetic processes from the bench-top to reactor-scale the following question arises: what scope is there for the application of microreactor devices to the bulk production of fine chemicals?

## Developmental constraints in the fine chemical industry

A fundamental tenet for the development scientist is that a new technology should exhibit clear advantages over existing methods. In the fine chemical industry potential improvements are generally perceived to occur in the following areas.

### Cost

Outlay on plant and operator time is almost always the largest overhead in the establishment of a chemical process. Any process which can reduce the need for a specialist plant and cut operator hours would be seen as a clear improvement. Savings on expensive starting materials would also be a cost advantage.

### Safety

The safe operation of a process is of paramount importance in the modern chemical industry. Accidents and reaction run-aways incur huge expense. Furthermore, many reactions that work efficiently on a bench-top scale are deemed too dangerous to perform on a reactor-scale. Examples of these can include formation of anhydrous diazonium solutions or the use of pure oxygen as a reagent gas. This often dictates that less efficient reaction pathways must be utilised for bulk chemical production.

### Specificity

Lack of regio-, chemo-, or stereospecificity in reactions often leads to decreased product yields, and an increase in the complexity of separating product from unwanted materials.

### Utility and applicability

Some chemistry is deemed too sensitive, dangerous or costly to be operated on the fine-scale, despite showing clear utility on the lab-scale. Examples of this include the Grubbs and Schrock catalysts, which are notoriously difficult to handle in their original forms.

In this mini-review we aim to show how microreactor technology can be and has been adapted to meet the needs of the fine chemical industry, as typified by the requirements of clear advantage.

## Microreactor developments in synthetic methodology

Much work has been done on the process of understanding and taming difficult reactions on the micro-scale. Highlighted below are some representative examples of areas in which the application of microreaction technology shows promise or accomplishment of real improvements in areas of industrial concern.

### Direct fluorination

The direct fluorination of organic compounds has long been considered to be too dangerous for an industrial setting.<sup>5</sup> Indeed, many explosions have been reported on a lab-scale.<sup>6</sup> Fluorine is notoriously toxic and corrosive, and is considered a major safety hazard. Fluorination of aromatics is most commonly undertaken using the Schiemman process,<sup>7</sup> involving the decomposition of diazonium tetrafluoroborates. This process is itself

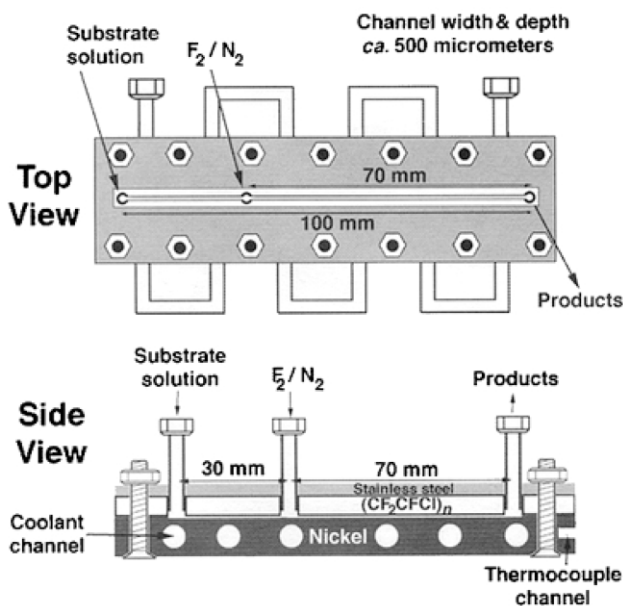


Fig. 1 A single channel microreactor for two-phase gas-liquid direct fluorination reactions.

somewhat hazardous as it involves diazonium chemistries,<sup>8</sup> but generally gives acceptable yields. In addition, it is limited to amines that will form stable diazonium salts, such as aryl amines. The process must also be conducted on dry diazonium tetrafluoroborates, since the presence of moisture leads to a runaway decomposition. Consequently, on the fine-scale, lengthy drying times are necessary. A typical procedure for the production of fluorobenzene from aniline gives a 51% yield and takes in excess of 24 h.<sup>9</sup> All these factors suggest that a method for the safe, controllable direct fluorination of organic compounds would, therefore, be of real advantage.

Richard Chambers and Robert Spink from the University of Durham have directly addressed the problems associated with direct fluorination by fabricating a nickel microreactor (Fig. 1).<sup>10</sup> Using this simple device the authors have demonstrated selective fluorinations of organic compounds. These included the monofluorination of a 1,3-dicarbonyl compound with yields in excess of 70% (Scheme 1). This significant result shows that the excellent interfacial and heat transfer properties of microscale devices can be used to advantage for controlled direct fluorination. More recent studies by the same group have reported the use of gas-liquid thin film microreactors for selective fluorination of a range of 1,3-dicarbonyl and aromatic substrates and, additionally, the conversion of aromatic disulfides to the corresponding sulfur pentafluorides. Furthermore, the authors demonstrate the potential for scale-up through application of a three-channel microreactor device

fabricated by replication of a single channel system.<sup>11</sup>

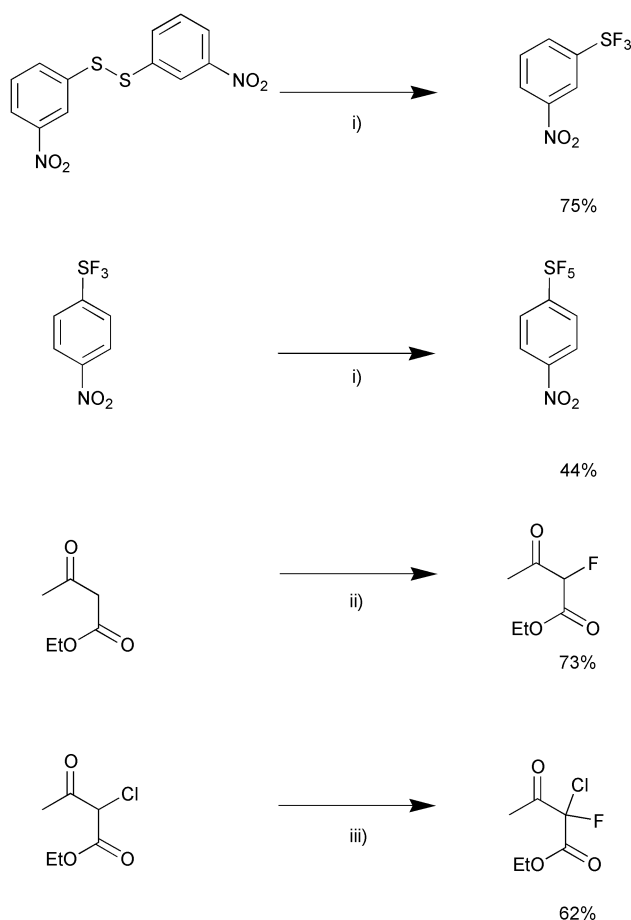
Volker Hessel and co-workers have also described a detailed analysis of microreactor performance with respect to the direct fluorination of toluene.<sup>6</sup> Studies evaluated the performance of a falling

film reactor (analogous to those used in refs. 10 and 11), a micro bubble column (operating in slug flow) and a laboratory-scale bubble column (Fig. 2). Results indicated that the space-time yields for both microreactors were considerably higher than for the laboratory column, supporting the idea that fluorination reactions were potentiated by virtue of the properties of micro-scale operation.

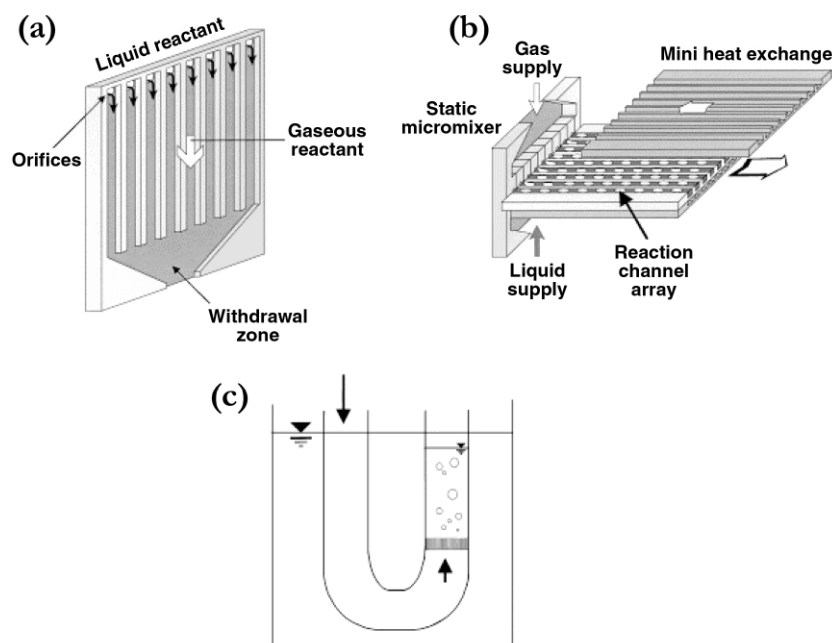
### Nitration reactions

The nitration of organic and, in particular, aromatic compounds plays an important role in the chemical industry. Nitro groups can be easily transformed into a wide variety of functionalities such as amines, halides and cyanides,<sup>12</sup> as well as functioning as activating groups for otherwise difficult  $S_N(Ar)$  reactions.<sup>13</sup> Unfortunately, the dangers inherent in the nitration of organic compounds are notorious. Even on the laboratory scale, careful control of the stoichiometry of the nitration mix must be maintained, as safety cannot be guaranteed with more than a 10% excess of nitric acid.<sup>14</sup>

Nitration chemistries have been an area of interest for microchemists for some



Scheme 1 Direct fluorination reactions. (i) MeCN ( $5 \text{ ml h}^{-1}$ ), 10%  $F_2$  in  $N_2$  ( $10 \text{ ml min}^{-1}$ ), room temperature.



**Fig. 2** Schematic diagram of a falling film microreactor, a micro-bubble column and a laboratory bubble column. (a) Vertically oriented falling film microreactor: a thin liquid film is fed through orifices into the reaction channels, generating a relatively large surface for contact with the gas. (b) Micro-bubble column: the liquid and gaseous reactants are contacted through a static micromixer, and, subsequently, fed into the reaction channels. (c) In the laboratory bubble column the gas is dispersed through a porous frit into the liquid.

quantitative product analysis.<sup>18</sup> Although this was developed specifically for gas-phase reactions, it is not difficult to envisage its application to liquid phase systems. The approach shows clear advantages over systems such as bead-based IR screening, as it allows direct detection of products as opposed to detection of catalysis.

The advantages that microreactors can bring to a catalytic system are many. One of the most outstanding characteristics of a microfabricated reaction system is its large surface-to-volume ratio (4–5 orders of magnitude greater than a conventional batch reactor). This means that heat can be rapidly transported into or out of a microreactor with little change in local temperature. Consequently, even highly exothermic reactions may be performed under isothermal conditions. A good example of the application of this advantage to an industrial process is in the oxidative dehydrogenation of alcohols (Scheme 2). One of the most industrially important oxidative dehydrogenation reactions is the synthesis of formaldehyde. This process was developed by BASF over 100 years ago, and involves a heterogeneously catalysed gas-phase reaction of feedstock (methanol) over a silver catalyst at 550 °C.

Otto Worz and colleagues at the BASF Central Research Laboratory in Ludwigshafen recently described the development of a microreactor for oxidative dehydrogenation of alcohols to aldehydes.<sup>19</sup> Since the authors required the aldehyde to be produced as part of a multi-step process an efficient synthesis was essential. Previously, use of pan-like reactors with a diameter of 5 cm led to a conversion rate of 50% and a selectivity of 90%. Based on these studies a prototype process reactor was built with a diameter of 3 m and a catalyst bed depth of 2 cm. Unfortunately, selectivity fell to 40%. This effect was ascribed to the poor heat loss (or conversely good insulation) experienced in the large scale. Use of tubular reactors did not help, as residence times were excessive. When the reaction

time. John Burns and Colin Ramshaw at the University of Newcastle have reported the nitration of benzene and toluene in PTFE and stainless steel microreactors.<sup>15</sup> In addition, the authors have implemented a device for the nitration of aromatic compounds, consisting of multiple parallel channels.<sup>16</sup> The device operates in a twin phase, laminar flow mode, and yields complete conversion of benzene to nitrobenzene in 50 s, with a product stream contamination of less than 600 ppm. The nitration of toluene on the same device was 43% complete after 1 s, with complete conversion achieved after 4 s (with a ratio of nitrotoluene isomers of 57% 2-nitrotoluene, 6% 3-nitrotoluene and 37% 4-nitrotoluene). It should also be noted that the degree of control conferred on the nitration of aromatics through the use of microreactors is significant, particularly in respect of over-nitration. The increase in safety conferred by the reduced instantaneous volumes is notable.

Methods for online monitoring of nitration reactions within microfabricated structures have also been investigated, since feedback control of nitration conditions would allow for far cleaner reactions than comparable large-scale processes. Tobias Tuercke and colleagues at the Fraunhofer Institut Chemische Technologie recently announced the use of on-line FT-IR monitoring for mechanistic studies of nitration in microreactors, utilizing the mid IR

permeability of silicon to image through a silicon microreactor.<sup>17</sup>

### Catalytic reactions

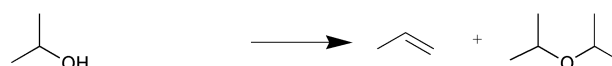
Many catalytic processes of interest to the chemical industry have been studied in micro-scale domains. The vast majority of these have been under heterogeneous catalysis conditions. This allows for clean reactions with little need for work-up. The catalyst can be immobilised in a variety of ways, including porous supports and membranes. In fact the ease of performing some catalytic reactions on chip has led to the development of the microchip as a catalyst test-bed.

For example Peter Claus and co-workers at the Institute of Applied Chemistry in Berlin have recently described microreactor systems for the rapid screening of heterogeneously catalysed gas-phase reactions (Fig. 3). In all cases, the authors used a scanning mass spectrometry technique for

Oxidative dehydrogenation of Alcohols



Dehydration of isopropanol



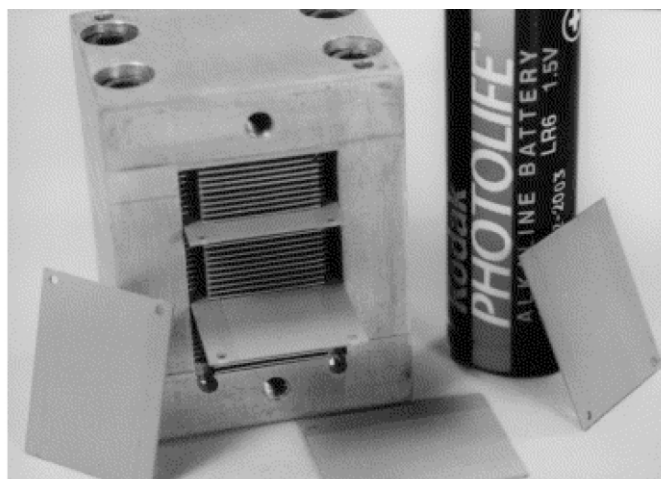
**Scheme 2**

was transferred to a microreactor format, with a residence time one order of magnitude lower and a heat transfer rate one order of magnitude higher than a short tube reactor, the conversion jumped to 55% and the selectivity to 96%. The authors state that the use of microreactors as a catalytic test-bed would have enabled them to develop the process with greater celerity than was the case; however, they have some reservations as to whether the technology could be utilized on an industrial scale due to problems with channel blockages. The results gained show that a valuable contribution as a development tool can be made by relatively simple microstructures.

Another area in which microreactors can demonstrate beneficial characteristics in catalytic processes is in periodic operation. It has long been recognized that unsteady state, or periodic operation of fixed bed reactors can lead to increased yields or selectivities.<sup>20</sup> The optimal cycle period is fundamentally related to reaction kinetics and may vary from a few hours down to a fraction of a second. The fastest frequencies at which standard fixed bed devices can be oscillated range between about  $10^{-2}$  to  $10^{-4}$  Hz. Rouge and co-workers at the Swiss Federal Institute of Technology, Lausanne, have reported the fabrication and characterisation of a first generation microchannel reactor specifically designed for periodic operation.<sup>21</sup> The kinetics of the dehydration of isopropanol to propene was initially studied in a conventional fixed-bed reactor (Scheme 2). Based on experimental results a kinetic scheme was proposed and used to successfully describe dehydration under periodic operation (at frequencies of 1 Hz) in the microreactor.

### Exothermic gaseous catalytic reactions

Oxidation reactions are legendarily ill tempered. Reactions are frequently dangerous, often explosive and radical run-away reactions are often the norm rather than the exception. Perhaps the classic example of such a reaction is the oxidation of hydrogen. The potential hazards of this process are graphically illustrated in Fig. 4. As discussed previously the large surface-to-volume ratios associated with microfabricated reaction systems result in short pathlengths for both heat and mass transport. In addition, free surfaces can act as binding sites for radical species (crucial as chain carriers for explosive gas-phase reactions). Consequently, microfabricated reaction systems should be ideally suited



**Fig. 3** Photograph of the reactor module and the microstructured inlays for rapid screening of heterogeneously catalysed gas-phase reactions.

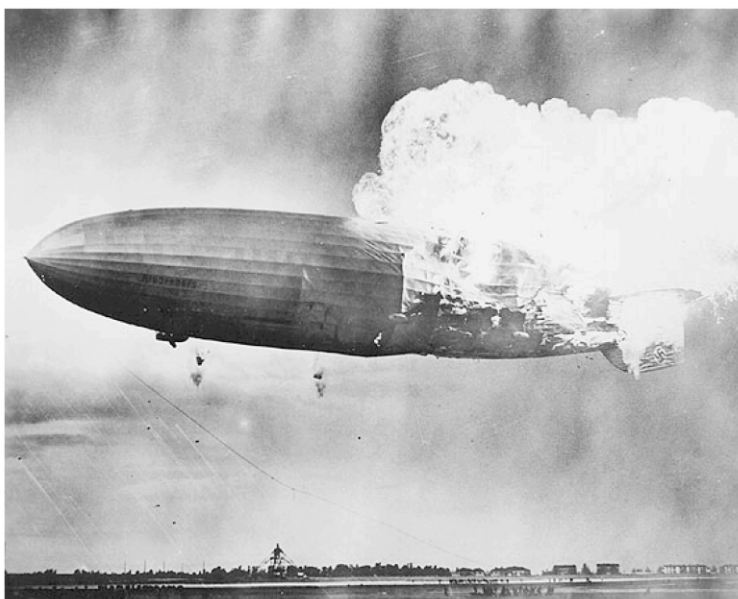
to suppressing explosive gas-phase reactions. Götz Vesper has addressed this issue by demonstrating increased safety aspects of highly exothermic catalytic reactions in microreactor environments.<sup>22,23</sup> Studies on the platinum catalysed oxidation of hydrogen in quartz/glass microreactors demonstrated efficient operation at temperatures in excess of 1000 °C without any signs of degradation. In addition, no homogeneous flames or explosions were observed under any reaction conditions. Further theoretical analysis of the system showed that for reactors with characteristic dimensions in the sub-millimetre range  $H_2$  oxidation is intrinsically safe.

In a related study J. Schouten and colleagues have conducted an analysis of the influence of microreactors on the extremely exothermic oxidation of ammonia.<sup>24</sup> Using an aluminium reactor

hot spot temperatures were within 5 °C at full conversion of 6% volume ammonia. Temperature gradients were considerably larger in an analogous platinum reactor, due to the smaller intrinsic conductivity. Selectivity for  $N_2O$  was concomitantly lower. The authors subsequently designed a microreactor/heat exchanger operating almost isothermally even when operated with a reaction mixture corresponding to an adiabatic temperature rise of 1400 °C.<sup>24</sup>

### Catalytic hydrogenations and dehydrogenations

Hydrogenations reactions are of widespread importance in the chemical industry. The selectivity of hydrogenation catalysts is a key factor in their development, and is often dependent upon reactor environments. Catalyst evaluation can often take a week or more per



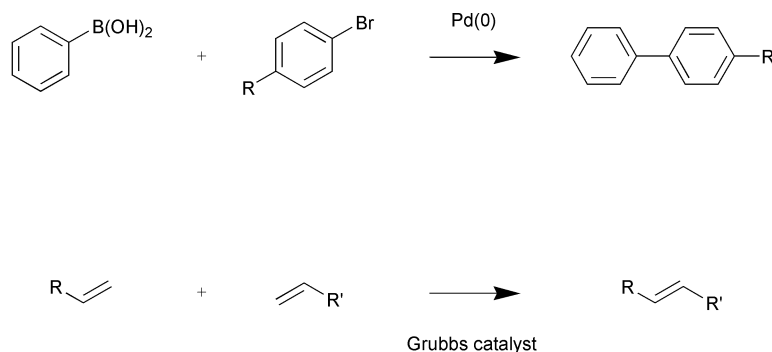
**Fig. 4** An illustration of the dangers of hydrogen–oxygen oxidation reactions. The *Hindenburg* explodes on its approach to Lakehurst on May 6, 1937.

catalyst. As has been shown above, microreactors have an important role to play in catalyst development, and may find application in industrial syntheses. This role has been further confirmed by their use in partial hydrogenations and dehydrogenations. For example, Dieter Honicke and associates have reported the gas-phase hydrogenations of benzene and cyclododecatriene over metal catalysts.<sup>25</sup> Results demonstrate that high yields and, in some cases, high selectivities can be achieved with very short reactor residence times. Furthermore, Ronald Besser and co-workers at Louisiana Tech University have investigated the application of silicon microreactors for catalyst development. In a model study on the hydrogenation of cyclohexene they show that the turnover frequency and reaction probability compare well with the literature.<sup>26</sup> More recent work by the same group demonstrates that a platinum reactor system could be effectively biased towards either the hydrogenation product or the dehydrogenation product, depending on reaction conditions.<sup>27</sup>

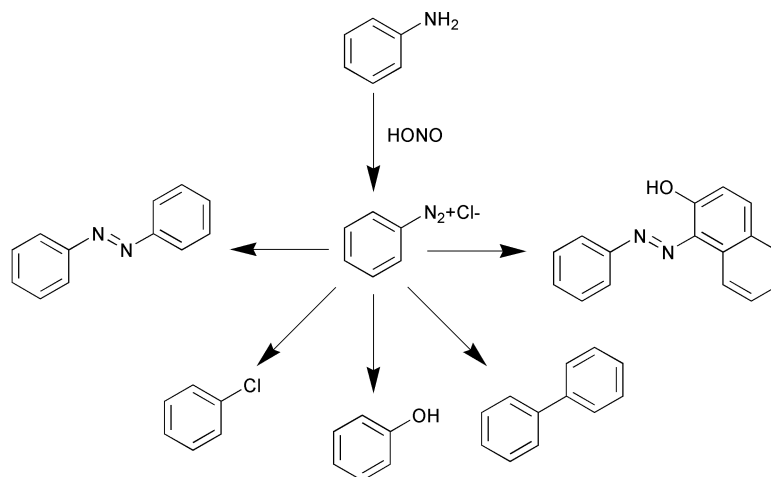
At least one palladium membrane reactor has been developed for hydrogen separation and hydrogenation–dehydrogenation reactions. This sophisticated device is perhaps an example of the future trend of ‘catalysis-on-chip’, with integrated sensors and heaters engineered onto monolithic chip structures.<sup>28</sup>

### Liquid phase catalytic reactions

A number of liquid phase catalytic reactions have been transferred to microreactor formats. Examples that represent reactions often undertaken on the fine-scale are the Suzuki coupling,<sup>29</sup> the notoriously sensitive yet useful Grubbs metathesis<sup>30</sup> (Scheme 3) and the Kumada–Corriu coupling.<sup>31</sup> Both coupling reactions show increased yields when performed on the micro-scale under EOF control, and even at an early stage of development microreactors represent the



**Scheme 3** The Suzuki coupling, and alkene metathesis reactions.



**Scheme 4** Diazonium displacement reactions.

most promising approach to performing metathesis on an industrial scale.

### Diazotisations

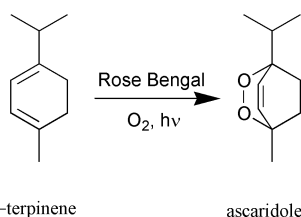
The diazotisation of aromatic amines is an industrial process of vast importance. The range of functionalities that can be introduced *via* dediazonation reactions is diverse (Scheme 4), but the dangers of diazotisation are well known. The explosive nature of diazonium intermediates necessitates extreme care in reaction processing. This is even true of the generally more stable diazonium tetrahaloborates. The low instantaneous volumes associated with all microfabricated reactors and the ability to integrate multiple reactions affords a simple and safe route to diazotisation of an amine and the reactive quench of the unstable diazonium intermediate on chip. The azo coupling reaction between diazonium salts and suitable electron-rich aromatic rings has been studied on chip using EOF motivation.<sup>32</sup> In addition, two alternative processes for continuous-flow synthesis of azo dyes have been developed. One system, utilising a fast flowing microreactor to produce azo dyes in suspension or solution has been patented by Clariant.<sup>33</sup> This system uses a

series of mixer vanes to combine a solution of diazonium salt and coupling agent, such as a naphthol. Heat exchangers for temperature control are included in the structure, and the ease of scale-out from such a device is noted. Researchers at Imperial College of Science, Technology and Medicine have also recently reported a simple monolithic chip device for synthesis of azo dyes.<sup>34</sup> In this case the transport distances are minimised by incorporating both generation of the unstable intermediate and reactive quenching on a monolithic glass chip. This approach has obvious safety advantages over conventional methods, and can be adapted to a combinatorial style approach. Research is currently underway to extend the methodology to other reactive intermediates.

### Photochemistry

The utility of microreactors for photochemistry is an area of expanding interest. The difficulty in scaling photochemistries is often one of light penetrance. Large-scale photochemical reactors are usually performed using macro-scale lamps immersed in the reaction vessel. In most cases considerable effort is necessary to transform a successful lab-scale reaction to an industrial scale, due to poor illumination uniformity and excessive sample heating.<sup>35</sup> Recently, Klavs Jensen and co-workers at MIT implemented an elegant microsystem for the photo-pinacol reaction of benzophenone.<sup>36</sup> By integrating photoreaction and detection the authors showed that the reactions could be efficiently performed on-chip, with conversions comparing well with those produced on the lab-scale.

The (4 + 2) cycloaddition of singlet oxygen, and related photooxidations,



Scheme 5 Singlet oxygen addition.

represent a useful way of introducing a peroxy function into an organic molecule (see Scheme 5). The difficulty with the process on any scale larger than a gram is the requirement for an oxygenated organic solvent. Oxygenated organic solvents are potent fire and explosion hazards. Coupled with this is the difficulty in introducing enough light into the reaction medium. Sensitising dyes for this process are often compounds with large extinction coefficients and so light penetration can be limited to a matter of centimetres. One approach to these reactions utilizes a small pipe reactor to optimize light penetration, but this still relies on large stocks of oxygenated solvent being pumped through the system, and the concomitant safety hazards.<sup>37</sup>

Work at Imperial College of Science, Technology and Medicine has recently led to the development of a simple reaction system whereby oxygen saturation and irradiation are performed within microchannels. Initial studies on the synthesis of the natural product ascaridole demonstrate very high conversion after only 5 s irradiation.<sup>38</sup> The system features a simple microfluidic channel network that can be readily duplicated, and eliminates most safety concerns attached to the system.

### ‘Scale-out’: fact, fiction or folly?

Most studies in the field of microreactor development have focussed on the design and implementation of individual reaction units. However successful these systems are at generating a desired product, their use in chemical production applications will primarily be determined by how easy it is to fabricate reactor systems that can generate significant volumes of product in relatively short time periods (the well known concept of ‘scale-out’).

On an initial inspection the notion of performing fine synthesis using microfabricated devices appears nonsensical. Within typical microreactor structures instantaneous reaction volumes can be conveniently measured in the picolitre to nanolitre range, which appears

incompatible with kilogram or even multi-gram scale synthesis. This is to ignore the possibilities of multiparallel synthesis (facilitated by facile mass production individual devices) and the ability to run individual reactors for extended periods of time. For example, a microreactor generating product at a concentration of 2.8% at a flow rate of 20 ml h<sup>-1</sup> will yield 0.56 ml of product in 1 h. One hundred reactors operating in parallel will therefore produce 56 ml h<sup>-1</sup>, a rate comparable to many fine processes. This calculation is based upon an actual example of a reaction with a low yield<sup>6</sup> and demonstrates that fine-scale processes can be simulated on chip arrays that are within the bounds of current technological development.

Unfortunately, this cursory analysis omits to take account of new challenges that have not previously been encountered in chemical system scale-up. In particular, as the size of a microreactor array increases both reaction monitoring and process control become increasingly difficult. This dictates that the control architecture surrounding the ‘microfluidics’ becomes more expensive and complex. Consequently, fluidic and electronic interfacing will most likely be the crucial issue in defining how widespread microreactors become in the area of fine-chemical production. Currently opinions are divided. Companies such as DuPont and Merck KGaA have already implemented microreactor technology for commercial chemical production.<sup>3,39</sup> Other companies such as BASF see more potential in using microreaction systems as a route to accelerating process design and improving current production methods.<sup>39</sup> What is clear though, is that microreactors undoubtedly have an important role to play in the modern day chemical industry.

### The outlook

The application of microreactor technology to synthesis on the fine-scale is a technology still in its infancy and yet, as has been shown above, significant progress has already been made in addressing many identified needs of the chemical industry. Processes can now be developed more rapidly, operated more cleanly and run in safer conditions thanks to the use of submillimetre devices, and the surge in patented processes over the last few years demonstrates a ‘real’ industrial interest. On a more fundamental level, new reaction pathways can be explored, leading to more economical and

environmentally friendly processing. As stated, microreactors are sure to play a significant role in the chemical industry, but the nature of that role is currently not defined.

In many ways the primary difficulty for today’s industrial chemist is accessing relevant microreactor literature. More work is published in conference abstracts than in paper form, limiting the readership. It is that lack that this journal (*Lab on a Chip*) was conceived in part to address.

### References

- 1 S. C. Jakeway, A. J. de Mello and E. Russell, *Fresenius’ J. Anal. Chem.*, 2000, **366**(6/7), 525–539.
- 2 S. J. Haswell, R. J. Middleton, B. O’Sullivan, V. Skelton, P. Watts and P. Styring, *Chem. Commun.*, 2001, 391.
- 3 K. F. Jensen, *Chem. Eng. Sci.*, 2001, **56**, 293.
- 4 H. Löwe and W. Ehrfeld, *Electrochim. Acta*, 1999, **44**, 3679.
- 5 R. D. Chambers, J. Hutchinson and G. Sandford, *J. Fluorine Chem.*, 1999, **100**, 63.
- 6 K. Jahnisch, M. Baerns, V. Hessel, W. Ehrfeld, V. Haverkamp, H. Lowe, Ch. Wille and A. Guber, *J. Fluorine Chem.*, 2000, **105**, 117; for hazards of decomposing diazonium tetrafluoroborates see C. F. Coates, *Runaway Reactions*, 1981, paper 4/Y, 1.
- 7 G. Balz and G. Schiemann, *Ber. Dtsch. Chem. Ges.*, 1927, **60**, 1186.
- 8 W. H. Doyle, *Loss Prev.*, 1969, **3**, 14; Anon., *Sichere Chemiearbeit*, 1993, **45**(1), 8.
- 9 D. T. Flood, *Organic Syntheses, 5th Collected Volume*, John Wiley & Sons, London, 1943, p. 295.
- 10 R. D. Chambers and R. C. H. Spink, *Chem. Commun.*, 1999, 883.
- 11 R. D. Chambers, D. Holling, R. C. H. Spink and G. Sandford, *Lab Chip*, 2001, **1**(2), 132.
- 12 M. P. Doyle, B. Siegfried and J. F. Dellaria, *J. Org. Chem.*, 1977, **42**, 2426.
- 13 See Fyfe in S. Patai, *Chemistry of the Hydroxyl Group*, Wiley, New York, 1971, pp. 83–124.
- 14 U. Worsdorfer, *Prax. Sicherheitstech.*, 1997, **4**, 355; *Chem. Abs.*, 1998, **128**, 77116m.
- 15 J. R. Burns and C. Ramshaw, *A Microreactor for the Nitration of Benzene and Toluene, Proceedings of the 4th International Conference on Microreaction Technology*, 2000, pp. 133–140.
- 16 P. Harston, J. R. Burns and C. Ramshaw, *Reactions of Aromatic Compounds*, International Patent WO 99/22858, 1999.
- 17 T. Tuercke, W. Schweickert, D. Boskovic, H. Krause and S. Loebbecke, *Micro Total Analysis Systems 2001*, Kluwer Academic Publishers, 2001, p. 581.
- 18 P. Claus, D. Honicke and T. Zech, *Catal. Today*, 2001, **67**, 319.
- 19 O. Worz, K. P. Jackel, T. Richter and A. Wolf, *Chem. Eng. Sci.*, 2001, **56**, 1029.

- 20 P. Silveston, R. R. Hudgins and A. Renken, *Catal. Today*, 1995, **25**, 91.
- 21 A. Rouge, B. Spoetzel, K. Gebauer, R. Schenk and A. Renken, *Chem. Eng. Sci.*, 2001, **56**, 1419.
- 22 G. Vesper, *Chem. Eng. Sci.*, 2001, **56**, 1265.
- 23 G. Vesper, G. Friedrich, M. Freyging and R. Zengerle, in *Reaction Kinetics and the Development of Catalytic Processes*, ed. G. F. Froment and K. C. Waugh, Elsevier, Amsterdam, 1999.
- 24 E.V. Rebrov, M. H. J. M. de Croon and J. C. Schouten, *Catal. Today*, 2001, **69**, 183.
- 25 E. Dietzsch, D. Honicke, M. Fichtner, K. Schubert and G. Weissmeier, *IMRET 4: 4th International Conference of Micro Reaction Technology Topical Conference Proceedings, AIChE Spring National Meeting, March 5–9 2000, Atlanta, GA, USA*, p. 89.
- 26 R. S. Besser, *Chem. Eng. Commun.*, January, 2001, accepted.
- 27 R. S. Besser, X. Ouyang and H. Surangalikal, *Hydrocarbon Hydrogenation and Dehydrogenation Reactions in Microfabricated Catalytic Reactors*, WWW.latech.edu/~rbesser/research/hydrocarbon%20reactions%20draft.pdf.
- 28 K. F. Jensen, S. Firebaugh, A. J. Franz and M. A. Schmidt, World Patent WO0032512/2000.
- 29 G. M. Greenway, S. J. Haswell, D. O. Morgan, V. Skelton and P. Styring, *Sens. Actuators B*, 2000, **63**, 153.
- 30 N. Schwesinger, G. Pieper and H. Wurziger, World Patent WO0170387, 2001.
- 31 S.J. Haswell, B. O'Sullivan and P. Styring, *Lab Chip*, 2001, **1**, 164.
- 32 H. Salimi-Moosavi, T. Tang and K. Jensen, *J. Am. Chem. Soc.*, 1997, **119**, 8716.
- 33 R. Jung, U. Nickel, K. Saitmacher and L. Unverdorben, U.S. Patent US2001029294.
- 34 R. C. R. Wootton, R. Fortt and A. J. de Mello, *Lab Chip*, 2002, **2**, 5.
- 35 H. Lu, M. A. Schmidt and K. F. Jensen, *IMRET 5: 5th International Conference of Micro Reaction Technology Topical Conference Proceedings*, Dechema e.V., Frankfurt am Main, 2001, p. 39.
- 36 H. Lu, M. A. Schmidt and K. F. Jensen, *Lab Chip*, 2001, **1**, 22.
- 37 H.-D. Scharf, P. Esser, W. Kuhn and R. Pelzer, U.S. Patent US5620569, 1997.
- 38 R. C. R. Wootton, R. Fortt and A. J. de Mello, *Org. Process Res. Dev.*, 2002, in the press.
- 39 P. Fairley, *Chem. Week*, 1998, **160**, 37.