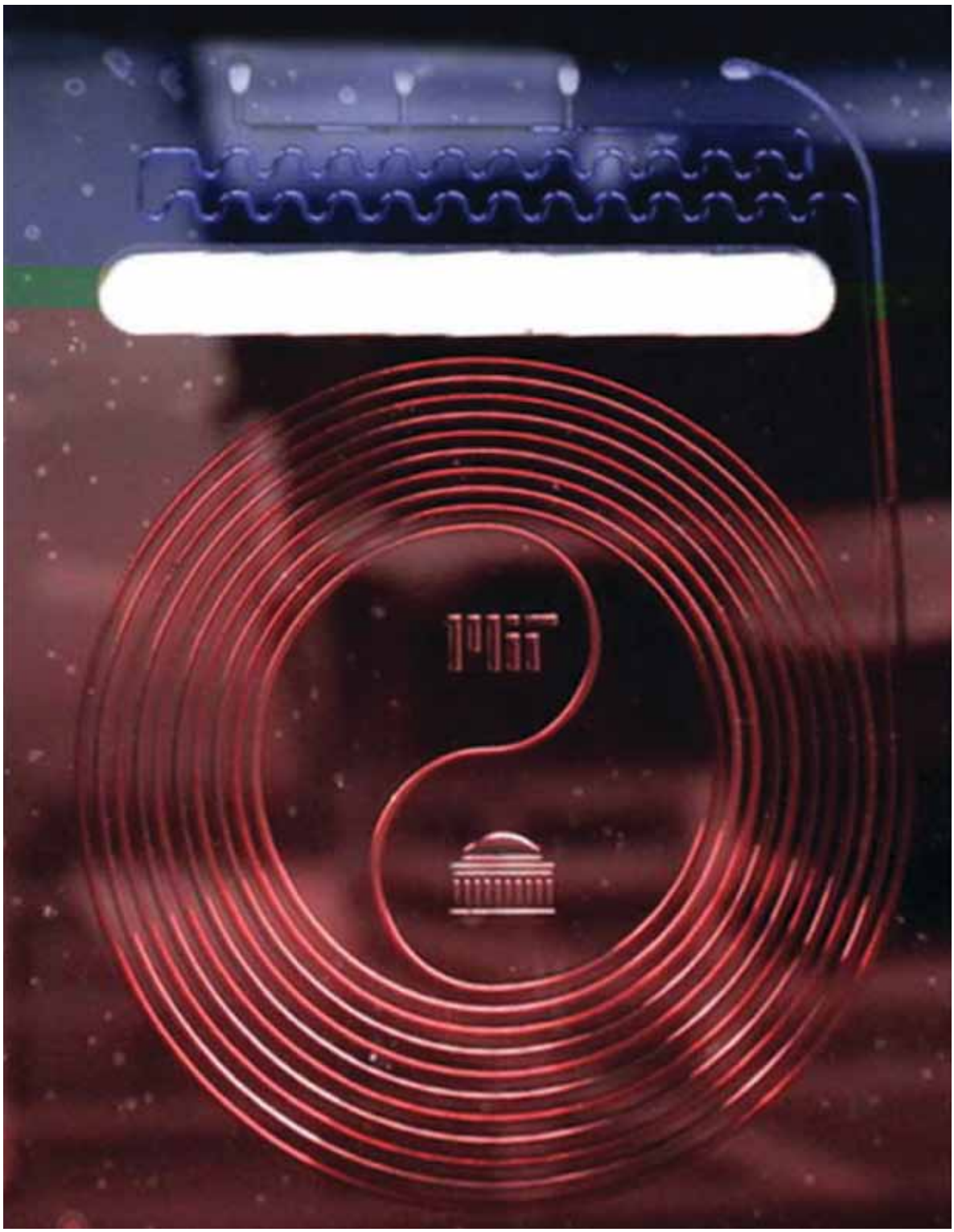
Going with the flow

When it comes to scaling up organic synthesis, it pays to think small. James Mitchell Crow explains



KLAVS JENSEN

It is not so many years ago that flow chemistry was considered a bit of a curiosity, the domain of a few hardcore dabblers. A growing number of reports began to appear in the mid-1990s – home-built microfluidic devices that could pump reactants and reagents through a microreactor, producing a continuous stream of product. Today, barely a decade and a half later, numerous commercial microreactor systems and add-ons are available, and virtually every commercial molecule-maker is now assessing or adopting the technology, from the discovery labs of pharma firms to the process chemists in the fine chemicals industry. Flow synthesis is poised to break through into the mainstream, with a trajectory of uptake that might ultimately consign the venerable round-bottomed flask to the back of the cupboard.

Reducing waste

The technology couldn't have come along at a better time. As attention increasingly focuses on sustainability and the principles of green chemistry, conventional batch-based chemistry frequently fails to hit the mark. 'Synthetic chemistry today just isn't good enough,' says Steve Ley, a synthetic organic chemist at the University of Cambridge, UK, whose overarching research goal is to change that situation. 'We want to improve the tools of synthesis so that we generate less waste, need less chromatography, can cut down on solvent usage, and avoid crystallisations and distillations and all the labour-intensive and wasteful practices of the past.' And so for Ley, the attraction of flow chemistry was irresistible.

Efficiency is the essence of flow chemistry's appeal. The rapid heating, mixing and cooling offered by microreactors can mean that reaction times are slashed, and product yields can be improved. 'In our flow lab we are using about one sixth of the solvent that my main synthesis lab uses, and we're generating about a tenth of the waste,' Ley says. Computer control makes flow reactions highly repeatable, and hands some of the grunt work of lab life over to automated machines. Method development is also simplified, and re-optimisation for scale-up can be avoided – to get more product, simply run the reaction for longer, or run several devices in parallel (a concept called 'numbering up').

The latest research promises to push this list of advantages even further, as flow chemists move from adapting batch-based reactions to developing new chemistries that fully exploit the latest flow reactor capabilities. Its drawbacks are also beginning to be conquered; not least the issue of handling solid without the flow tubes blocking up and the whole process coming to a sudden, dramatic halt.

Industrial backing

However, the real measure of the technology will be industry's interest in it. 'A technology can be too innovative, especially when you are dealing with a conservative industry like chemistry – conservative because it is a capital-intensive industry where you exchange chemical plants maybe every 40 or 50 years,' says Volker Hessel, who researches flow chemistry and microreactor technology at Eindhoven University of Technology (TUE) in the Netherlands.

Even so, the switch has started. 'Many big pharma and most agrichemical companies are really looking at these continuous processing methods, it's really catching on,' says Ley. A growing list of examples confirms that flow microreactor technology is starting to take hold.

For certain classes of reaction, flow chemistry holds clear advantages over batch, and when a new industrial process is being developed, these areas are where microreactors are beginning to get the nod over big flasks. One of those niches is the handling of hazardous reactions – things like nitration reactions, highly exothermic processes that can generate highly explosive by-products and undergo thermal runaway if the reaction temperature is not carefully controlled.

In the late 2000s, the small French pharmaceutical firm NicOx was looking for a way to produce commercial-scale quantities of the experimental drug naproxcinod, a nitroxy-substituted version of the anti-inflammatory drug naproxen. The company struck a process development deal with Netherlands-based chemical company DSM to develop a large-scale route to naproxcinod, and attention turned quickly to flow chemistry.[1]

For such reactions, microreactor technology's advantages over batch processes are myriad. By definition, microreactors generate only tiny amounts of reactive material at a time, which can be continually processed rather than accumulating as they would in a bulk reaction vessel. If the reactive compound is the desired intermediate then it can be immediately reacted to form the desired product without ever having to be isolated. In the case of nitration reactions where it is by-products that cause the problem, these can be extracted and neutralised as soon as they are generated, removing the risk. Throughout the process, heat generated during the exothermic reaction can be efficiently removed to keep the reaction temperature under strict control.

'Companies are really looking at continuous processing – it's really catching on'

However, the added benefit of microreactor technology was the speed with which the process could be developed into a high-volume process. Once the process was optimised at small scale, the companies could simply number up rather than having to re-optimise. After about six months' work, DSM had a pilot-scale process that could supply hundreds of kilograms of material.

It's an example that marks the tip of the

RICHARD TURNER/UNIVERSITY OF CAMBRIDGE

DSM

Flow microreactors are equally at home in academic labs (top) and industrial synthesis plants (bottom)

VOLKER HESSEL

The home-built microreactor rigs of the pioneers, such as this one in Volker Hessel's lab, are slowly translating into commercially available products

iceberg. Swiss chemical company Lonza, a leader in the industrial use of flow technology, has already transferred at least 10 reactions to flow production, says Hessel. And Bayer is leading a consortium of Europe's largest chemicals companies in an EU-project called F³ Factory, which aims to exploit continuous flow to develop a new paradigm in efficient chemical plants based on modular plug-and-play chemical production technology.

Increased productivity

However, Hessel believes that the real value of microreactor technology is still to be tapped. Until March 2011, Hessel worked at the Mainz Institute of Microtechnology in Germany, a research institute part-funded by industry and with a heavily industrial focus. Today, his research at TUE is funded by Europe's biggest research award, the €2.5 million (£2.1 million) ERC Advanced Grant. 'We are now working on process chemistry. The idea is to bring microreactors to a productivity level that is suitable for industry.

'In every textbook you will find that you have to do numbering up - that you have to put small reactors in parallel,' Hessel adds. It is an expensive proposition - and an unnecessary one, Hessel believes. 'My intension is first to boost the productivity of a single channel to the very limit. This is not [currently] done.' So far, flow chemistry has been largely about 'transport intensification', Hessel argues - better mixing and better heat transfer. 'In this way you can have a considerable boost in productivity, you can go from one hour processing to a few minutes.'

However, Hessel is working towards reactions that work on a timescale of seconds, by exploiting microreactors' amenability to aggressive conditions - high concentration, high temperatures and high pressures. 'In the lab we always limit ourselves by making reflux operations, and there is not any logic behind it. I don't limit myself by the boiling point of the solvent but by the best chemistry. [Using microreactors] we can go up to 300°C, and then we come into timescales of seconds, for virtually any organic reaction,' he says. 'If you bring the chemistry into this timescale, then you will find that for many reactions you don't need any numbering up, you can do all this in one slightly larger channel.'

Making waves

The high temperature and pressure reaction space offered by microreactor technology is also being explored by Oliver Kappe at the University of Graz in Austria, an expert in such conditions thanks to his experience with microwave chemistry.[2] 'We got into the field of flow chemistry because microwave chemistry in batch was not scaleable,' Kappe says.

On a small scale, using microwaves to heat sealed reaction flasks can give excellent results, slashing reaction times and improving yields. However, because microwaves only penetrate a short way into the flask, scaling-up these batch processes has proved difficult.

'We got into flow chemistry because microwave batch chemistry was not scaleable'

'Much of our research over the last 10 years was devoted to the so-called "magic microwave effect",' Kappe explains. 'The evidence that we and others gathered was that microwave chemistry is really exclusively about heat transfer - being able to rapidly heat something in a sealed environment. And if it's just heat, then microreactor technology, where the heat transfer is rapid and you can run a pressurised system, is the ideal tool to mimic microwave chemistry at scale.'

In his research lab, Kappe exclusively uses conventionally heated microreactors, and says that he sees no benefit to using microwave heating at this scale. However, production-scale flow reactors like the kind that Hessel envisages, which use high temperatures and pressures combined with wider flow channels to avoid the need for numbering up, could be ideally suited to microwave heating, he says.

'When you get to production scale, there is a very nice synergy between microwave and flow,' Kappe says. 'When you have a tube of 1-2cm or more, with conventional heating there is always the danger you overheat [your reaction mixture] from the outside and destroy something. With microwaves you heat from the inside, and if that is done with a very powerful microwave, then this makes sense again because the heat transfer is very efficient.'

Kappe is currently working with Clariant on just such a project. The Swiss speciality chemical company is developing an industrial-scale continuous flow microwave reactor to make reactions such as amidations more efficient. Generating an amide from a carboxylic acid and an amine has conventionally required the acid to first be activated by converting it into an acyl chloride

or similar. But under high temperature microwave flow conditions, this activation step is no longer required, saving time, money and resources. 'I think that very soon we will see something coming out where this idea is really implemented in industry,' Kappe says.

Multi-step records

Aggressive reaction conditions aside, the other key development that could spur industry's increased adoption of microreactor technology is the ability to link together multiple synthetic steps into a single, continuous, automated flow process. 'It is absolutely essential that we can do multi-step flow synthesis,' says Klavs Jensen, a chemical engineer specialising in microreactor technology at Massachusetts Institute of Technology (MIT) in Cambridge, US. 'Chemists build molecules – to put together a pharmaceutical product you have to carry out multiple steps.'[3]

Ley agrees that establishing flow reactors as a useful tool for multi-step synthesis is an essential step in their uptake. Ley is particularly proud of his research group's achievements in the area, especially his 2006 publications on the multi-step synthesis of natural products grossamide and oxomaritidine.[4,5] 'The oxomaritidine synthesis is still a world record, it's a seven-step synthesis of a natural product done in flow, all done by connected and automated machinery,' says Ley.

The fact that Ley's oxomaritidine synthesis still stands as a record also testifies to the challenges of multi-step flow synthesis. As Ley is the first to acknowledge, setting up such multi-step synthesis is not simple to do without first building up a fair bit of background knowledge and experience. 'I think a lot of people that have come into the area have really underestimated, certainly for multi-step mode, the importance of that knowledge that we had acquired,' says Ley. 'We often take people into our labs for three months to get them up to speed. But if they attempt to do it themselves, it's going to take them years of learning all the mistakes that we've all learned, about blockages, about how long you cut a piece of tube, and all the tricks of the trade that don't always find their way easily into the literature.'

However, the ongoing improvement in microreactor technology is helping to make multi-step synthesis easier to run. Ley has been pioneering the use of in-line infrared (IR) spectrometers. 'These allow us to measure in real time the compounds that we are making, and then use that signal to switch on a third pump.' The IR data allows a computer to control the addition of the reagent for the second step to match the concentration of product produced by the first step, automating reaction set-up and reducing waste.[6]

No plunger required

Avoiding reactor blockages – a notorious problem for flow reactors – is also beginning to become more routine. 'For solving clogging, we're doing well on small scale,' says Jensen.

'It would take years to pick up the tricks that don't always find their way into the literature'

Jensen and Ley are both developing the use of ultrasonication for reactions where components threaten to crash out of solution and block the reactor. 'Acoustic irradiation generates little hot-spots within the channel, which cause cavitation, generating pressure pulses,' Jensen explains. These pressure pulses keep solids moving until they can be extracted at the end of the reactor. Jensen and long-term MIT collaborator Steve Buchwald recently demonstrated that the technique could handle the inorganic salt by-products generated by palladium-catalysed carbon–nitrogen cross-coupling reactions, which are insoluble in the non-polar solvents used for these reactions.[7]

'For bigger tubes, acoustic irradiation is difficult to scale, you don't get the penetration,' Jensen adds. But for larger systems, there are other options, he adds. 'Eli Lilly has been using valves to create pressure pulses to keep solids moving in bigger pipes, and bigger pipes are less likely to clog anyway.'

So if flow chemistry continues to develop apace, and realise its potential, could round-bottomed flasks ultimately be out of a job? Undoubtedly, given industry's investment in batch-based processes, the shift will be gradual, and there will always be reactions that are better suited to flasks, especially those involving precipitations.

However, we might not be so far away from a time when flow rather than batch processes become the default choice for most syntheses. Batch-based reaction steps might even deliberately be avoided. 'Looking forward, you're not going to want a batch reaction in the middle of your flow process,' says Jensen.

Given the technology's relative immaturity, talk of the end of the era in which synthesis has been dominated by batch chemistry might not be so far-fetched.

'In just 15 years or so we've moved a long way,' says Ley. 'We can even use our cell phones to control our reactors, and watch reactions over webcams in real time. It's a different world now, and I'm excited by what can be achieved over the next 15 years.'

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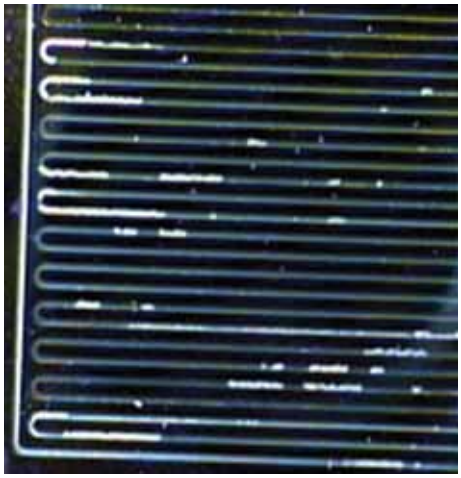

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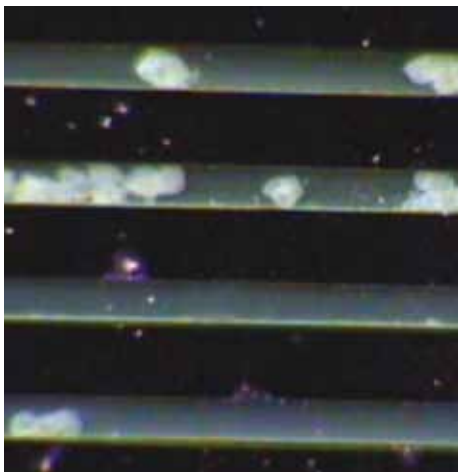

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Blockages can be a problem in microfluidic reactors, but ultrasound can keep precipitated solids moving

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