Greener Approaches to Organic Synthesis Using Microreactor Technology

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1. Introduction and Scope

Recently, microreactor technology has received a great deal of attention. However, most of the research carried out in this field is concerned with engineering aspects of microreactors,[1] not their potential for improving organic chemistry. Organic chemists have not fully embraced this technology, either because of the high cost of building and maintaining microreactors or because of the fact that organic

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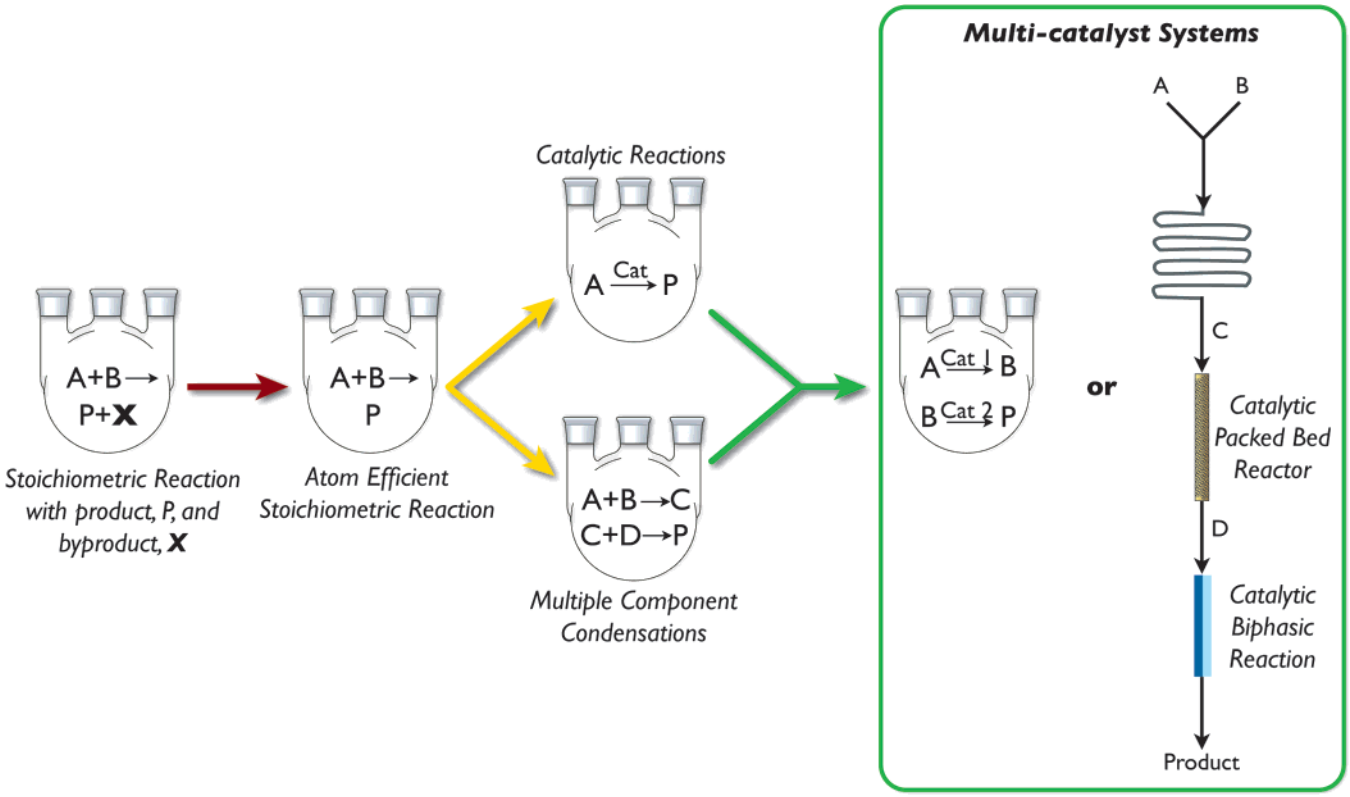
Scheme 1. Toward More Sustainable Organic Synthesis



chemists already have successful and productive strategies for building molecules. However, it is becoming clear that the traditional methods for doing organic chemistry are not sustainable and must be changed. Microreactors offer a solution because they are inherently less wasteful than traditional methods and because they provide unprecedented reaction control. We will show that although devices used for microreactor flow reactions can be costly, new microreactors for doing synthetic chemistry do exist that are inexpensive, simple to build, and easy to modify.

Chemists have been using essentially the same equipment to run reactions for the last several hundred years. The glassware that served Wöhler for his synthesis of urea, for instance, would not have been wildly different from the glassware that Woodward's group used for the synthesis of Vitamin B_{12} some 140 years later. Syntheses in round-bottom flasks and complementary large-scale batch reactors are mainstays of modern fine chemical and pharmaceutical synthesis.[2] Using these traditional synthetic methods, organic chemists can access almost any organic molecule, leading to widespread availability of drugs that save lives and improve quality of life for billions.

While traditional synthesis has been incredibly successful, it is inherently wasteful, and as raw materials become more limited, it is essential that we strive to make synthetic organic chemistry more efficient. It is estimated that more than 98% of the organic chemicals currently used in synthesis arise from petroleum feedstocks.[3] Once thought to be a practically limitless resource, petroleum is an exhaustible starting material whose cost will continue to increase as volumes diminish. The ballooning costs of starting materials will hamper our ability to carry out synthesis unless new technologies are developed to make large-scale synthesis more efficient. Beyond the rising price of oil, it is estimated that between 25 and 100 kg of waste result from every 1 kg of active pharmaceutical product synthesized, creating both a significant disposal cost and an environmental burden.[4]

Given the amount of waste resulting from these highly optimized syntheses, every increase in synthetic efficiency can serve to lessen the environmental impact of the chemical enterprise.[3] In recent years, new strategies have been introduced to advance the sustainability of organic synthesis. These include metrics to analyze reaction efficiency,[5] catalytic reactions,[6] multicomponent condensations,[7] multicatalyst systems in the form of multistep, one-pot reactions,[8] and microreactors, which will be the focus of this review (Scheme 1). We will briefly review each of these advances below to place microreactors into context.

To evaluate and compare these new technologies and the resulting syntheses, quantitative metrics have been introduced.[5,9] Whether considering a single step or an entire sequence of steps, Trost's concept of atom economy (AE) is one of the simplest ways to evaluate relative efficiency before running a reaction.[10−12] The AE of a reaction is a ratio comparing the mass of product relative to the mass of reaction byproducts (eq 1). In this context, an efficient

$$\%\ \text{atom economy} = \frac{\text{MW of desired products}}{\text{MW of all products}} \times 100\% \quad (1)$$

reaction produces very little byproduct, whereas an inefficient reaction produces significant amounts of byproduct. The AE metric has been modified to account for stoichiometric excess, solvent usage, and catalyst recycling to give metrics such as Sheldon's environmental impact factor[13,14] and reaction mass efficiency.[15,16] These account for raw materials usage, reaction conditions, waste, and purification. Andraos has recently defined each metric and expressed their relationships to each other in a detailed review.[5,9] Quantitative

treatment of reaction efficiency pinpoints wasteful steps, inspiring improvements in synthetic design.

Excellent technologies are emerging to make syntheses more efficient. The biggest innovation is the use of catalysts for organic reactions. Catalytic reactions that replace stoichiometric reagents increase atomic efficiency and decrease the amount of waste produced. Enantioselective catalysis eliminates the need for kinetic resolution, enabling the synthesis of enantiopure materials from simple prochiral starting materials.[6,17−22]

Attempts to further increase efficiency and lower costs have driven chemists to load expensive catalysts onto solid supports. The solid supports used for catalyst systems vary widely: inorganic materials (i.e., charcoal, alumina, zeolites, and silica),[23−26] soluble polymers,[27] cross-linked polymers,[28−31] or recently developed catalysts that are supported on or within microcapsules.[32−34]

Multiple reactions run in one reactor also significantly reduce the solvent demand during synthesis and workup. Multiple component condensation (MCC) reactions such as the Passerini or Ugi reaction couple three or four small molecule organic components into a single product (Scheme 1).[7] Related to MCC reactions are domino reaction sequences,[35] tandem catalysis (TC), and concurrent tandem catalysis (CTC).[36,37] Catalyst site-isolation can take CTC further, allowing traditionally incompatible catalysts, such as acids and bases, to operate in tandem.[38−46] The field of multicatalyst, one-pot reactions has only recently begun to tap its potential for creating more efficient, sustainable organic chemistry.[8]

Related to multicatalyst tandem reactions are the many examples of process intensification.[47−50] Process intensification involves optimizing the reaction engineering, specifically changing the instrumentation or chemical methods to decrease the equipment, energy usage, and waste associated with a synthesis.[50] One of the simplest methods for process intensification involves running two or more processes in a single piece of equipment. This provides two steps in one reactor, which is similar to an MCC reaction or a two-catalyst system. Another example is continuous processing, which uses continuously stirred tank reactors, spinning disk reactors, static mixing reactors, and flow reactors.[48−50] Through continuous processing, a desired product is produced via multiple transformations. Continuous processing is common in bulk chemical production but is somewhat uncommon in fine chemical and pharmaceutical synthesis.[2]

Microreactors are tools that can combine the advantages of continuous processing with the scale and complexity of pharmaceutical synthesis[2,51−54] in that they facilitate reactions by passing reagents and starting materials through channels on the order of 10−1000 μm. The narrow channel dimensions combined with static mixers provide millisecond mixing times. Their small size also prevents hot spots typically generated in batch reactors, offering better selectivity and yield for many organic reactions. Rapid mixing and heat transfer allow the use of highly concentrated reagent streams, providing opportunities to run reactions with minimal waste. Microreactors enable both process optimization and library generation to be done rapidly on small scale, further reducing waste. More importantly, however, microreactors eliminate scale-up—instead output is increased by "numbering up" with many reactors. Safety is increased and production enhanced by avoiding large reactors.[55] For industrial chemical production, microreactors often provide larger space−time yields than batch reactors, that is, a greater amount of product per unit volume and per unit time (typically given in kg m^{-3} s^{-1}).[56] Once synthetic methods are developed in microreactors, synthetic transformations can be tied together in continuous processes, creating far more efficient syntheses.

This review details the unique aspects of microreactors that make them efficient tools for organic chemistry on both small and large scale. The types of reactions that have been run in microreactors are also surveyed. We limit our discussion to those reactions we thought would be of interest to organic chemists, and we have not reviewed bulk chemical processes performed in microreactors and keep discussion of engineering aspects to a minimum. Also, although the term "microreactor" has been loosely defined in dimensional terms, we have tried to discuss reactors using 10−1000 μm channels, and we make individual exceptions only when a particularly challenging issue has been addressed. For this reason, monolithic and fluid-bed reactors have not been reviewed here.

2. Microreactor Structure: Design, Fabrication, and Operation

Microreactors consist of a series of small (10−1000 μm) channels connected in various geometries that allow for the spatial and temporal manipulation of small amounts of fluids and reagents. Unlike the case of macroscale laboratory equipment, fluid behavior is dominated by nonconvective, laminar flow wherein diffusion alone affects mixing. Physically, microreactors are usually planar objects roughly the size of a deck of playing cards or a small dinner plate (Figure 1). Microreactors are typically self-contained devices, other

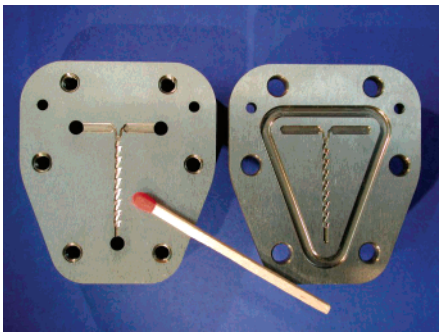


Figure 1. A caterpillar microreactor device from the Institute for Molecular Manufacturing, Mainz (IMM). Reprinted with permission from Institut für Mikrotechnik Mainz GmbH (IMM).

than auxiliary pumps and fluid ports, that can control factors such as reagent addition, mixing, reaction time, separation, and analysis. Microchannel junctions are often simple T- or Y-shaped geometries joining channels with rectangular or trapezoidal cross sections, but more complex channel shapes and configurations are also possible (Figure 2).[1]

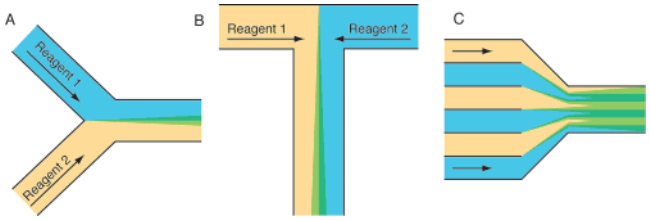


Figure 2. Various channel geometries: (A) Y-junction, (B) T-junction, and (C) interdigitated multilamellar mixer.

To an organic chemist accustomed to the world of stirred reaction vessels, the vast amount of literature on microfluidic device geometries and materials may seem daunting. Most microreactors are designed and fabricated using methods borrowed from the well-established field of semiconductor microelectronics. Though we will discuss these methods below, we acknowledge that microfabrication, clean rooms, and photolithography are foreign to the typical organic chemist. However, the exciting world of the small may be explored using tools that are ubiquitous in organic laboratories. Our group has introduced a simple microreactor system constructed of poly(vinyl chloride) (PVC) tubing and small-gauge needles mounted on plastic or Gastight syringes.[57] Other than the syringe pumps that drive the fluids, all of these components are common tools in the organic chemist's laboratory. Moreover, the system requires only minutes to construct while offering great flexibility in the positioning of fluid junctions and, therefore, reagent addition. We have found that our system replicates fluid behavior observed in smaller microreactors and is useful for carrying out organic synthesis with space−time yields that exceed those of corresponding batch reactions by a factor of 20.[58] Ismagilov and co-workers recently used a similar system to rapidly screen reagents for the hydrolysis of a complex molecule using only micrograms of material for each reaction.[59] Given these examples, organic chemists should feel confident trying their hand at the field of microreactors without worrying about the details of complex device fabrication.

Though simplified microreactors are accessible to all organic chemists, smaller dimensions, greater device complexity, or certain solvent requirements may require the use of traditional microreactor devices. The microfabrication tools of lithography, resist layers, and wet and dry etching are instrumental in the fabrication of many such systems. These methods have been used to create microreactor systems in both direct and indirect ways. In the direct method, the microfabricated component is used directly as channels in a device. Direct methods have the disadvantage that each completed fabrication yields only one device. However, if the fabrication is fast, this can allow for rapid prototyping of many designs. On the other hand, indirect methods use the microfabricated component as a master to transfer the design to a secondary material in a replication step. This molded material is then used in the final device. Indirect methods have the advantage of needing only one master to create many (up to hundreds of) final devices.

Most device fabrication strategies begin with a lithography step. Lithography is the process of using a mask that contains a desired pattern to expose specified areas of a photosensitive material to X-ray or ultraviolet (UV) radiation.[60] The mask pattern is thereby transferred to the underlying material. After exposure, the resist is developed and washed to remove either the exposed or the unexposed portion. At this point, various etching techniques may be employed to remove substrate material that is no longer shielded by the resist, reproducing the original mask pattern (or its negative) in the substrate.

The most common substrate for microreactor master production is elemental silicon. Silicon may be removed by wet etching,[61] using aqueous acids or bases, or dry etching,[62] which employs reactive plasmas. For certain applications, the disadvantages of silicon, namely its lack of durability and potentially poor release properties,[63] may preclude its use as a master. However, a patterned silicon substrate may be electroplated with a metal,[64] which is then removed from the silicon and used as a master in later replication steps instead of the silicon master. A prominent method that avoids the use of silicon altogether is the so-called LIGA (*Lithographie* [lithography], *Galvanoformung* [electroplating], *Abformung* [molding]) process.[65] In the LIGA process, a polymeric substrate, usually poly(methylmethacrylate), is ablated with either X-rays or a UV laser through a patterned mask. After patterning, the resulting structures are electroplated with a metal, the polymeric substrate is removed, and the metalized master is used in subsequent replication steps.

Once a suitable master has been produced, the replication of the pattern into the device material is achieved by one of several methods. Injection molding,[66] hot embossing,[67] and the use of elastomeric stamps[68] are common indirect methods of device fabrication. Poly(dimethylsiloxane) (PDMS) is commonly used as a material for microreactors (Figure 3),

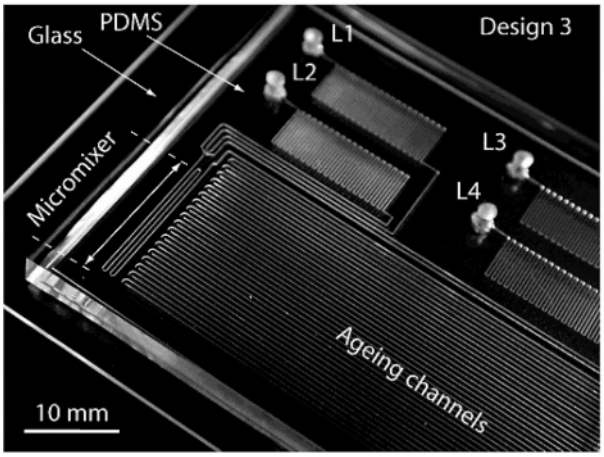


Figure 3. A PDMS and glass microreactor. The PDMS was molded from a polymer master made via soft lithography and was then bonded to the glass, forming an irreversible seal. Reprinted with permission from Khan, S. A.; Günther, A.; Schmidt, M. A.; Jensen, K. F. *Langmuir* **2004**, *20*, 8604. Copyright 2004 American Chemical Society.

though it swells in most organic solvents and cannot be used in such cases.[69] However, a recently developed perfluorinated elastomer is compatible with at least methanol, dichloromethane, and toluene.[70]

Direct fabrication methods do not rely on master patterns created in prior steps; rather, the patterned material is used directly in the final device. Microreactors may be fabricated directly via the LIGA process discussed above, by lithography of polymer materials[71] or the photosensitive glass FOTURAN,[72] and also by chemical etching of various other glasses. Alternatively, microfluidic devices may also be fabricated by milling techniques, thereby obviating the need for lithography altogether. Mechanical[73,74] and ion beam[75] milling techniques have successfully patterned channels in polymers and various metals with relatively high resolution.

Once a microreactor has been fabricated, a variety of techniques may be employed to interface the device to macroscopic instruments (Figure 4). These include fluid wells incorporated directly into the device design, ferrule-type connectors, HPLC fittings, and larger-scale barbed connectors for laboratory tubing. A review by Fredrickson and Fan provides more examples.[76]

Control of fluids in microreactors is achieved by one of two broad classes of pumping techniques: hydrodynamic flow and electrokinetic flow.[68] Hydrodynamic flow, also

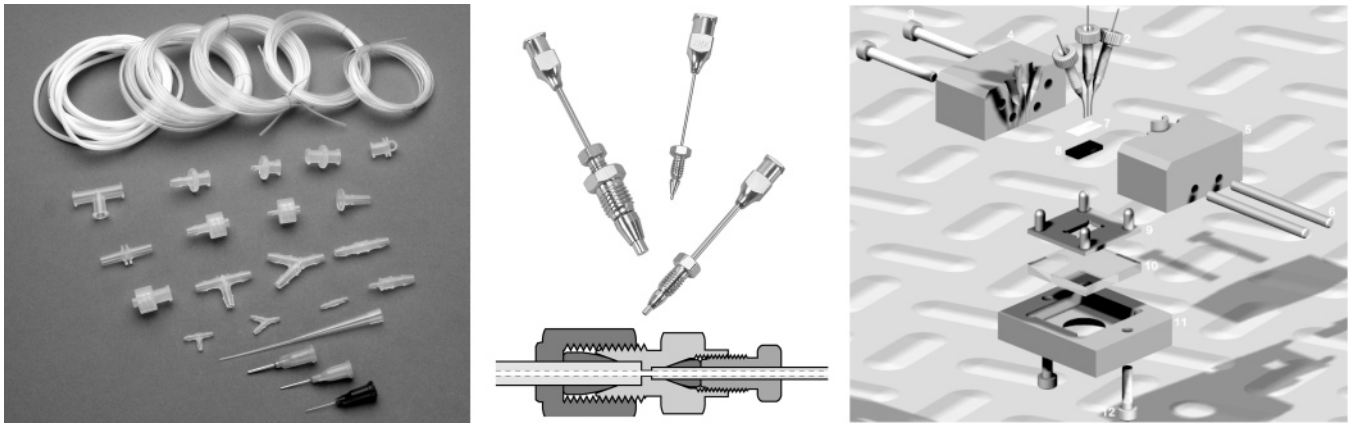


Figure 4. Various fittings used to interface microreactors to macroscopic fluid handling devices. From left to right: Luer-to-barb and Luer-to-Luer connectors (reproduced with permission from Warner Instruments); common HPLC fittings (reproduced with permission from Valco Instruments Company Inc.); and a high-pressure interconnect designed to interface with standard capillary tubing (Nittis, V.; Fortt, R.; Legge, C. H.; de Mello, A. J. *Lab Chip* **2001**, *1*, 148. Reproduced by permission of The Royal Society of Chemistry).

called pressure-driven flow, occurs due to a pressure difference between the inlet and outlet of a channel. Usually positive pressure is applied to the inlet while the outlet is open to atmospheric pressure. Syringe pumps and peristaltic pumps can both infuse and withdraw fluids and are a popular means of applying pumping pressure, though pulsing of flow can be problematic at low flow rates. Advantages of hydrodynamic flow are that it may be used with any liquid and with devices constructed of any material. However, capillary resistance to pressure-driven flow increases exponentially with decreasing channel dimensions. Thus, with small channels, only very slow flow rates may be used, if pumping is possible at all. Also, the velocity profile in hydrodynamic flow is parabolic in shape; that is, fluid in the center of the microchannel moves faster than that near the walls (Figure 5). This dispersion in flow rates leads to a distribution of residence times that can decrease yields and selectivities of reactions run in flow.

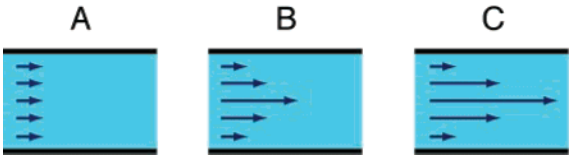


Figure 5. Parabolic flow profile of hydrodynamic flow. (A) At the beginning of the channel, the velocity vectors are equal across the channel, but further down the channel (B, C), fluid flows faster in the center of the channel than near the sides.

An alternative to hydrodynamic flow is electrokinetic flow, wherein a potential bias is applied between the channel inlet and outlet. This type of flow arises from two distinct mechanisms.[77,78] The first is the direct movement of ions in solution toward the electrode of opposite charge, as with gel electrophoresis. The second component of electrokinetic flow, electroosmotic flow, arises from the electrical double layer that forms on channels with charged surfaces (Figure 6). For example, at neutral to basic pH, glass and silica surfaces bear a negative charge due to partial ionization of surface hydroxyl groups. In response to the negative surface charge, positive species in the solution form an electrical double layer near the surface of the channel. When an electric potential is applied between the channel end points, the mobile positive ions in solution migrate toward the negative electrode. Viscous drag between the moving ions and the

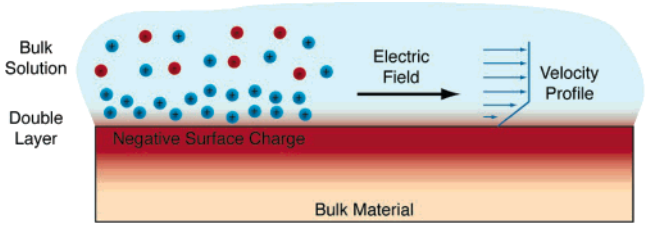


Figure 6. Principles of electroosmotic flow. At appropriate pH, a negative surface charge is present on the microreactor walls, which attracts positive ions from solution and forms an electrical double layer. When an electric field is applied along a microreactor's channel, the mobile cations move toward the negative electrode, dragging along the rest of the solution. The flow velocity profile is nearly flat across the channel except for a thin (few nanometer) diffusive layer immediately adjacent to the channel wall.

rest of the solution causes net flow of the fluid toward the negative electrode. The velocity of electroosmotic flow is linearly proportional to the applied voltage,[77] allowing precise fluid handling and facile computerized automation even with many interconnected channels. Also, the velocity profile is nearly flat across the channel, leading to greatly reduced dispersion of reagents relative to hydrodynamic flow. Unfortunately, the use of electroosmotic flow is restricted to polar solvents such as water, methanol, acetonitrile, dimethylformamide, and tetrahydrofuran,[79] as well as to device materials that develop surface charges such as glass, silicon, and treated PDMS.

3. Advantages of Microreactors: Added Efficiency, Control, and Safety

3.1. Increased Yields and Selectivity

3.1.1. Mixing in Batch versus Microreactors

Typically, to run an organic reaction with high yield and selectivity, both mass and heat transport must be carefully controlled. Chemists and chemical engineers manipulate these processes mainly by convection, the millennia-old practice of stirring. Stirring in classical reactors, such as round-bottom flasks and larger batch reactors, is limited by inhomogeneities in the flow fields created by the stirring mechanism. As fluid approaches the stirrer, convection is induced, resulting in turbulence and chaotic mixing.[51,80] The shear forces that cause the convection are significantly

dampened away from the stirrer and the majority of the round-bottom flask or reactor experiences little or no mixing. Several studies have directly visualized the mixing of dyes in vessels stirred either by impellers[81−83] or by stir bars.[84] These investigations found that small changes in vessel geometry or stirring conditions can unexpectedly change mixing efficiency. Also, inhomogeneities in the fluid and convective dead zones can persist for hours in certain cases.[83] These idle portions in a reaction environment lead to concentration gradients, poor heat transfer, "hot spots" in the reactions,[85] and ultimately inefficient chemistry. If productivity is not an issue, longer reaction times may be used to drive reactions to completion, decreasing temporal efficiency. However, concentration and temperature gradients in a reactor can lead to decreases in both selectivity and yield, despite greater reaction times.[86−88]

On the other hand, continuously flowing microreactors allow for rapid and homogeneous mixing because of their small dimensions. Microreactors can achieve complete mixing in microseconds, whereas classical reactors mix on the time scale of seconds or longer.[52] Microreactors achieve this rapid mixing using a variety of strategies. Researchers at Battelle in the U.S. and at the Institute for Molecular Manufacturing in Germany have created devices that mix fluids using a multilamellar approach (Figure 2C, section 2), where layers of fluids ranging in thickness from 50 to 200 μm are sandwiched together. The small dimensions allow rapid diffusional mixing to occur in as little as 100 μs. Such rapid mixing occurs because these lamellar systems achieve surface-to-volume ratios of 30,000 m^2 m^{-3}, compared to laboratory beakers and batch reactors, which typically have surface-to-volume ratios of 100 and 4 m^2 m^{-3}, respectively. As discussed below, these surface-to-volume ratios impact thermal and mass transport. Other strategies that complement the lamellar design are twisted or undulating tubes, impinging flows, or static mixers placed in flow.[89,90]

3.1.2 Thermal Management

Heating and cooling a reaction is an important variable that, if left uncontrolled, can lead to either very slow reactions (needing heat) or runaway reactions that can lead to explosions (needing cooling). Also, reactions that offer two potential products from either kinetic or thermodynamic pathways are very sensitive to temperature. Batch reactors often provide broad temperature profiles that can allow access to multiple pathways when only one pathway is desired. Figure 7 compares the temperature distributions in batch and in a microreactor to the kinetic energy needed to access a byproduct-forming pathway.[91] Whereas the batch reactor's broad temperature distribution allows the undesired side reaction to occur, the narrow temperature distribution in the microreactor restricts the reaction to the target product. Microreactors achieve such efficient input or removal of heat and nearly constant reaction temperatures because of their high surface-to-volume ratios. Rapid temperature changes[92] and heat exchange coefficients up to 25 kW m^{-2} K^{-1} are possible depending on the materials and heat exchanger used.[52]

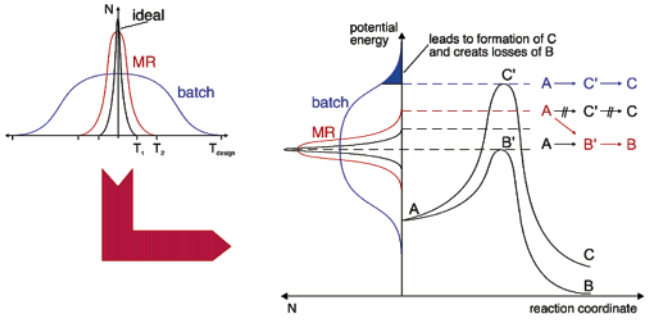
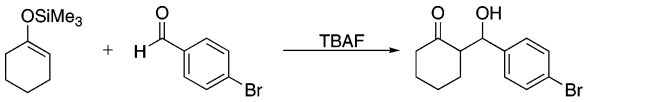


Figure 7. (left) Comparison between ideal temperature distributions for a hypothetical reaction (black) and actual temperature distributions in a batch reactor (blue) and a microreactor (red). (right) Schematic comparison of these temperature distributions to two product-forming pathways. The batch reactor's broad temperature distribution allows the production of the undesired product C, but the narrow temperature distribution in the microreactor restricts the reaction to the target product B. Reprinted with permission from ref 91. Copyright 2004 American Chemical Society.

3.1.3. Increased Rates of Reaction, Yields, and Selectivities

Because of the rapid heat transfer and mixing in microreactors, reactions can be carried out significantly faster than those in batch, typically with increases in both yield and selectivity.[54] The difference in reaction time is dramatic in some cases. Haswell's group has demonstrated that the aldol reaction between an aldehyde and a silyl enol ether in the presence of tetrabutyl ammonium fluoride (TBAF) reaches completion in only 20 min when using a microreactor, versus 24 h in a typical reactor (Scheme 2).[93]

Scheme 2. Haswell's Aldol Reaction in a Microreactor

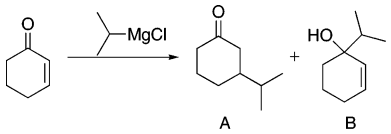


Time Needed to Reach 100% Conversion
Flow: 20 minutes Batch: 24 hours

When examining rapid reactions that allowed equivalent reaction times in flow and batch modes, we see that many show improvements in yield. Significant increases in yield have been demonstrated in Wittig reactions,[94,95] reductions and oxidations,[96−99] coupling reactions,[100,101] heterocycle formations,[102,103] and many others.[104] Schwalbe and co-workers offer a direct comparison of microreactor and batch yields for many reaction types run using the Cytos system in their review.[85] Pennemann and co-workers have also summarized many batch/microreactor comparisons from the literature in their recent review.[53]

Besides high yields, microreactors provide environments for highly selective chemistry, most likely due to the precise temperature control. One example of the type of regioselectivity possible is the Grignard reaction run by Taghavi-Moghadam and co-workers (Scheme 3).[51]

Scheme 3. Optimized Grignard Reaction of Taghavi-Moghadam

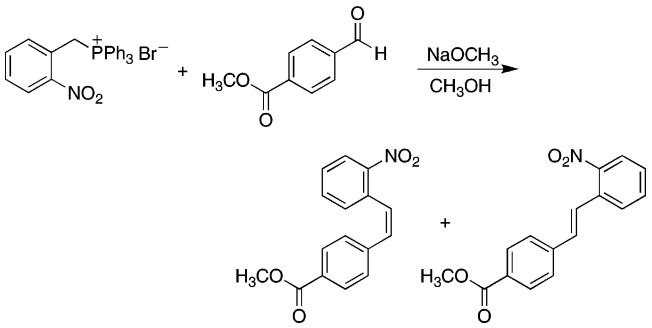


Optimized Conditions: 78% Yield
Regioisomer Ratio: 95:5 A:B

Another example is the Wittig reaction run by Haswell's group, which illustrates the tunability of a flow system.[95] In this case, the *E*/*Z* ratio could be reproducibly varied from

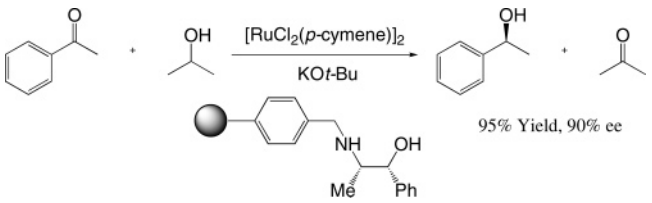
0.5 to 5 using different reagent concentrations, whereas the batch reaction was limited to a ratio of ~3 (Scheme 4).

Scheme 4. Haswell's Wittig Reaction



Very few enantioselective reactions have been run in microreactors. Recently, Reetz and co-workers used epoxide hydrolase to generate a diol at high enantiomeric excess in flow.[105] A number of examples exist in larger-volume flow reactors with diameters on the order of millimeters or centimeters. Hodge and co-workers have demonstrated a highly enantioselective (up to 97% ee) diethyl zinc addition to benzaldehyde using an ephedrine-functionalized polystyrene resin as the source of chirality.[106] Also, Mandoli and co-workers have demonstrated an enantioselective ene reaction in an HPLC-based flow reactor.[107] The investigation of enantioselective reactions in these larger flow systems has been extended to organometallic catalysts. Reek, van Leeuwen, and co-workers designed a chiral ruthenium catalyst, supported on silica gel, that has been shown to give higher yield and ee than the related batch reactor (Scheme 5).[108] In these examples, the ee provided by flow is typically as good as or better than that obtained from batch.

Scheme 5. Reek's Asymmetric Transfer Hydrogenation Reaction



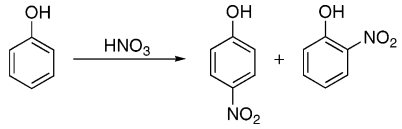
Enantioselective systems using smaller diameter flow reactors have been seldom used and have been proven to be less successful. De Bellefon and co-workers have studied a number of soluble catalysts in flow, including a known enantioselective and water-soluble rhodium catalyst.[109] The goal of de Bellefon and co-workers was to use a microfluidic device to study the mechanism of catalysis. As a result, the enantioselectivity was never optimized beyond 48% ee. Generally, the potential of enantioselective reactions in microreactors is still largely unexplored, but it is promising given the results in larger flow systems.

3.2. Accessibility of Exothermic and Runaway Reactions

The unique heat transfer properties of microreactors allow reactions to be controlled that were previously inaccessible on scale. By rapidly cooling microreactors, large exotherms can be minimized, creating a safer and more selective process.[48]

One of the most common reactions used to illustrate control over exothermicity is nitration of aromatic species. Nitrations are often dangerous in industrial processes, since they can be uncontrollably exothermic and can generate explosive byproducts.[110] A number of groups have carried out nitration reactions in microreactors, controlling both yield and selectivity.[110−113] Ducry and Roberge used calorimetry to compare the autocatalytic nitration of phenol in a microreactor with that of similar reactions run in batch (Scheme 6).[110] In batch, the nitration reaction showed two

Scheme 6. Ducry and Roberge's Nitration of Phenol



Yield of mononitrate mixture increased from 55% to 75%.
Purity increased from 56% to 78%.
Polymeric byproducts reduced by a factor of 5.
Exotherms eliminated.

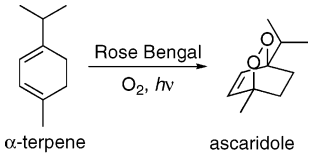
large exotherms which, despite the small scale (1 L), caused an increase of 55 °C in reaction temperature. The microreactor temperature, in contrast, increased by less than 5 °C after arriving at the bath temperature. This strict temperature control provided greater selectivity and higher yields. The yield increased from 55% in batch to 75% in flow. Notably, the purity also increased and the fraction of polymeric byproducts was reduced by a factor of 5.

Other exothermic or autocatalytic processes have also benefited from the controlled microreactor environment, including polmerizations[1,114−116] and elemental fluorinations (*vide infra*).[117−123]

3.3. Increased Safety

Besides offering careful control of exotherms, the small volumes used by microreactors enable the safe use of highly toxic or explosive reactants. Fluorination reactions, requiring F_2 addition and producing HF as a byproduct, are particularly well suited to microreactors because of their toxicity.[117] In addition, microreactors can provide safe containment to carry out singlet oxygen addition reactions, which are complicated by the necessity of high-intensity light exposure. These reactions are hazardous in batch because they require liters of toxic and potentially explosive organic solutions.[124] De Mello and co-workers have used a microreactor system for the addition of oxygen to α-terpene (Scheme 7), eliminating the need for presaturation of α-terpene with oxygen and increasing the yield of ascaridole by almost 20%.[124]

Scheme 7. de Mello's Ascaridole Synthesis



Yield of Ascaridole increased:
67% batch to 85% in microreactor

Microreactors allow diazomethane reactions and reactions of other highly reactive compounds, such as high-energy nitration reactions and diazo ring expansions, to be performed safely.[125−127] These reactions are now safer because of the small volumes and rapid reactions associated with micro-

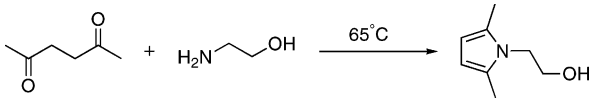
reactors. Previously unscalable and hazardous, this chemistry can be reduced to practice and be introduced into new synthetic pathways with microreactor technology. The reactors can then be "numbered up" to produce appropriate quantities of material.

3.4. Increased Efficiency

3.4.1. Decreased Inputs and Waste

As mentioned earlier, reactions run in microreactors typically provide higher yields and selectivity than batch reactions. They are also run at higher concentrations, accessible due to rapid heat transfer. With smaller volumes of solvents and byproducts per unit of product, microreactors create significantly less waste than reactions run in traditional reactors, especially as new *in situ* purification procedures are developed.[51,128,129] An excellent method for waste reduction is the use of neat conditions, often inaccessible in batch reactors because of exothermicity. Taghavi-Moghadam and co-workers have demonstrated an exothermic Paal−Knorr reaction in a Cytos microreactor under *solvent-free* conditions (Scheme 8).[51]

Scheme 8. Solvent-Free Paal−Knorr Reaction



3.4.2. Low-Volume Optimization Experiments

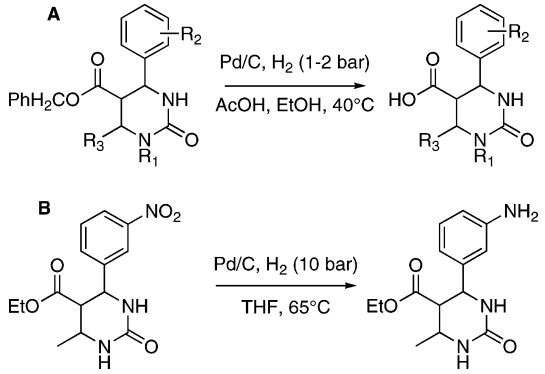
When surveying high-yielding, selective reactions, it is essential to consider the optimization that preceded the result. Like every reaction run in a batch reactor, every reaction run in flow requires adjustments to optimize yield and selectivity. Microreactors offer significant advantages for optimization because of the short reaction times and small volumes involved. Taghavi-Moghadam and co-workers demonstrated a selective Grignard reaction in flow (Scheme 3, section 3.1.3).[51] This reaction was optimized in 6 h using 14 different reactor conditions, transforming the reaction from 49% (65:35 ratio of A/B) to 78% yield (95:5 ratio of A/B). Optimization is an essential part of every step in the synthesis of fine chemicals and pharmaceutical agents. Any reduction of material input and waste makes the optimization experiments faster, less wasteful, and less costly.

Microreactors are also ideally suited to generating libraries of related compounds with minimal input and waste. Fernandez-Suarez and co-workers have demonstrated that, by varying the reactant inputs, a small collection of three cycloadducts could be generated from a single run on a microreactor.[130] Garcia-Edigo and co-workers have applied this technology to generate a larger 7 × 3 library of pyrazoles.[102] Pushing the technology further, Schwalbe and co-workers developed a library of Ciprofloxacin derivatives. This library differs from others in that each library member is taken through multiple microreactor-based transformations (Scheme 10, section 3.4.5).[131] A number of other libraries have been generated, including peptide-based libraries covered extensively by Watts.[54,132] De Bellefon and co-workers have demonstrated that microreactors can also serve as a venue for rapid catalyst screening[133] and for running low-volume, low-waste kinetic investigations.[109]

3.4.3. On-Line Reaction Monitoring

The rapid optimization associated with microreactors is made even more efficient when the effluent can be analyzed as the reaction or reaction series progresses. Product distribution can be constantly monitored for reactions being optimized or those already in production. One could of course monitor a large batch reaction to ensure product quality, but by the time unwanted impurities were generated, the whole reaction would already be contaminated. Constant monitoring of small flow reactions guarantees that no large reaction mixtures would have to be discarded as waste. A number of groups have used HPLC and electrophoresis for reactions that generate complex mixtures and that require separation after the reaction.[102,134] Kappe and co-workers used rapid HPLC feedback to adjust hydrogen pressures, temperatures, and reagent concentration to maximize yields in hydrogenations and hydrogenolysis reactions (Scheme 9).[135]

Scheme 9. Kappe's Hydrogenation and Hydrogenolysis



HPLC analysis can be relatively slow compared to many reactions in microreactors, and as a result, *in situ* UV/vis or IR analysis can provide a constant handle on product distribution as the reaction progresses. Jensen and co-workers have used online UV detection to determine conversion for a photochemical reaction as a function of flow rate. These results were later confirmed by HPLC analysis.[136]

3.4.4. No Scale-up Necessary

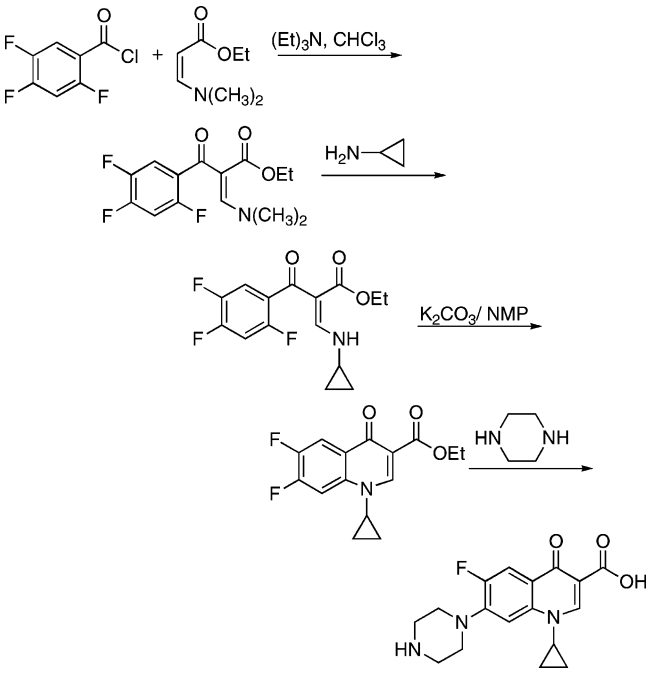
Because many of the properties of microreactors are unique to their micron-sized dimensions, scale-up is not possible. To increase production of a desired compound, multiple reactors can be used in parallel (numbering up), and more reactors can be brought on-line as needed to scale from grams to kilograms.[52,53] Unlike typical benchtop chemistry, microreactors have a modular design that enables mass production, as well as a small size that allows for multiple units to run in a small footprint.[53] Since material of consistent quality is obtained from one microreactor or many, time and cost savings can be realized because a reaction does not require additional optimization once it is moved onto production scale, as demonstrated with CPC Systems's pilot plant reactors.[51]

3.4.5. Introduction of Multiple Transformations with Continuous Flow

Microreactor reactions, similar to larger scale continuous processes, can be connected in series, so that a reactant undergoes many transformations prior to isolation. The development of continuous processing using microreactors is relatively recent. Haswell and co-workers have successfully

carried out two compatible steps of peptide generation in a single device, greatly reducing the waste.[54] The groups of Lectka[137−139] and Ley[140] have successfully carried out multistep syntheses using larger scale flow reactors. These systems, unlike many of the microreactor reactions discussed, use immobilized reagent columns and scavengers that require exchange once their contents are exhausted. Schwalbe and co-workers from CPC have developed a multistep microreactor synthesis of the antibacterial API Ciprofloxacin (Scheme 10).[131,141] This synthesis, which included five

Scheme 10. Schwalbe's Synthesis of Ciprofloxacin



microreactor transformations, required aqueous workups between all but the final two steps and has not yet been optimized for completely continuous synthesis. Even with the minimal workup used to eliminate salt byproducts, the synthesis required no chromatography and generated Ciprofloxacin in 57% overall yield with a purity exceeding 90%. This synthesis is another example of the high yields and selectivities associated with flow reactions and illustrates the promise for completely continuous microreactor syntheses of fine chemicals.

4. Survey of Organic Reactions in Microreactors

The use of microreactors for organic synthesis was only pioneered in the mid-1990s, but in the ensuing decade, it has burgeoned into a widely studied field in industrial and academic environments.[52] The following section reviews examples from some of the major classes of organic transformations carried out in microreactors. The first section details stoichiometric reactions, and the second details catalytic reactions in flow.

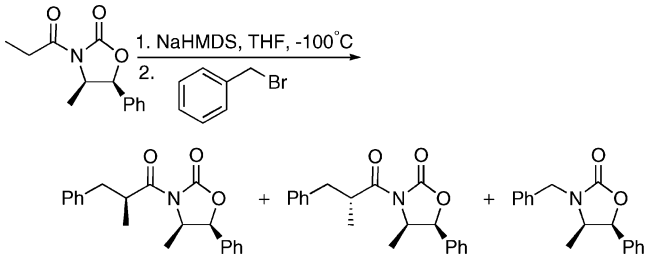
4.1. Stoichiometric Reactions

4.1.1. Carbon–Carbon Bond-Forming Reactions

Carbon−carbon bond-forming reactions allow complex skeletons to be built from relatively simple starting materials. Although useful, many C−C bond-forming reactions produce significant amounts of byproducts, making them excellent candidates for the carefully controlled conditions associated with microreactors. A number of common C−C bond-forming reactions have been demonstrated in flow, including Grignard reactions,[51,125,142] Wittig reactions,[85,143] addition of aryl and alkyl lithium salts,[85] Aldol reactions,[93] Claisen condensations,[144] Michael additions,[145] Diels−Alder and other cyclization reactions,[99] as well as alkylation of enolates.[146] Microreactors have also proven useful for the generation of carbon nucleophiles such as enolates,[85,147] enamines,[148] and Grignard reagents.[142]

Watts and co-workers have improved a tricky reaction involving alkylation (Scheme 11).[146] Under batch conditions,

Scheme 11. Alkylation of an Evans's Chiral Auxiliary



Flow: 41% Yield, 91:9 ratio of diastereomers, only starting material present
Batch: 31% Yield, 85:15 ratio of diastereomers, >10% byproduct
Raising the temperature in batch caused >50% byproduct formation.

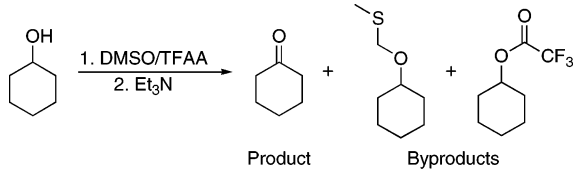
the enolate quickly decomposes. At −100 °C, there is still significant byproduct formation. The final yield under batch conditions is ∼31% with 10% byproduct formation and a ratio of 85:15 of diastereomers. By running this reaction in a microreactor without optimization, the diastereometric ratio improved to 91:9 and the yield improved to 41%. The most exciting part of this improved yield was that the remaining material was starting material, not byproduct, implying that the time for enolate formation was not sufficient. Since residence times are easily modified by changing the flow rate in a microreactor, it should be possible to optimize the yield.

4.1.2. Oxidations and Reductions

Redox transformations play an essential part in modern synthetic chemistry. This chemistry can also be significantly improved with the controlled temperatures and mixing associated with flow reactors. Schwalbe and co-workers have demonstrated improved yields with many common redox reactions, including sodium borohydride reductions, Dess-Martin oxidations, pyridine oxidations, Nef reactions, and others.[85,99] Other groups have demonstrated oxidation with singlet oxygen[124] and hydrogen peroxide.[149]

Oxidations, such as the Swern, Moffatt, and Corey−Kim reactions, are useful because they work with substrates that are sensitive to harsh metal oxidants and prevent overoxidation.[150] The drawback to these reactions is the cryogenic conditions, often lower than −70 °C, required to prevent Pummerer rearrangement from hindering their industrial utility.[96] Yoshida and co-workers have demonstrated that, by using a microreactor, high-yielding Swern oxidations can be run at −20 °C, 0°C, and room temperature (Scheme 12).[96] The authors deliver the reagents sequentially using four syringe pumps. The trifluoroacetic anhydride and DMSO are mixed first, and then the alcohol is introduced into the flow, followed by triethylamine addition. The sequential additions and a brief residence time of 10 ms prior to alcohol addition provided Swern products in 70−90% yield at each of the

Scheme 12. Yoshida's Swern Reaction in a Microreactor



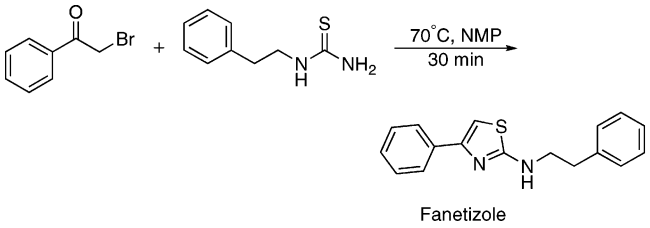
At -20 °C:
Microreactor yields 88% product
Batch yields 19% product, 72% rearrangement products

three temperatures, whereas batch reactions at −20 °C provided yields in the range of 10−50%. By eliminating the cryogenic conditions, this Swern oxidation is more suited to industrial syntheses with the added advantage of eliminating scale-up.

4.1.3. Heterocycle Formations

Since many bioactive natural products and pharmaceutical agents contain heterocycles, the ability to efficiently synthesize one heterocycle or a library of many heterocycles is incredibly valuable. A number of groups have pursued heterocyclization reactions in flow, generating pyrroles,[51,85] thiazoles,[103] lactams,[85] pyridones,[85] and pyrazoles.[102] Garcia-Egido and co-workers have demonstrated the formation of thiazoles using a Hantzsch reaction in a glass microreactor controlled by electroosmotic flow.[103] In this case, a variety of substrates were tested and the yield of the aminothiazole products was higher in the microreactor than that in a traditional batch reactor once the EOF voltage had been optimized. A known pharmaceutical agent, Fanetizole, was synthesized as a proof-of-concept reaction (Scheme 13).

Scheme 13. 2-Aminothiazole Synthesis in Microreactor



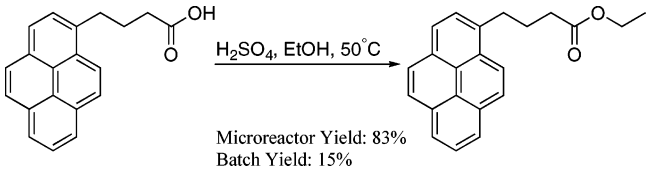
Garcia-Egido and co-workers followed their Hantzsch reaction study with the use of the Knorr reaction to generate a 21-member library of pyrazoles that had quantitative conversions for 16 out of 21 compounds.[102]

4.1.4. Carbon–Nitrogen and Carbon–Oxygen Bond-Forming Reactions

Amide and ester formation reactions are often high-yielding under traditional batch conditions and play an important part in the synthesis of many bioactive compounds. Despite high yields, these reactions still can require long reaction times and can benefit from the high concentrations, reduced waste, and increased reaction rates associated with microreactors.

Reinhoudt and co-workers have recently demonstrated dramatic improvements in yield and rate for the Fisher esterification of 9-pyrene butyric acid with ethanol (Scheme 14).[151] In this case, syringe pumps were used to control fluid movement in the borosilicate microreactor. The authors found that, by increasing the residence time to 40 min, the yield of the reaction was increased to 83%. Under identical

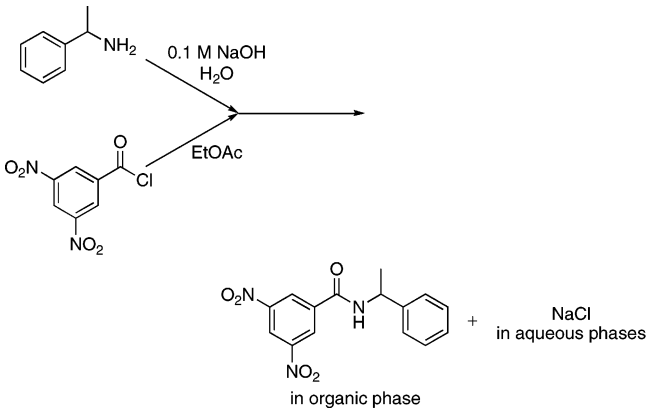
Scheme 14. Reinhoudt's Fisher Esterification



concentration conditions, the batch reactor, which included silica gel to simulate the glass walls of the microreactors, only went to 15% yield in 40 min. The authors concluded that the excess of SiOH groups present in the microreactor assist in the ethanol activation.

Amide formation reactions can also be run successfully in microreactors. Kitamori and co-workers synthesized four amides in parallel in their specially designed microreactor.[152] The authors used modified Schotten−Baumann conditions in which the amine was combined with the aqueous phase in the presence of NaOH and an organic phase containing the acid chloride (Scheme 15). The biphasic nature of the

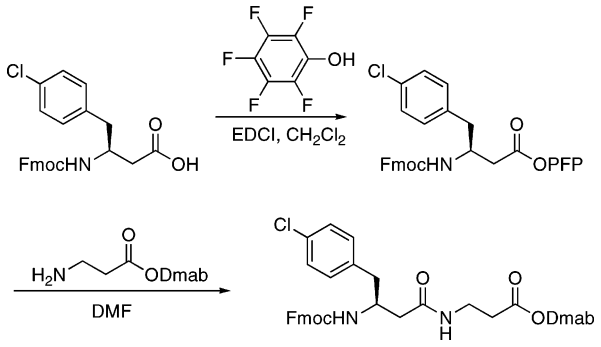
Scheme 15. Kitamori's Schotten−Baumann Reaction in a Microreactor



reaction effectively separated the unreacted amine and salt byproduct from the amide in the microreactor effluent. By adding multiple inlets and a second plate for stream splitting to their microreactor, the authors simultaneously added two different amine solutions and two different acid chloride solutions, generating a total of four products in parallel with a single microreactor chip. The four amides were made in 82−93% yields when run in parallel or 83−98% yields when the reactions were separated.

There have been a number of studies specifically focused on the synthesis of short oligopeptides in flow as an alternative to solid-phase synthesis. The stepwise generation of oligos was greatly simplified with the development of Merrifield resin and iterative solid-phase synthesis. Solid-phase synthesis is incredibly powerful but somewhat impractical on larger scale due to the cost of the resins and the additional steps to first link an amino acid to the resin and to cleave the final product.[153] Haswell and co-workers have designed a single microreactor capable of sequentially adding reagents to carry out multiple steps of peptide synthesis (Scheme 16).[54,153,154] Besides eliminating the need for resin, the amount of reagents required for each step is drastically reduced while high conversions are maintained. An example is the FMOC deprotection that can be carried out with a single equivalent of base, rather than the usual excess, when run in the microreactor.

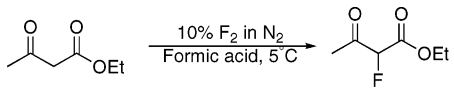
Scheme 16. Haswell's Peptide Synthesis in Flow



4.1.5. Fluorinations

Elemental fluorinations typically cannot be run on large scale because of their exothermicity, potential for explosion, and lack of selectivity.[122] Chambers and co-workers were among the first to demonstrate direct fluorination in microreactors, carrying out the controlled fluorination and perfluorination of β-dicarbonyl compounds (Scheme 17) and

Scheme 17. Chambers's Fluorination of β-Dicarbonyl Compounds



99% Conversion, 73% Yield

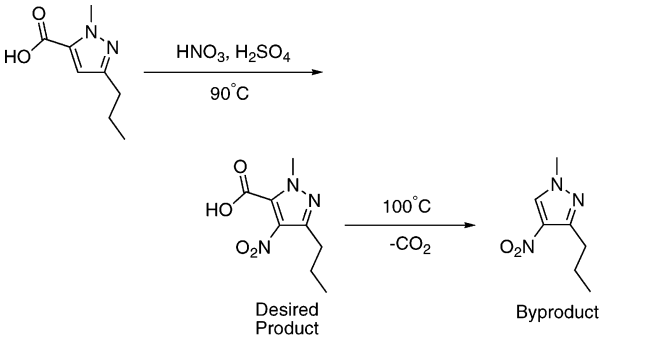
sulfides.[117] In this example, the fluids were driven through a nickel microreactor using a syringe pump and F_2 was brought in with a stream of N_2. This system, with channels of $\sim$500 μm, provided cylindrical flow, with the solution coating the channel walls and the gas traveling in the center, giving a high surface area for fluorine exposure. The high surface area allowed for short residence times and high throughput. The microreactor also minimized the volumes of F_2 and HF, making the reactor safer to operate. Chambers and co-workers have extended their work to include a number of other substrates.[118−120,155]

Aromatic substrates are particularly difficult to fluorinate. In industry they are generated using the Scheimann process, which first involves conversion of an aryl amine to diazonium tetrafluoroborate salts and then subsequent thermal decomposition to the monofluoro aromatic species.[122] Hessel, Jahnisch, and co-workers have been able to use microreactor-based fluorination to synthesize fluorinated toluene directly.[122]

4.1.6. Nitration Reactions

Nitration reactions, similar to fluorinations, are typically limited on large scale by their extreme exothermicity and potential for explosion (see section 3.2).[110] Despite this exothermicity, nitration reactions are essential for the synthesis of pharmaceutical intermediates such as the pyrazole carboxylic acid precursor to sildenafil citrate (Viagra).[113] In the sildenafil synthesis, the exothermic nitration is further complicated by a degradation pathway that becomes accessible above 100 °C. The decomposition involves the loss of CO_2, that both releases heat and causes pressure to build in the reactor. In order to safely run this reaction on scale, the nitrating agent is added over 2 h followed by 8 h of reaction time at 50 °C, to give the product in a 96% yield. When run in a microreactor under unoptimized conditions, Taghavi-Moghadam and co-workers could run the same nitration with a yield of 73% in only 35 min with a throughput of 5.5 g/h from a single reactor (Scheme 18).[113] By running the reaction

Scheme 18. Nitration of Sildenafil Citrate Precursor



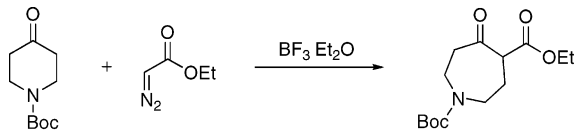
73% Yield in Microreactor, 35 minutes retention, 5.5 g/hour
75% Yield in Batch, 10 hours

in a microreactor, excess heat was quickly dissipated, allowing the reaction temperature to be carefully maintained at 90 °C, which provided a rapid rate without degradation. The small volumes also limited the hazards presented by the highly acidic conditions and CO_2 generation, should the reaction become overheated.

4.1.7. Reactions with Diazo Reagents

Reactions with diazo reagents, similar to nitrations and fluorinations, are typically highly exothermic, and in some cases, they can release significant quantities of N_2 gas, creating hazardous conditions.[125] Zhang and co-workers recently applied microreactor technology to improve the yield and safety of a diazo ring expansion reaction (Scheme 19).[125]

Scheme 19. Zhang's Diazo-Ring Expansion Reaction



89% Yield, 1.8 minute residence time
91 g/hour throughput

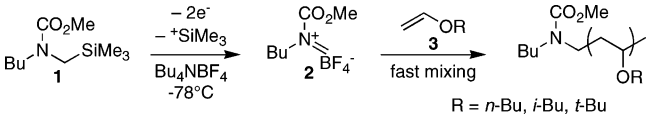
Although the reaction of *N*-Boc-4-piperidone with ethyl diazoacetate proceeded to 90% yield at −25 °C in batch, the reaction was limited to small scale because temperature increases of up to 45 °C occurred with addition of the diazo species and because the evolution of N_2 caused overpressurization of the reactor. As a result, the authors used a microreactor in which it was hoped that rapid heat transfer and small volumes would prevent hazards as well as byproduct formation. The ring expansion was found to run to 89% yield in 1.8 min in the microreactor with a total throughput of 91 g/h.

4.1.8. Polymerizations

Cationic, ring opening, and free-radical polymerization are three polymerization mechanisms that have benefited from the rapid mixing and precise temperature control found in microreactors. Yoshida and co-workers showed that microreactors could improve the yield of polymerizations. By using the cation-pool-initiated polymerization, a reactive initiator,

N-methoxycarbonyl-*N*-(trimethylsilylmethyl)butylamine (**1**), decomposed to cation **2** that was irreversibly formed and collected (Scheme 20). Using a multilamellar IMM micro-

Scheme 20. Cation-Pool-Initiated Polymerization



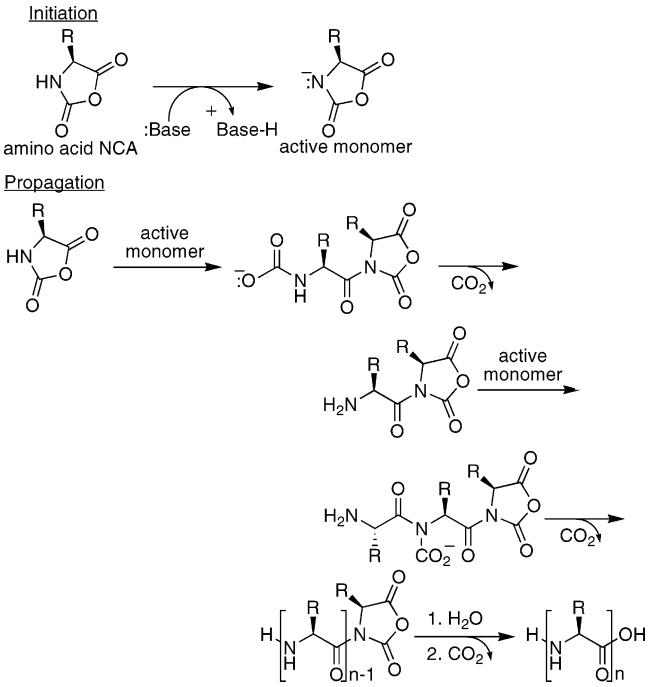
reactor, which effected mixing within 0.5 s, the addition of a vinyl ether to cation **2** resulted in a cationic polymerization that provided narrow PDIs (1.14−1.40) relative to the case for a batch process (2.25−2.56).[156] The authors demonstrated that, by adjusting flow rates, rapid mixing of initiator and monomer controlled PDI. Mixing in multilamellar microreactors increased with flow rate, and as the flow rates were lowered, the resulting polymers exhibited broadened PDIs. Thus, more efficient mixing at high flow rates yielded the narrowest PDIs.

Yoshida and co-workers went on to show that microreactors are also useful in radical polymerization, generally yielding lower PDIs than those observed in batch reactions.[114] The authors compared the free-radical polymerizations of various acrylates (butyl acrylate, benzyl methacrylate, and methyl methacrylate) and vinyl monomers (vinyl benzoate and styrene) in tubular, stainless steel microchannels. They found that the more highly exothermic polymerizations showed the most improvement in polydispersity relative to the corresponding batch reactions. On the other hand, the less exothermic polymerizations showed little improvement in PDI when run in the microreactor. The authors concluded that the microreactor's ability to transfer heat more efficiently than the batch reactor resulted in fine control of the polymerization exotherms and, thus, PDI.

Not all radical reactions in flow provide significant improvements in polydispersity. Jones and Schork,[157,158] using reversible addition−fragmentation chain-transfer polymerization (RAFT), and Cunningham,[159] using nitroxide-mediated polymerizations (NMPs), observed the same or higher PDIs in tubular reactions as with batch reactors. These investigations found similar reaction kinetics in batch and microreactor systems, which both retained the living natures of the RAFT and NMP polymerizations. However, in both of these cases, reagent mixing was performed prior to introduction into the microreactor, and the reactions were performed in microemulsions flowed through the microreactors. Thus, the advantage of rapid, homogeneous mixing inherent to microreactors was forfeited. Jones and Schork suggested that the PDI erosion found in their microreactor system was due to axial dispersion of the reaction plugs and thus a distribution of residence times. As larger tubing was used, the plugs became larger, and the PDIs approached the batch values. This result is consistent with axial dispersion of plug velocity causing increased PDIs.

Miyazaki and Maeda showed that the benefits of microreactors are not limited to cationic and radical polymerizations by creating homo-polymers of N^{ϵ}-benzyloxycarbonyl-L-lysine, alanine, leucine, or glutamic acid (NCA).[160] Reactions were run in batch and microreactors by combining NCA and triethylamine to initiate the polymerization (Scheme 21). Instead of using an IMM microreactor, a PDMS multilayered system was used.[161] In all cases, the microreactor provided slightly higher molecular weights and much better PDIs. Again, the NCA polymerization was strongly affected by

Scheme 21. Miyazaki and Maeda's NCA Polymerization



mixing and potentially by temperature control, though no experiments directly tested this hypothesis. The authors noted that their device could produce ~15 g/day.

Beers and co-workers showed that microreactors are useful for systematically varying the molecular weight of both homopolymers and block copolymers. They developed microfluidic methods to carry out controlled radical polymerizations in which variables such as monomer ratios or monomer/initiator ratios were altered to produce gradients of molecular weights or monomer ratios in copolymers.[162] The homopolymer synthesis was achieved using a two-channel microreactor with the two channels meeting in a reservoir containing a magnetic flea stir bar for active mixing. The mixing chamber emptied into a much longer microchannel reactor. One inlet channel contained the monomer and catalyst, and the other contained the initiator. Both were dissolved in 50:50 water/methanol. Initiator/monomer ratios were varied by changing relative concentrations, and the polymerization at a fixed initiator/monomer ratio was then monitored as a function of flow rate. The authors observed

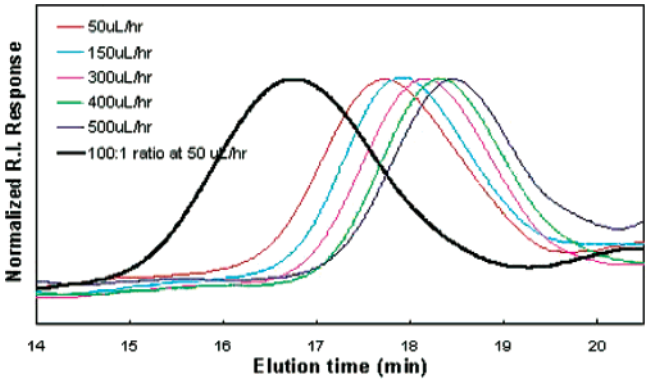


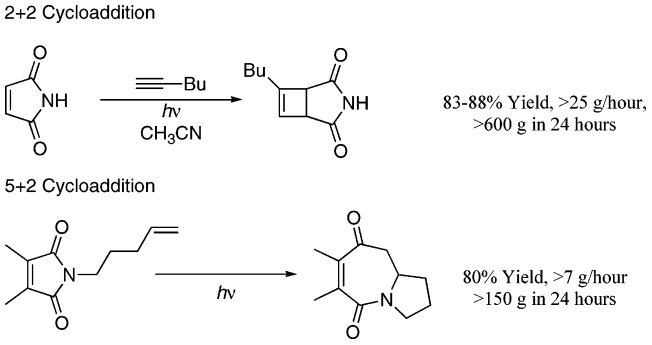
Figure 8. Size-exclusion chromatograms of polymers synthesized in the microfluidic device at various flow rates. Increasing flow rates resulted in shorter residence times and lower molecular weight polymers (thin lines). Molecular weight was further tunable by decreasing the amount of initiator (thick line). Reprinted with permission from ref 162. Copyright 2004 American Chemical Society.

that the molecular weight decreased as a function of flow rate, which is inversely proportional to residence time (Figure 8). The PDIs under all conditions were quite good, ranging from 1.19 to 1.32. Using a similar approach with three channels instead of two, Beers and co-workers[163] created poly(ethylene oxide)-*b*-poly(2-hydroxypropylmethacrylate) on a chip with excellent control over conversion, PDI, and block ratios.

4.1.9. Photochemical Reactions

Photochemical reactions can produce extremely complex organic molecules from simple starting materials, in many cases without catalysts or additional reagents.[164] When run in the laboratory, the lamp is typically submerged directly into a cooled reaction mixture. This design, although efficient on small scales, limits scaling up because the lamps are limited in size and heat and mass transfer become more difficult as the reaction is scaled.[136] A few photochemical reactions have been successfully transferred to production, including Vitamin D synthesis and caprolactam synthesis for nylon production, but flow reactors may make large-scale photochemical synthesis more general.[164] A number of photochemical reactions have been demonstrated in flow, including formation of singlet oxygen (see section 3.3),[124,165] photocyanation reactions,[166] cycloadditions,[167] cyclizations,[164,168] and dimerization reactions.[136] Berry, Booker-Milburn, and co-workers have recently demonstrated [5 + 2] and [2 + 2] cycloadditions in a flow reactor with outputs of more than 100 g of product in 24 h (Scheme 22).[164]

Scheme 22. High-Throughput Photochemistry in a Flow Reactor



Interestingly, instead of using a transparent device with a light source over the reactor (similar to de Mello's singlet oxygen formation), the authors wrapped the tubing that composed their device around a traditional photochemistry lamp in a cooling jacket (Figure 9).

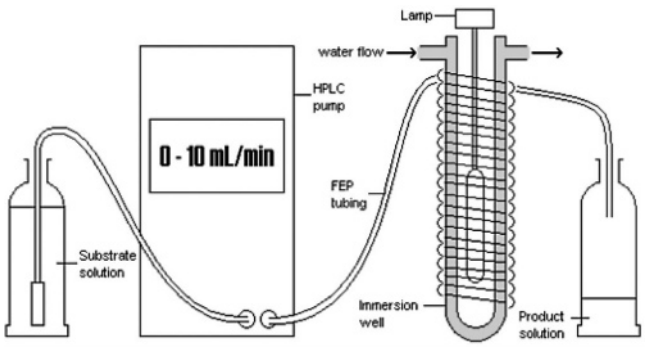
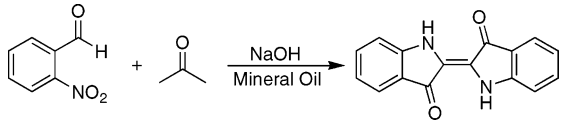


Figure 9. Schematic of Berry and Booker-Milburn's FEP Continuous Flow Reactor. Reprinted with permission from ref 164. Copyright 2005 American Chemical Society.

4.1.10. Precipitate-Forming Reactions

One drawback to using microreactors for chemical synthesis is that solid-forming reactions can clog the small reactor channels.[169] Our group recently offered a solution to this problem by running reactions in relatively large diameter (1.59 mm) PVC tubing, where reagents were introduced into the channels by blunt-end needles (0.15 mm i.d.) controlled by syringe pumps.[57] We found that this setup replicated the flow phenomena of small diameter reactors. With the larger diameter channels, precipitate-forming reactions could be carried out without clogging or building back-pressure.[58] The synthesis of indigo in mineral oil, for example, did not clog the reactor and also failed to contact the channel walls (Scheme 23).

Scheme 23. Synthesis of Indigo in Flow



4.1.11. Electrosyntheses

The geometries of microreactors lend themselves to performing electrochemistry on organic molecules in flow. Specifically, the inherently small channels in microreactors allow for relatively short distances between the cathode and anode, thus decreasing the energy requirements for performing redox chemistry. Also, the high surface area-to-volume ratio of the channels naturally creates high-surface-area electrodes. Such reactions in batch reactors have traditionally required supporting electrolytes,[170,171] although recent advances have been made with "self-supported", or electrolyte-free, systems.[172−176] Because there is already a recent and excellent review of electrolysis reactions in microreactors by Marken and co-workers, this subject will not be reviewed.[177]

4.2. Catalytic Reactions

4.2.1. Methods for Including Catalysts in Microreactor Syntheses

There are generally two ways to introduce catalysts into microreactors. One method is to dissolve a homogeneous catalyst directly into the reaction mixture; the other is to immobilize the catalyst on solid supports through which the reagents can flow. These two approaches have each been applied extensively, and each has unique advantages.

Flowing a soluble catalyst with the reaction mixture through microreactors offers the advantages that all reactions performed in microreactors enjoy. Like many stoichiometric reactions, running catalytic reactions in flow allows small-scale batch conditions to serve as a starting point for the first trials in flow. By using a microreactor, catalysts can be screened for activity and undergo mechanistic studies with minimal use of costly catalysts and ligands.[109,178] Once the catalyst's activity is determined, the catalyst can be applied in either microreactor or batch reactions as necessary.

The drawback to homogeneous catalysts, whether in microreactor or batch reactions, is the catalyst's cost and removal from the product. Since the catalysts are soluble, they cannot simply be filtered off, and they can therefore be

quite difficult to recycle. On the other hand, if catalysts are immobilized to an insoluble support in the reaction mixture, simple filtration removes the catalyst from the product, which introduces the possibility for catalyst recycling. Packing a tube with a supported catalyst and flowing the reaction mixture through it takes this idea a step further. In fact, such systems have been in use industrially for decades in the form of packed-bed reactors (PBRs), and much of the work with immobilized catalysts in microreactors is based on these. PBRs are commonly used in the bulk chemical industry and consist of a length of pipe loaded with solid or solid-supported catalysts through which a reactant may flow.[179] Typically, the catalyst or supported catalyst in a PBR is compressed into beads on the order of 1 cm in diameter and loaded into the reactor tubes.[23] Inorganic supports are often favored over polymeric supports because of increased strength and decreased solvent-dependent swelling.[180] When adapted to microreactors, the pipes are scaled to channels with dimensions of 10−1000 μm.[181] As a result, the catalyst particles must be appropriately scaled for the microreactor.[23] In the case of packed-bed microreactors, the catalyst is instantly (and constantly) recycled, and greater space−time yields are achieved relative to those for the batch mode. In addition, reactions performed in these reactors often achieve greater turnover numbers.

It is no surprise then that much of the engineering work with packed-bed microreactors involves such industrially significant reactions as the steam re-formation of methane over rhodium,[182] the cracking of alkanes over silica and alumina,[183] or the hydrogenation of cyclohexene over platinum,[184] for example. The bulk of this literature is concerned with the engineering aspects of microreactors and not the chemistry itself; therefore, discussion will be limited to processes involving the synthesis of fine chemicals only.

Typically, lightly cross-linked organic supports are inappropriate for use in microreactors because they clog the device, causing irreproducibility and high back-pressure.[180,185,186] This is unfortunate, since there is a great deal of precedent for catalysts bound to such polymeric supports as Merrifield resin.[187] It should be noted that researchers have attempted to find a way around this problem by simply increasing the diameter of the reactors (up to the centimeter scale),[106,188] adding inert and nonswelling media (such as sea sand) to the reactor channels, or using fluid-bed reactors, where supports are given more room to swell and are not pressurized as in a microreactor.[189] These solutions naturally limit the amount of catalyst that can be loaded into the reactors and nullify the advantages of working on smaller scale.

A method for packing a reactor with solid-supported catalyst similar to PBRs is through the use of monoliths. Generally, the term "monolith" refers to any single-body structure that contains repeating cells, channels, or pores to which a catalyst may be attached and through which a reaction mixture may flow.[190−193] As with fluid-bed reactors, monolithic reactions are typically carried out on a larger diameter size regime than is typical for microreactors, and so no specific systems demonstrating these methods will be discussed here.

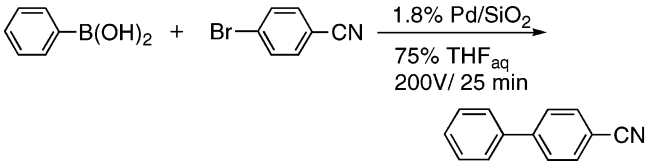
Finally, the catalyst can be packed not onto a solid support contained within the microreactor, but on the inner walls of the microreactor itself. This generally solves the issue of back-pressure build-up on the microreactor as the reaction mixture is forced through, but it necessarily reduces the surface area of the support and thus the amount of catalyst that can be loaded.

A number of catalytic reactions have been run in microreactors using soluble or supported catalysts. Reactions will be discussed by type.

4.2.2. Carbon–Carbon Bond-Forming Reactions

To increase catalyst turnover numbers and reduce loading, Haswell and co-workers have studied Suzuki coupling in packed-bed microreactors using electroosmotic flow (EOF)[100] and syringe-pump-driven flow reactors.[185] They showed that for the EOF device it was possible to catalyze the coupling of phenylboronic acid and 4-bromobenzonitrile at room temperature, using 1.8% palladium on silica gel as a catalyst, with no base (Scheme 24).[100] The palladium on silica was

Scheme 24. Haswell's Suzuki Reaction in Flow

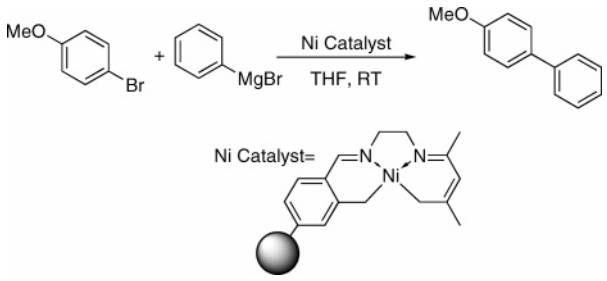


immobilized between microporous silicate frits within the device. The Suzuki reaction reached 68% conversion in the microreactor, a significant increase relative to the batch reaction (10% yield, excess base added). The authors hypothesized that the water, under high voltage, generated free hydroxide ions about the palladium metal surface, alleviating the typical requirement for excess base when the reaction was run in flow. Notably, the product generated with the microreactor showed very low Pd content (1.2−1.6 ppb), indicating that the Pd remained within the microreactor.

Recently, Haswell's group developed a more general method for running Suzuki reactions in microreactors using syringe-pump-driven flow.[185] In this case, Pd on alumina served as the catalyst. To effectively heat the reaction, the authors chose to use microwave (MW) irradiation and implanted a thin gold patch directly over the packed channel. In this case, the gold served to absorb the MW radiation and heat the interior of the channel to approximately 100 °C. Even though the gold patch showed degradation after extended MW exposure, the reaction achieved 58−99% conversion with catalyst and heat exposures of only 60 s. The authors found that 4% Pd anchored on polystyrene beads was also effective, giving similar conversions and providing more practical filling.

Haswell, Styring, and co-workers have also successfully demonstrated Kumada−Corriu coupling reactions in microreactors (Scheme 25).[180,194] The reaction is similar to the Suzuki coupling in that it also formed a biphenyl linkage, but it relied on a Grignard reagent in place of the boronic

Scheme 25. Haswell and Styring's Kumada−Corriu Reaction



acid. The authors chose to investigate the coupling of 4-bromoanisole with phenyl magnesium bromide in the presence of a nickel(II) salen catalyst in a packed-bed reactor with a diameter of 1−2 mm. Both silica gel and Merrifield resin supports were tested for this catalyst.

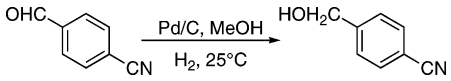
Although rate enhancements for the packed-bed microreactor compared to the traditional batch reactor were achieved with Merrifield resin, solvent-induced swelling of the resin caused an unacceptable pressure drop in the microreactor, for which the only solution was to include less catalyst in the system, which limited conversion to product. A solution was sought by immobilizing the catalyst onto silica, which did not swell and exhibited more robust mechanical properties than the polymeric resin. Although this system worked reasonably well, it was found that salt build-up on the silica surface gradually deactivated the catalyst. In this way, the best catalyst may have to be compromised to be appropriate for the given microreactor system.

Nontraditional solvents have also been used for palladium-catalyzed coupling reactions. For example, Ryu and co-workers have used low-viscosity ionic liquids in microflow to carry out Sonogashira and Mizoroki−Heck reactions in high yields.[195,196]

4.2.3. Catalytic Oxidations and Reductions

Hydrogenation reactions and related hydrogenolysis represent another major class of catalysis in microreactors. For traditional hydrogenations, heterogeneous catalysts are frequently used, making packed-bed reactors an obvious choice for hydrogenations in flow, as has been successfully illustrated by a number of groups.[135,197] Sato and co-workers have applied a 1 mm tube reactor packed with palladium on carbon (5 wt %) to the continuous hydrogenation of 4-cyanobenzaldehyde in methanol (Scheme 26).[197] Since this

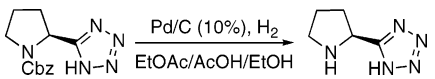
Scheme 26. Aldehyde Reduction in a Microreactor



reaction required hydrogen gas, the authors cited the added safety of using a series of small pressurized tubes (in this case, 6.3 mm × 1.0 mm) rather than one large pressurized autoclave. At 25 °C, the flow reactor yielded 72% of the product, improving over the batch yield of 51%. The same microreactor, when heated to 90 °C could reduce the nitrile to the corresponding amine in 71% yield in less than 2 min. The drawback to this highly active hydrogenation catalyst was the prevalence of byproducts; at both temperatures the ∼30% of nonproduct material was over-reduced and could not be recycled.

Hydrogenolysis reactions, often using the same heterogeneous catalysts used in hydrogenations, have similarly been carried out with packed-bed microreactors.[135,198] Ley and co-workers successfully used a Pd/C packed-bed microreactor to carry out the hydrogenolysis of the benzyl carbamate (Cbz) protecting group on the proline-based organocatalyst, (s)-pyrrolidin-2-yl-1H-tetrazole (Scheme 27).[198] This

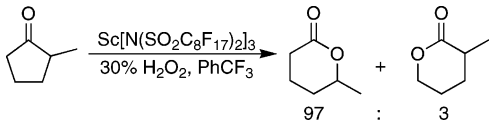
Scheme 27. Ley's Synthesis of (s)-Pyrrolidin-2-yl-1H-tetrazole



reaction, which took 3 days to reach completion in batch, could be taken to 98% conversion in only 3.5 h using the microreactor.

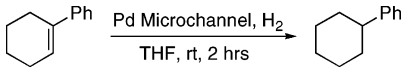
A notable example of an oxidation performed in microreactors is the Baeyer−Villiger reaction catalyzed by scandium bis(perfluorooctanesulfonyl)amide.[199] Mikami and co-workers showed that they could achieve higher yields and regioselectivities than were possible in the analogous batch reactions. For example, the oxidation of 2-methylcyclopentanone proceeded to essentially quantitative yield in the microreactor with a regioselectivity of 97:3, versus a yield of 53% and a regioselectivity of 67:33 in the traditional batch reactor (Scheme 28), even at 20 times the catalyst loading.

Scheme 28. Mikami's Baeyer−Villiger Oxidation in Flow



Kobayashi and co-workers have made headway in the area of reduction in flow. By using a Pd-catalyzed multiphase system, numerous substrates were hydrogenated in nearly quantitative yield.[200,201] The use of these microreactors is beneficial due to the lack of palladium contamination often associated with palladium-catalyzed reactions. No palladium leaching was detected, which enabled the microreactor to be reused several times. Although a small amount of product was generated over time, the system could easily be numbered up to achieve the desired output. Palladium was encapsulated in a glycidyl ether functionalized polystyrene matrix and immobilized on microchannel walls functionalized with (3-aminopropyl)triethoxysilane.[202] The substrate stream and hydrogen were consequently introduced into the microchannel, where the reaction occurred. The system successfully reduced a wide variety of substrates (mono-, bi-, and trisubstituted olefins and triple bonds) (Scheme 29), as well as deprotected benzyl ether and carbamate protecting groups, quantitatively within a matter of minutes.

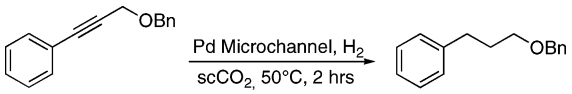
Scheme 29. Kobayashi's Olefin Reduction



The high yields were attributed to the small dimensions of the microreactor. Narrow channels enabled greater interaction between the solid, liquid, and gaseous states than in batch, increasing the reaction kinetics. Batch reactions were subsequently run on a number of substrates, reaching a maximum yield of only 11%.

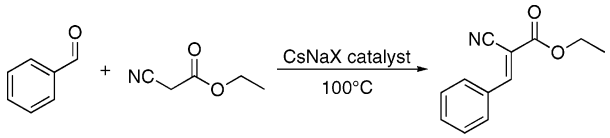
Kobayashi later optimized the system by use of supercritical carbon dioxide ($scCO_2$) as the solvent.[203] The use of $scCO_2$ ensured dissolution of all reagents, including hydrogen gas, resulting in reaction times of less than 1 s. In the triphasic system, the hydrogen stream passed through the middle of the channel and the substrate stream coated the walls. Reduced mass transport rates therefore increased the reaction times. The monophasic system had far fewer transport limitations, as the hydrogen and substrate were homogeneous, ensuring a maximum amount of interaction with the Pd-coated microchannel walls. Kobayashi showed the selective reduction of a triple bond in the presence of a benzyl ether protecting group (Scheme 30).

Scheme 30. Alkyne Reduction without Debenzylation



Zhang and co-workers performed a Knoevenagel condensation using a microreactor coated with a zeolite catalyst (Scheme 31).[204] This reaction, typically catalyzed by organic bases, was shown to be cleaner than normal methods since solid-phase catalysts precluded catalyst removal from product.

Scheme 31. Zhang's Use of Catalyst-Functionalized Zeolite Coatings



The zeolite catalyst was deposited onto the microchannels by use of ionic interactions. A layer of polydiallyldimethyl ammonium chloride (PDAMAC) was first coated on the microreactor. A solution of negatively charged zeolite particles was passed through the channel, which absorbed onto the positively charged PDAMAC.

These zeolite-coated microreactors catalyzed the Knoevenagel condensation between benzaldehyde and ethyl cyanoacetate in yields up to 80% (Scheme 31). Different zeolites afforded different conversions, the most active of which was functionalized with aminopropyl groups. Higher conversions were also obtained with the implementation of a hydrophilic membrane that was used to constantly remove water from the system. With the use of this membrane reactor, conversions improved up to 25%.

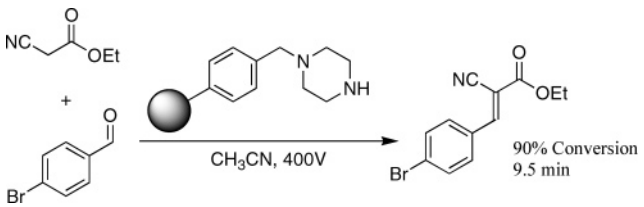
Nonetheless, Zhang determined that, due to larger catalyst loadings, higher yields could be achieved using a packed-bed microreactor. Zhang goes on to state, however, that the benefit of his system was the increased productivity, meaning less catalyst was required to produce a given number of moles of product per unit time.

4.2.4. Reactions Using Organocatalysts

While the majority of solid-supported catalysts used in packed-bed and wall-coated microreactors feature metal-catalyzed reactions, there are examples of organocatalysts that have been used in flow.

Watts and Nikbin have carried out a reaction similar to Zhang's using immobilized piperazine on silica. They used this solid-supported catalyst to perform the Knoevenagel reaction between ethyl cyanoacetate and 4-bromobenzaldehyde (Scheme 32).[186] The condensation was done in an 800 μm $\times$ 100 μm catalyst channel in borosilicate glass, where the reaction was driven by electroosmotic flow. The authors first attempted the reaction using piperazine loaded on

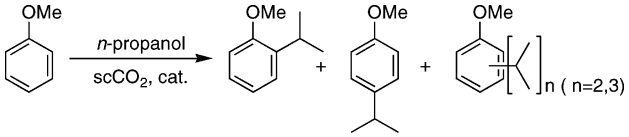
Scheme 32. Knoevenagel Reaction Catalyzed by Solid-Supported Piperizine



Merrifield resin, Tentagel, and Argopore, but they found that these organic supports swelled in the reaction channel, causing irreproducible flow rates and conversions. However, they found that using silica, a nonswelling support, solved these problems, and increasing the field strength applied to the reaction brought conversions to as high as 90%. Watts's group has gone on to generate several amine-based catalysts for performing the Knoevenagel reaction,[205] and Clark and co-workers have done similar work with amine-functionalized silica coatings on microreactor walls.[206]

Organic catalyst supports make a difference in reactivity even when the supports do not swell. Poliakoff and co-workers have carried out the Friedel–Crafts alkylation of anisole with various commercially available Brønsted solid acid catalysts (Amberlyst 15, Purolite CT-175, Nafion SAC-13, Deloxan ASP I/7, and Zeolyst CBV 600) in supercritical CO_2 (Scheme 33).[207,208] They found that the organic-based

Scheme 33. Friedel–Crafts Alkylation



supports (Amberlyst and Purolite) worked best within the temperature range 100–150 °C, but the inorganic supports (Nafion, Deloxan, and Zeolyst) performed better at higher temperatures. They also observed that the inorganic supports gave better yields at higher pressures (300–400 bar) but that the organic supports exhibited a pseudoconcentration effect, where yields were high at relatively low and high pressures but lessened at intermediate pressures.

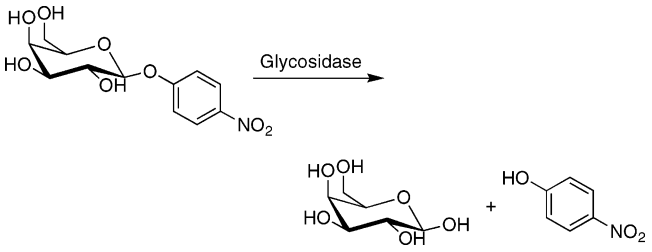
One may also use unsupported organocatalysts in flow. Although such catalysts would not be easily recycled, these reactions could still exploit the same advantages that all microreactor systems have, such as efficient mixing and rapid optimization. Seeberger and co-workers, for instance, have designed 50–100 μm diameter reactors that could withstand pressures of up to 100 bar and have used them to run such reactions such as DMAP-catalyzed acylations, DBFD-catalyzed Diels–Alder reactions, and the TBD-catalyzed Henry reaction, among others.[209] Although yields for most of the reactions performed were not significantly better than those in batch, the authors note the time-saving potential for microreactors, estimating that they were able to run 59 different reactions in about half the time it takes to run the reactions in batch.

4.2.5. Enzymatic Reactions in Microreactors

A number of researchers have used enzymes, immobilized and in free solution, in microreactors. Typically, enzymes are applied to microreactor technology for the purposes of protein mapping, enzyme kinetics studies, or proof-of-principle biotransformations (for example, degradation of *p*-chlorophenol[210] or conversion of urea to ammonia[211]). These systems will not be reviewed here because they do not involve the generation of synthetically useful small organic molecules and because they have been thoroughly reviewed elsewhere.[212] A short discussion of enzymatic catalysis in microchannels may be useful, however. For example, Kanno and co-workers have shown that an enzyme-catalyzed reaction performed homogeneously in flow can yield higher conversions than those in the batch counterpart.[213] In this case, a solution of β-galactosidase in pH 8

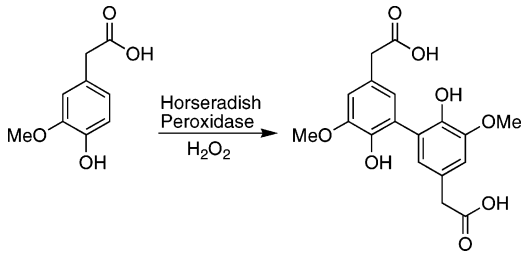
phosphate buffer was combined with a similarly buffered solution of *p*-nitrophenyl-β-D-galactopyranoside (PNPGal) in a 200 μm $\times$ 200 μm microreactor (Scheme 34). The authors were able to show that the hydrolysis in the microreactor was 5-fold faster than the analogous batch reaction, performed in a micro-test tube.

Scheme 34. Kanno's β-Galactosidase-Promoted Hydrolysis



Solid-supported enzymes for use in batch reactions are well-known,[214−216] and these have been applied to microreactor technology. Heule and co-workers have immobilized the relatively robust enzyme horseradish peroxidase onto crystals of aldehyde-functionalized alumina.[217] Loading this catalyst into a microchannel, they performed the oxidation of homovanillic acid (Scheme 35). Since achieving efficient mixing appeared to be a problem in the microreactor, they found that adding alumina "microstruts", essentially porous baffles that effect mixing, increased conversions by 300−500%.

Scheme 35. Enzymatic Oxidation of Homovanillic Acid



5. Conclusions and Outlook

The burgeoning field of microreactor technology can have a significant impact when applied to organic synthesis, not only for industrial chemists but also for the bench chemist designing new methodologies. The advantages inherent to microreactors—increased safety, decreased inputs and waste, the potential for catalyst recycling, and the opportunity for low-volume optimization—make them ideal for doing more environmentally benign chemistry. Moreover, the increased control over reactions in microreactors, in the form of thermal stability and mixing control, means that new reactions can be made more reproducible from inception, and may offer better regioselectivity and chemical selectivity than traditional batch synthesis.

All of the reactions surveyed here have been single-step reactions, but we see no reason why microreactors cannot be coupled to generate true multistep syntheses, wherein relatively simple starting materials can be fed into a series of microreactors, and relatively complex and synthetically difficult products result.[139] However, the microreactor community, comprised of chemists and engineers, must confront many issues before this can happen, including catalyst deactivation and incompatibility with reagents and intermediates, back-pressures developed in flow, and the removal or elimination of unwanted side products.

6. Acknowledgment

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7. References

(1) Ehrfeld, W.; Hessel, V.; Lowe, H. *Microreactors*; Wiley-VCH: Weinheim, 2000.
(2) Roberge, D. M.; Ducry, L.; Bieler, N.; Cretton, P.; Zimmermann, B. *Chem. Eng. Technol.* **2005**, *28*, 318.
(3) Anastas, P. T.; Kirchhoff, M. M. *Acc. Chem. Res.* **2002**, *35*, 686.
(4) Dunn, P. J.; Galvin, S.; Hettenbach, K. *Green Chem.* **2004**, *6*, 43.
(5) Andraos, J. *Org. Process Res. Dev.* **2005**, *9*, 519.
(6) Denmark, S. E.; Jacobsen, E. N. *Acc. Chem. Res.* **2000**, *33*, 324.
(7) Domling, A. *Chem. Rev.* **2006**, *106*, 17.
(8) Broadwater, S. J.; Roth, S. L.; Price, K. E.; Kobaslija, M.; McQuade, D. T. *Org. Biomol. Chem.* **2005**, *3*, 2899.
(9) Andraos, J. *Org. Process Res. Dev.* **2005**, *9*, 404.
(10) Trost, B. M. *Science* **1991**, *254*, 1471.
(11) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259.
(12) Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, 695.
(13) Sheldon, R. A. *Pure Appl. Chem.* **2000**, *72*, 1233.
(14) Sheldon, R. A. *Green Chem.* **2005**, *7*, 267.
(15) Constable, D. J. C.; Curzons, A. D.; Cunningham, V. L. *Green Chem.* **2002**, *4*, 521.
(16) Curzons, A. D.; Constable, D. J. C.; Mortimer, D. N.; Cunningham, V. L. *Green Chem.* **2001**, *3*, 1.
(17) Borman, S. *Chem. Eng. News* **2001**, *79*, 5.
(18) Jacobsen, E. N. *Acc. Chem. Res.* **2000**, *33*, 421.
(19) Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345.
(20) Fu, G. C. *Acc. Chem. Res.* **2004**, *37*, 542.
(21) Denmark, S. E.; Stavenger, R. A. *Acc. Chem. Res.* **2000**, *33*, 432.
(22) Notz, W.; Tanaka, F.; Barbas, C. F. *Acc. Chem. Res.* **2004**, *37*, 580.
(23) Wittcoff, H. A.; Reuben, B. G.; Plotkin, J. S. *Industrial Organic Chemicals*, 2nd ed.; Wiley-Interscience: Hoboken, NJ, 2004; p 662.
(24) Song, C. E.; Lee, S. G. *Chem. Rev.* **2002**, *102*, 3495.
(25) Duchateau, R. *Chem. Rev.* **2002**, *102*, 3525.
(26) De Vos, D. E.; Dams, M.; Sels, B. F.; Jacobs, P. A. *Chem. Rev.* **2002**, *102*, 3615.
(27) Dickerson, T. J.; Reed, N. N.; Janda, K. D. *Chem. Rev.* **2002**, *102*, 3325.
(28) McNamara, C. A.; Dixon, M. J.; Bradley, M. *Chem. Rev.* **2002**, *102*, 3275.
(29) Barrett, A. G. M.; Hopkins, B. T.; Kobberling, J. *Chem. Rev.* **2002**, *102*, 3301.
(30) Benaglia, M.; Puglisi, A.; Cozzi, F. *Chem. Rev.* **2003**, *103*, 3401.
(31) Leadbeater, N. E.; Marco, M. *Chem. Rev.* **2002**, *102*, 3217.
(32) Ley, S. V.; Baxendale, I. R.; Bream, R. N.; Jackson, P. S.; Leach, A. G.; Longbottom, D. A.; Nesi, M.; Scott, J. S.; Storer, R. I.; Taylor, S. J. *J. Chem. Soc., Perkin Trans.* **2000**, *1*, 3815.
(33) Kobayashi, S.; Akiyama, R. *Chem. Commun.* **2003**, 449.
(34) Price, K. E.; Mason, B. P.; Bogdan, A. R.; Broadwater, S. J.; Steinbacher, J. L.; McQuade, D. T. *J. Am. Chem. Soc.* **2006**, *128*, 10376−10377.
(35) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115.
(36) Wasilke, J. C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001.
(37) Lee, J. M.; Na, Y.; Han, H.; Chang, S. *Chem. Soc. Rev.* **2004**, *33*, 302.
(38) Sarussi, L.; Blum, J.; Avnir, D. *J. Sol-Gel Sci. Technol.* **2000**, *19*, 17.
(39) Blum, J.; Gelman, F.; Abu-Reziq, R.; Miloslavski, I.; Schumann, H.; Avnir, D. *Polyhedron* **2000**, *19*, 509.
(40) Gelman, F.; Blum, J.; Avnir, D. *Angew. Chem., Int. Ed.* **2001**, *40*, 3647.
(41) Gelman, F.; Blum, J.; Avnir, D. *J. Am. Chem. Soc.* **2002**, *124*, 14460.
(42) Gelman, F.; Blum, J.; Schumann, H.; Avnir, D. *J. Sol-Gel Sci. Technol.* **2003**, *26*, 43.
(43) Gelman, F.; Blum, J.; Avnir, D. *New J. Chem.* **2003**, *27*, 205.
(44) Helms, B.; Guillaudeu, S. J.; Xie, Y.; McMurdo, M.; Hawker, C. J.; Frechet, J. M. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6384.
(45) Motokura, K.; Fujita, N.; Mori, K.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *J. Am. Chem. Soc.* **2005**, *127*, 9674.
(46) Phan, N. T. S.; Gill, C. S.; Nguyen, J. V.; Zhang, Z. J.; Jones, C. W. *Angew. Chem., Int. Ed.* **2006**, *45*, 2209.

(47) Laird, T. *Org. Process Res. Dev.* **2001**, *5*, 612.
(48) Anderson, N. G. *Org. Process Res. Dev.* **2001**, *5*, 613.
(49) Spear, M. *Chem. Ind.* **2006**, 16.
(50) Stankiewicz, A. I.; Moulijn, J. A. *Chem. Eng. Prog.* **2000**, *96*, 22.
(51) Taghavi-Moghadam, S.; Kleemann, A.; Golbig, K. G. *Org. Process Res. Dev.* **2001**, *5*, 652.
(52) Jahnisch, K.; Hessel, V.; Lowe, H.; Baerns, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 406.
(53) Pennemann, H.; Hessel, V.; Lowe, H. *Chem. Eng. Sci.* **2004**, *59*, 4789.
(54) Watts, P.; Haswell, S. J. *Chem. Soc. Rev.* **2005**, *34*, 235.
(55) Bayer, T.; Jenck, J.; Matlosz, M. *Chem. Eng. Technol.* **2005**, *28*, 431.
(56) Gritzner, G.; Kreysa, G. *J. Electroanal. Chem.* **1993**, *360*, 351.
(57) Quevedo, E.; Steinbacher, J.; McQuade, D. T. *J. Am. Chem. Soc.* **2005**, *127*, 10498.
(58) Poe, S. L.; Cummings, M. A.; Haaf, M. R.; McQuade, D. T. *Angew. Chem., Int. Ed.* **2006**, *45*, 1544.
(59) Hatakeyama, T.; Chen, D. L. L.; Ismagilov, R. F. *J. Am. Chem. Soc.* **2006**, *128*, 2518.
(60) Madou, M. *Fundamentals of Microfabrication*; CRC Press: Boca Raton, Fl, 1997.
(61) Kern, W.; Deckert, C. A. Chemical Etching. In *Thin Film Processes*; Vossen, J. L., Werner, K., Eds.; Academic Press: New York, 1978; pp 401.
(62) Jansen, H.; Gardeniers, H.; deBoer, M.; Elwenspoek, M.; Fluitman, J. *J. Micromech. Microeng.* **1996**, *6*, 14.
(63) Becker, H.; Gartner, C. *Electrophoresis* **2000**, *21*, 12.
(64) Becker, H.; Locascio, L. E. *Talanta* **2002**, *56*, 267.
(65) Ehrfeld, W.; Lehr, H. *Radiat. Phys. Chem.* **1995**, *45*, 349.
(66) McCormick, R. M.; Nelson, R. J.; Alonso-Amigo, M. G.; Benvegnu, J.; Hooper, H. H. *Anal. Chem.* **1997**, *69*, 2626.
(67) Martynova, L.; Locascio, L. E.; Gaitan, M.; Kramer, G. W.; Christensen, R. G.; MacCrehan, W. A. *Anal. Chem.* **1997**, *69*, 4783.
(68) McDonald, J. C.; Duffy, D. C.; Anderson, J. R.; Chiu, D. T.; Wu, H. K.; Schueller, O. J. A.; Whitesides, G. M. *Electrophoresis* **2000**, *21*, 27.
(69) Lee, J. N.; Park, C.; Whitesides, G. M. *Anal. Chem.* **2003**, *75*, 6544.
(70) Rolland, J. P.; Van Dam, R. M.; Schorzman, D. A.; Quake, S. R.; DeSimone, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 2322.
(71) Lorenz, H.; Despont, M.; Fahrni, N.; LaBianca, N.; Renaud, P.; Vettiger, P. *J. Micromech. Microeng.* **1997**, *7*, 121.
(72) Dietrich, T. R.; Freitag, A.; Scholz, R. *Chem. Eng. Technol.* **2005**, *28*, 477.
(73) Kussul, E.; Baidyk, T.; Ruiz-Huerta, L.; Caballero-Ruiz, A.; Velasco, G.; Kasatkina, L. *J. Micromech. Microeng.* **2002**, *12*, 795.
(74) Schubert, K.; Brandner, J.; Fichtner, M.; Linder, G.; Schygulla, U.; Wenka, A. *Microscale Thermophys. Eng.* **2001**, *5*, 17.
(75) Vasile, M. J.; Friedrich, C. R.; Kikkeri, B.; McElhannon, R. *Precis. Eng., J. Am. Soc. Precis. Eng.* **1996**, *19*, 180.
(76) Fredrickson, C. K.; Fan, Z. H. *Lab Chip* **2004**, *4*, 526.
(77) Jorgenson, J. W.; Lukacs, K. D. *Anal. Chem.* **1981**, *53*, 1298.
(78) Li, D. *Electrokinetics in Microfluidics*; Elsevier: Amsterdam, 2004; Vol. 2.
(79) Haswell, S. J.; Middleton, R. J.; O'Sullivan, B.; Skelton, V.; Watts, P.; Styring, P. *Chem. Commun.* **2001**, 391.
(80) Baldyga, J.; Pohorecki, R. *Chem. Eng. J.* **1995**, *58*, 183.
(81) Fountain, G. O.; Khakhar, D. V.; Ottino, J. M. *Science* **1998**, *281*, 683.
(82) Alvarez, M. M.; Zalc, J. M.; Shinbrot, T.; Arratia, P. E.; Muzzio, F. J. *AIChE J.* **2002**, *48*, 2135.
(83) Alvarez, M. M.; Arratia, P. E.; Muzzio, F. J. *Can. J. Chem. Eng.* **2002**, *80*, 546.
(84) Bilgen, B.; Chang-Mateu, I. M.; Barabino, G. A. *Biotechnol. Bioeng.* **2005**, *92*, 907.
(85) Schwalbe, T.; Autze, V.; Wille, G. *Chimia* **2002**, *56*, 636.
(86) Nagaki, A.; Togai, M.; Suga, S.; Aoki, N.; Mae, K.; Yoshida, J. *J. Am. Chem. Soc.* **2005**, *127*, 11666.
(87) Suga, S.; Nagaki, A.; Yoshida, J. *Chem. Commun.* **2003**, 354.
(88) Hessel, V.; Hofmann, C.; Lowe, H.; Meudt, A.; Scherer, S.; Schonfeld, F.; Werner, B. *Org. Process Res. Dev.* **2004**, *8*, 511.
(89) Bayer, T.; Himmler, K. *Chem. Eng. Technol.* **2005**, *28*, 285.
(90) Hessel, V.; Lowe, H.; Stange, T. *Lab Chip* **2002**, *2*, 14N.
(91) Schwalbe, T.; Autze, V.; Hohmann, M.; Stirner, W. *Org. Process Res. Dev.* **2004**, *8*, 440.
(92) Sue, K.; Murata, K.; Kimura, K.; Arai, K. *Green Chem.* **2003**, *5*, 659.
(93) Wiles, C.; Watts, P.; Haswell, S. J.; Pombo-Villar, E. *Lab Chip* **2001**, *1*, 100.
(94) Skelton, V.; Greenway, G. M.; Haswell, S. J.; Styring, P.; Morgan, D. O.; Warrington, B.; Wong, S. Y. F. *Analyst* **2001**, *126*, 7.
(95) Skelton, V.; Greenway, G. M.; Haswell, S. J.; Styring, P.; Morgan, D. O.; Warrington, B. H.; Wong, S. Y. F. *Analyst* **2001**, *126*, 11.
(96) Kawaguchi, T.; Miyata, H.; Ataka, K.; Mae, K.; Yoshida, J. *Angew. Chem., Int. Ed.* **2005**, *44*, 2413.
(97) Van Meenen, E.; Moonen, K.; Acke, D.; Stevens, C. V. *Arkivoc* **2006**, 31.
(98) Walter, S.; Malmberg, S.; Schmidt, B.; Liauw, M. A. *Chem. Eng. Res. Des.* **2005**, *83*, 1019.
(99) Cellular Process Chemistry Systems, www.cpc-net.com/reactions/.
(100) Greenway, G. M.; Haswell, S. J.; Morgan, D. O.; Skelton, V.; Styring, P. *Sens. Actuators, B* **2000**, *B63*, 153.
(101) Fletcher, P. D. I.; Haswell, S. J.; Pombo-Villar, E.; Warrington, B. H.; Watts, P.; Wong, S. Y. F.; Zhang, X. L. *Tetrahedron* **2002**, *58*, 4735.
(102) Garcia-Egido, E.; Spikmans, V.; Wong, S. Y. F.; Warrington, B. H. *Lab Chip* **2003**, *3*, 73.
(103) Garcia-Egido, E.; Wong, S. Y. F.; Warrington, B. H. *Lab Chip* **2002**, *2*, 31.
(104) CPC systems have many examples of different reaction types run in their Cytos system on their Web site listed in ref 64.
(105) Belder, D.; Ludwig, M.; Wang, L. W.; Reetz, M. T. *Angew. Chem., Int. Ed.* **2006**, *45*, 2463.
(106) Hodge, P.; Sung, D. W. L.; Stratford, P. W. *J. Chem. Soc., Perkin Trans.* **1999**, *1*, 2335.
(107) Mandoli, A.; Orlandi, S.; Pini, D.; Salvadori, P. *Tetrahedron: Asymmetry* **2004**, *15*, 3233.
(108) Sandee, A. J.; Petra, D. G. I.; Reek, J. N. H.; Kamer, P. C. J.; van Leeuwen, P. *Chem.—Eur. J.* **2001**, *7*, 1202.
(109) de Bellefon, C.; Pestre, N.; Lamouille, T.; Grenouillet, P.; Hessel, V. *Adv. Synth. Catal.* **2003**, *345*, 190.
(110) Ducry, L.; Roberge, D. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 7972.
(111) Doku, G. N.; Haswell, S. J.; McCreedy, T.; Greenway, G. M. *Analyst* **2001**, *126*, 14.
(112) Antes, J.; Boskovic, D.; Krause, H.; Loebbecke, S.; Lutz, N.; Tuercke, T.; Schweikert, W. *Chem. Eng. Res. Des.* **2003**, *81*, 760.
(113) Panke, G.; Schwalbe, T.; Stirner, W.; Taghavi-Moghadam, S.; Wille, G. *Synthesis* **2003**, 2827.
(114) Iwasaki, T.; Yoshida, J. *Macromolecules* **2005**, *38*, 1159.
(115) Hessel, V.; Sera, C.; Loewe, H.; Hadziioannou, G. *Chem. Ing. Tech.* **2005**, *77*, 1693.
(116) Steinbacher, J. L.; McQuade, D. T. *J. Polym. Sci.* **2006**, *44*, 6505—6533.
(117) Chambers, R. D.; Spink, R. C. H. *Chem. Commun.* **1999**, 883.
(118) Chambers, R. D.; Holling, D.; Spink, R. C. H.; Sandford, G. *Lab Chip* **2001**, *1*, 132.
(119) Chambers, R. D.; Fox, M. A.; Holling, D.; Nakano, T.; Okazoe, T.; Sandford, G. *Lab Chip* **2005**, *5*, 191.
(120) Chambers, R. D.; Fox, M. A.; Holling, D.; Nakano, T.; Okazoe, T.; Sandford, G. *Chem. Eng. Technol.* **2005**, *28*, 344.
(121) Kawai, K.; Ebata, T.; Kitazume, T. *J. Fluor. Chem.* **2005**, *126*, 956.
(122) Jahnisch, K.; Baerns, M.; Hessel, V.; Ehrfeld, W.; Haverkamp, V.; Lowe, H.; Wille, C.; Guber, A. *J. Fluor. Chem.* **2000**, *105*, 117.
(123) Lob, P.; Lowe, H.; Hessel, V. *J. Fluor. Chem.* **2004**, *125*, 1677.
(124) Wootton, R. C. R.; Fortt, R.; de Mello, A. J. *Org. Process Res. Dev.* **2002**, *6*, 187.
(125) Zhang, X. N.; Stefanick, S.; Villani, F. J. *Org. Process Res. Dev.* **2004**, *8*, 455.
(126) Ferstl, W. F.; Schwarzer, M. S.; Loebbecke, S. *Chem. Ing. Tech.* **2004**, *76*, 1326.
(127) Antes, J.; Tuercke, T.; Marioth, E.; Lechner, F.; Scholz, M.; Schnurer, F.; Krause, H.; Loebbecke, S. In *Microreaction Technology—IMRET 5: Proceedings of the 5th International Conference on Microreaction Technology*; Springer-Verlag: Berlin, 2001; pp 446.
(128) Haswell, S. J.; Watts, P. *Green Chem.* **2003**, *5*, 240.
(129) DeWitt, S. H. *Curr. Opin. Chem. Biol.* **1999**, *3*, 350.
(130) Fernandez-Suarez, M.; Wong, S. Y. F.; Warrington, B. H. *Lab Chip* **2002**, *2*, 170.
(131) Schwalbe, T.; Kadzimirsz, D.; Jas, G. *QSAR Comb. Sci.* **2005**, *24*, 758.
(132) Watts, P. *QSAR Comb. Sci.* **2005**, *24*, 701.
(133) de Bellefon, C.; Abdallah, R.; Lamouille, T.; Caravieilhes, S.; Grenouillet, P. *Chimia* **2002**, *56*, 621.
(134) George, V.; Watts, P.; Haswell, S. J.; Pombo-Villar, E. *Chem. Commun.* **2003**, 2886.
(135) Desai, B.; Kappe, C. O. *J. Comb. Chem.* **2005**, *7*, 641.
(136) Lu, H.; Schmidt, M. A.; Jensen, K. F. *Lab Chip* **2001**, *1*, 22.
(137) Hafez, A. M.; Taggi, A. E.; Dudding, T.; Lectka, T. *J. Am. Chem. Soc.* **2001**, *123*, 10853.
(138) France, S.; Weatherwax, A.; Taggi, A. E.; Lectka, T. *Acc. Chem. Res.* **2004**, *37*, 592.
(139) France, S.; Bernstein, D.; Weatherwax, A.; Lectka, T. *Org. Lett.* **2005**, *7*, 3009.
(140) Baxendale, I. R.; Griffiths-Jones, C. M.; Ley, S. V.; Tranmer, G. K. *Synlett* **2006**, 427.

(141) Schwalbe, T.; Taghavi-Moghadam, S.; Ruger, R. EP 1 160 241 A2, 2001.
(142) Wakami, H.; Yoshida, J. *Org. Process Res. Dev.* **2005**, *9*, 787.
(143) Comer, E.; Organ, M. G. *J. Am. Chem. Soc.* **2005**, *127*, 8160.
(144) Wiles, C.; Watts, P.; Haswell, S. J.; Pombo-Villar, E. *Chem. Commun.* **2002**, 1034.
(145) Wiles, C.; Watts, P.; Haswell, S. J.; Pombo-Villar, E. *Lab Chip* **2002**, *2*, 62.
(146) Wiles, C.; Watts, P.; Haswell, S. J.; Pombo-Villar, E. *Lab Chip* **2004**, *4*, 171.
(147) Wiles, C.; Watts, P.; Haswell, S. J.; Pombo-Villar, E. *Tetrahedron* **2005**, *61*, 10757.
(148) Sands, M.; Haswell, S. J.; Kelly, S. M.; Skelton, V.; Morgan, D. O.; Styring, P.; Warrington, B. *Lab Chip* **2001**, *1*, 64.
(149) Yube, K.; Mae, K. *Chem. Eng. Technol.* **2005**, *28*, 331.
(150) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemisry Part B: Reactions and Synthesis*, 3rd ed.; Plenum: New York, 1990; p 800.
(151) Brivio, M.; Oosterbroek, R. E.; Verboom, W.; Goedbloed, M. H.; van den Berg, A.; Reinhoudt, D. N. *Chem. Commun.* **2003**, 1924.
(152) Kikutani, Y.; Horiuchi, T.; Uchiyama, K.; Hisamoto, H.; Tokeshi, M.; Kitamori, T. *Lab Chip* **2002**, *2*, 188.
(153) Watts, P.; Wiles, C.; Haswell, S. J.; Pombo-Villar, E.; Styring, P. *Chem. Commun.* **2001**, 990.
(154) Watts, P.; Wiles, C.; Haswell, S. J.; Pombo-Villar, E. *Tetrahedron* **2002**, *58*, 5427.
(155) Chambers, R. D.; Fox, M. A.; Sandford, G. *Lab Chip* **2005**, *5*, 1132.
(156) Nagaki, A.; Kawamura, K.; Suga, S.; Ando, T.; Sawamoto, M.; Yoshida, J. *J. Am. Chem. Soc.* **2004**, *126*, 14702.
(157) Russum, J. P.; Jones, C. W.; Schork, F. J. *Ind. Eng. Chem. Res.* **2005**, *44*, 2484.
(158) Russum, J. P.; Jones, C. W.; Schork, F. J. *AIChE J.* **2006**, *52*, 1566.
(159) Enright, T. E.; Cunningham, M. F.; Keoshkerian, B. *Macromol. Rapid Commun.* **2005**, *26*, 221.
(160) Honda, T.; Miyazaki, M.; Nakamura, H.; Maeda, H. *Lab Chip* **2005**, *5*, 812.
(161) Yamaguchi, Y.; Ogino, K.; Yamashita, K.; Maeda, H. *J. Chem. Eng. Jpn.* **2004**, *37*, 1265.
(162) Wu, T.; Mei, Y.; Cabral, J. T.; Xu, C.; Beers, K. L. *J. Am. Chem. Soc.* **2004**, *126*, 9880.
(163) Wu, T.; Mei, Y.; Xu, C.; Byrd, H. C. M.; Beers, K. L. *Macromol. Rapid Commun.* **2005**, *26*, 1037.
(164) Hook, B. D. A.; Dohle, W.; Hirst, P. R.; Pickworth, M.; Berry, M. B.; Booker-Milburn, K. I. *J. Org. Chem.* **2005**, *70*, 7558.
(165) Jahnisch, K.; Dingerdissen, U. *Chem. Eng. Technol.* **2005**, *28*, 426.
(166) Ueno, K.; Kitagawa, F.; Kitamura, N. *Lab Chip* **2002**, *2*, 231.
(167) Fukuyama, T.; Hino, Y.; Kamata, N.; Ryu, I. *Chem. Lett.* **2004**, *33*, 1430.
(168) Maeda, H.; Mukae, H.; Mizuno, K. *Chem. Lett.* **2005**, *34*, 66.
(169) Boswell, C. *Chem. Mark. Rep.* **2004**, *266*, 8.
(170) Suga, S.; Okajima, M.; Fujiwara, K.; Yoshida, J. *J. Am. Chem. Soc.* **2001**, *123*, 7941.
(171) Suga, S.; Okajima, M.; Fujiwara, K.; Yoshida, J. *QSAR Comb. Sci.* **2005**, *24*, 728.
(172) Paddon, C. A.; Pritchard, G. J.; Thiemann, T.; Marken, F. *Electrochem. Commun.* **2002**, *4*, 825.
(173) He, P.; Watts, P.; Marken, F.; Haswell, S. J. *Electrochem. Commun.* **2005**, *7*, 918.
(174) Horii, D.; Atobe, M.; Fuchigami, T.; Marken, F. *Electrochem. Commun.* **2005**, *7*, 35.
(175) Horcajada, R.; Okajima, M.; Suga, S.; Yoshida, J. *Chem. Commun.* **2005**, 1303.
(176) He, P.; Watts, P.; Marken, F.; Haswell, S. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 4146.
(177) Paddon, C. A.; Atobe, M.; Fuchigami, T.; He, P.; Watts, P.; Haswell, S. J.; Pritchard, G. J.; Bull, S. D.; Marken, F. *J. Appl. Electrochem.* **2006**, *36*, 617.
(178) de Bellefon, C.; Tanchoux, N.; Caravieilhes, S.; Grenouillet, P.; Hessel, V. *Angew. Chem., Int. Ed.* **2000**, *39*, 3442.
(179) Schmidt, L. D. *The Engineering of Chemical Reactions*; 1998; p 592.
(180) Phan, N. T. S.; Brown, D. H.; Styring, P. *Green Chem.* **2004**, *6*, 526.
(181) Haswell, S. J.; Middleton, R. J.; O'Sullivan, B.; Skelton, V.; Watts, P.; Styring, P. *Chem. Commun.* **2001**, 391.
(182) Cao, C.; Wang, Y.; Rozmiarek, R. T. *Catal. Today* **2005**, *110*, 92.
(183) Hall, W. K.; MacIver, D. S.; Weber, H. P. *J. Ind. Eng. Chem.* **1960**, *52*, 421.
(184) Losey, M. W.; Schmidt, M. A.; Jensen, K. F. *Ind. Eng. Chem. Res.* **2001**, *40*, 2555.
(185) He, P.; Haswell Stephen, J.; Fletcher Paul, D. I. *Lab Chip* **2004**, *4*, 38.
(186) Nikbin, N.; Watts, P. *Org. Process Res. Dev.* **2004**, *8*, 942.
(187) Shuttleworth, S. J.; Allin, S. M.; Sharma, P. K. *Synthesis* **1997**, 1217.
(188) Bonfils, F.; Cazaux, I.; Hodge, P.; Caze, C. *Org. Biomol. Chem.* **2006**, *4*, 493.
(189) Hodge, P. *Ind. Eng. Chem. Res.* **2005**, *44*, 8542.
(190) Lubbad, S.; Mayr, B.; Mayr, M.; Buchmeiser, M. R. *Macromol. Symp.* **2004**, *210*, 1.
(191) Boger, T.; Heibel, A. K.; Sorensen, C. M. *Ind. Eng. Chem. Res.* **2004**, *43*, 4602.
(192) Nijhuis, T. A.; Beers, A. E. W.; Vergunst, T.; Hoek, I.; Kapteijn, F.; Moulijn, J. A. *Catal. Rev.—Sci. Eng.* **2001**, *43*, 345.
(193) Roy, S.; Bauer, T.; Al-Dahhan, M.; Lehner, P.; Turek, T. *AIChE J.* **2004**, *50*, 2918.
(194) Haswell, S. J.; O'Sullivan, B.; Styring, P. *Lab Chip* **2001**, *1*, 164.
(195) Liu, S. F.; Fukuyama, T.; Sato, M.; Ryu, I. *Org. Process Res. Dev.* **2004**, *8*, 477.
(196) Fukuyama, T.; Shinmen, M.; Nishitani, S.; Sato, M.; Ryu, I. *Org. Lett.* **2002**, *4*, 1691.
(197) Yoswathananont, N.; Nitta, K.; Nishiuchi, Y.; Sato, M. *Chem. Commun.* **2005**, 40.
(198) Franckevicius, V.; Knudsen, K. R.; Ladlow, M.; Longbottom, D. A.; Ley, S. V. *Synlett* **2006**, 889.
(199) Mikami, K.; Islam, N.; Yamanaka, M.; Itoh, Y.; Shinoda, M.; Kudo, K. *Tetrahedron Lett.* **2004**, *45*, 3681.
(200) Kobayashi, J.; Mori, Y.; Kobayashi, S. *Adv. Synth. Catal.* **2005**, *347*, 1889.
(201) Kobayashi, J.; Mori, Y.; Okamoto, K.; Akiyama, R.; Ueno, M.; Kitamori, T.; Kobayashi, S. *Science* **2004**, *304*, 1305.
(202) Akiyama, R.; Kobayashi, S. *J. Am. Chem. Soc.* **2003**, *125*, 3412.
(203) Kobayashi, J.; Mori, Y.; Kobayashi, S. *Chem. Commun.* **2005**, 2567.
(204) Zhang, X. F.; Lai, E. S. M.; Martin-Aranda, R.; Yeung, K. L. *Appl. Catal., A: Gen.* **2004**, *261*, 109.
(205) Wiles, C.; Watts, P.; Haswell, S. J. *Tetrahedron* **2004**, *60*, 8421.
(206) Jackson, T.; Clark, J. H.; Macquarrie, D. J.; Brophy, J. H. *Green Chem.* **2004**, *6*, 193.
(207) Amandi, R.; Licence, P.; Ross, S. K.; Aaltonen, O.; Poliakoff, M. *Org. Process Res. Dev.* **2005**, *9*, 451.
(208) Hitzler, M. G.; Smail, F. R.; Ross, S. K.; Poliakoff, M. *Chem. Commun.* **1998**, 359.
(209) Snyder, D. A.; Noti, C.; Seeberger, P. H.; Schael, F.; Bieber, T.; Rimmel, G.; Ehrfeld, W. **2005**, *88*, 1.
(210) Maruyama, T.; Uchida, J.; Ohkawa, T.; Futami, T.; Katayama, K.; Nishizawa, K.; Sotowa, K.; Kubota, F.; Kamiyaa, N.; Goto, M. *Lab Chip* **2003**, *3*, 308.
(211) Jones, F.; Forrest, S.; Palmer, J.; Lu, Z. H.; Elmore, J.; Elmore, B. B. *Appl. Biochem. Biotechnol.* **2004**, *113-16*, 261.
(212) Urban, P. L.; Goodall, D. M.; Bruce, N. C. **2006**, *24*, 42.
(213) Kanno, K.; Maeda, H.; Izumo, S.; Ikuno, M.; Takeshita, K.; Tashiro, A.; Fujii, M. *Lab Chip* **2002**, *2*, 15.
(214) Yiu, H. H. P.; Wright, P. A. *J. Mater. Chem.* **2005**, *15*, 3690.
(215) Moelans, D.; Cool, P.; Baeyens, J.; Vansant, E. F. *Catal. Commun.* **2005**, *6*, 307.
(216) Crumbliss, A. L.; Stonehuerner, J.; Henkens, R. W.; Odaly, J. P.; Zhao, J. *New J. Chem.* **1994**, *18*, 327.
(217) Heule, M.; Rezwan, K.; Cavalli, L.; Gauckler, L. J. *Adv. Mater.* **2003**, *15*, 1191.

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