Integrated Microreactors for Reaction Automation: New Approaches to Reaction Development

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Key Words

microfabrication, online reaction monitoring, chemical synthesis, reaction optimization

Abstract

Applications of microsystems (microreactors) in continuous-flow chemistry have expanded rapidly over the past two decades, with numerous reports of higher conversions and yields compared to conventional batch benchtop equipment. Synthesis applications are enhanced by chemical information gained from integrating microreactor components with sensors, actuators, and automated fluid handling. Moreover, miniaturized systems allow experiments on well-defined samples at conditions not easily accessed by conventional means, such as reactions at high pressure and temperatures. The wealth of synthesis information that could potentially be acquired through use of microreactors integrated with physical sensors and analytical chemistry techniques for online reaction monitoring has not yet been well explored. The increased efficiency resulting from use of continuous-flow microreactor platforms to automate reaction screening and optimization encourages a shift from current batchwise chemical reaction development to this new approach. We review advances in this new area and provide application examples of online monitoring and automation.

1. INTRODUCTION

Applications for microfluidics have significantly advanced from its roots in microanalytical chemistry to include high-throughput screening (1), biological analysis of cells (2) and proteins (3, 4), portable energy devices (5), and reaction kinetics and mechanisms studies (6, 7). Enhanced heat- and mass-transfer rates, continuous-flow operations, and the potential inline analysis inherent in microsystems for chemistry (microreactors) have enabled chemical researchers to investigate myriad reactions under experimental conditions not easily achieved with conventional laboratory batch equipment, such as glass flasks and test tubes. As a result, microreactor systems are attracting attention in pharmaceutical and fine-chemical industries as a platform technology to be used for discovery and reaction development in research laboratories and scales to satisfy production throughput requirements (8, 9). Reported economic advantages and improved safety metrics from microreactors for production purposes have further encouraged the adoption of microreactors for these industries (10–12).

Novel microfabrication techniques and reactor peripherals are continuously being developed as microreactor applications expand. Micromixers are designed to use interdigitated multilamellae (13, 14), chaotic advection (15, 16), segmented flow of immiscible fluids (17, 18), or active micromixing techniques (19, 20). Separation of homogenous mixtures on the microscale is achieved via distillation (21, 22) or crystallization (23), whereas multiphase mixtures are separated by taking advantage of the dominating surface forces (24–26). Microchemical systems are established by integrating microdevices with the appropriate fluidic interfacing scheme (27–29). The advantages of using these miniaturized reaction networks for multistep chemical synthesis have been demonstrated in several case studies (30–33). Selected examples of current microfluidic devices for reaction and separation are shown in **Figure 1**.

Incorporation of chemical and physical sensors with a microreactor leads to so-called integrated or instrumented microreactors and enables online monitoring of the reaction conditions and the extent of reaction (38). Moreover, incorporating logic and feedback control with instrumented microreactors provides a system capable of performing numerous experiments in a fully automated manner. Benefits from automation and microreactors, including reductions in material and time, have been demonstrated for reaction screening and reaction optimization (39–41). Consequently, process lead times are accelerated, and associated developmental costs can be reduced by gathering a wealth of reaction knowledge with integrated microreactors in the research laboratory and translating the results to production systems (42). The ability to rapidly identify a reaction path, optimize the reaction conditions, and scale up and/or scale out the results for manufacturing could engender a shift from reaction development in glass flasks to continuous-flow operations in microreactors. However, several challenges remain to be resolved in order for this transition to be successful.

Thorough reviews describing the range of reactions performed in microreactors have been published in the past decade (43–49). **Table 1** lists examples in which the reaction performance is enhanced through operations in a microreactor. In the present review, we focus on microfabrication and microfluidic devices, with an emphasis on integration techniques for online measurement and reaction enhancement. More comprehensive reviews in the general area of miniaturized systems for chemistry and life sciences (micro total analysis systems) have been published by Manz and coworkers (50–52). We provide several examples of microreactors and reactions with online detection capabilities and describe automated operations for reaction screening and optimization. We conclude by discussing the outlook of instrumentation and automation in microchemical systems and the anticipated challenges.

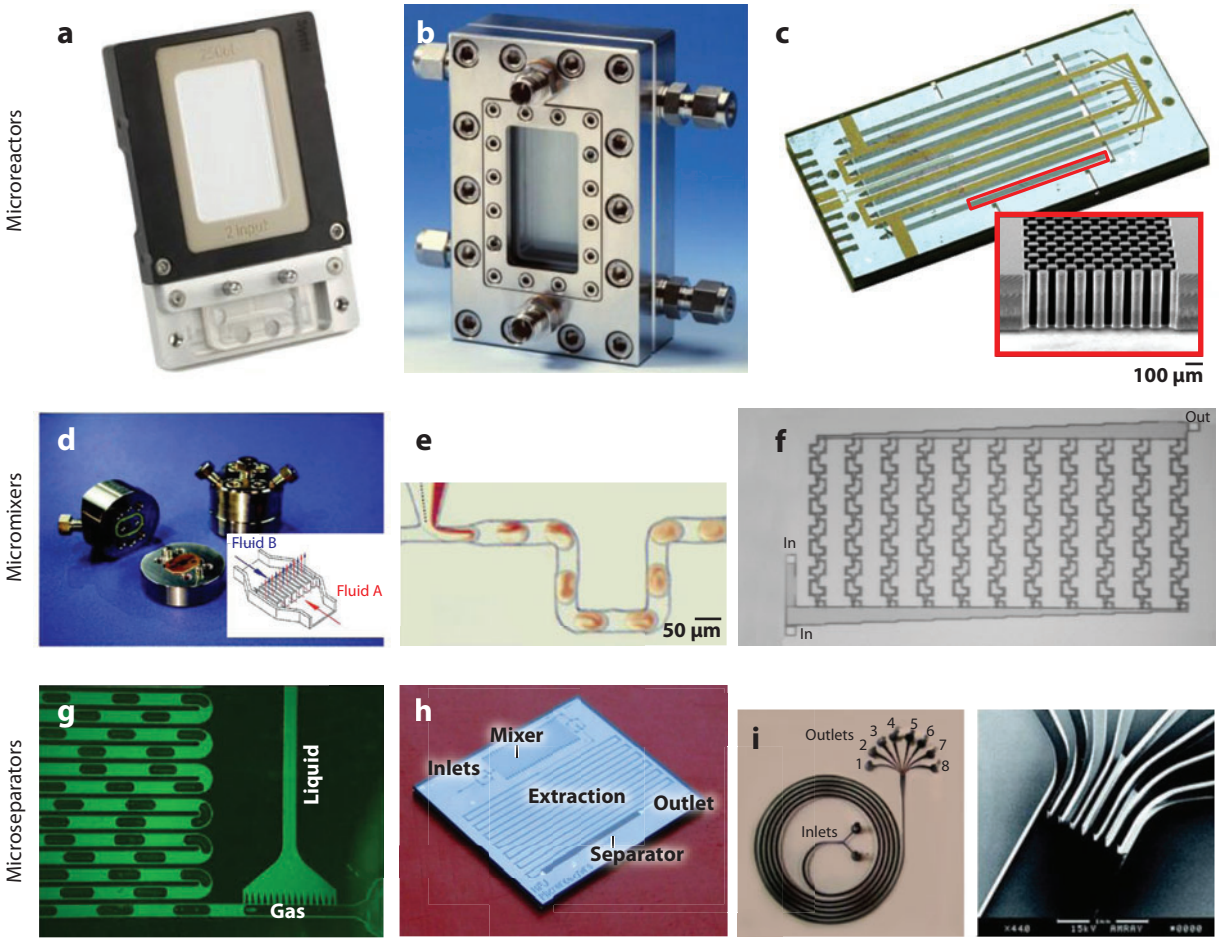


Figure 1

Selected examples of microfluidic devices. (*a*) Glass microreactor used in Syrris's Africa Flow Chemistry System. Reproduced with permission from Syrris Ltd. (*b*) Stainless steel reactor fabricated by Institut für Mikrotechnik Mainz GmbH. Reproduced with permission from IMM GmbH. (*c*) Multichannel silicon microreactor, highlighting in-channel, platinum catalyst–coated pillars (34). (*d*) Interdigital micromixer by Institut für Mikrotechnik Mainz GmbH, with flow patterns inset. Adapted with permission. Copyright 2009, American Chemical Society. (*e*) Example of chaotic advection with liquid-liquid segmented flow. Reproduced with permission from Reference 15. Copyright 2003, American Institute of Physics. (*f*) Split-and-recombine mixer (36). Copyright Wiley-VCH Verlag GmbH & Co. Reproduced with permission. (*g*) Microseparator for gas-liquid slug flow (24). (*h*) Integrated liquid-liquid extractor and separator (25). (*i*) Size-based particle separator (37). Reproduced with permission from the Royal Society of Chemistry.

2. MICROREACTOR TECHNOLOGY

2.1. Microfabrication Techniques and Microfluidic Devices

Microreactors are fabricated in a range of materials, including ceramics, polymers, stainless steel, and silicon. Common fabrication techniques and the advantages and disadvantages of these different materials are listed in **Table 2** and discussed in further detail by Madou (61). Polymer-based microfluidic systems, especially systems based on poly(dimethyl siloxane) (62), are frequently

Table 1 Selected examples of chemical reactions performed in microreactors

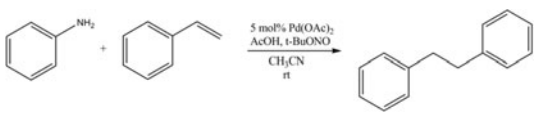
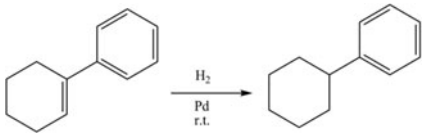
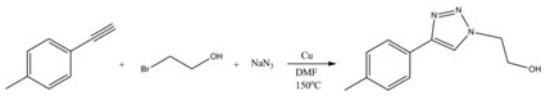
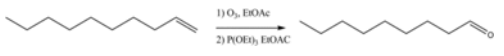
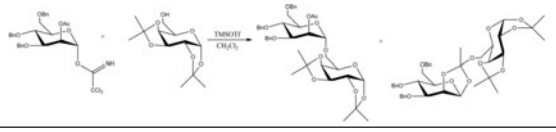
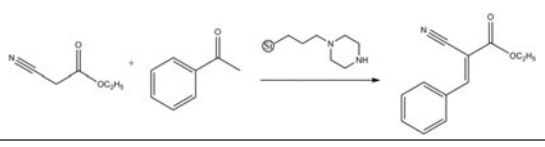
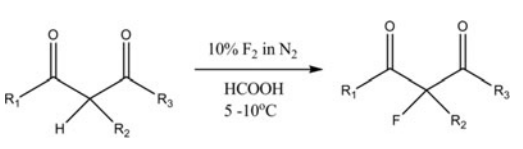
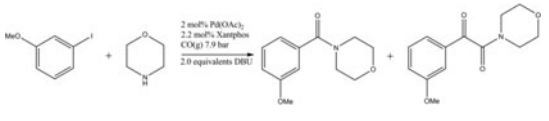
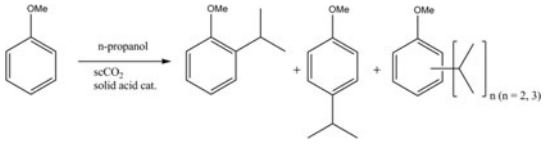
Reaction type	Reaction	Reactor material	Highlight	Reference
Heck		Poly(methyl methacrylate)	Enhanced mixing through segmented flow	53
Hydrogenation		Silica	Fast, triphasic reaction by enhancing mass transfer	54
Click		Copper	Reactor material used as catalyst	55
Ozonolysis		Silicon	Demonstration of improved safety with microreactors	56
Glycosylation		Silicon	Synthesis of desired product at warmer temperatures	57
Enolation		Glass	Faster reaction and fewer work-up stages from immobilized base	49
Halogenation		Metal	Selective fluorination at accelerated reaction times; 11 examples	58
Amino-carbonylation		Silicon	Exploration of reaction selectivity at temperature above normal boiling point	59
Friedel-Crafts alkylation		Metal	Investigation of reaction selectivity with different solid-acid catalysts and supercritical CO_2	60

Table 2 Fabrication and highlighted features of various microreactors

Material	Fabrication techniques	Advantages	Disadvantages	References
Ceramic	Stereolithography; powder molding; electrodischarge machining; laser machining	Stable at high temperatures with low heat loss; chemically resistant	High development costs; shrinkage after sintering	68, 69
Glass	Photolithography; powder blasting; wet etching; ultrasonic machining	High chemical resistance; direct visualization of reaction	Deep, anisotropic etch is difficult; incompatible with strong aqueous bases at moderate temperature	70, 71
Plastic	Soft lithography; injection molding; hot embossing	Fast fabrication; inexpensive development costs	Incompatible with organic solvents; not suitable for high temperatures and pressures	72, 73
Silicon	Photolithography; wet and dry etching	Operation at high pressure and temperature; superior heat conductivity; high–aspect ratio designs	Incompatible with strong aqueous bases at moderate temperature	74, 75
Stainless steel	Lithography, electroplating, and molding; stamping; micromachining	Operation at high pressure and temperature	Incompatible with acidic media except for expensive, specialized steels	76, 77

used for biological applications because of their reduced cost and the potential for one-time use to avoid cross-contamination. However, most polymers swell or dissolve in common solvents used in chemical synthesis. Ceramic systems are often difficult to microfabricate and are typically limited to high-temperature applications. Consequently, organic chemical synthesis is typically performed in metal, glass, and silicon. Stainless steel microreactor networks range from simple systems comprising T-shaped micromixers and narrow tubing (63) to commercial systems with microfabricated components (64–67). Glass microreactors offer the benefit of allowing one to visualize the reaction progress, but they are limited in reactor designs by their difficulty in creating high–aspect ratio structures. Alternatively, a glassy, inert reaction environment with high thermal conductivity can be produced by oxidizing the channel walls of silicon microreactors. Additional benefits from these reactors include the ability to operate at elevated temperatures and pressures (59).

2.2. Sensor-Integration Methods

Reaction temperature, residence time, and stoichiometry can be measured through integrated sensors and controlled with on-chip or modular components. Thin layers of platinum are deposited on microreactors to record and adjust reactor temperatures (**Figure 2*a***) (78). Resistive electrical heaters (34) and heat exchangers (7) are also used to control temperatures. Additionally, temperature gradients created by exotherms from mixing or reaction are closely monitored by fabricating thin-film calorimeters (**Figure 2*b***) (79) or by monitoring hot spots thermographically with an infrared (IR) camera.

Flow rates are measured with micropressure sensors (80), microflow anemometers (81), or optical fiber cantilevers (**Figure 2*c***) (82) and can be adjusted in several manners. Electroosmotic flow (EOF) is used in glass microreactors to generate precise plug flow (83), but it is typically only applicable for aqueous systems, low flow rates, and small channel dimensions (84). Alternative flow-control methods include commercial syringe pumps and pneumatic (85, 86), peristaltic (87), and passive pumping (88) systems. Gas-liquid segmented flow in microreactors is characterized by integrating microfluidics with an inverted fluorescence microscope and a charge-coupled device

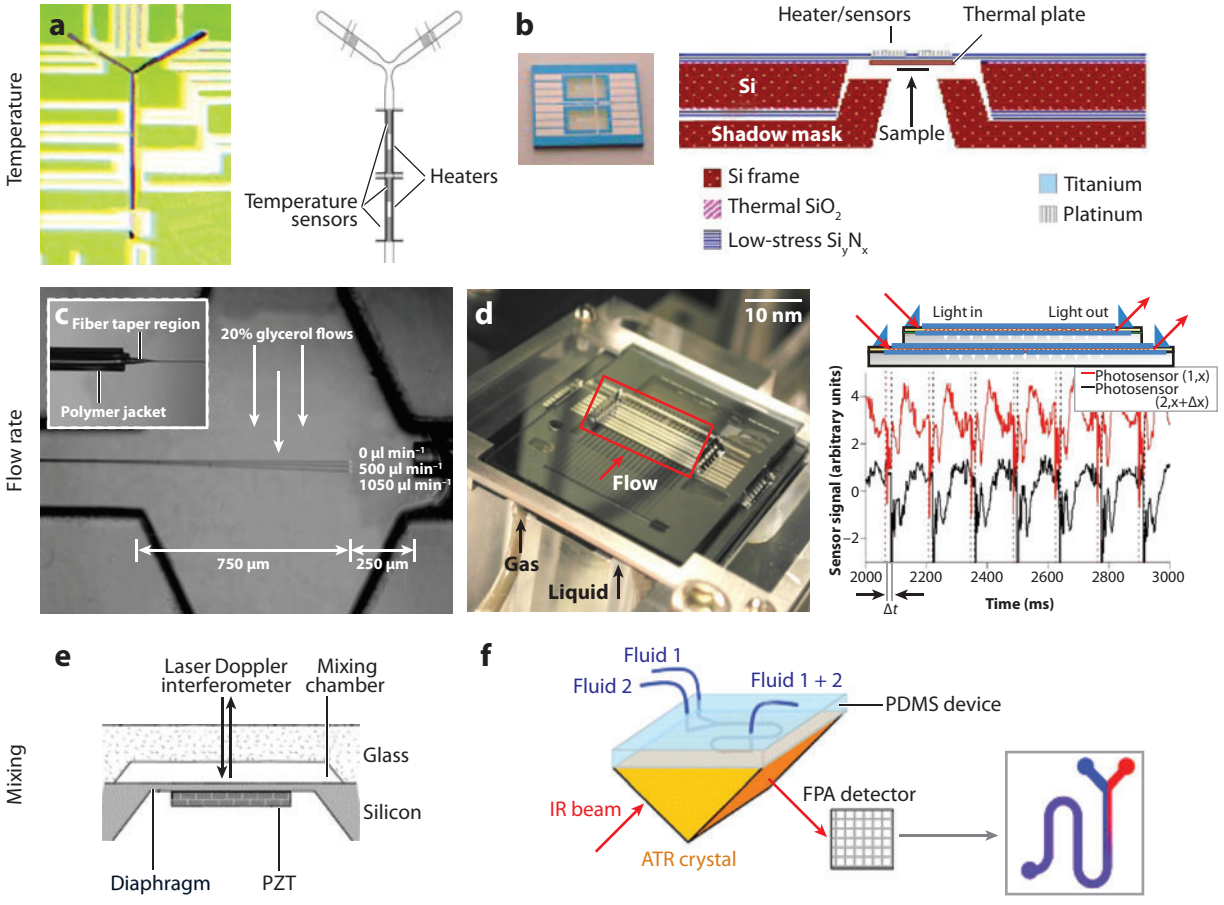


Figure 2

Selected examples of microfluidics systems integrated with sensors for measuring physical properties. (*a*) Microreactor integrated with platinum-deposited temperature sensors and heaters (*left*) and a schematic of the device (*right*) (78). (*b*) Microcalorimeter capable of measuring exotherms (79). (*c*) Microoptofluidic flow measurement with optical position marked at 0, 500, and 1050 µl min^{-1} (82). Reproduced with permission from the Royal Society of Chemistry. (*d*) Gas-liquid flow sensor that uses attenuated total reflectance–Fourier transform infrared spectroscopy (ATR-FTIR) spectroscopy and waveguides (90). (*e*) Ultrasonic micromixer schematic with fluorescent imaging of mixing for water and uranine. Reprinted from Reference 91 with permission from Elsevier. Copyright 2001, Elsevier. (*f*) Schematic microfluidic device capable of monitoring mixing throughout the device via ATR-IR spectroscopy (93). Reproduced with permission from the Royal Society of Chemistry. Abbreviations: FPA, focal plane array; PDMS, polydimethylsiloxane; PZT, lead zirconate titanate.

(CCD) camera (89). This approach is also used to measure gas-liquid slug velocity and uniformity in multichannel, scaled-out microreactors by including a waveguide that uses internal reflection (**Figure 2*d***), as has been demonstrated by de Mas et al. (90). Fluorescent measurements are used to characterize mixing (**Figure 2*e***) (91) and dispersion (92) in transparent microreactors. Recently, Chan et al. (93) characterized the mixing profiles of H_2O and D_2O throughout an entire polydimethylsiloxane (PDMS) microreactor with attenuated total reflectance–Fourier transform infrared spectroscopy (ATR-FTIR) by placing the device above an ATR crystal and using a focal plane array for spatial imaging (**Figure 2*f***). Advances in this technology will lead to faster methods for determining reaction kinetics and optimal conditions.

A variety of spectroscopic methods have also been integrated with microreactors. Advances in fiber optics and flow-cell technology allow continuous monitoring of the reaction stream with ultraviolet/visible/near-infrared (UV/vis/NIR) (94), Raman (95), ATR-IR (7), X-ray absorption spectroscopy (96), and nuclear magnetic resonance (NMR) (97). The potential to monitor the entire reaction progress in a microreactor is exemplified in Damean et al. (98). In this study, the authors used diffraction grating and an array of microlenses to disperse light from a bright-field microscope through a PDMS microreactor. They obtained absorbance spectra of components at multiple locations in a microarray or microchannel by collecting and resolving the diffracted light images with a CCD camera.

Microfluidic devices for the separation of analytes are coupled with microreactors to improve chemical detection on the miniaturized scale. Separation of proteins, metabolites, and other biological macromolecules can be quickly performed in devices that use a form of electrophoresis (52, 99). A common technique to separate smaller molecules is liquid chromatography. Basic designs for this technique involve packing the microfluidic channel with high-performance liquid chromatography (HPLC) beads (100), coating the channel walls with adsorbent material (101), or creating a functionalized monolith as the separation column (102). Chiral separation is achieved in EOF microfluidics through addition of a chiral selector to the mixture (103). Common problems associated with gradient methods in reversed-phase chromatography, such as long equilibration times, can be avoided on the microscale through use of an isocratic method and temperature-gradient interaction chromatography, as shown by Shih et al. (100). In this study, the authors fabricated an integrated column separator from silicon and parylene that was 8 mm long by 100 μm wide, had a 25-μm-deep channel, and was packed with 5-μm C18 silica beads. Platinum was deposited on the silicon to create a resistive heater, a temperature sensor, and an electrochemical analyte sensor. Through use of a variable power source, a constant temperature gradient across the column allowed the separation and detection of five derivatized amino acids.

2.3. Integration of Microreactors with Other Process-Intensification Methods

In addition to analytical instruments and microdevices, microreactors are integrated with other process-intensification equipment to enhance reaction rates through superior mixing or superheating. Mixing in silicon-based devices is promoted by acoustics through the attachment of a piezoelectric element directly to the micromixer (104). The combination of a gas phase and acoustics reduces the mixing time to milliseconds (105). Microreactor and microwave technology have been coupled to reduce reaction times from hours to minutes. By inserting a glass U-tube packed with microencapsulated palladium into a microwave cavity, Baxendale and coworkers (106) performed numerous Suzuki cross-coupling reactions that resulted in decreased rates of side-product formation and thermal degradation of the catalyst and product, compared with their batch investigations. Other carbon-carbon bond–forming reactions have also been enhanced through microwave technology (107). Moreover, mixing and reaction rates are drastically increased in silicon and stainless steel reactors when supercritical fluids are used as solvents (29, 108).

3. REACTIONS WITH INLINE ANALYTICAL MONITORING

We have presented a selection of the different inline measurement techniques important in reducing sample volume, increasing experimental throughput, and removing work-up procedures required for offline detection. Because microreactors allow greater control over reaction conditions, information acquired with these instrumented devices can be of a higher quality than data collected in traditional batch experiments. Furthermore, incorporating multiple in situ

measurements increases the amount of information gained per experiment performed. Obtaining a concentration profile throughout the microreactor provides insight into the mechanisms, the kinetics, and the optimal conditions for reactions that are traditionally difficult to perform in batch but easily achieved in microreactors, such as highly hazardous (30) or explosive reactions (109); reactions with highly energetic, unstable intermediates (110); and extremely fast reactions (111). In the following subsections, we illustrate these points with selected applications in which inline analytical methods were used for online monitoring of chemical reactions.

3.1. Integration with Optical Sensors

3.1.1. Reaction monitoring with fluorescent measurements. Laser-induced fluorescence (LIF) is a common method for in situ detection because of the high sensitivity and minimal mass required for sampling. An example of this sensitive measurement is that performed by Stavis et al. (112), who developed a microfluidic system with a 500-al focal volume for multicolor detection and characterization of single-molecule binding of quantum dots (QDs) to fluoromolecules. Recent applications of in situ LIF have been used for kinetic parameter estimations for enzymatic reactions. Kerby et al. (113) calculated the Michaelis-Menten kinetic constants, K_m and V_{max}, by integrating fluorescent measurements with a glass microreactor that was packed with immobilized, enzyme-coated silica beads. Another illustration is provided by Song & Ismagilov (114), who combined fluorescent measurements with slug-flow operations in a PDMS microreactor to enhance mixing and calculate millisecond kinetics.

Very high degrees of process integration have been made possible with the development of Quake and colleagues' (115, 116) PDMS valves. Examples include the preparation of 1024 click chemistry reactions with a PDMS microfluidic circuit by Wang et al. (117) and the multistep synthesis of an [^{18}F]fluoride-radiolabeled molecular imaging probe by Lee and coworkers (118). Integration of fluorescent measurements with these devices reduces the number of experiments required to estimate kinetic parameters of enzyme-catalyzed reactions. Jambovane and coworkers (119) fabricated a PDMS microreactor capable of performing experiments in parallel with in situ monitoring of the product formation through use of β-galactosidase and its substrate, resorufin-β-D-galactopyranoside. In this work, the authors performed 11 experiments, each at different substrate-to-enzyme ratios, by varying the metering lengths for each processor (microreactor). As the reaction proceeded in each processor, the fluorescence emitted by the product, resorufin, was recorded and analyzed. The authors thus obtained a reaction profile in each processor, allowing them to estimate the Michaelis-Menten parameters in a single experimental trial.

3.1.2. Reaction monitoring with inline ultraviolet spectroscopy. Typically coupled with chromatography, UV detection is a commonly used analytical method in chemical synthesis. Faster analysis is made possible by integrating the fiber optics in the reaction flow path. Alignment of fiber optics for in-plane UV detection is achieved in silicon microfluidics through use of standard photolithography deep-reactive ion-etching techniques, and mounting is secured with epoxy. Such a method was used by Park and coworkers (120) for the investigation of the Berthelot reaction, which involved monitoring indophenol-formation rates over a range of ammonia concentrations in the parts-per-million range and a range of reaction temperatures. Out-of-plane UV detection was demonstrated by Lu et al. (121), who investigated the photochemical synthesis of benzopinacol in a quartz/silicon/quartz microreactor. By machining a compression packaging chuck with standard optical SMS connections, the authors mounted UV optics for online monitoring of benzophenone consumption. Conversion data obtained from inline measurements were in good agreement with off-chip HPLC analysis and indicated that the reaction in the microreactor

results in a higher effective quantum efficiency due to equal light penetration and sufficient heat dissipation.

Development of a more secure packaging scheme of the fiber optics has expanded the applications of UV integrated microfluidics to high-pressure reaction applications. Oosterbroek and coworkers (122) designed a glass chip for high-pressure analytical and synthetic chemistry that withstood 100 bar. Alternatively, a simpler approach involving a silica capillary microreactor system and common HPLC equipment can be used to monitor reaction conditions, as exemplified by Benito-Lopez et al. (123). In this system, the reaction performance was monitored via a stainless steel cross so that the reaction flow path was perpendicular to the UV/vis fiber optics. Using a high-pressure generator to explore reactions at up to 600 bar, the authors computed the reaction-rate constants and activation volumes for a nucleophilic substitution and a Diels-Alder reaction.

3.1.3. Reaction monitoring with inline infrared spectroscopy. Because IR spectroscopy can be used to determine chemical structure and to quantify concentrations, integrating this analytical technique with microreactors has numerous benefits. An NIR flow cell was fabricated by Ferstl et al. (94) for online analysis of a nitration reaction. Inline FTIR measurements have also been applied by Hübner et al. (96) to quickly optimize an ozonolysis reaction in a two-step synthesis for a vitamin D analog. Clever fabrication and integration techniques have led to numerous advances in in situ monitoring. Exploiting the transparency of silicon to IR radiation in the range of 4,000 to 10,000 cm^{-1}, Floyd et al. (7) achieved in situ FTIR monitoring for the hydrolysis of propionyl by loading a silicon microreactor directly into the sample compartment of an IR spectrometer. Further integration of temperature control was accomplished with this device through the fabrication of an on-chip heat exchanger. Additionally, detection by multiple internal reflection–FTIR in silicon microreactors has been accomplished through use of a potassium hydroxide wet etch to create the beveled silicon edges needed for the technique (124).

3.1.4. Reaction monitoring with inline Raman spectroscopy. Integration of Raman spectroscopy with microreactors enables online monitoring of chemical reactions with compounds that do not contain any chromophores and is advantageous over IR for aqueous reactions. In situ reaction monitoring for the synthesis of ethyl acetate from ethanol and acetic acid using confocal Raman spectroscopy was performed by Fletcher and coworkers (125). Operating with a glass microreactor with a T-junction mixer, the authors scanned a portion of the entrance region from 200 to 1450 cm^{-1}. With this arrangement, the authors were able to visualize the consumption of reactants and the formation of ethyl acetate along the T-mixer in the microreactor. Such information-rich data could be used to quickly model reaction parameters.

Online confocal Raman spectroscopy was also used by Leung and coworkers (95) to monitor the catalytic oxidation of isopropyl alcohol to acetone by tetra-*N*-propylammonium perruthanate (TPAP) and *N*-methylmorpholine *N*-oxide (NMO) in a glass, radial, interdigitated micromixer. Through monitoring of the reactant and product concentrations for varying residence times and ratios of TPAP/NMO, reaction insight on conversion and turnover numbers was obtained. Raman spectroscopy has also been used to monitor hydrogenation of cyclohexene in supercritical CO_2 in a silicon microreactor by Urakawa et al. (126). Conversion information for this heterogeneous reaction was recorded with a Raman probe at several points along the microreactor channel by adjusting the microreactor position with a motorized *x*-*y*-*z* stage. Liquid-, gas-, and supercritical fluid–phase transitions of CO_2 were also observed through monitoring of abrupt changes in the Fermi dyad bands at different temperatures and pressures when only CO_2 was flowed through the microreactor.

3.1.5. Reaction monitoring with inline nuclear magnetic resonance. Integrating NMR measurements with microreactors facilitates reaction discovery and development because product structure and reaction yield can be measured simultaneously. To improve signal sensitivity for the minute mass samples available on the microscale, instrumented microreactors with smaller NMR coils have been developed. Wensink and colleagues (127) fabricated a device with high sensitivity and resolution by using a flat, helical coil above a glass microchannel. Standard photolithography, sputtering, and electroplating of copper were used to create an NMR coil with 24 windings, a width and separation of 20 μm, and an inner diameter (i.d.) of 200 μm. A conventional NMR magnet was used to detect components of the imine-producing reaction between benzaldehyde and aniline. The authors (127) also estimated the second-order rate constant by obtaining the time profile of these concentrations.

Measurement sensitivity can be improved through modifications of the NMR coil design. A NMR probe that uses a stripline design was integrated with a glass microreactor for real-time monitoring of acetylation of benzyl alcohol by acetyl chloride (128). These authors also demonstrated the possibility of studying mass-limited biological samples by using the probe to detect 1.21 mM of human cerebrospinal fluid. Incorporating a waveguide NMR with microfluidic devices also leads to improved sensitivity (97). A more complete discussion of microdevices integrated with NMR detection is provided by Kentgens et al. (129).

3.2. Reaction Monitoring with Inline Chromatography

Inline chromatographic methods can be performed by fabricating microchips capable of separation and detection or by transferring samples from the microreactor system to commercial HPLC equipment. While studying the nitration of toluene, Antes et al. (130) used a valve or an automated microsyringe system to continuously monitor the reaction. Examples of inline chromatography are more frequently observed with gas chromatography analysis. Mills & Nicole (131) used a multiport gas-switching valve to sample heterogeneous gas-phase oxidation from six parallel packed-bed microreactors. Benson et al. (132) also used online gas chromatography for real-time evaluation of catalytic transformations of lipids to biodiesel via several different zeolites in a glass microreactor.

3.3. Reaction Monitoring with Inline Mass Spectrometry

A variety of microchips have been fabricated for sample preparation, separation, and nebulization for electrospray ionization–mass spectrometry (133, 134) and atmospheric pressure chemical ionization (135). In the field of chemical synthesis, online matrix-assisted laser/desorption ionization–time-of-flight mass spectrometry analysis is achieved by coupling a microreactor onto a standard sample plate. This approach was used by Brivio et al. (136) to monitor a Schiff's base reaction and oligonucleotide and peptide digestion. Using a second-generation design of this device (137), the authors measured the kinetics of 4-nitro-7-piperazino-2,1,3-benzoxadiazole with various isocyanates in a glass microreactor and observed faster reaction rates due to the enhanced mixing (138). Enzyme inhibition was measured by de Boer et al. (139), who monitored the products of an enzyme-substrate reaction with online electrospray ionization–mass spectrometry.

4. AUTOMATION WITH INTEGRATED MICROREACTORS

Incorporating feedback control with instrumented microreactors leads to full automation of continuous-flow experiments, thereby reducing the time and the material costs associated with

reaction discovery and development. Selected examples follow to illustrate the utility of automated microfluidic platforms for reaction screening and optimization.

4.1. Reaction Screening with Automated Microfluidic Platforms

The use of automated microreactors and combinatorial chemistry to build reaction libraries has been demonstrated for the synthesis of cycloadducts (140), pyrazoles (40), and ciprofloxacin analogs (141). Griffiths-Jones and coworkers (142) developed an automated multistep, continuous-flow system to generate a 48-member sulfonamide reaction library. In this platform, monoalkylation of a Boc-protected primary sulfonamide was performed in a glass reactor column packed with polystyrene-supported 1,5,7-triazabicyclo[4.4.0]dec-5-ene (PS-TBD), followed by deprotection in a second column packed with the polystyrene-supported sulfonic acid Amberlyst^{TM} H-15 (**Figure 3**). By integrating these columns with a liquid handler/fraction collector, syringe pumps, four-way valves, and necessary computer logic, the authors (142) automated the loading of the Boc-protected primary sulfonamide on the PS-TBD column, the loading of the monomer on the PS-TBD column for reaction, the detection and collection of the final product following deprotection, and the regeneration of the PS-TBD column. Although some manual intervention was required to remove the spent H-15 and the eventually deactivated PS-TBD column, this application shows that numerous experimental steps can be automated with a continuous-flow system.

Recently, Goodell et al. (39) developed a microfluidic platform for multidimensional screening (**Figure 4*a***). Communications between the platform's hardware and central computer enabled automated sequential reaction screening, in which reactions are evaluated by varying reaction compounds, reaction temperature, and residence time. The transformations of functionalized bicyclo[3.2.1]octanoid scaffolds involving two different substrates and 55 reaction partners were investigated to rapidly generate reaction libraries with the automated system.

Reaction screens were initiated by withdrawing a reagent from the 96-well reagent block with the liquid handler and injecting the compounds into the microreactor system via actuated six-way valves. The pressure drops across the microreactor and the compression-packaging chuck were designed to ensure that the injected reagents merged at the T-mixers in the microreactor (**Figure 4*b*,*c***). This coalescence of reagents created a so-called reaction pulse that moved throughout the microreactor system, using solvent as the carrier fluid. Other reaction-screening applications have successfully used immiscible solvents as carrier fluids (143), but Goodell et al. (39) chose not to use this approach due to solubility concerns of the fluids at higher reaction temperatures. The miscible-solvent method, however, results in axial dispersion of the reaction pulse and requires programmed delays between injections to eliminate cross-contamination and in-line UV detection to capture the central part of the reaction pulse. After surpassing a specified

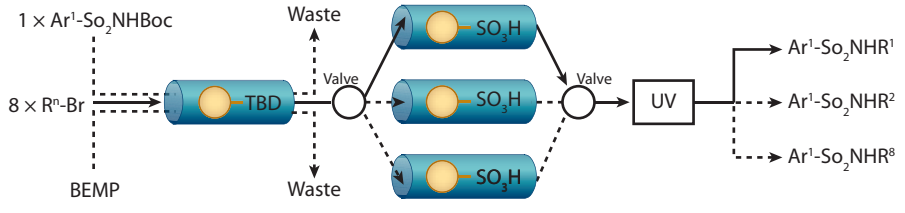


Figure 3

Schematic of an automated platform for reaction screening to create a 48-member sulfonamide reaction library. Abbreviation: BEMP, 2-tert-2-diethylamino-1,3-dimethyl-perhydro-1,2,3-diazophosphorine. Adapted with permission. Copyright 2007, American Chemical Society.

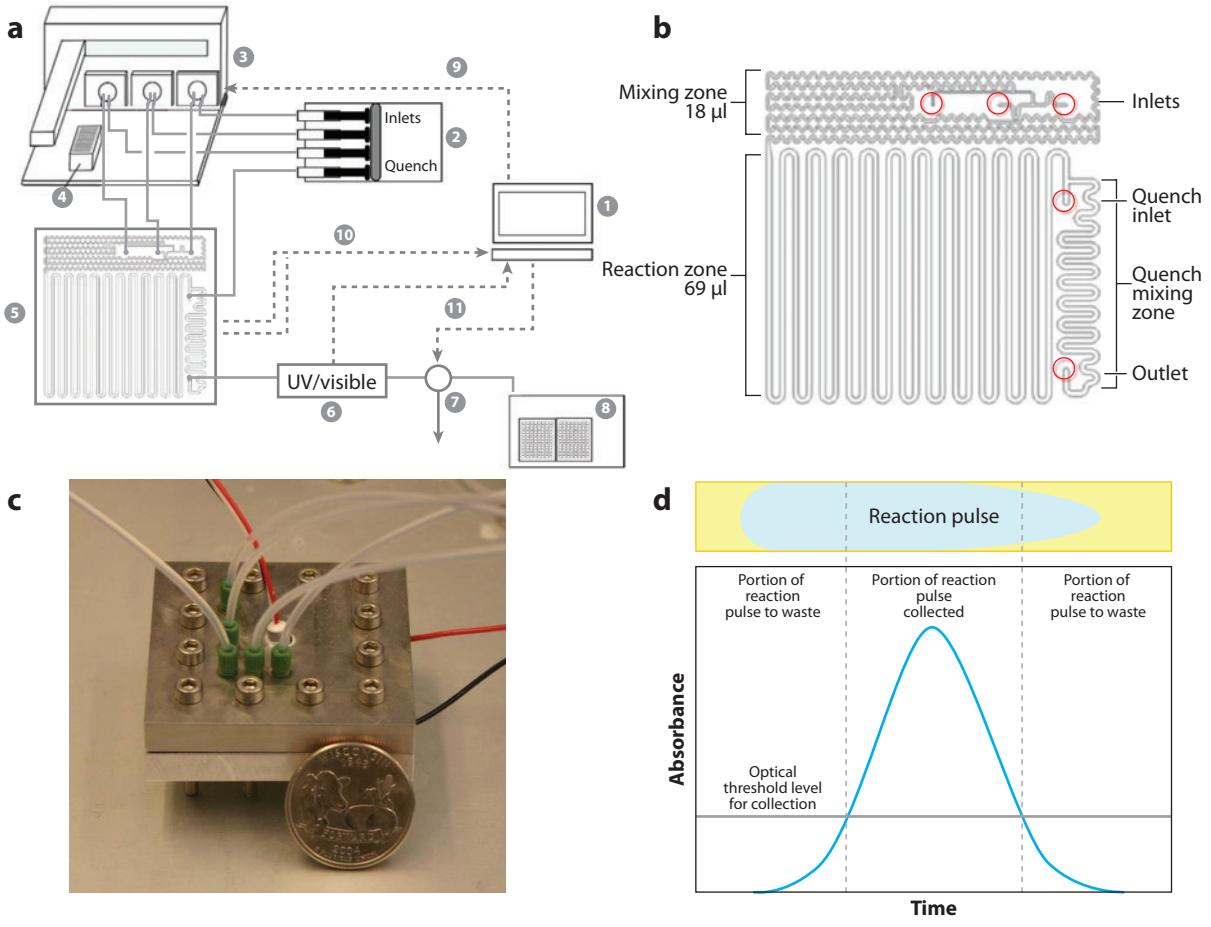


Figure 4

(*a*) Automated microfluidic platform for reaction screening. Components include (*1*) computer with operating software, (*2*) multihead syringe pump, (*3*) liquid handler, (4) 96-well reagent block, (*5*) compression packaging that houses the microreactor and the thermoelectric module, (*6*) UV detection for optical triggering, (7) sampling valve, (*8*) 96-well-plate fraction collector, and (*9–11*) feedback-control loops for reagent injection, temperature control, and sample collection, respectively. (*b*) Layout of a silicon microreactor designed with equivalent pressure drops to ensure merging of screen pulses. (*c*) Image of a compression-packed reactor and thermoelectric module. (*d*) Illustration of a detection technique used to collect reaction pulses.

UV-absorbance threshold, the authors collected the reaction pulses with a fraction collector and monitored them offline by ultraperformance LC (**Figure 4*d***).

This microfluidic platform automated approximately 800 experiments through use of two different substrates, 55 reaction partners (23 heteroatom nucleophiles, 16 carbon nucelophiles, and 16 electrophiles), two organic bases, two reaction times, two solvents, and two reaction temperatures. Each reaction screen was performed with 1 µmol of substrate, 2.0–3.0 equivalents of reaction partner, and 1.2 equivalents of base. Residence times were controlled by quenching the reaction pulses on chip with a 10%-by-volume acetic anhydride solution. Insight into the reactivity of the substrates with the different nucleophilic reaction partners and solvents was obtained in this application, whose results exemplify the ability to generate comprehensive reaction library data quickly with minimal amounts of material.

4.2. Reaction Profiling with Automated Microfluidic Platforms

Following identification of the successful "hits" involved in reaction screening, the next step in reaction development is profiling the parameter space to evaluate the reaction rate, to determine the optimal operating speed, and to calculate the kinetic parameters. This information-driven approach for characterizing reaction influences has recently received more attention with the quality-by-design initiative by the U.S. Food and Drug Administration (144). Automation of microfluidic platforms adheres to the principles of this program and gathers the required reaction information without the need for significant time or resources.

An automated microreactor system that can quickly profile the parameter space of a Sonogashira reaction was designed by Sugimoto and coworkers (145). This personal computer–controlled system consisted of two HPLC pumps for fluid handling, a temperature control, a 500-μm × 1000-μm micromixer followed by a 1000-μm-i.d. × 10-m–residence time unit, and a fraction collector. Following input of the desired experimental matrix, namely the set of reaction temperatures and residence times of interest, the system performed the specified reactions and collected samples in an automated fashion. The fractions were then analyzed offline by HPLC.

This system was first used to investigate reactions with 0.225 M bromothiophene derivative, 1.08 equivalents of *p*-tolyacetylene, 1-mol% Pd and 2-mol% Cu catalysts, and 2.5 equivalents of base with temperatures of 70°C and residence times of 20, 40, and 60 min; 90°C at 20 and 60 min; and 110°C at 20 and 60 min. The best yield for this set of experiments was 88%; it occurred at 110°C and 60 min. A second set of experiments was performed at 1.3 equivalents of *p*-tolyacetylene at reaction temperatures of 110 and 120°C with residence times of 10, 20, and 40 min. The best reaction performance for these more aggressive conditions corresponded to 82% yield at 120°C and 20 min. While a reaction temperature of 120°C was maintained, experiments with residence times of 10 and 20 min at 1.15, 1.20, and 1.25 equivalents of *p*-tolyacetylene were explored, with a maximum yield of 91% occurring at 20 min and 1.25 equivalents. Experiments with varying base concentrations and residence times (2.0 and 3.0 base equivalents at 10 and 20 min) were then performed at the best observed temperature (120°C) and *p*-tolyacetylene equivalents (1.25 equivalents). The optimal yield of 96% was obtained at 3.0 equivalents and 20 min. These optimal conditions were then translated to a larger system consisting of a stainless steel, 200-μm-i.d. micromixer and a 2-mm-i.d. × 20-m–residence time unit. This scaled-up system was operated for 6 h at the previously determined optimal conditions to provide 113 g of product after recrystallization.

A recent work by Koch et al. (146) demonstrated the use of an automated microfluidic platform to profile the removal of a *p*-methoxyphenyl-protecting group. The microfluidic system consisted of syringe pumps for control over residence time and reagent stoichiometry, a 7.02-μl glass microreactor, a thermoelectric module for temperature control, and a fraction collector for sampling. Offline analysis was used to quantify the reaction yield. The authors applied an optimal experiment design to investigate reaction temperatures between 60 and 90°C, residence times between 0.5 and 4 min, and 1.0 to 4.0 equivalents of acid.

On the basis of the authors' design approach, the platform performed 51 experiments in an automated fashion. Interestingly, the required material for these automated experiments was minimal—each sample required only 0.2 mg. Furthermore, the total sampling time for this profiling investigation was only 5.6 h. A polynomial response surface was fitted to these experiments and indicated that a conversion greater than 99% combined with the shortest reaction time occurred at 1.3 min, 3.2 equivalents of acid, and a reaction temperature of 90°C. These optimal results were repeated on a larger stainless steel reactor with a volume of 950 μl. However, on this larger system, the authors noted that the solvent boiled at 90°C; they therefore lowered the reaction

temperature to 80°C and increased the reaction time to 4 min to obtain 100%, as specified by their profiling experiments in the microreactor. Under these conditions, the system produced approximately 213 mg h^{-1} of the deprotected product.

4.3. Reaction Optimization with Automated Microfluidic Platforms

Incorporating a feedback algorithm with automated microfluidic platforms enables real-time optimization of a chemical reaction, as has been shown by McMullen & Jensen (147). Using a Nelder-Mead simplex optimization algorithm to intelligently select sequential experiments, the authors developed a silicon microreactor system to determine the operating conditions that would maximize a user-specified objective function for reaction. The optimization platform included syringe pumps for fluid delivery; thermoelectric modules for heating and cooling; and a downstream, interdigital micromixer to prepare the reaction sample for online HPLC analysis (**Figure 5*a***). An integrated compression packaging scheme housing the microreactor, thermoelectric module, and baffled heat exchanger investigated a wide range of temperatures during the optimization procedure and minimized thermal equilibration times between experimental conditions (**Figure 5*b*,*c***). The latter property maximized the throughput rate of experiments and minimized the amount of reagent material consumed during an optimization trial.

The oxidation pathway of benzyl alcohol to benzaldehyde to benzoic acid by chromium trioxide in an acidic solvent was used as the model reaction for this automated platform. The objective function of this reaction was to maximize the yield of benzaldehyde. Although numerous oxidation pathways that produce the intermediate aldehyde in an excellent yield exist, this model reaction was selected to demonstrate the benefits of using the automated platform for identifying the optima in aggressive reaction conditions. This example also demonstrates the improved safety of microreactors associated with the minimal handling of the hazardous material CrO_3 and the caustic solvent.

A two-dimensional optimization with temperature and residence time as variables was performed starting from an initial condition of 50°C and 60 s. Following the selection of sequential experiments according to the Nelder-Mead simplex algorithm, the platform moved from reaction conditions that gave a 21% benzaldehyde yield to conditions that yielded 46% (**Figure 5*d***). A four-dimensional optimization with temperature, residence time, and inlet concentrations of chromium trioxide and benzyl alcohol as variables was then performed starting from the same initial condition (temperature of 50°C, time of 60 s, 1.0 equivalent CrO_3, 8 mM benzyl alcohol). Including more variables in the optimization procedure enabled the platform to perform 46 automated experiments to find an optimal benzaldehyde yield of 80%, corresponding to a temperature of 88°C, a time of 48 s, 0.65 equivalent CrO_3, and 8.24 mM benzyl alcohol. Interestingly, the general trend of running this reaction at longer residence times and cooler temperatures in batch was not observed in the microreactor. The higher degree of control over reaction parameters with microreactors enabled the automated platform to explore reaction conditions that could not easily be monitored in batch.

Another example of faster reaction development through automated microfluidic platforms involves the controlled synthesis of cadmium selenium (CdSe) QDs. Creating reproducible CdSe QDs in batch is difficult because addition processes, agitation, and local temperature gradients are all key factors in nucleation and growth. Alternatively, monodisperse nanoparticles can be produced via microreactors due to the increased mixing and heat-transfer rates (18, 148–150). By incorporating inline detection and feedback with a microreactor, Krishnadasan and coworkers (151) developed an automated platform capable of determining optimal operating conditions of CdSe QD synthesis of different sizes. This automated system consisted of a Y-shaped glass

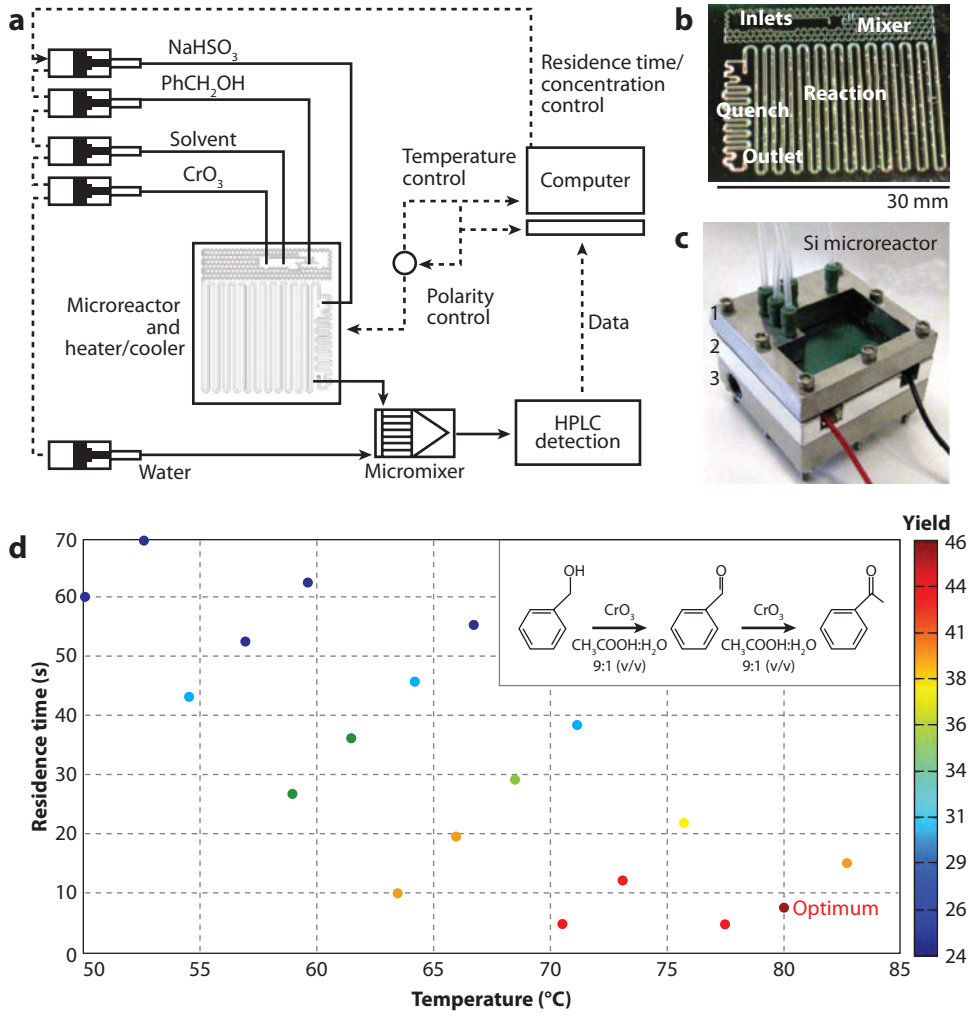


Figure 5

(*a*) Schematic of a microfluidic platform used for optimization of a chemical reaction. (*b*) Image of the microreactor. (*c*) Image of the integrated compression chuck, including the fluidic connection, the housing unit for the microreactor and the thermoelectric modules, and the baffled heat exchanger for additional heating or cooling. (*d*) Results from the automated microfluidic platform were used to maximize the yield of the intermediate, benzaldehyde. A two-dimensional optimization procedure varied reaction temperature and residence time to find the optimal benzaldehyde yield of 46%, whereas a four-dimensional optimization procedure varied temperature, residence time, and inlet concentrations of chromium trioxide and benzyl alcohol to obtain an 80% benzaldehyde yield. Abbreviation: HPLC, high-performance liquid chromatography.

microreactor, syringe pumps for fluid handling, a stabilized hot plate for temperature control, and a 355-nm Nd:YAG laser and CCD spectrometer. Sequential experiments were determined through the Stable Noisy Optimization by Branch and Fit (SNOBFIT) optimization algorithm, which combines local and global search methods through response-surface modeling and random experimentation, respectively. A weighted objective function aimed at maximizing CdSe QD production and minimizing the size distribution was established by assigning a so-called dissatisfaction

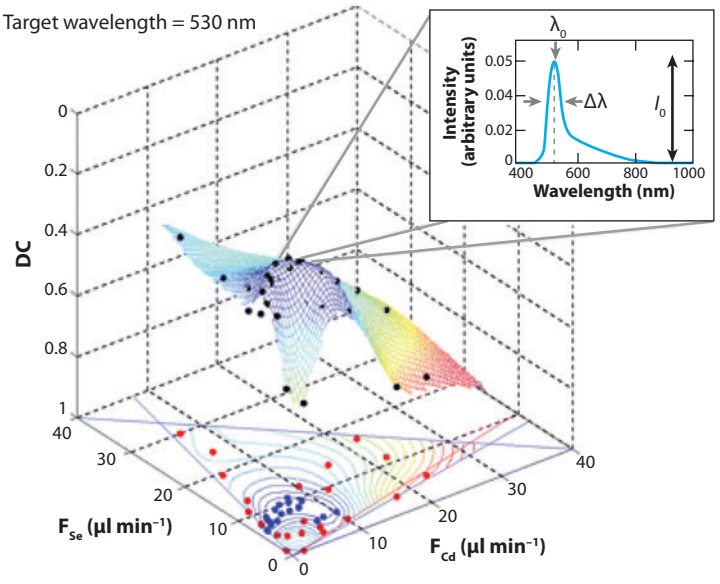


Figure 6

Results from an automated microfluidic platform used for cadmium selenium (CdSe) quantum dot synthesis. The two-dimensional optimization results for 530-nm target synthesis, where precursor flow rates were varied to minimize a dissatisfaction coefficient (DC) with a reaction spectrum inset. Abbreviation: F, volumetric-flow rate. Reproduced with permission from the Royal Society of Chemistry.

coefficient to each reaction result. Using this metric, the authors used the automated platform to perform multidimensional optimizations.

First, two-dimensional optimizations in which the optimum was discovered by varying the flow rates of the Cd and Se precursors (**Figure 6**) were performed. Each optimization trial involved 43 automated experiments and investigated the conditions that would result in the best reaction performance for CdSe QDs with target emissions of 500, 510, 520, 530, 540, and 550 nm. A three-dimensional optimization search in which reaction temperature was included in the set of variables was then performed. As expected, reaction performance improved through operation with fewer constraints. For the larger optimization, the authors performed 106 automated experiments to identify the optimal conditions for CdSe QDs at the various target emission wavelengths. In addition to demonstrating automated optimization operations, this study nicely illustrates the ability to quickly acquire an abundance of reaction data with these platforms.

5. OUTLOOK AND CHALLENGES

We have reviewed a small fraction of the current microfluidic devices, inline reaction-monitoring techniques, and applications being explored for reaction development and optimization. This is a rapidly emerging field, with research groups continuously improving reactor designs to transfer current and new laboratory batch processes to miniaturized, continuous-flow operations. It is closely related to process-intensification efforts within the chemical industry (152). However, a number of challenges remain. Perhaps the most important ones for chemical synthesis are the design of flow reactors and the development of methods to (*a*) handle solids generated as by-products in many common organic chemistry reactions and (*b*) introduce solid reagents. Increasing

the channel size often reduces the chance that solids will accumulate and clog a microreactor but at the cost of slower diffusion time scales and reduced heat-transfer rates. Solutions to handling solids in microsystems will require innovative designs, new operating procedures, and advances in surface-coating techniques. Furthermore, for microreactors to lead to a paradigm shift in reaction development in the industry setting, scale-up and scale-out strategies must be developed and understood in detail.

Integration of physical and chemical sensors with microreactors for continuous monitoring of the reaction conditions will be a critical first step in implementing automated microreactor systems. Subsequent implementation of logic and feedback algorithms will enable automated screening, process control, and optimization. The resulting automated microreactor system will become a platform technology that could revolutionize development and production chains across the laboratory and production scales. Benefits from automated continuous-flow systems for reaction screening and intelligent systems capable of determining the optimal operating conditions have already been realized. However, embedding the mind and decision-making skills of a chemical researcher into an automated microreactor system for reaction development is a clear challenge when the objective function is not obvious or when the trade-offs among yield and catalyst consumption, production throughput, and ultimately profit are uncertain. Alternatively, this information could be accumulated indirectly through use of automated microfluidic systems to estimate kinetic parameters or to construct a comprehensive, multiresponse surface. Increased automation and data acquisition will require advances in efficient extraction, storage, and utilization of reaction data warehouses. Development of experimental protocol to identifying experimental failures, such as clogged microreactors or analytical errors, to avoid tainting these reaction libraries with misinformation will also be necessary.

Complications for automated microfluidic systems compound as the size of the microchemical network grows. Inline pumps, multistage counter-current separation systems, and actuated valves with minimal dead volume that are compatible with conditions for typical organic reactions represent a set of unit operations required to realize multistep chemical synthesis. Furthermore, control schemes for these microdevices that offer stable operation with fast dynamics are required for the adoption of multistage microchemical systems in total synthesis research. Realization of effective complex systems will require multidisciplinary collaborations among chemists, engineers, microfabricators, and software developers.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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Contents

Indexes

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