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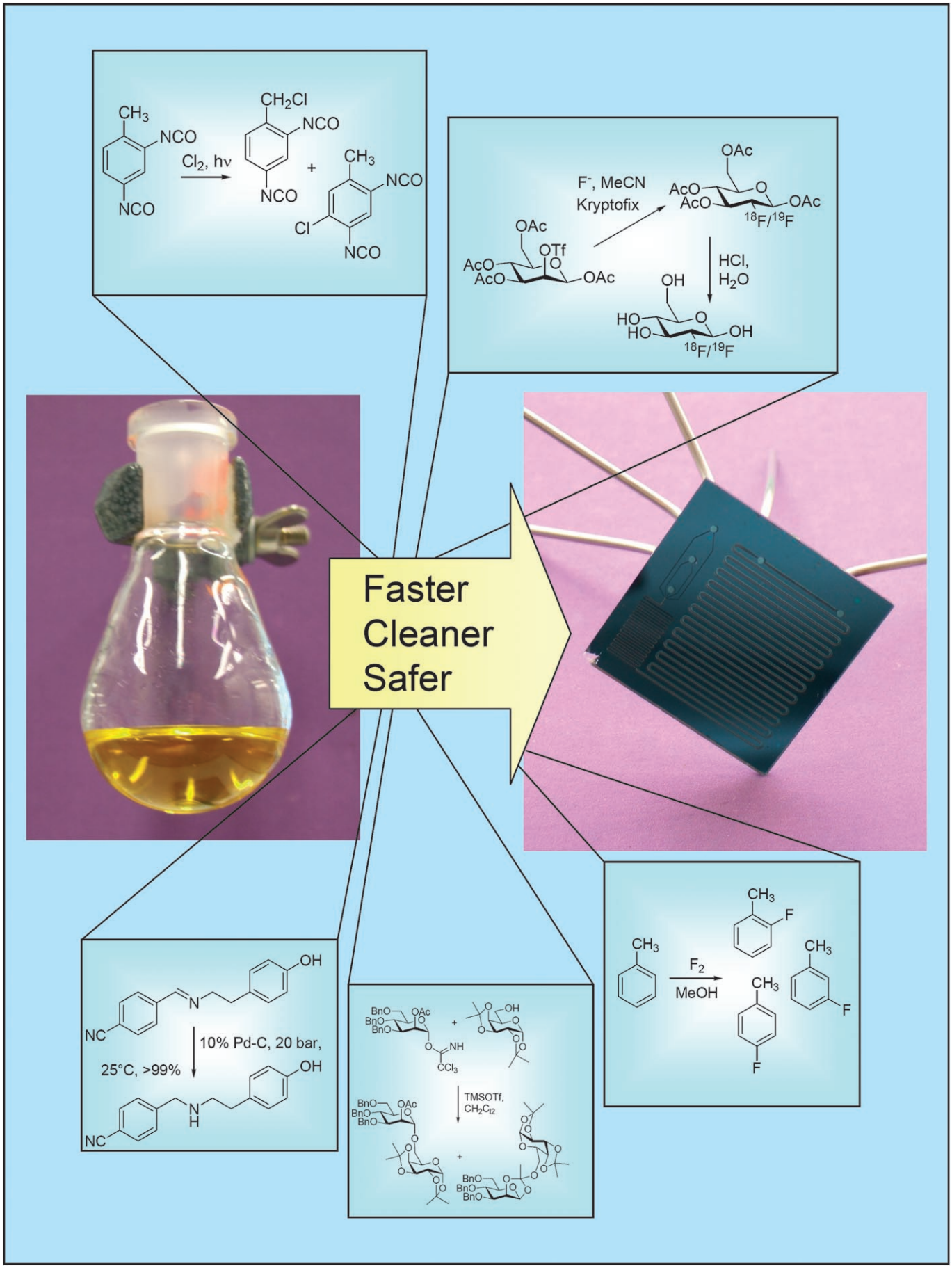

Microreactors as Tools for Synthetic Chemists—The Chemists' Round-Bottomed Flask of the 21st Century?

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Abstract: Will microreactors replace the round-bottomed flask to perform chemical reactions in the near future? Recent developments in the construction of microstructured reaction devices and their wide-ranging applications in many different areas of chemistry suggest that they can have a significant impact on the way chemists conduct their experiments. Miniaturizing reactions offers many advantages for the synthetic organic chemist: high-throughput scanning of reaction conditions, precise control of reaction variables, the use of small quantities of reagents, increased safety parameters, and ready scale-up of synthetic procedures. A wide range of single- and multiphase reactions have now been performed in microfluidic-based devices. Certainly, microreactors cannot be applied to all chemistries yet and microfluidic systems also have disadvantages. Limited reaction-time range, high sensitivity to precipitating products, and new physical, chemical, and analytical challenges have to be overcome. This concept article presents an overview of microfluidic devices available for chemical synthesis and evaluates the potential of microreactor technology in organic synthesis.

Keywords: automation · continuous-flow · integrated microchemical systems · microreactors · process optimization

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Introduction

Ever since the dawn of chemistry, chemists have relied on round-bottomed flasks to perform their experiments. Synthetic chemists typically perform transformations on a scale ranging from several milligrams to many grams in reaction volumes from less than one milliliter to several liters. Much time and energy is consumed for the optimization of chemical transformations and the search for ideal reaction conditions. Having found the optimal conditions to achieve a certain reaction on a small scale, process scale-up often poses additional challenges and requires further adjustment of the reaction parameters. To come up with an adequate general solution to these classic hurdles in synthetic chemistry, microstructured continuous-flow reactors and chip-based microreactors are becoming increasingly popular.[1] The small dimensions of microreactors allow for the use of minimal amounts of reagent under precisely controlled conditions, and make it possible to rapidly screen reaction conditions and improve the overall safety of the process. To obtain synthetically useful amounts of material, the reactors are simply allowed to run for a longer period of time, the so-called "scale-out" principle.[2] Alternatively, several reactors are placed in parallel ("numbering up"), assuring identical conditions for the "analytical" and "preparative" modes. Several aspects of microreactor chemistry have been reviewed previously.[2–14] Here, we focus on some recent developments and conceptual implications of microreactor technology for synthetic chemists. Using some selected examples, this concept article illustrates how this new technological platform can be utilized in organic synthesis, with a focus on academic applications. Microreactor technology is now being investigated widely in fine chemical and pharmaceutical industry,[13] where microreactors are employed for specific production processes, and several success stories have already been reported.[2,15]

Types of Microfluidic Reactors

Generally, microreactors consist of a network of miniaturized channels, often embedded in a flat surface, the "chip".[1,3,17–23] In recent years, a variety of reactors have been developed and several of them are now commercially available. The applicability of a reactor is defined by its size, the chemical and physical properties of the material used for its construction, and the mode of reagent and solvent introduction to the system. To illustrate the diversity in miniaturized reaction devices reported to date, a small selection of microreactors is presented in Table 1 and Figure 1.[24] A range of materials, including glass, silicon, stainless steel,

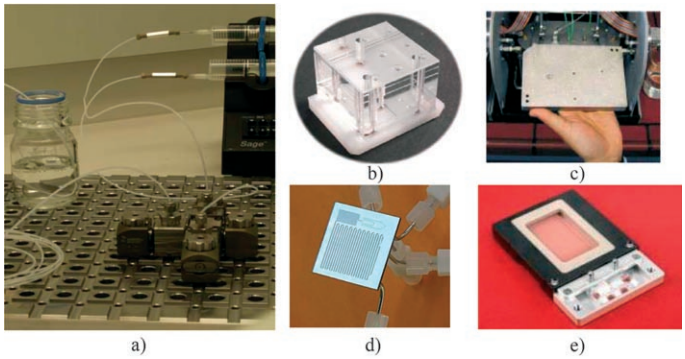


Figure 1. Selected microreactors; a) Stainless steel microreactor system designed by Ehrfeld Mikrotechnik; b) Glass microreactor made by Haswell;[7] c) Stainless steel microreactor of the CYTOS® Lab system;[35] d) Silicon-based microreactor designed by Jensen;[33] e) Glass microreactor of the AFRICA-System.[30]

metals, and polymers have been used to construct microreactors.[3,25] For synthetic chemists, glass has been traditionally the most popular material to work with in the lab, since it is chemically inert to most reagents and solvents and its transparency enables the visual inspection of a reaction. The favourable material properties and the availability of well-established fabrication procedures, such as photolithography,[7,26–29] have made glass one of the most popular materials for the construction of microreactors. The commercially available AFRICA[30] microreactor system for example can be equipped with glass reactors of different sizes (60 μL, 250 μL, and 1.0 mL).[30]

Silicon has also found widespread use in the construction of microreactors, since methods developed for semiconductor chip production can be readily applied to create a host of three-dimensional architectures.[9,31,32] When oxidized, silicon behaves very similar to glass and is chemically inert to most reagents and solvents. Due to the excellent thermal conductivity of silicon, in contrast to glass, microreactors can be constructed with outstanding heat-transfer capabilities. Therefore, silicon microreactors are attractive for exothermal reactions as well as reactions that require very high or low temperatures.[33] In addition, silicon-based microsensors can be readily incorporated in the reactors.[9]

Stainless steel is the material of choice for process chemistry. Consequently, stainless steel microreactors have been developed, including complete reactor process plants and modular systems, to tailor reactor configurations from a set of micromixers, heat exchangers and tube reactors. The dimensions of these reactor systems are generally larger than the previously mentioned glass and silicon reactors. These mesoscale reactors are primarily of interest for pilot-plant and fine-chemical applications, but are rather large for academic synthesis laboratories. Commercially available systems include the CYTOS® Lab system,[35] with an internal volume of 1.1 mL and 0.1 mL, and the modular microreactor system designed by Ehrfeld Mikrotechnik.[36] The different types of microreactors for this reactor system include capillary and cartridge reactors, that have internal volumes in the 0.5–11.0 mL range.[36] IMM provides a wide variety of stainless steel microreaction systems including micromixers, heat exchangers, and reactors for multiphase reactions.

Polymer-based microreactor systems, made of poly(dimethylsiloxane) (PDMS), for example, with inner volumes in the nanoliter to microliter range,[37] are relatively inexpensive and easy to produce. Injection-molding, hot-embossing, or phase-separation-micromolding techniques are used to prepare polymer-based reactors. The polymers do not tolerate many solvents used for organic transformations, and show limited mechanical stability and low thermal conductivity. Thus, the application of these reactors is mostly restricted to aqueous chemistry at atmospheric pressure and temperatures in the area of biochemical applications.[37–39]

Flow Types and Introduction of Solvents and Reagents

Fluids can be moved through the channels of microreactors by using methods such as hydrodynamic pumping, electrokinetic pumping, or capillary flow. The most straightforward approach to operate a microreactor from the synthetic chemist's point of view is to drive solutions through the reactor by hydrodynamic pumping. A broad range of flow speeds from $\mu L\,min^{-1}$ to $L\,min^{-1}$ can be achieved readily by the use of either syringe or HPLC pumps. In glass microreactors, fluids can be immobilized by using electroosmotic flow (EOF), in which a voltage is applied to the reagent and collection reservoirs. This mode of "pumping" has certain advantages over hydrodynamic pumping as it involves no moving parts and can be readily miniaturized and carefully computer controlled. However, EOF requires polar solvents, depends on the solute concentration, may cause unwanted electrochemical transformations and/or separations, and can only be applied to analytical scale reactors. Capillary flow techniques are also of limited use in organic synthesis. Although precise control over fluid amounts can be achieved, the volumes transported through the capillary reactors are very small.[5,40]

Independent of the mode of pumping, the flow inside the channel network of chip-based microreactors is generally laminar and the mixing of reagents occurs by diffusion and convection.[41] Given the small dimensions of the devices,

Table 1. Pros and cons of selected types of microreactors.

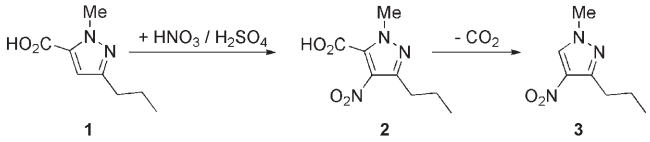
Material	System	Fabrication	Flow	Internal volume	Advantages	Disadvantages	Applications	References
glass	Haswell–Watts	photolithography	electroosmotic flow, hydrodynamic pumping	nL–μL range	reaction optimization, chemically inert, visible light detection, electrophoresis[a]	not a real continuous-flow process, electrophoresis,[a] small reactor dimensions	peptide synthesis, nitrations, Suzuki coupling, aldol chemistry, olefinations	[4, 7, 28, 42–48]
glass	SYRRIS		hydrodynamic pumping	60 μL, 250 μL, 1 mL	reaction optimization, chemically inert, lab scale, automated system, variable system concerning reactor size	only for temperatures above 0 °C	cycloadditions, cross couplings, Claisen reactions, oxidations, reductions	[30]
silicon	Jensen–Seeberger	wet/dry etching	hydrodynamic pumping	80 μL	reaction optimization, chemically inert, simple system, coating of the channel walls possible		peptide synthesis, fluorinations, glycosylations, photochemistry, hydrogenation	[31–33]
stainless steel	Ehrfeld	etching, μ-EDM	hydrodynamic pumping	0.5–11 mL	chemically inert, lab scale, large scale syntheses reported, modular to special purpose	not comfortable for small-scale synthesis	cross-couplings, cycloadditions, nitrations, acylations, alkylations, olefinations	[50–52]
stainless steel	CPC		hydrodynamic pumping	100 μL, 1.1 mL	reaction optimization, chemically inert, lab scale, automated system, large scale syntheses reported, variable reactor sizes		hydroborations, cross-couplings, cycloadditions, Wittig reaction, Mitsunobu reaction	[53]
stainless steel	Thales		hydrodynamic pumping	2.5 mL	reaction optimization, lab scale, automated system, continuous-flow hydrogenation, several catalyst cartridges (Pd, Pt, Rh), no external hydrogen source	unstable to THF, CH_2Cl_2, DMSO; use only for hydrogenations	selective hydrogenations	[54–58]
plastic	no special supplier	soft-lithography	osmosis, "pumping"	nL–mL range	cheap and fast fabrication	not stable to organic solvents, limited mechanical stability	protein crystallisation, assembly of polyelectrolyte, microcapsule patterns, protein digestion	[37–39]

[a] Electrophoretic separation may occur due to the voltage applied, this might be either an advantage or a disadvantage.

diffusion is generally very efficient, and mixing is effected within milliseconds.

Synthesis in Microchemical Systems

Due to the small dimensions and the increased surface to volume ratio of microreactors, mass and heat transport are significantly more efficient than in the classic round-bottomed flask. Efficiency is even higher when compared to an industrial production plant. The mixing of reagents by diffusion is very fast, and heat exchange between the reaction medium and reaction vessel is highly efficient. As a result, the reaction conditions in a continuous-flow microchannel are very homogenous, and can be precisely controlled. Highly exothermic and even explosive reactions can be readily harnessed in a microreactor. The careful control of reaction temperature and residence time has a beneficial effect on the outcome of a reaction with respect to yield, purity, and selectivity. In the following section, some selected examples of mono-, bi-, and triphasic reactions are presented to illustrate the potential application of microreactors to organic synthesis. It should be mentioned that most progress has been made in process and production chemistry. Until now, the application of microreactors to academic total synthesis is still limited.

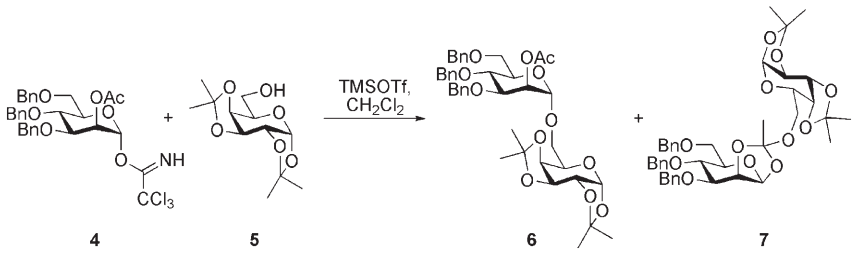


Scheme 1. Nitration of substituted pyrazole-5-carboxylic acid **1** in a stainless steel reactor.

carbon dioxide is generated by the undesired decarboxylation and long reaction times (10 h) are required.

Synthesis in the stainless steel microreactor of the CYTOS® lab system resulted in the highly controlled formation of nitropyrazole **2**. Side reactions such as decarboxylation were minimized due to accurate temperature control in the continuous-flow microreactor. The process was operated with a residence time of 35 min and a throughput rate of 5.5 g h^{-1}, yielding 73% of the desired product.[16]

The use of microreactors for reaction optimization is illustrated for a glycosylation reaction (Scheme 2). In general, glycosylations are very challenging, since their stereochemical outcome depends on a wide variety of factors, such as



Scheme 2. Glycosylations in a microreactor.

Liquid-Phase Reactions

A wide range of liquid-phase reactions have been performed in microreactor devices, such as Grignard reactions,[59] nitrations,[16,49] glycosylations,[60] olefinations,[46,47,60] peptide couplings,[28,61,62] aldol reactions,[44] epoxidations,[60] multicomponent reactions,[63] and Swern oxidations[64] to name just a few. As mentioned above, liquid-phase reactions carried out in microstructured devices benefit from the efficient mass and heat transport characteristics of microreactors and the fact that only small amounts of the reactants are in the system at any given time. In general, reactions performed in microreactors should be reasonable fast and should not produce precipitating products or byproducts that might clog up the reaction channel.[34]

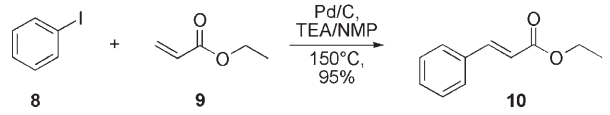
The development of improved processes for the electrophilic nitration of aromatic compounds is highly desirable from an industrial viewpoint, since these reactions are difficult to perform on large scale due to safety concerns. The nitration of 1-methyl-3-propyl-1*H*-pyrazole-5-carboxylic acid **1** (Scheme 1), a key intermediate in the synthesis of the drug Sildenafil®, is problematic in large batches. Temperature control during quenching is difficult, a large amount of the nature of the coupling partners, temperature, solvent and concentration. Furthermore, the building blocks used for oligosaccharide assembly often require multistep syntheses and are precious synthetic intermediates themselves. By using a Jensen silicon microreactor system, the reaction progress of the coupling between mannoside **4** and galactoside **5** was monitored as a function of temperature and time.[33] It was revealed that at low temperatures (−80 °C to −70 °C) and short reaction times (<1 min) the formation of orthoester **7** was favoured, whereas higher temperatures (−40 °C) and longer reaction times (~4 min) led to the formation of the desired α-linked product **6**. Using as little as 100 mg of starting materials, 40 different reaction conditions were scanned within one day. The crude reaction mixtures were analyzed off-line using LCMS.

Liquid–Solid-Phase Reactions

Chemical transformations requiring solid starting materials, intermediates, or products are difficult to carry out in microreactors, since solids may clog the channel network and hamper the continuous flow. To carry out reactions that use

solid catalysts, several different approaches have been reported. Catalytically active metals may be used to cover the inner walls of a reactor or may be placed on miniaturized poles in the reactor channels.[9,43] Alternatively, catalysts can be loaded on polymer beads in pre-packed reaction cartridges that are placed in the reactor channel.[58,60,65] Independent of the way of immobilization, all approaches benefit from a very high surface to volume ratio, characteristic of the microreactor platform. Highly effective interaction of the phases leads to considerable reaction rate enhancements.

Metal-catalyzed cross-coupling reactions are key transformations for carbon–carbon bond formation. The applicability of continuous-flow systems to this important reaction type has been shown by a Heck reaction carried out in a stainless steel microreactor system.[60] A solution of phenyliodide **8** and ethyl acrylate **9** was passed through a solid-phase cartridge reactor loaded with 10% palladium on charcoal (Scheme 3). The process was conducted with a residence time of 30 minutes at 130°C, giving the desired ethyl cinnamate **10** in 95% isolated yield. The batch process resulted in 100% conversion after 30 minutes at 140°C using a pre-conditioned catalyst.



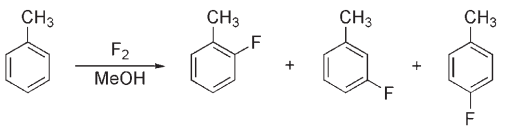
8 **9** **10**

Scheme 3. Heck reaction forming ethyl cinnamate (**10**) in a stainless steel flow-through reactor.

Liquid–Gas Reactions

Synthetic transformations that make use of corrosive and toxic gases are generally difficult to perform, because of the hazardous and highly reactive nature of the gases. Specially designed liquid–gas microreactors allow for the careful control of gas flow in the reactor and to regulate the contact time between gas and liquid. Integrated gas–liquid separators can be introduced to separate the gaseous phase at the end of the reaction.[6] The utility of microreactors for this chemistry has been illustrated for fluorination,[32,66–71] chlorination,[72,73] nitration,[74] and oxygenation reactions.

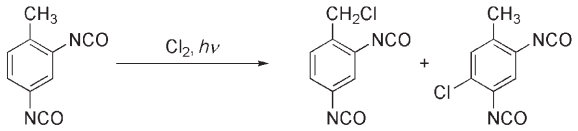
The direct fluorination of toluene was performed at room temperature in a silicon microreactor that was internally coated with nickel to render it compatible with the corrosive gas (Scheme 4).[32] Fluorination reactions that make use of elemental fluorine are highly exothermic and difficult to control using conventional equipment. Taking full advantage of the highly efficient mass and heat transport as well as the presence of only a small amount of fluorine at any given time in the reactor, monofluorination of toluene was achieved with very good selectivity. By using five equivalents of elemental fluorine in methanol as solvent, 96% conversion was reported, yielding the monofluorinated toluenes *ortho*-**12**, *meta*-**13**, *para*-**14** in a ratio of 3:1:2.[32]



11 **12** **13** **14**

Scheme 4. Direct fluorination of toluene in a microreactor.

In a photochemical reaction, the side-chain chlorination of toluene-2,4-diisocyanate **15** was investigated (Scheme 5).[72] A nickel microreactor was equipped with a quarz window to allow for the irradiation of the reaction mixture and to generate chlorine radicals from gaseous chlorine. Light penetrates through most of the reactor depth of the miniaturized reaction channels. Due to the high surface to volume ratio, the local concentration of chlorine radicals is significantly lower and results in higher selectivities. 1-Chloromethyl-2,4-diisocyanatobenzene (**16**) was generated with 55% conversion and a selectivity of 80%, almost suppressing the formation of the undesired side product **17**. When the reaction was performed in a traditional glass vessel, a higher conversion (65%) was achieved, but the selectivity was seriously reduced (45%).[72]



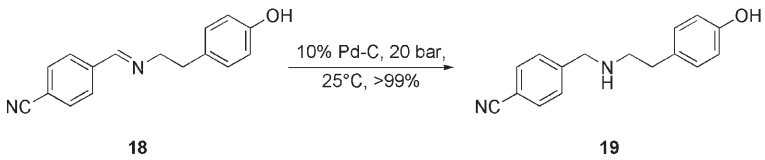
15 **16** **17**

Scheme 5. Photochlorination of toluene-2,4-diisocyanate (**15**).

Liquid–Gas–Solid Reactions

Multiphase catalytic reactions, such as catalytic hydrogenation and oxidation reactions, are important in academic research laboratories, and chemical and pharmaceutical industries alike. The reaction times are often long due to poor mixing and interactions between the different phases. The use of gaseous reagents itself may cause various additional problems (see above). As mentioned previously, continuous-flow microreactors ensure higher reaction rates due to an increased surface to volume ratio and allow for the careful control of temperature and residence time.

Reductive amination reactions are key transformations en route to many drug substances. However, reversibility, functional group incompatibility, and over-reduction can create problems. The reduction of aryl imines often gives rise to secondary amines that are contaminated with the corresponding primary amine, due to over-reduction. A commercially available hydrogenation reactor (H-cube®), which combines continuous-flow microchemistry with on-demand hydrogen generation, allows for the catalytic reduction of imines with high chemoselectivity (Scheme 6).[58,75]

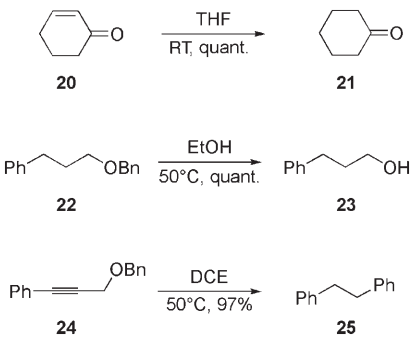


18 19

Scheme 6. Chemoselective hydrogenation of imine **18** in a hydrogenation reactor.

Hydrogenation of imine **18**, by employing a catalyst cartridge with 10% palladium on charcoal at 20 bar hydrogen pressure, yielded the desired amine **19** quantitatively and in high purity. Notably, other functional groups such as the nitrile and the benzyl were not affected.[58]

Using a palladium-coated micro channel reactor, Kobayashi et al. reduced benzyl groups, and double and triple bonds through effective gas–liquid–solid reactions (Scheme 7). The alkyne in **24** was chemoselectively reduced in the presence of the benzyl ether.[76]



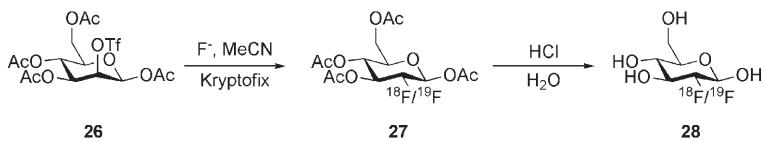
20 21 22 23 24 25

Scheme 7. Examples of hydrogenation reactions carried out in a palladium-coated microreactor.

Multistep Syntheses

Multistep syntheses that make use of interconnected microreactors will eventually be a way to create complex molecules in a flow through mode. It also allows the use of unstable intermediates, which can be generated in the first reactor and then immediately fed onto the second one. Some multistep syntheses performed with microreactor technology have already been carried out. The radiolabeled imaging probe 2-deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]FDG; **28**) was prepared in a poly(dimethylsiloxane) (PDMS)-based microreactor, whereby all reaction steps were conducted in one single device (Scheme 8).[77] A highly sophisticated, tailor-made chip was designed that sequentially executed the following steps: 1) concentration of the dilute [^{18}F]fluoride solution by using anion exchange column techniques; 2) solvent change, water to acetonitrile; 3) nucleophilic substitution of the mannosyl triflate **26**; 4) solvent change, acetonitrile to water; 5) acidic hydrolysis of the acetate protecting groups to obtain the [^{18}F]FDG (**28**). The entire process was automated and required 14 minutes; for comparison the existing batch process takes 50 minutes. This acceleration is significant when taking the half-life of [^{18}F]fluorine, 110 minutes, into account. Compound **28** was produced in 38% radiochemical yield and radiochemical purity of 97.6%, and was directly used for positron emission tomography (PET) imaging studies in mice.[77]

Although the synthesis of **28** serves as an impressive example to illustrate the potential of microreactor synthesis, it is by no means a routine operation. Notably, the reaction conditions had previously been optimized extensively for the batch process.



26 27 28

Scheme 8. Synthesis of the radiolabeled imaging probe [^{18}F]FDG (**28**) in a PDMS-based microfluidic reactor.

Conclusion and Outlook

Many chemical reactions can become faster, safer, and cleaner. The down-scaling of reaction volumes in a microreactor offers a means to superbly control reaction conditions, including temperature, time, mixing, and to use minute amounts of precious compounds to rapidly screen a variety of conditions, generating a wealth of information on reaction kinetics and pathways. Microreactors present opportunities to apply conditions that are inaccessible with conventional laboratory equipment, such as super heated solvents, and reactions in "explosive" regimes. However, there are also inherent drawbacks associated with the miniaturized format: the reactors are incompatible with solid reagents, very sensitive to precipitating products,[34] and are synthetically mainly useful for relatively fast reactions (in turn, slow reactions can be turned into fast ones by using unconventional conditions only achievable in microreactors!). The efficient and effective analysis of reaction mixtures in a high-throughput format represents a major outstanding issue. Real-time on-line analysis has been accomplished by using mass spectrometry, IR spectroscopy, and UV/VIS absorbance, and currently on-chip NMR technology is being developed. However, organic synthesis of complex molecules requires analytical methods that can distinguish between regio- and stereochemically different compounds, for which MS, IR, UV/VIS and low-resolution NMR techniques are inadequate. Off-line HPLC, LCMS, or GC-MS are currently the most commonly applied techniques to analyze reactions conducted in microreactors.

Before microreactor technology will be employed as a standard academic synthetic re-

search tool, it will have to become more readily commercially available. Eventually, cheap, easy-to-use, flexible microreactors will be used as a valuable alternative to the round-bottomed flask.

[1] The term "microreactor" is generally used to describe microstructured reactors. In fact the reactors are often a lot bigger then the term "microreactor" suggests, having internal volumes of several milliliters. So far microstructured reactors have found most applications in process and development chemistry. Chip-based microreactors incorporate much smaller channels and are therefore more suitable for synthetic purposes in an academic setting.

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[24] A wide variety of other microreactors is available from other manufacturers and suppliers, for example: Institute for Microtechnology Mainz (IMM), Fraunhofer Alliance for Modular Microreaction Systems (FAMOS), the New Jersey Centre for MicroChemical Systems (NJCMCS), the MicroChemical Process Technology Research Association (MCPT). The selection presented here is by no means exhaustive and only serves to indicate the diversity in systems developed to date.

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