Reviews

Benchmarking of Microreactor Applications

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Abstract:
At present, the aims of the investigations with microchemical processing devices are changing from simply proving feasibility for one chemical reaction towards more in-depth scientific studies and industrial piloting. In this way, large data sets are gathered, providing multifaceted information on the topic. To enable industrial exploitation of the technology, future investigations should aim to complete the economic evaluation of the methodology for plant engineering. Hence, commercially oriented studies have to be undertaken, not with the aim to further broaden the scope of information, but rather to achieve a new system-oriented level of know-how. Since this involves the interaction of many parties with many different skills, it is a bridging function that is needed to bring the vast amount of findings documented to a compact format and to compare it to the state of the art in the chemicals-producing industry. Accordingly, this contribution reviews many chemical reactions carried out in either credit-card-sized microdevices or in larger microflow processing tools for reasons of screening/analysis and organic synthesis/industrial piloting, respectively. Quantities which characterize the process itself, the product on a molecular and supramolecular level, and the downstream processing are compared for both microreactor and conventional processing, benchmarking the performance of microflow devices at minute and large throughput levels.

Introduction

Microchannel process devices gain interest not only for academic investigations but also for uses in the chemical industry.[1-9] MEMS (*m*icroelectro *m*echanical *s*ystems)-based chips with a microchannel architecture in one plane serve for chemical screening or analysis (Figure 1); precision-engineered microflow devices having a three-dimensional
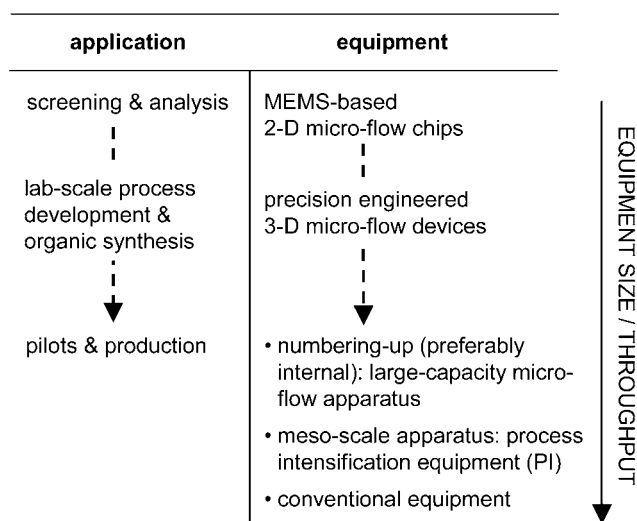

Figure 1. Stages of microreaction technology.

(3D) microchannel architecture are used for lab-scale development or organic synthesis, as the investigations may refer to the process itself or the material to be produced, respectively. Pilot operation and production with chemical microprocessing apparatus is not directly evident for a large number of cases since the companies involved keep this as secret as possible. However, the increasing practice can be deduced from the growing number of industrial patents, the larger number of industrial participants at microreactor conferences, and the increasing sales of the supplier companies in the field. This feeling that the business is expanding steers the foundation of platforms worldwide which promotes a breakthrough in the microreaction technology.

However, the way to achieve this is not clear at present. Hence, in the future, probably a multitude of processing solutions will cope with the tasks, which differ in scale as the most distinctive feature (the *multiscale concept*). This includes the simple numbering up of microchannels, done preferentially in an internal manner, mesoscale processing, preferably by process intensification (PI) equipment, or even using conventional equipment. Concerning the first approach, one has to be aware that the first large-capacity devices such as microflow mixers and heat exchangers have been reported, achieving liquid throughputs in the m^3 h^{-1} range.[10-14]

However, newcomers still consider the technique to be inscrutable, due to its interdisciplinary nature, and fear unforeseen consequences of an abrupt change in their way of processing, when switching from large batch tanks to

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(1) Ehrfeld, W.; Hessel, V.; Löwe, H. *Microreactors*; Wiley-VCH: Weinheim, 2000.
(2) Hessel, V.; Hardt, S.; Löwe, H. *Micro Chemical Process Engineering*; Wiley-VCH: Weinheim, 2004.
(3) Jensen, K. F. *Chem. Eng. Sci.* **2001**, *56*, 293.
(4) Gavriilidis, A.; Angeli, P.; Cao, E.; Yeong, K. K.; Wan, Y. S. S. *Trans. Inst. Chem. Eng.* **2002**, *80/A*, 3.
(5) Hessel, V.; Löwe, H. *Chem. Eng. Technol.* **2003**, *26*, 13.
(6) Hessel, V.; Löwe, H. *Chem. Eng. Technol.* **2003**, *26*, 391.
(7) Hessel, V.; Löwe, H. *Chem. Eng. Technol.* **2003**, *26*, 531.
(8) Fletcher, P. D. I.; Haswell, S. J.; Pombo-Villar, E.; Warrington, B. H.; Watts, P.; Wong, S. Y. F.; Zhang, X. *Tetrahedron* **2002**, *58*, 4735.
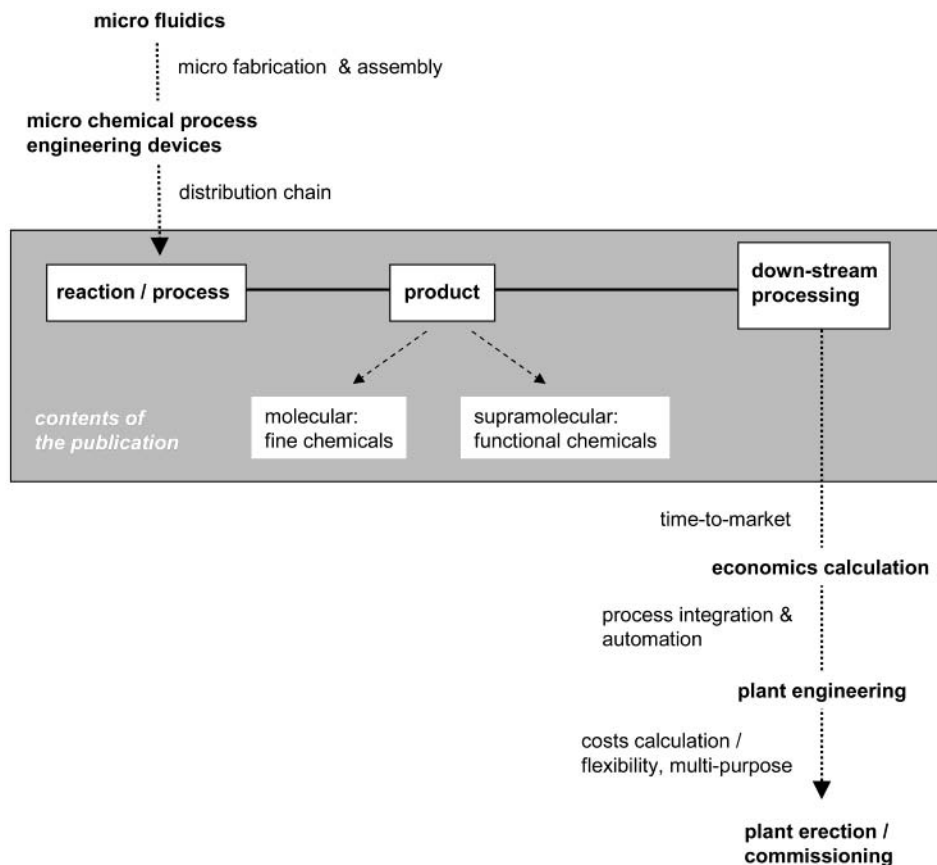(9) Haswell, S. J.; Watts, P. *Green Chem.* **2003**, *5*, 240.

Figure 2. Contents of the present publication.

smaller continuous-flow devices (see also the Conclusions of this article and Table 27). Nobody wants to take the lead on his own; thus, the situation can be described as "wait-and-see". While more and more decision makers believe in the performance of the microprocessing devices themselves and do not consider the technology to be immature any more, they ask at the same time for a complete picture of the processing, i.e., including a detailed engineering design and economics calculation (Figure 2).

For such a comprehensive view, initially all performance data are required. Most initial investigations were concerned with comparing selectivity and space-time yields, thus proving the feasibility of carrying out a chemical reaction in a microchannel. When the devices changed from scientists' playthings to accepted professional processing tools, this led to further requests on more in-depth data, e.g., with regard to loss of catalyst during longer runs, spectra and morphology of crystallites, and product purity. Besides specification on molecular quantities, information on supramolecular properties was now desired. Having raised commercial interest in this way, one nowadays is faced with questions on outlining a whole production process scenario, e.g., regarding the impact of other processing operations (i.e., separation), energy efficiencies of the process, consequential costs for equipment, process controllability and safety, overall profitability of the process and multipurpose flexibility. This includes such detailed aspects as how using the microreactor affects and simplifies downstream separation or how much this may help to decrease the amount of coolant water, for instance. It therefore stands to reason that we need more

information and preferably more qualified data on micro-reactor processing, the latter being based on existing knowledge of chemical processes in industry. Accordingly, qualified data should first of all allow benchmarking of microreactor information.

After five years of intensive research with now more than 1000 publications (among them about 450 peer-reviewed) microreactor benchmarking can be done with regard to the following: (1) the reaction/process, (2) the product properties, and (3) the impact on downstream processing (Figure 2). These issues will be addressed in this publication; however, giving an economic calculation or details on the plant engineering behind the technique is out of the scope of this paper.

Typical parameters which can be derived from the reaction/process are the experimental protocol of an organic reaction (e.g., temperature or reaction time), performance parameters of the process (e.g., selectivity or space-time yield), product features (e.g., isomer ratios or particle size distribution), and finally features of downstream processing (e.g. energy efficiency or safety measures) (Figure 3).

In the following sections, the benchmarking of these parameters will be discussed for microreactor vs conventional processing. It will be given as a short text for each reaction and will be summarized as a table, comparing the performance data of a microreactor with those of traditional chemical apparatus. The reactions are put into two classes, one referring to small-scale applications and one to lab- and pilot-scale synthesis. The first class have flow rates typically up to several milliliters per hour, and the flow rates of the
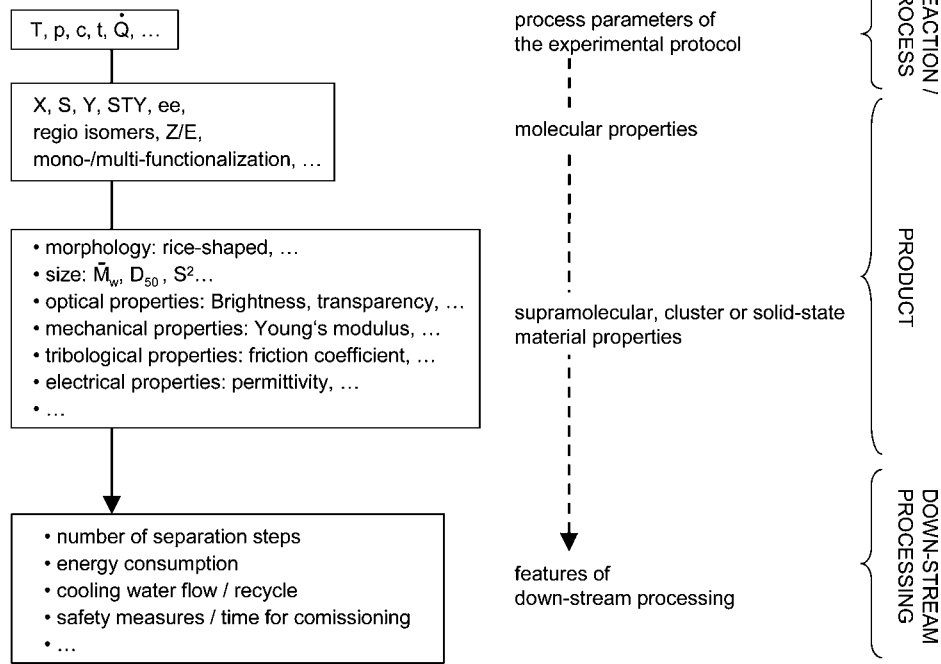
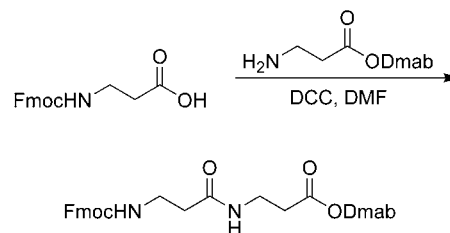**Figure 3.** Parameters suitable for benchmarking of microreactors.[15]

latter range from several milliliters per hour up to several tens of liters per hour (Table 1).

Microreactors Used for Small-Scale Applications: Liquid Reactions

Peptide Synthesis. Peptides and peptide-related molecules are present in many pharmaceutically important compounds, and consequently, the pharmaceutical industry is particularly interested in developing improved methodology for their preparation.

Watts et al. have recently demonstrated multistep peptide synthesis in a borosilicate glass microreactor operating under electrokinetic control.[16,17] The authors evaluated their device using a carbodiimide coupling reaction of Fmoc-β-alanine with an amine to give the dipeptide (Scheme 1). When stoichiometric quantities of the reagents were used, approximately 10% conversion to the dipeptide was achieved. By using two equivalents of DCC however, an increase in
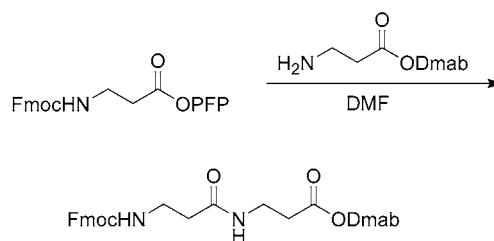
(10) Schubert, K.; Brandner, J.; Fichtner, M.; Linder, G.; Schygulla, U.; Wenka, A. *Microscale Thermophys. Eng.* **2001**, *5*, 17.
(11) Löb, P.; Drese, K. S.; Hessel, V.; Hardt, S.; Hofmann, C.; Löwe, H.; Schenk, R.; Schönfeld, F.; Werner, B. *Chem. Eng. Technol.* **2003**. In press.
(12) Haynes, B. S.; Wegeng, R. S. In *Topical Conference Proceedings*; IMRET 6, 6th International Conference on Microreaction Technology, AIChE Spring National Meeting, March 11–14, 2002, New Orleans, LA; American Institute of Chemical Engineers: New York, NY, 2002; pp 223–237.
(13) Edge, A. M.; Pearce, I.; Phillips, C. H. In *Proceedings of 1st International Conference on Process Intensification for the Chemical Industry*; Green, A., Ed.; BHR Group Conference Series, Vol. 38, pp 175–189; Professional Engineering Publishing Ltd., 1997.
(14) Information about Atotech's heat exchanger can be found on the homepage (http://www.atotech.com) or in a patent: Breuer, N.; Meyer, H. (Atotech Deutschland GmbH). WO 98/37457, Priority: February 20, 1997.
(15) *T*: temperature, *p*: pressure, *c*: concentration, *t*: reaction time, $\dot{Q}$: flow rate, X: conversion, S: selectivity, Y: yield, STY: space-time yield, ee: enantiomeric excess, *Z/E*: isomers with a C=C-bond, $\bar{M}_w$: weight-average molecular weight, D_{50}: median particle diameter, S^2: mean square radius of gyration.
(16) Watts, P.; Wiles, C.; Haswell, S. J.; Pombo-Villar, E.; Styring, P. *Chem. Commun.* **2001**, 990.
(17) Watts, P.; Wiles, C.; Haswell, S. J.; Pombo-Villar, E. *Tetrahedron* **2002**, *58*, 5427.

Scheme 1. Dipeptide synthesis with β-amino acids

conversion to 20% was observed, and by applying a stopped-flow technique (2.5 s injection length with stopped-flow for 10 s), the conversion of the reaction was further increased to approximately 50%. Using five equivalents of DCC, a conversion of up to 93% for the dipeptide was obtained using the stopped-flow technique described, as summarized in Table 2.

The authors also demonstrated that the dipeptide could be prepared from preactivated carboxylic acids.[16,17] They report that the reaction of the pentafluorophenyl (PFP) ester of Fmoc-β-alanine with the amine gave the dipeptide quantitatively in 20 min (Scheme 2). This represented a significant increase in yield compared with the traditional batch synthesis, where only a 60% yield was obtained in 120 h.

Scheme 2. Dipeptide synthesis with activated β-amino acids

Table 1. Summary of the published parameters and properties of organic reactions in microreactors

x = parameter or property mentioned in this review

+ = additional information in the citation

[a] down-stream processing

Column groups — **small-scale applications**: peptide synthesis … hydrogenation reactions. **lab-scale synthesis**: hydrolysis & transglycosylation … fluorination of non-aromatics.

group	parameter	peptide synthesis	Suzuki reaction	Kumada–Corriu reaction	aldol reaction	Michael addition	enamine synthesis	Hantzsch reaction	dehydration reactions	hydrogenation reactions	hydrolysis & transglycosylation	diazotation & diazo coupling	aromatic nitration	nitration of urea derivatives	phenylboronic acid formation	Sonogashira coupling	polyacrylate formation	addition of organometallic reagents	cumene hydroperoxide rearrangement	methylation of aromatics	oxidation of ethanol	photo chlorination of alkyl aromatics	chlorination of acetic acid	hydrogenation of nitro compounds	fluorination of aromatics	fluorination of non-aromatics
process parameter	temperature					x	x			x			x	x	x	x	x	x	+	x	x	x	x	x	x	x
	pressure																		+	x			x	x	x	
	reactant concentration	x			+	+	+						x		+	+			x	x					x	x
	flow rate			+									x		x	x	x	x		x	x	x	x	x	x	x
	reaction time	x	x	x	x	x	x	x	x	x	x		x	x	x		x	x	+	x	x	x			x	+
	reaction rate			+							x		x													
	interfacial area											x													+	
	heat transfer area																		x							
molecular properties	conversion	x	x	x	x	x	x	x	x	x	x	x	x									x			x	x
	yield			+											x	x		x		x	x	x		x	x	
	selectivity									x				x						x	x				x	x
	space-time yield																			x	x				+	
	isomeric ratio	x											x												x	
supramolecular properties	color strength											x														
	brightness											x														
	transparency											x														
	particle size											x														
	molecular weight distribution																x									
d.-s. proc.[a]	recycle ratio																				x				x	
	purification											x												x		

Table 2. Benchmark of the microreactor

	microreactor	batch reactor
1. DCC coupling reactions (5 equiv)		
reaction time	20 min	24 h
conversion	up to 93%	92%
2. active ester coupling reaction		
reaction time	20 min	120 h
conversion	100%	60%
3. deprotection chemistry (DBU or hydrazine)		
reaction time	20 min (1 equiv)	several hours (100 equiv)
conversion	100%	100%

Having demonstrated that peptide bonds could be successfully formed using a microreactor, the authors then found that they could extend the methodology to the preparation of longer-chain peptides.[18] Using the microreactor, the Dmab ester of Fmoc-β-alanine was reacted with one equivalent of piperidine or 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU) to give the free amine in quantitative conversion. This is in comparison to the solid-phase peptide synthesis where 20% piperidine in DMF is frequently employed. The authors then reacted the amine in situ with a pentafluorophenyl ester derivative to give the dipeptide (Scheme 3) in 96% overall conversion.

Scheme 3. Methodology for the preparation of longer-chain peptides
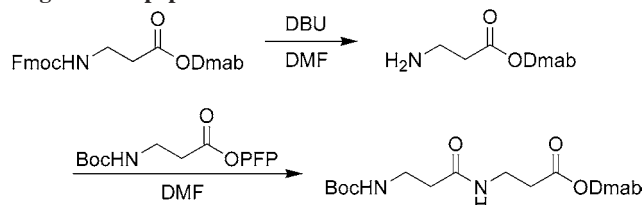
Having shown that more complex peptides could be produced by removal of the *N*-protecting group, the authors then demonstrated that they could remove the Dmab ester using hydrazine.[18] The reaction of the Dmab ester with one equivalent of hydrazine gave quantitative deprotection to afford the carboxylic acid (Scheme 4). This is in comparison

**Scheme 4.** Deprotection by hydrazinolysis
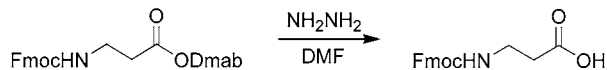
to the solid-phase peptide synthesis where 2% hydrazine in DMF is generally used to effect deprotection.

The authors have further extended the approach to the synthesis of tripeptides. Reaction of a pentafluorophenyl ester with an amine formed a dipeptide, which was reacted with DBU to effect Fmoc deprotection. The amine was then reacted in situ with another equivalent of the pentafluorophenyl ester to prepare the tripeptide in 30% overall conversion (Scheme 5). The approach clearly demonstrates that intermediates may be generated in situ and used in

Scheme 5. Synthesis of tripeptides
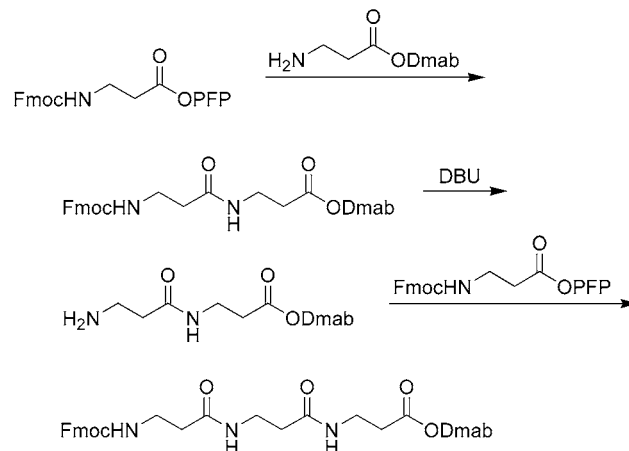
subsequent reactions. Although in the above examples the intermediates are relatively nontoxic, it is postulated that the approach may be used to generate highly toxic reagents in situ, consequently, this is an approach that one would like to use in a large-scale synthesis.

Synthesis of peptides containing α-amino acids is far more problematic as a result of racemization. Having demonstrated that peptide bonds could be successfully formed when using a borosilicate glass microreactor, the authors then investigated racemization in a model compound, namely α-phenylbutyric acid.[19] Reaction of the pentafluorophenyl ester of *R*-2-phenylbutyric acid (0.1 M concentration) with α-methyl-benzylamine gave the product in quantitative conversion with 4.2% racemization (Scheme 6). Significantly this was less

Scheme 6. Racemization control experiment
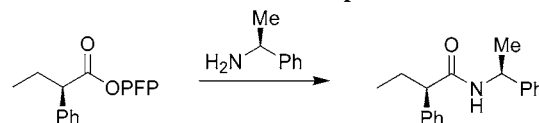
racemization than observed in the batch reaction at the same concentration and temperature. The reduced level of race-mization was attributed to the reduced reaction times observed within the microreactors.

Furthermore, the authors have reported that it is possible to purify the reaction mixture within the microreactor by exploiting the differential electrophoretic mobilities of the individual components of the reaction mixture.[20]

Suzuki Reaction. Heterogeneous catalysis is of significant industrial importance for the synthesis of fine chemicals and pharmaceuticals. However, to isolate the product it is necessary to remove the catalyst from the reaction mixture, which further complicates the procedure. Consequently, microreactors involving the use of immobilized catalysts represent a method to overcome this problem.

Greenway et al. have demonstrated the Suzuki reaction within a borosilicate glass microreactor in which electro-osmotic flow was used as the pumping mechanism.[21] The

(18) Watts, P.; Wiles, C.; Haswell, S. J.; Pombo-Villar, E.; Styring, P. In *Topical Conference Proceedings*; IMRET 5, 5th International Conference on Microreaction Technology, AIChE Spring National Meeting; Matlosz, M., Ehrfeld, W., Baselt, J. P., Eds.; Springer-Verlag: Berlin, 2001; pp 508−519.

(19) Watts, P.; Wiles, C.; Haswell, S. J.; Pombo-Villar, E. *Lab Chip* **2002**, *2*, 141.

(20) George, V.; Watts, P.; Haswell, S. J.; Pombo-Villar, E., *Chem. Commun.* **2003**, 2886.

catalyst, 1.8% palladium on silica, was immobilized between microporous silica frits prepared from potassium silicate and formamide. The boronic acid derivative was reacted with an aryl bromide to give a 68% conversion to cyanobiphenyl at room temperature within the microreactor (Scheme 7).

Scheme 7. Suzuki coupling
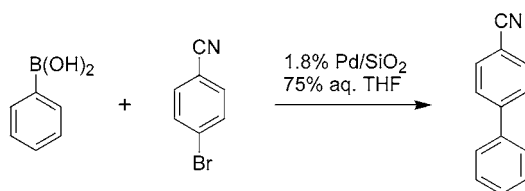
Traditionally, tetrahydrofuran (THF) is used as the solvent in this reaction; however, as has been found with many organic solvents, THF has very low natural EOF properties, and for this reason it was mixed with water (75:25) for use in these experiments. The yields obtained were comparable with those from Suzuki reactions on a batch scale using homogeneous catalysis. Importantly, there were negligible levels of the palladium catalyst in the product, demonstrating the environmental benefits of the technology (Table 3).
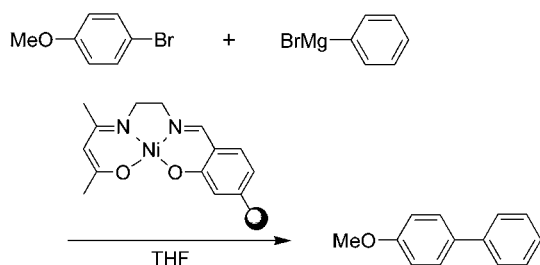
Table 3. Benchmark of the microreactor

	microreactor	batch reactor
reaction time	6 s	8 h
conversion	68%	60%
solvent	water/THF (1:3)	THF

One of the interesting observations of the reaction was that, unlike conventional Suzuki reactions, an additional base was not required. Although the exact reason for this is unclear, it is postulated that the electric field may be sufficient to cause ionization of the water at the metal surface. It is feasible that the hydroxide formed in this way may be sufficient to perform the function of the conventional base.

Kumada−Corriu Reaction. In another example of heterogeneous catalysis, O'Sullivan et al. have recently investigated the Kumada−Corriu reaction in a pressure-driven microreactor.[22] The reactor was constructed by placing a plug of catalyst into a length of polypropylene tubing. A syringe pump was used to drive a premixed solution containing equimolar quantities of the aryl halide and Grignard reagent through the reactor.

The authors reacted p-bromoanisole with phenylmagnesium bromide, in the presence of the nickel catalyst which was supported on Merrifield resin, to give 4-methoxybiphenyl (Scheme 8). When the reaction was conducted in the

Scheme 8. Kumada−Corriu reaction

microreactor, an enhanced reaction rate was observed compared to that of the batch reactions (Table 4). Since the

Table 4. Benchmark of the microreactor

	microreactor	batch reactor
reaction time	10 min	25 h
conversion	60%	70%

concentrations were the same in the both cases, the authors postulated that the dimensions of the microreactor were solely responsible for the enhanced rate of reaction.

Aldol Reaction. Carbanion chemistry is one of the most common methods of C−C bond formation used in the pharmaceutical industry. In such reactions, large volumes of highly pyrophoric bases are frequently employed. In many cases the selectivity of the reaction is temperature dependent; consequently, microreactors have a considerable attraction for these reactions because the reactor enables excellent temperature control of the reaction.

Wiles et al. have recently demonstrated the use of silyl enol ethers in the aldol reaction within a borosilicate glass microreactor operating under electrokinetic control.[23] Quantitative conversion of the silyl enol ethers to β-hydroxy-ketones was observed in 20 min compared to traditional batch systems, where quantitative yields were only obtained when extended reaction times of up to 24 h were employed (Table 5). One example involved the treatment of the TMS enol

Table 5. Benchmark of the microreactor

	microreactor	batch reactor
reaction time	20 min	24 h
conversion	100%	100%

ether with tetra-n-butylammonium fluoride (TBAF) to generate the tetra-n-butylammonium enolate in situ, followed by condensation with p-bromobenzaldehyde to give the β-hydroxyketone in 100% conversion (Scheme 9).

Scheme 9. Aldol reaction
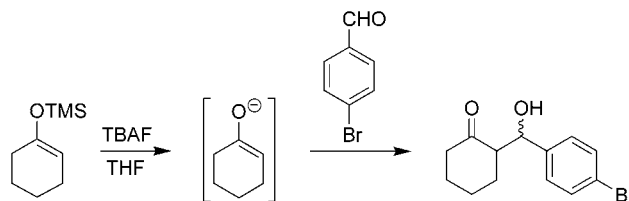
Michael Addition. Another example of enolate-type chemistry performed within a microreactor has been reported by Wiles et al.[24] The authors reported the preparation of enolates from a series of 1,3-diketones using an organic base

(21) Greenway, G. M.; Haswell, S. J.; Morgan, D. O.; Skelton, V.; Styring, P., *Sensors Actuators B* **2000**, *63*, 153.
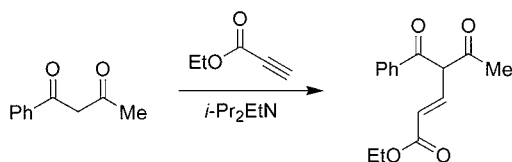(22) Haswell, S. J.; O'Sullivan, B.; Styring, P. *Lab Chip* **2001**, *1*, 164.
(23) Wiles, C.; Watts, P.; Haswell, S. J.; Pombo-Villar, E. *Lab Chip* **2001**, *1*, 100.
(24) Wiles, C.; Watts, P.; Haswell, S. J.; Pombo-Villar, E. *Lab Chip* **2002**, *2*, 62.

and their subsequent reaction with a variety of Michael acceptors to afford 1,4-addition products within a microreactor (Scheme 10).

Scheme 10. Michael addition

When using a continuous flow of the reagents, 15% conversion to the adduct was observed. The authors, however, demonstrated enhancements in conversions through the application of the stopped-flow technique. This procedure involved the mobilization of reagents through the device for a designated period of time, using an applied field, and the flow was subsequently paused by the removal of the applied field, prior to reapplying the field. Using the regime of 2.5 s on and 5 s off, the conversion to the product was improved to 34%, while lengthening the stopped-flow period to 10 s, resulted in a further increase to 100% (Table 6). The authors

Table 6. Benchmark of the microreactor

	microreactor	batch reactor
reaction time	20 min	24 h
conversion	100%	89%

proposed that the observed increase in conversion, when using the technique of stopped-flow, was due to an effective increase in residence time within the device and hence an increase in the diffusive mixing of the reagent streams.

Enamine Synthesis. Sands and co-workers have recently reported the preparation of enamines within a microreactor.[25] Enamines are traditionally prepared under Dean and Stark conditions, where the ketone and secondary amine are heated to reflux in toluene. These conditions remove the water from the reaction to produce the equilibrium-dependent enamine; however, it is difficult to perform the reaction on a large scale. To remove the water from the reaction by distillation it is necessary to use a high-boiling point solvent and to heat the reaction at typically 120 °C, which clearly requires large amounts of energy.

By using a borosilicate glass microreactor operating under electrokinetic control cyclohexanone was reacted with pyrrolidine using methanol as the solvent to form the enamine (Scheme 11) in 42% conversion at room temperature (Table

Scheme 11. Enamine synthesis
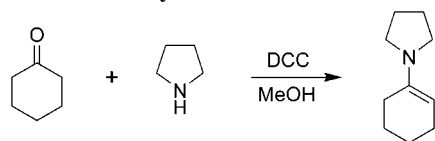
7), rather than at the elevated temperatures discussed above. To assist in removing the water, one equivalent of DCC was used in the reaction. Clearly, the use of methanol as solvent

(25) Sands, M.; Haswell, S. J.; Kelly, S. M.; Skelton, V.; Morgan, D.; Styring, P.; Warrington, B. *Lab Chip* **2001**, *1*, 64.

Table 7. Benchmark of the microreactor

	microreactor	batch reactor
reaction time	20 min	not reported (probably several hours)
conversion	42%	not reported
temperature	25 °C	120 °C

at room temperature, compared with the traditional conditions, represents a more environmentally friendly procedure. In this case also, the electrophoretic mobility of the product is thought to be greater than that of water, thus enabling product separation in situ. Consequently exploitation of the individual electrophoretic mobilities of the individual reactants and products enables control of the thermodynamics of the reaction.

Hantzsch Reaction. Industrially, special equipment is required when performing large-scale reactions at elevated temperature, such as reflux condensers. Consequently, the ability to use microreactors at elevated temperatures using the scale-out principle is of commercial interest.

Garcia-Egido et al. have demonstrated the synthesis of a series of 2-aminothiazoles using a Hantzsch reaction within a microreactor.[26] During the experiments the T-shaped microreactor was heated to 70 °C using a Peltier heater, which was aligned with the channels, and the heat generated by the device was applied to the base of the microreactor. Reaction of an α-bromoketone with a thiourea derivative, using NMP as solvent, resulted in the preparation of an aminothiazole in 85% conversion (Scheme 12 and Table 8).
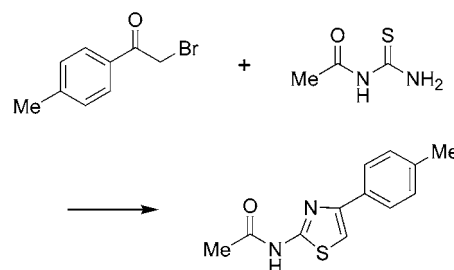
Scheme 12. Hantzsch reaction

Table 8. Benchmark of the microreactor

	microreactor	batch reactor
reaction time	30 min	not reported
conversion	85%	up to 99%
temperature	70 °C	70 °C

A range of aminothiazole derivatives were prepared using alternative α-bromoketones as starting materials.

Dehydration Reactions. Wilson and McCreedy have reported the use of a microreactor to perform the dehydration of alcohols using a sulfated zirconia catalyst.[27] The microreactor was fabricated from a glass plate, which was etched using photolithography. A PDMS top block, with predrilled holes to act as reservoirs for the reagents, was then aligned

(26) Garcia-Egido, E.; Wong, S. Y. F.; Warrington, B. H. *Lab Chip* **2002**, *2*, 31.
(27) Wilson, N. G.; McCreedy, T. *Chem. Commun.* **2000**, 733.

with the channel geometry. To introduce the catalyst into the microreactor, it was dusted over the surface of the PDMS face before the base plate was joined to the top plate. This process immobilized the catalyst, while simultaneously increasing its surface area. The overall effect was to produce a catalytically active wall of the microchannel. A heater, fabricated from Nichrome wire, was also immobilized in the PDMS top plate. Pumping was produced with a syringe pump, and the products were analyzed by gas chromatography (GC). The conversion of hexan-1-ol to hex-1-ene was between 85 and 95%, and no additional products were detected (Scheme 13). This yield is extremely good when

Scheme 13. Dehydration of alcohols
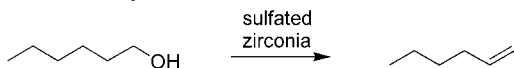
compared to the 30% expected for the industrially used process (Table 9).

Table 9. Benchmark of the microreactor

	microreactor	batch reactor
reaction time	20 min	not reported
conversion	85−95%	30%

The reaction was also applied to ethanol. At a reaction temperature of 155 °C and using a syringe pump at a flow rate of 3 μL min^{-1}, the product was found to contain 68% ethene, 16% ethane, and 15% methane, together with trace amounts of ethanol. When electroosmotic pumping was used, the flow rate obtained was between 0.9 and 1.1 μL min^{-1} at a field strength of 200 V cm^{-1}. The only detectable product was methane, indicating that the reaction had progressed beyond dehydration to complete cracking of the ethanol. Additionally, trace amounts of methanol were present in the product. It is proposed that the slow flow rate of the electroosmotic pumping method results in longer residence times in the reactor, thus offering a significant advantage over the syringe pump. Electroosmotic flow (EOF), however, cannot be applied to all reactions because organic reactants, such as hexanol, exhibit no natural EOF under an applied potential.
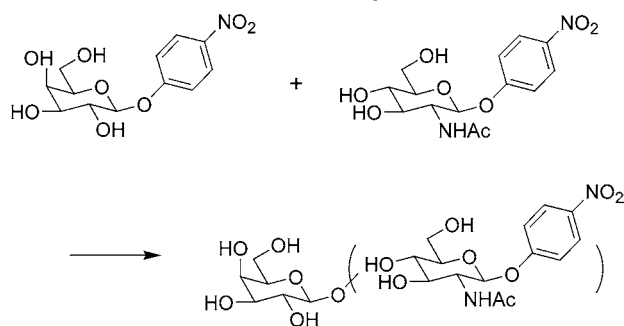
Hydrolysis and Transglycosylation of β-D-Galactopyranoside Derivatives. Two enzyme-catalyzed reactions were carried out in a microchip reactor by Kanno et al. At first p-nitrophenyl-β-D-galactopyranoside was hydrolyzed with a β-galactosidase from *Escherichia coli* (Scheme 14) and a

Scheme 14. Hydrolysis of p-nitrophenyl-β-D-galactopyranoside
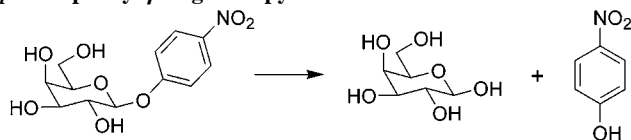
transgalactosylation of a p-nitrophenyl-2-acetamide-2-deoxy-β-D-glucopyranoside was carried out (Scheme 15).[28]

(28) Kanno, K.; Maeda, H.; Izumo, S.; Ikumo, M.; Takeshita, K.; Tashiro, A.; Fujii, M. *Lab Chip* **2002**, *2*, 15.

Scheme 15. Transglycosylation of β-D-galactopyranoside

As a microreactor, a mechanically fabricated microchip made of PMMA was used. The chip consisted of a two-plate assembly. One plate featured the microchannels having a cross section of 200 μm × 200 μm and length of 40 cm, and the second plate covered the microchannel. The microchip is designed for contacting two liquids, whereas the mixing is realized by a micro Y-piece. For temperature control a hot plate is used.

For the hydrolysis, the p-nitrophenyl-β-D-galactopyranoside solution and the enzyme solution were pumped into the microchip using microsyringes with identical flow rates (several μL min^{-1}). The microchannel was maintained at 37 °C. After leaving the microchip, the reaction mixture was quenched into hot water to inactivate the enzyme. The resulting raw product was analyzed by LC−MS. For the second experiment, the transgalactosylation, the pure p-nitrophenyl-β-D-galactopyranoside solution was replaced by a mixture of p-nitrophenyl-β-D-galactopyranoside and nitrophenyl-2-acetamide-2-deoxy-β-D-glucopyranoside.

Due to different flow rates, the residence times of the reaction mixture inside the microchip were varied. It was found that the hydrolysis of p-nitrophenyl-β-D-galactopyranoside (Scheme 14) in the microchip was 5 times faster than in a batch reactor. According to this, a higher conversion was determined by the use of the microchip reactor (Table 10). Although the reaction rate of the transgalactosylation

Table 10. Comparison of the microchip reactor with respect to a microtest tube concerning the hydrolysis and transgalactosylation of β-D-galactopyranoside derivatives

	microchip reactor (continuous)	microtest tube (batch)
	1. hydrolysis	
reaction rate	5 times faster than batch	
conversion	0.16 (after 8 min)	0.01 (after 8 min)
	2. transgalactosylation	
reaction rate	faster than batch	
conversion	0.04 (after 11 min)	0.01 (after 10 min)

(Scheme 15) is comparably low, an acceleration of the latter could be detected in the case of the microchip reactor.

Microreactors Used for Lab- and Pilot-Scale Synthesis: Liquid or Liquid/Liquid Reactions

Diazotization and Diazo Coupling. Previous publications refer to various process conditions. Salimi-Mososavi et al. conducted diazotization reactions under EOF, while Wootton

Table 11. Diazo coupling in various microreactors
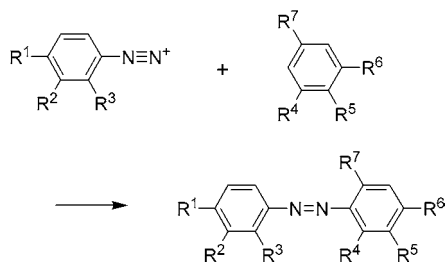
entry	ref	R¹	R²	R³	R⁴	R⁵	R⁶	R⁷
1	25	NO$_2$	H	H	H	H	NMe$_2$	H
2	26)	H	H	H	naphthyl	H	OH	
3	26	H	Me	H	naphthyl	H	OH	
4	26	H	H	Me	naphthyl	H	OH	
5	27	NO$_2$	H	H	OH	H	OH	Me
6	28	substituents not disclosed						

et al. used a microreactor operating under hydrodynamic flow conditions for a similar reaction (Table 11, No. 1−4).[29,30] In comparison, Hisamoto et al. realized the azo chemistry using phase-transfer synthesis in a glass microchip (Table 11, No. 5).[31] A first attempt to transfer a microreactor-based azo-pigment process from lab scale into a pilot-plant process was described by Wille et al. (Table 11, No. 6).[32]

Whereas the experimental results obtained within microchip reactors based on EOF were not compared with those from batch experiments, the publication referring to the glass microchip published by Hisamoto et al. provides such information (Table 11, No. 5).[31] The latter reactor consisted of a microchannel (cross section: 250 μm × 100 μm, length: 3 cm) fabricated on a glass chip. The contacting of the two phases was realized by a micro Y-piece on the chip, which ensured the formation of a stable two-phase flow consisting of two lamellae.

To determine the efficiency of the glass-chip reactor (Table 11, No. 5) the diazo coupling was carried out in the microreactor and a glass vessel (diameter: 3.5 cm). In the first case syringe pumps were used to realize a total flow rate of 10 μL min^{-1} for each phase. The macro-scale benchmark test using a glass vessel was carried out with 10 mL of both phases and different stirring conditions. The product was analyzed by reversed phase HPLC.

Using the glass-chip reactor (Table 11, No. 5) it was found that the conversion is close to 100% within 2.3 s, whereas the strongest stirring of the glass vessel leads to approximately 80% conversion after 10 min (Table 12). This is in accordance with the specific interface surface area of the microreactor, which is twice as high as that of the glass vessel. Furthermore, the high conversion in connection with the short reaction time demonstrates that the phase-transfer

(29) Salimi-Moosavi, H.; Tang, T.; Harrison, D. J. *J. Am. Chem. Soc.* **1997**, *119*, 8716.
(30) Wootton, R. C. R.; Fortt, R.; de Mello, A. J. *Lab Chip* **2002**, *2*, 5.
(31) Hisamoto, H.; Saito, T.; Tokeshi, M.; Hibara, A.; Kitamori, T. *Chem. Commun.* **2001**, 2662.
(32) Wille, C.; Autze, V.; Kim, H.; Nickel, U.; Oberbeck, S.; Schwalbe, T.; Unverdorben, L. In *Topical Conference Proceedings*; IMRET 6, 6th International Conference on Microreaction Technology, AIChE Spring National Meeting, March 11−14, 2002, New Orleans, LA; American Institute of Chemical Engineers: New York, NY, 2002; pp 7−17.

Table 12. Diazo coupling in a strong stirred vessel as benchmark for the glass microchip

	glass microchip	strong stirred glass vessel
conversion	~100%	80%
reaction time	2.3 s	~10 min
interfacial area	80 cm^{-1}	40 cm^{-1}

conditions in the glass-chip reactor were instrumental in suppressing the formation of the bis-azo product, a literature-known side reaction.

As a microreactor for the lab-scale and pilot-plant azo-pigment process (Table 11, No. 6) the standard laboratory reactor CYTOS provided by CPC, Germany was used.[32] The latter was stacked-plate units comprising of mixing and reaction zones, as well as including an integrated heat exchanger. For the pilot plant a numbering-up concept by connecting three reactors in parallel was realized.

The laboratory-scale reactor (Table 11, No. 6) was used with flow rates of 20 and 80 mL min^{-1}, leading to residence times of several seconds. In the case of the pilot plant the total flow rate was increased up to 500 mL min^{-1}, resulting in an output of 10 t a^{-1}. All experiments were carried out at laminar flow as well as isothermal conditions. Although preliminary experiments have indicated that the diazotization and the pigmenting step can also be carried out in a microreactor, only the results of the diazo coupling are described. The coupling of two azo pigments, one red and one yellow, were investigated. In the case of the first one, a homogeneous diazo solution was used, and a pigment suspension was formed in the course of the reaction. In contrast, the yellow pigment was synthesized starting with a suspended diazo solution which resulted also in a suspended pigment solution.

Concerning the red pigment synthesized in a lab-scale reactor (Table 11, No. 6) an increased brightness and transparency were determined, which were mainly based on a smaller particle size of the pigments. Even better results were achieved for the yellow pigment, whose color strength was increased by up to 139% (Table 13). For the latter

Table 13. Comparison of the diazo coupling in the microreactor (lab-scale) with respect to the traditional batch reactor

|	microreactor red pigment	microreactor yellow pigment
color strength	119%	139%
brightness	5 steps glossier	6 steps glossier
transparency	5 steps more transparent	6 steps more transparent
particle size: D_{50} (σ)	(not given)	<250 nm (1.5)/batch: 598 nm (2.0)

pigment, a particle size less than 250 nm was found which is significantly smaller compared with that from the batch process (598 nm).

A further reduction of the particle size D_{50} down to 90 nm was achieved by applying the yellow pigment process to the pilot-scale microreactor. Due to the smaller particles,

the color strength of the pigments was increased by up to 149%.

Nitration of Aromatics. Previously investigated reactions refer to the nitration of naphthalene, by Antes et al.[33,34] (Scheme 16, No. 1), of benzene and toluene (Scheme 16,

Scheme 16. Nitration reactions carried out in different microreactors
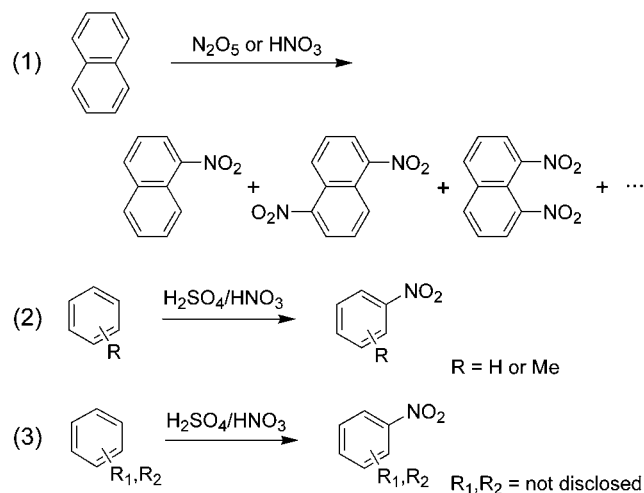
No. 2) by Burns et al.,[35,36] and substituted aromatic compounds (Scheme 16, No. 3) by Dummann et al.[37]

Antes et al. used three micromixers which were connected to tubular reactors (PTFE capillary of length: up to 150 cm) (Scheme 16, No. 1). The micromixers were based on different mixing principles such as multilamination (interdigital micromixer, Institut für Mikrotechnik Mainz GmbH, Germany (IMM)), split-recombine (silicon-based micromixer, University of Ilmenau, Germany), and T-piece mixing (glass micromixer, mgt mikroglas technik Mainz, Germany (mgt)).

The nitrations (Scheme 16, No. 1) were carried out at −10 to 50 °C using gaseous dinitrogen pentoxide as a nitration agent, or at 30 °C using fuming HNO_3 diluted in dichloromethane. Typical residence times were in the range of 15−45 s using a flow rate of 1 mL min^{-1}. After a quenching and an extraction step, the product composition was determined by HPLC and GC analysis.

If gaseous dinitrogen pentoxide was used for the nitration (Scheme 16, No. 1), the highest conversion was achieved by the interdigital micromixer, resulting in dinitrated naphthalene as the main product. By applying fuming nitric acid as the nitration agent, the selectivity changed to the mono-

substituted product, whereas the highest yield was obtained using the glass microreactor. Overall, the results indicate that the selectivity was sensitive to the reaction conditions as well as to which microreactor was used. A brief comparison of these results with those from batch processes is given in Table 14.

Table 14. Nitration of naphthalene in a batch reactor as benchmark for the microreactor

	microreactor	batch reactor
typical reaction temperature for nitrations using N_2O_5	30 °C	−50 to −20 °C
product ratio: 1,5-dinitro:1,8-dinitro	1:2.8	1:3.6
product ratio: 1-mono-nitro:2-mono-nitro	32:1	20:1

To generate a liquid/liquid slug flow various T-pieces (i.d.: 0.5 or 0.8 mm) connected to a capillary reactor (i.d.: 127, 178, or 254 μm; length: 45−135 cm)[35,36] and Y-pieces (inner diameter: 0.5−1 mm) connected to a capillary reactor (i.d.: 0.5−1 mm, length: 1−8 m)[37] were used (Scheme 16, Nos. 2 and 3). The latter reactor featured a heating jacket, which allowed isothermal operation of the reactor.

The nitrations of benzene and toluene[35,36] (Scheme 16, Nos. 2 and 3) were carried out in a temperature range of 60−90 °C using different ratios of nitric acid and sulfuric acid (H_2SO_4: 70−85 wt %) as nitration agents, and different acid/organic solution ratios (2:1 to 7:1). The nitration studies published by Dummann et al. were carried out with mixtures of concentrated sulfuric and nitric acid as a nitration agent and various undisclosed substrates.[37] An isothermal capillary reactor was used to realize reactions temperatures in a range of 60−120 °C. The reactor was operated at 4 bar using total flow rates in the range of 9−36 mL h^{-1}. A GC was used for the analysis.

For the nitration of benzene and toluene (Scheme 16, Nos. 2 and 3) it was found that the reaction rate could be increased by several parameters, e.g. a smaller inner diameter of the tube implying a better mass transfer, a higher sulfuric acid ratio, and a low acid/organic solution ratio. If two of the experiments were compared with patent data, it can be seen that the capillary reactor-based process is competitive (Table 15).[35,36] Especially the high reaction rate in the case of the capillary reactor promises room for improvement if smaller inner diameters are used.

By investigating the nitration reaction in a capillary reactor, Dummann et al. confirmed the published reaction mechanism, which explains the detection of two by-products, a dinitrated and a phenolic one. Further experiments at 60 and 120 °C outline that the amount of by-products can be decreased at lower temperatures. The use of various flow rates show that the by-product composition can be affected by the flow velocity.[37]

Nitration of Urea Derivatives. Due to application of nitrated *N,N′*-dialkyl ureas as new energetic plasticizers, the nitration step was investigated in two microreactors by Antes et al.[33,38,39] It was found that the direct nitration of *N,N′*-diethyl urea resulted in a mixture of mono- and dinitro

(33) Antes, J.; Tuercke, T.; Marioth, E.; Schmid, K.; Krause, H.; Loebbecke, S. *Topical Conference Proceedings*; IMRET 4, 4th International Conference on Microreaction Technology, AIChE Spring National Meeting, March 5−9, 2000, Atlanta, GA; American Institute of Chemical Engineers: New York, NY, 2000; pp 194−200.
(34) Löbbecke, S.; Antes, J.; Türcke, T.; Marioth, E.; Schmid, K.; Krause, H. In *Proceedings of the 31st International Annual Conference ICT: Energetic Materials-Analysis, Diagnostics and Testing*, June 27−30, 2000, Karlsruhe, Germany.
(35) Burns, J. R.; Ramshaw, C. *Trans. Inst. Chem. Eng.* **1999**, 77, 206.
(36) Burns, J. R.; Ramshaw, C. In *Topical Conference Proceedings*; IMRET 4, 4th International Conference on Microreaction Technology, AIChE Spring National Meeting, March 5−9, 2000, Atlanta, GA; American Institute of Chemical Engineers: New York, NY, 2000; pp 133−140.
(37) Dummann, G.; Quittmann, U.; Gröschel, L.; Agar, D. W.; Wörz, O.; Morgenschweis, K. *Catal. Today* **2003**, 79−80, 433.

Table 15. Comparison of the performance of the micro T-piece/capillary reactor with published patent data concerning the nitration of aromatics

type of nitration process	inlet/°C	outlet/°C	H_2SO_4/wt %	conversion/%	by-product/ppm	time/s	rate/min^{-1}
traditional equipment	80	128	60.6	89.5	1000	120	0.9
traditional equipment	80	134	65.2	99.1	2090	120	2.1
traditional equipment	95	120	69.5	90.0	1750	25	4.6
T-piece and 178 μm capillary	90	90	77.7	94.0	4600	24.4	5.9
T-piece and 178 μm capillary	90	90	72.2	60.7	<1000	26.1	1.6

derivatives (Scheme 17, No. 1), which is in accordance to the batch process. Furthermore, a new two-step route to the dinitrated products using thiourea derivatives as the starting compounds was described (Scheme 17, No. 2).

**Scheme 17.** Nitration of *N,N′*-dialkyl urea derivatives
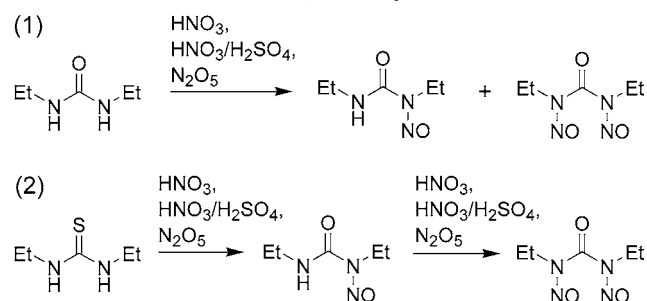
The silicon-based microreactors described in the former section "nitration of aromatics" were used. The nitration was carried out at defined temperatures between 0−20 °C using various nitrating agents such as nitric acid, mixtures of nitric and sulfuric acid, and dinitrogen pentoxide. PTFE capillaries of different lengths were used as residence time loops to realize different reaction times (0.6−82 s).

In accordance with the batch process, the nitration of *N,N′*-diethyl urea in a microreactor resulted in a mixture of mononitro and dinitro derivatives (Scheme 17, No. 1). In comparison, the nitration of corresponding thioureas was successfully carried out in a two-step procedure, resulting at first in the mononitro urea derivative with nearly 100% selectivity (Scheme 17, No. 2). By a second nitration step the respective dinitro derivative was obtained. The latter process was transferred to a batch process using sodium nitrate and sulfuric acid as a nitrating agent, and similar results were achieved, albeit the heat management could be more easily realized in a microreactor setup.

Phenylboronic Acid Formation. The formation of phenylboronic acid by Grignard addition of phenylmagnesium chloride to trimethyl borate was investigated in three micromixers by Hessel et al. and Koch et al. (Scheme 18).[40,41]

To ensure a fast mixing of the substrate solutions, both were contacted by various micromixers. Two mixers made of glass and stainless steel respectively, featured an inter-

Scheme 18. Grignard addition to trimethyl borate and the consecutive hydrolysis step
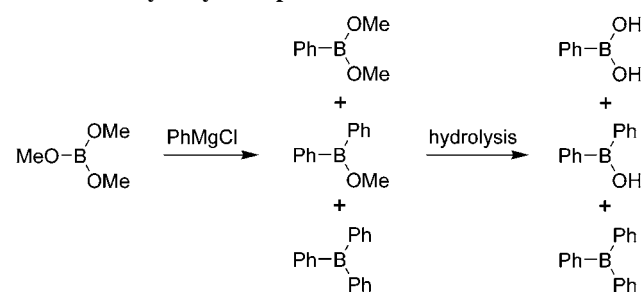
digital channel structure and a geometric focusing section to generate a multilamellae flow with thin lamellae. The third micromixer was based on the split-recombine principle of fluid lamellae and was made of stainless steel. As residence time loops, different tubular reactors were applied. In a typical lab-scale setup the glass micromixer[40] was connected to a PTFE tube (length: 70 cm, i.d.: 2 mm). The caterpillar mixer[40] was used with various stainless steel tubular reactors of 100 cm length (i.d.: 0.7−21.2 mm), resulting in residence times in the range of 1−120 s. The flow rates were chosen with respect to the micromixer.[42] The temperature range was varied between −12 up to 50 °C. Analogous investigations were carried out by Koch et al. using the stainless steel micromixer.[41] The reaction temperature was varied in the range of −20−30 °C, and residence times between 5 and 180 s were realized by applying different flow rates.

The best results for each microreactor are listed in Table 16. It was found that the experimental setups based on micromixers provided higher yields than the batch process using traditional laboratory glassware. Furthermore, the amount of the disubstituted by-product can be decreased from 11% (batch process) down to 0.6% in the case of the stainless steel micromixer.[41] Besides a detailed analysis of by-products, also the fouling in the microstructured devices was addressed by Hessel et al.[40] It was found that the glass mixer can be operated for 15 min only as long as deposition of a white precipitate was visible.

In addition, it is reported that, by achieving high purity of the crude product (99.2%), downstream processing could be considerably facilitated. The previously required distil-

(38) Antes, J.; Tuercke, T.; Marioth, E.; Schmid, K.; Krause, H.; Loebbecke, S. In *Topical Conference Proceedings*; IMRET 4, 4th International Conference on Microreaction Technology, AIChE Spring National Meeting, March 5−9, 2000, Atlanta, GA; American Institute of Chemical Engineers: New York, NY, 2000; pp 194−200.

(39) Löbbecke, S.; Antes, J.; Türcke, T.; Marioth, E.; Schmid, K.; Krause, H. In *Proceedings of the 31st International Annual Conference ICT: Energetic Materials-Analysis, Diagnostics and Testing*, June 27−30, 2000, Karlsruhe, Germany.

(40) Hessel, V.; Löwe, H.; Hofmann, C.; Schönfeld, F.; Wehle, D.; Werner, B. In *Topical Conference Proceedings*; IMRET 4, 4th International Conference on Microreaction Technology, AIChE Spring National Meeting, March 5−9, 2000, Atlanta, GA; American Institute of Chemical Engineers: New York, NY, 2000; pp 39−54.

(41) Koch, M.; Wehle, D.; Scherer, S.; Forstinger, K.; Meudt, A.; Hessel, V.; Werner, B.; Löwe, H. (Clariant GmbH). DE 10140857, Frankfurt, Priority: August 21, 2001.

(42) Flow rates: glass mixer: 3.3−25 mL min^{-1}, caterpillar mixer: 23−167 mL min^{-1}.

Table 16. Comparison of the Grignard addition using different microreactors and traditional laboratory glass ware

	interdigital glass mixer[40]	caterpillar mixer[40]	stainless steel interdigital micromixer[41]	traditional glass ware[41]
yield: $PhB(OH)_2$	83%[a]	89%[a]	95%[b]	83%[b]
by-product yield: $Ph_2B(OH)$	1.4%	0%	0.6%	13.8%
temperature	22 °C	10 °C	20 °C	20 °C
residence time	8 s	10 s	5 s	not given

[a] Determined by HPLC. [b] Isolated yield.

lation step is not needed anymore; instead, purification can be performed by crystallization or extraction. The latter two processes are favorably performed at room temperature, while distillation requires an additional energy supply, rendering the whole process more costly.

Sonogashira Coupling. The coupling reaction was based on a transition metal-catalyzed conversion of aryl halides and monosubstituted acetylenes to disubstituted acetylenes. A copper-free catalyst for this reaction was found by Fukuyama et al. (Scheme 19).[43] The latter was used in the

Scheme 19. Pd-catalyzed coupling of iodo benzene and phenyl acetylene
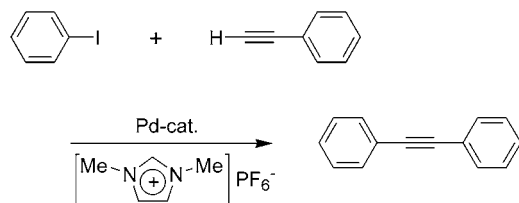
connection with an ionic liquid as the solvent to realize a continuous catalyst recycling system.

The coupling reaction was carried out in an interdigital micromixer having a microstructured mixing device (30 microchannels, width: 40 μm, depth: 200 μm) to generate a multilamellae flow. Furthermore, a T-shaped tubular reactor made of glass (length: 40 mm, i.d.: 2 mm) was used.

The low flow rates of 1.7 μL min⁻¹ for both the substrate solution containing the aryl halide and the acetylene and the Pd-catalyst dissolved in an ionic liquid was realized by syringe pumps. After the liquids were contacted at 110 °C, the reaction mixture was extracted, and the yield was determined by GC analysis.

Concerning catalyst recycling, the results indicate that the microflow system provides yields nearly equal to those of the batch setup using traditional glassware (20 mL round-bottomed flask) (Table 17). In contrast a continuous process

Table 17. Comparison of a microflow system with respect to a batch process in traditional laboratory glass ware concerning the Sonogashira coupling

	microflow system/%	batch process/%
yield of the first run	93	96
yield of the second run	83	80

based on a T-shaped tubular reactor resulted in a low conversion of the substrate.

Formation of Polyacrylates. A radical polymerization of acrylates was investigated by Bayer et al. (Scheme 20).[44,45]

Scheme 20. Radical polymerization of acrylates

Since fouling limited the continuous polymerization process of a lab-scale tubular reactor, investigations were carried to enhance the homogenization of the monomer and initiator by a micromixer.

The setup for polymerization consisted of a tubular reactor (i.d.: 5−20 mm, length: 23−60 m) with static mixers inside and a premixing device. For the latter a Sulzer SMX or a mixer array, a numbering-up version of the stainless steel interdigital micromixer from IMM comprising 10 mixing units, was used.

The polymerization of acrylates was carried out with various monomers and initiators (preferential ratio 9:1) which were not disclosed. As typical reaction conditions, a reaction temperature up to 150 °C and a pressure up to 16 bar were mentioned. The flow rate was adjusted in the range of 6−8 kg h⁻¹ which resulted in a typical residence time of 40 min. The molecular weight distribution was determined by size exclusion chromatography.

In comparison to the Sulzer SMX, it was found that the use of a micromixer array as a premixing device led to an important improvement of the polymerization process. Due to an enhancement of the mixing of monomer and initiator, no molecular weights $>6 \times 10^4$ g mol⁻¹ were found, which prevented fouling inside the tubular reactor (Table 18).

Addition of Organometallic Reagents. The addition of organometallic reagents to carbonyl compounds was the target reaction of Krummradt et al. (Scheme 21).[46] The investigations included the optimization of process parameters using various micro- and ministructured devices.

For the lab-scale experiments the micromixer array from IMM comprising 10 mixing units which generate a multi-

(43) Fukuyama, T.; Shinmen, M.; Nishitani, S.; Sato, M.; Ryu, I. *Org. Lett.* **2002**, *4*, 1691.
(44) Bayer, T.; Pysall, D.; Wachsen, O. In *Topical Conference Proceedings*; IMRET 3, 3rd International Conference on Microreaction Technology, AIChE Spring National Meeting; Ehrfeld, W., Ed.; Springer-Verlag: Berlin, 2000; pp 165−170.
(45) Pysall, D.; Wachsen, O.; Bayer, T.; Wulf, S. (Axiva GmbH). DE 19816886 C1, Priority: April 17, 1998.
(46) Krummradt, H.; Koop, U.; Stoldt, J. In *Topical Conference Proceedings*; IMRET 3, 3rd International Conference on Microreaction Technology, AIChE Spring National Meeting; Ehrfeld, W., Ed.; Springer-Verlag: Berlin, 2000; pp 181−186.

Table 18. Comparison of premixers concerning the polymerization of acrylates

	micromixer	Sulzer SMX
molecular weight distribution	2×10^2–6×10^4 g mol^{-1}	2×10^2–7×10^6 g mol^{-1}
modality of the distribution	bimodal	trimodal
fouling	not found	fouling because of high-weight molecules

Table 19. Comparison of various reactors concerning the addition of organometallic reagents to carbonyl compounds

reactor type	surface/volume ratio/m^2 m^{-3}	T/°C	residence time	yield/%
flask (0.5 L) (lab-scale)	80	−40	0.5 h	88
stirred vessel (6 m^3) (production-scale)	4	−20	5 h	72
micromixer (lab-scale)	10000	−10	<10 s	95
minimixer (pilot-scale)	4000	−10	<10 s	92
5 parallel minimixer (production-scale)	5×4000	−10	<10 s	92

Scheme 21. Addition of organometallic reagents to carbonyl compounds
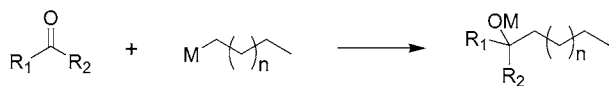
lamellae flow was applied. Due to the deposition of solids inside the microreactor a ministructured mixing unit was designed and used for the pilot-scale experiments. Finally a numbering-up concept containing five minireactors was realized for the production process.

The process optimization was carried out with the micromixer-array-based lab-scale setup. Two flow rates of 6.7 and 33.3 mL min^{-1} were used at different temperatures in the range of −10 to −40 °C and at various substrate concentrations.

The best results for the lab-scale experiments were obtained at a temperature of −10 °C using the higher flow rate. A comparison of this result with those from other experiments carried out in a flask, a stirred vessel, and in the minireactors is summarized in Table 19. It is evident that the continuously operating micro- and ministructured reactors result in much higher yields than the batch reactor. This was enabled by shorter reaction times which prevented side reactions and more efficient heat management by a larger surface/volume ratio.

Although the yield gained by the ministructured mixer was a little bit smaller than that of the micromixer, the minimixer was applied to the production process. Besides the still high surface/volume ratio and the short residence time, the latter device could better face the fouling issue.

Cumene Hydroperoxide Rearrangement. The synthesis of phenol and acetone by means of the acid-catalyzed rearrangement of cumene hydroperoxide was described in a patent by Weber et al. (Scheme 22).[47]

To contact the cumene hydroperoxide and the catalyst solution a multichannel reactor made of stainless steel was used. After splitting both feed streams into a multitude of reaction channels, two channels, one from each stream, were rejoined again. A typical cross section of the microchannels was 100 μm × 5000 μm. The dimensions of the cooling

Scheme 22. Acid-catalyzed rearrangement of cumene hydroperoxide
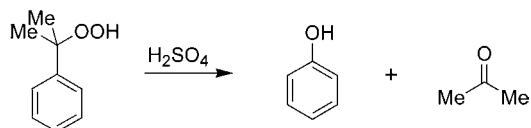
channels of the integrated heat exchanger also had a depth of 500 μm and a width of 5000 μm. Referring to the volume of the reaction channels, the specific heat-transfer area amounted to 10000 m^2 m^{-3}, which ensured sufficient heat transfer even if the cooling circuit failed.

The experiments were carried out with technical solution of 67 wt % cumene hydroperoxide and sulfuric acid as the catalyst. The catalyst feed stream was adjusted until the residual cumene hydroperoxide content was reduced to 1 wt %.

In the case of the microreactor the amount of high-boiling substances in the product stream was reduced down to 0.1 wt %. Conventional processing at a recycle ratio of 17 resulted in 0.21 wt % high-boiling substances (Table 20).

Table 20. Rearrangement of cumene hydroperoxide in a traditional tubular reactor as benchmark for the microreactor

|	microreactor	traditional tubular reactor
yield	0.5% higher than the traditional process	
high-boiling substances	0.12 wt %	0.21 wt %
recycle ratio	2	17

Methylation of Aromatics. The methylation of substituted aromatics was carried out by Wörz using tertiary methylamine (Scheme 23).[48] Since this process is proprietary, the nature of the substituents was not disclosed.

The reactor used for the methylation consisted of three parts. At first, both substrates were contacted in a short tubular pre-reactor (i.d.: 1 mm). Subsequently, the product

(47) Weber, M.; Tanger, U.; Kleinloh, W. (Phenolchemie GmbH & Co. KG). WO 01/30732, Priority: October 22, 1999.

(48) Wörz, O. In *Topical Conference Proceedings*; IMRET 5, 5th International Conference on Microreaction Technology, AIChE Spring National Meeting; Matlosz, M., Ehrfeld, W., Baselt, J. P., Eds.; Springer-Verlag: Berlin, 2001; pp 377−386.

Scheme 23. Methylation of aromatics by tertiarymethylamines
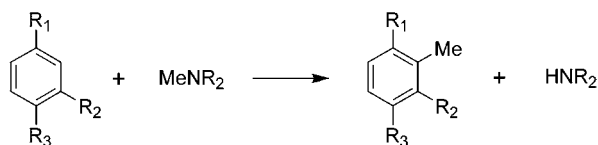
stream was divided into two parts, and both partial streams were guided into a micromixer array (microchannels: 40 μm) provided by IMM to ensure a complete homogenization. Third, a tubular postreactor (i.d.: 1 mm) completed the reaction. The methylation was conducted at 0 °C and was completed within a total residence time of 6 s.

Compared with a former investigated semi-batch process, an equal yield of 95% was achieved by the micromixer-based setup (Table 21). However, two major advantages were

Table 21. Methylation of aromatics in a semi-batch process as benchmark for the micromixer-based process

	micromixer-based process	semi-batch process
yield	95%	95%
temperature	0 °C	−70 °C
reaction time	6 s	15 min

achieved: the reaction temperature was increased from −70 °C (semi-batch) up to 0 °C, and the reaction time was diminished from 15 min down to 6 s.

Oxidation of Ethanol to Acetic Acid. The synthesis of acetic acid by the highly exothermic oxidation of ethanol was investigated by Kraut et al. (Scheme 24).[49] The reaction

Scheme 24. Synthesis of acetic acid by catalytic oxidation of ethanol
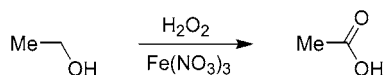
was catalyzed by ferric nitrate using hydrogen peroxide as the oxidant.

As a microdevice a modular microreactor composed of micromixers and microreactors was used. The latter were built as cross-flow heat exchangers. The section for the reactants consisted of 169 channels with a cross section of 150 μm × 300 μm and a length of 6 cm. The section used for the thermo fluid featured 1960 channels with a cross section of 150 μm × 300 μm and a length of 1.8 cm.

The experiments were performed using flow rates between 0.2 to 0.9 kg h^{-1} ethanol, 0.015 to 0.05 kg h^{-1} catalyst solution containing aqueous solutions of 1 mol L^{-1} ferric nitrate and 1 mol L^{-1} acetic acid, and 0.3 to 4 kg h^{-1} hydrogen peroxide solution (35%). The reactants were mixed successively by micromixers and passed through a series of four reaction modules (ignition, reaction, quenching) with cross-flow guided thermo fluids. The inlet temperatures of the modules were set to 70−115 °C. To prevent boiling, the

(49) Kraut, M.; Nagel, A.; Schubert, K. In *Topical Conference Proceedings*; IMRET 6, 6th International Conference on Microreaction Technology, AIChE Spring National Meeting, March 11−14, 2002, New Orleans, LA; American Institute of Chemical Engineers: New York, NY, 2002; pp 352−356.

pressure was adjusted in the range of 3−5 bar. Analysis was performed by in-line NIR flow-cell measurement.

As summarized in Table 22, a yield and a selectivity of

Table 22. Oxidation of ethanol in a continuous stirred tank as benchmark for the microreactor

	microreactor	continuous stirred tank
residence time	3 s	1760 s
pressure	3−5 bar	atmospheric
conversion	>99%	30−95% (oscillating)
selectivity	>99%	>99%
reaction volume	3 cm^3	2900 cm^3
throughput	4300 cm^3 h^{-1}	5930 cm^3 h^{-1}
space-time yield	500 h^{-1}	0.7−2.0 h^{-1}

>99% was obtained. On the basis of temperature measurements of the thermo fluids and the mass throughput a power output of 2.8−3.1 kW was found which is in good accordance with the theoretical value of 3.13 kW. A benchmark of the microreactor-based setup and a continuous stirred tank reactor for this oxidation process is given in Table 22.

Microreactors Used for Lab- and Pilot-Scale Synthesis: Gas/Liquid and Gas Reactions

Side-Chain Chlorination of Alkyl Aromatics. The side-chain chlorination of toluene-2,4-diisocyanate was investigated by Ehrich et al. in terms of a photochemical reaction (Scheme 25).[50] The reaction was started by irradiation to generate chlorine radicals from gaseous chlorine.

Scheme 25. Photo chlorination of toluene-2,4-diisocyanate
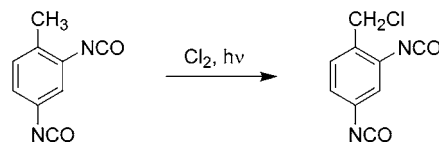
The nondispersive gas/liquid contacting of the photochlorination was carried out in a falling film microreactor comprising a vertically orientated reaction plate with 32 microchannels (width: 600 μm, depth: 300 μm, length: 66 mm). The latter was used to generate a small liquid film. Furthermore, the microreactor featured an integrated heat exchanger for heating and a quartz window to allow an irradiation of the microchannels by an external light source.

The flow rates of the reactants were adjusted in the range of 14 to 56 mL min^{-1} for the chlorine and 0.12 to 0.57 mL min^{-1} for the solution of toluene-2,4-diisocyanate in tetrachloroethane. The latter resulted in residence times of 4.8−13.7 s. By the use of an integrated heat exchanger, the reactor was held at a temperature of 130 °C. The raw product was analyzed by GC.

The highest conversion (81%) was obtained at the highest residence time. Furthermore, it was found that the amount of unidentified by-products was increased at higher residence times. In contrast, the amount of product resulting from an electrophilic chlorination reaction (by-product) was diminished. Hence, the best result was achieved at a residence

(50) Ehrich, H.; Linke, D.; Morgenschweis, K.; Baerns, M.; Jähnisch, K. *Chimia* **2002**, *56*, 647.

time of 8.9 s, resulting in a conversion of 55% and a selectivity of 80%. In comparison, a traditional glass vessel resulted in a conversion of 65%, but the selectivity of the desired product was reduced down to 45% (Table 23).

Table 23. Photochlorination in a glass vessel as benchmark for the falling film microreactor

	falling film microreactor	glass vessel
reaction time	8.9 s	30 min
space-time yield	401 mol $L^{-1} h^{-1}$	1.3 mol $L^{-1} h^{-1}$
conversion	55%	65%
selectivity (product)	80%	45%
selectivity (by-product)	5%	54%

Chlorination of Acetic Acid. The synthesis of monochloroacetic acid by the chlorination of acetic acid in the presence of acetyl chloride was described by Wehle et al. (Scheme 26).[51]

Scheme 26. Chlorination of acetic acid
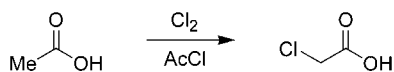
The reaction was carried out in a microreactor comprising different microstructured plates for the flow distribution and gas/liquid contacting. Typically, the reaction channels had a width of 1000 μm and depth of 300 μm. An integrated heat exchanger ensured an appropriate heat management.

The conversion of acetic acid with chlorine was carried out at 170−190 °C. At a pressure of 4−6 bar chlorine gas was passed into the reactor in a co-current or counter-current direction. The chlorine flow rate was adjusted such that the chlorine content of the waste stream was smaller than 0.1%. A typical liquid flow rate of 50 g min⁻¹ was chosen.

Compared to the traditional process, which required a further crystallization step to remove the unwanted 3.5% dichloroacetic acid, the amount of this by-product could be decreased down to 0.01% using the microreactor-based process. Due to the stacked plate design a numbering up approach could be easily realized by assembling two reactors. The latter resulted in a yield of 85% for the monochloroacetic acid with 0.1% of the dichloro product (Table 24).

Table 24. Comparison of the microcapillary reactor with respect to a traditional bubble column concerning the chlorination of acetic acid

	microcapillary reactor	microcapillary reactor (2×)	bubble column
flow rate	50 g min⁻¹	100 g min⁻¹	
yield: monochloroacetic acid	90%	85%	85%
by-product yield: dichloroacetic acid	<0.05%	<0.1%	3.5%

Fluorination of Aromatics. A microbubble column,[52−54] a falling film microreactor,[52−54] and a silicon-based micro-

channel reactor[55,56] were used by Jähnisch et al. and de Mas et al., respectively, for the direct fluorination of toluene. In both reactors the fluorination was carried out with elemental fluorine diluted in a nitrogen carrier gas, and pure or dissolved toluene (Scheme 27, No. 1). Furthermore, Cham-

Scheme 27. Direct fluorination of aromatics
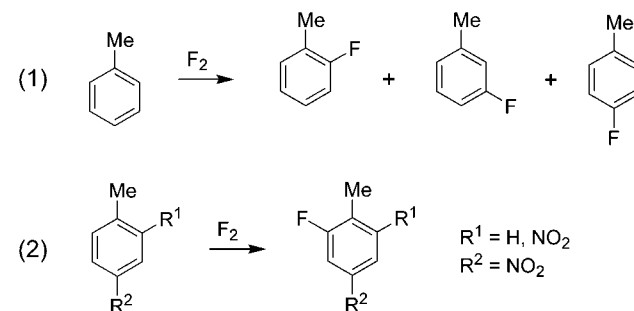
bers et al. demonstrated the fluorination of 4-nitrotoluene and 2,4-dinitrotoluene (Scheme 27, No. 2).[57]

Jähnisch et al. demonstrated the fluorination in two microreactors made of stainless steel. The microbubble column was composed of a dispersion device which ensured a uniform distribution of the gas and liquid flow to the reaction plate with a number of microchannels (width: 50 μm and depth: 50 μm or width: 300 μm, depth: 100 μm). For cooling, integrated heat exchangers were located on both sides of the reaction plates. The falling film microreactor featured a microstructured plate having 300 μm wide and 100 μm deep channels. A thin film of several 10 μm thickness was generated by means of gravity forces. de Mas et al. used a microreactor made by silicon microfabrication having two microchannels with a triangular cross section (width: 435 μm, depth: 305 μm, length: 2 cm). The inner volume of the reactor amounted to 2.7 μL. Chambers et al. fabricated a channel reactor, composed of nickel block with three parallel 0.5 mm wide and 0.5 mm deep channels covered by plastic plate. An integrated heat exchanger beneath the reaction channels allowed an adequate temperature control.

When using the microbubble column and the falling film microreactor the experiments were conducted at −50 to 15 °C, using liquid flow rates of 185−327 μL min⁻¹ and molar fluorine ratios from 0.2 to 2 equiv. The product mixture was analyzed by GC.

(51) Wehle, D.; Dejmek, M.; Rosenthal, J.; Ernst, H.; Kampmann, D.; Trautschold, S.; Pechatschek, R. DE 10036603 A1, Priority: July 27, 2000.

(52) Jähnisch, K.; Baerns, M.; Hessel, V.; Ehrfeld, W.; Haverkamp, W.; Löwe, H.; Wille, C.; Guber, A. *J. Fluorine Chem.* **2000**, *105*, 117.

(53) Jähnisch, K.; Baerns, M.; Hessel, V.; Haverkamp, V.; Löwe, H.; Wille, C. In *Proceedings of the 37th ESF/EUCHEM Conference on Stereochemistry*, April 13−19, 2002, Bürgenstock, Switzerland.

(54) Hessel, V.; Ehrfeld, W.; Golbig, K.; Haverkamp, V.; Löwe, H.; Storz, M.; Wille, C.; Guber, A.; Jähnisch, K.; Baerns, M. In *Topical Conference Proceedings*; IMRET 3, 3rd International Conference on Microreaction Technology, AIChE Spring National Meeting; Ehrfeld, W., Ed.; Springer-Verlag: Berlin, 2000; pp 526−540.

(55) de Mas, N.; Günther, A.; Schmidt, M. A.; Jensen, K. F. *Ind. Eng. Chem. Res.* **2003**, *42*, 698.

(56) de Mas, N.; Jackman, R. J.; Schmidt, M. A.; Jensen, K. F. In *Topical Conference Proceedings*; IMRET 5, 5th International Conference on Microreaction Technology, AIChE Spring National Meeting; Matlosz, M., Ehrfeld, W., Baselt, J. P., Eds.; Springer-Verlag: Berlin, 2001; pp 60−67.

(57) Chambers, R. D.; Holling, D.; Spink, R. C. H.; Sandford, G. *Lab Chip* **2001**, *1*, 132.

Table 25. Direct fluorination in a laboratory bubble column as benchmark for a microbubble column, a falling film microreactor, and silicon-based microchannel reactor

|	microbubble column[52]	falling film microreactor[52]	laboratory bubble column[52]	silicon-based microchannel reactor[55]
temperature	$-15\ ^{\circ}$C	$-16\ ^{\circ}$C	$-17\ ^{\circ}$C	rt
fluorine ratio	0.54 equiv	2.0 equiv	1.0 equiv	2.5 equiv
conversion	26%	76%	34%	58%
yield	11%	28%	8%	14%
selectivity	42%	37%	22%	24%

As a typical distribution of monofluorinated isomers a ortho:meta:para ratio of 5:1:3 was found. The experimental results with the highest yields are listed in Table 25. Both microreactors exceed the results gained by laboratory bubble column (volume: 20 mL), whereas the better results were achieved by the falling film microreactor.

The experiments of de Mas et al. were conducted at room temperature and nearly atmospheric pressure using flow velocities of 1.4 m s^{-1} for gas flow and 5.6×10^{-3} m s^{-1} for the liquid flow. The fluorine ratio was varied from 1 to 5 equiv. The best result is given in Table 25.

Chambers et al. applied flow rates of 50 and 100 μL min^{-1} for the dissolved substrate, and typically 10 mL min^{-1} for the fluorine/nitrogen mixture (10%). The reaction temperature was set to 5 °C. In the fluorination of 4-nitrotoluene a conversion of 40% was achieved. GC analysis resulted in a purity of 70%. The fluorination of 2,4-dinitrotoluene resulted in a conversion of 44%, whereas the purity amounted to 78%.

Fluorination of Non-aromatics. The fluorination of non-aromatics, namely the fluorination of 1,3-dicarbonyl compounds, the fluorination of sulfur trifluoride derivatives and the perfluorination of alkanes (Scheme 28) was also investigated by Chambers et al.[57,58]

Scheme 28. Direct fluorination of nonaromatics
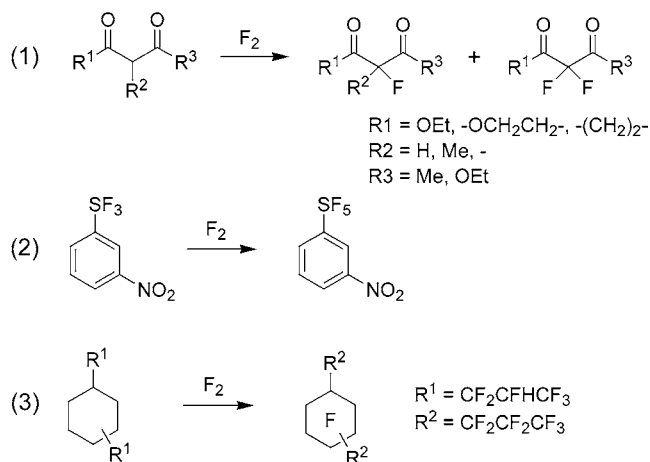
The reactions were carried out in a single-channel reactor having a 0.5 mm wide and 0.5 mm deep channel covered by a plastic plate. A numbered-up version with three parallel channels was fabricated to demonstrate the scale-up possibilities. In both cases an integrated heat exchanger beneath the reaction channel ensured the temperature control.

(58) Chambers, R. D.; Spink, R. C. H. *Chem. Commun.* **1999**, *10*, 883.

The experiments were conducted typically at 5 °C using liquid flow rates in the range of 4.2−83.3 μL min^{-1}. A mixture of 10% fluorine in nitrogen (typical flow rate: 10 mL min^{-1}) was used as the gaseous reactant.

It was demonstrated that the single-channel reactor provided conversions up to 98% (Scheme 28: R_1 = OEt, R_2 = H, R_3 = CH$_3$), whereas the three-channel device gave lower conversions up to 59% (Scheme 28: R_1 = OEt, R_2 = H, R_3 = CH$_3$). The fluorination of the sulfur trifluoride derivative led to a crude product which contained the pentafluorinated product in a ratio of 56%. The perfluorinated alkane was obtained with a purity of 70%.

Hydrogenation of Aromatic Nitro Compounds. The hydrogenation of aromatic nitro compounds, e.g., *p*-nitrotoluene and nitrobenzene, was investigated by Födisch et al.[59,60] (Scheme 29, R = Me) and by Yeong et al.[61,62] respectively (Scheme 29, R = H).

Scheme 29. Hydrogenation of aromatic nitro compounds
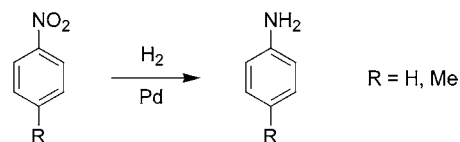
Födisch et al. used a stack of microstructured platelets which had 6×14 channels having a width of 300 μm, a depth of 700 μm, and a length of 400 μm. The aluminum platelets were anodically oxidized, and palladium was deposited using an electrochemical or chemical method. The reactor housing was used either with the stack of platelets or without this stack as a conventional fixed bed reactor.

Hydrogenation experiments were carried out at 70 °C and 20 bar. As a liquid reactant a 10% *p*-nitrotoluene solution in 2-propanol was used. To increase the conversion the reaction mixture was partly recycled in the loop reactor. In the case of the microreactor the recycle ratio was set to 43%. The residence time amounted to 280 s.

The experimental results illustrate that the chemical deposition of palladium resulted in a more efficient catalyst

(59) Födisch, R.; Hönicke, D.; Xu, Y.; Platzer, B. In *Topical Conference Proceedings*; IMRET 5, 5th International Conference on Microreaction Technology, AIChE Spring National Meeting; Matlosz, M., Ehrfeld, W., Baselt, J. P., Eds.; Springer-Verlag: Berlin, 2001; pp 470−478.
(60) Födisch, R.; Reschetilowski, W.; Hönicke, D. In *Proceedings of the DGMK-Conference on the Future Role of Aromatics in Refining and Petrochemistry*; Erlangen, Germany, 1999; pp 231−238.
(61) Yeong, K. K.; Gavriilidis, A.; Zapf, R.; Hessel, V. *Catal. Today* **2003**, *81*, 641.
(62) Yeong, K. K.; Gavriilidis, A.; Zapf, R.; Hessel, V. *Chem. Eng. Sci.* Manuscript submitted.

than the electrochemical deposition. In the first case using a recycle ratio of 43 a nearly quantitative conversion (98%) of *p*-nitrotoluene in combination with a *p*-toluidine selectivity of 100% was achieved in the microchannel reactor (Table 26). If the microchannel reactor is compared at smaller

Table 26. Comparison of a microchannel reactor with respect to a fixed bed reactor concerning the hydrogenation of aromatic nitro compounds

	conversion/ %	residence time/s	recycle ratio	*p*-nitrotoluene flow/geometric surface area/ g h^{-1} cm^{-2}
microchannel reactor	98	280	43	0.013
microchannel reactor	58	85	21	0.045
fixed bed	85	90	21	1.7×10^{-6}
coated aluminum wires	89	260	21	0.045

recycle ratios with a conventional fixed bed catalyst or with coated aluminum wires, it turned out that the conversion of the microreactor is lower. The latter was ascribed to an unequal distribution of gas and liquid in the microchannels.

Yeong et al. demonstrated the hydrogenation of nitrobenzene in a falling film microreactor. To generate a thin liquid film the reactor was equipped with a microstructured plate having 64 parallel, 300 μm wide, 100 μm deep, and 65 mm long channels. The temperature control was ensured by an integrated heat exchanger which is located behind the reaction plate. For a visual inspection of the liquid film, e.g. measuring the film thickness, the reactor housing was equipped with an inspection glass. Experiments were conducted at 60 °C and 1–6 bar pressure using liquid flow rates in the range of 0.2–3 mL min^{-1}. The analysis was carried out with a GC.

Because the liquid flow rate affected the thickness of the liquid film and the residence time, a dependency of the nitrobenzene conversion on liquid flow rate and the hydrogen pressure was ascertained. The best conversions greater than 85% were obtained at low flow rates of 0.5 mL min^{-1}. Furthermore, different catalyst preparation methods (Pd sputtering, UV-decomposition, wet impregnation, incipient wetness) were compared in long-term experiments, whereas the catalyst prepared by incipient wetness retained a nearly stable activity.

Hydrogenation Reactions. The use of gas-phase reactions in organic synthesis is problematic as a result of the difficulties associated with the safe handling of gaseous reagents. In addition, many such reactions are generally extremely exothermic, and it is difficult to control the temperature of such reactions when performed on a large scale. Microreactors have considerable attraction for such processes because there is only a small amount of reactants in the reactor at any given time. The microreactor enables excellent temperature control of the reaction as well as an opportunity for scale-up, by the simultaneous use of many such reactors.

Hönicke and co-workers have reported the gas-phase partial oxidation of cyclic dienes, to their corresponding

monoalkenes, over palladium and ruthenium/zinc catalysts.[63] The microreactors consisted of aluminium wafers, with mechanically etched channels, which were activated by anodic oxidation to obtain a porous oxide layer, which was used as the catalyst support. Impregnation of an organic solution of palladium(II) acetylacetonate resulted in microchannels consisting of an 18 μm thick layer of 0.18% Pd catalyst. The wafers were then stacked in a stainless steel housing to form a microreactor consisting of 672 microchannels for a stream of reagents to pass through. The authors used the device to investigate the hydrogenation of 1,5-cyclooctadiene to cyclooctene (Scheme 30). The diene was

Scheme 30. Hydrogenation of cyclooctadiene
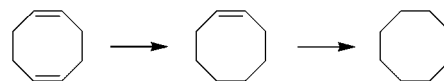
vaporized and mixed with hydrogen before being passed through the microreactor at a temperature of 150 °C. By increasing the residence time of the reaction from 35 to 115 ms the authors reported that the conversion increased from 75 to 99.5%. Although the increased residence time resulted in increased quantities of cyclooctane being formed, the selectivity of cyclooctene decreased from 99.5 to 98% under these conditions.

The authors used the same device to investigate the hydrogenation of *c,t,t*,1,5,9-cyclododecatriene to cyclododecene derivatives (Scheme 31). At a temperature of 150 °C, a

Scheme 31. Hydrogenation of cyclododecatriene
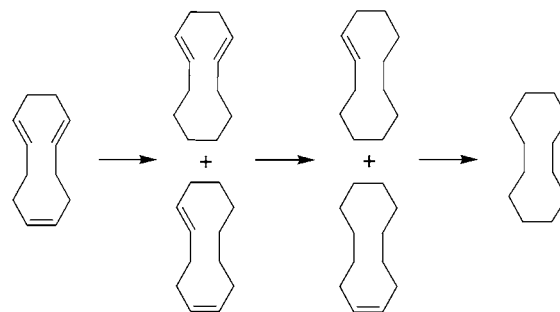
selectivity of 85–90% was reported, where the conversion was approximately 90%. The selectivity of this reaction was lower than the previous example because of the formation of the by-products. It was demonstrated, however, that there was a selectivity advantage of the microreactor compared to that of a fixed-bed reactor.

The catalytic hydrogenation of benzene was also investigated (Scheme 32), but complete reduction to cyclohexane

Scheme 32. Hydrogenation of benzene
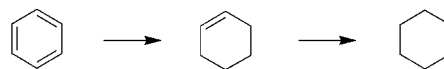
was observed to take place when using the Pd catalyst.[63]

(63) Dietzsch, E.; Hönicke, D.; Fichtner, M.; Schubert, K.; Weissmeier, G. *Topical Conference Proceedings*; IMRET 4, 4th International Conference on Microreaction Technology, AIChE Spring National Meeting, March 5–9, 2000, Atlanta, GA; American Institute of Chemical Engineers: New York, NY, 2000; pp 89–99.

The authors reported that hydrogenation of benzene to cyclohexene was accomplished using a microreactor system consisting of a ruthenium/zinc catalyst, which was incorporated into the microreactor using the same methodology, but the conversions were reported to be low (ca. 10%), with a maximum selectivity of 36%).

Conclusions

A large range of reactions have been carried out in microflow devices with success, among them many of the famous and industrially relevant organic processes. It is necessary to significantly change the experimental protocol of such reactions in order to adapt them to the needs of chemical microprocess engineering. Most prominent, the residence time of reactions has been notably shortened, usually by orders of magnitude, with the result that formerly hour-long processes may now be completed within seconds (Table 27).

Table 27. **Comparison of process parameters in batch and microreactors with exemplary citations**

parameter	batch quantity	microreactor quantity	exemplary citations
concentrated	c_b	$c_{mr} = c_b \; (<c_b)$	40, 41
temp	T_b	$T_{mr} = T_b + x \times 10\,°C$ [a]	34, 40, 46
time	t_b	$t_{mr} \ll t_b$	23, 46, 50
pressure	p_b	$p_{mr} = p_b \; (>p_b)$	41, 49
volume	V_b	$V_{mr} \ll V_b \; (V_{mr} \gg V_b)$	49, 52

[a] $x = 1-5$.

Since this task cannot be accomplished for every process by improving mass and heat transfer on its own (and undoubtedly can fail for some reactions), operation at higher temperatures is mandatory for some organic reactions in microreactors. This increase in reaction temperature may have other desired implications. When performing formerly cryogenic processes at ambient temperature, this may notably reduce energy costs. Typically, reactions may be carried out at temperatures up to 50 °C higher than done in a conventional way (albeit examples with larger gaps are still possible). Reactant concentrations (and pressure in the case of processing gaseous species) may be maintained or even increased; however, to avoid fouling in the tiny microchannels a slight reduction in concentration is generally advised. The sample volumes are nowadays flexible in a surprisingly large range when using microflow devices, and many systems are commercially available.

The microreactor benchmarking was described above in a multifaceted manner. The discussion was grouped per reaction. It is difficult at this stage to draw general, at best deductive, conclusions. Each chemical process and each company demands unique profiles and specifications. In addition, the data set is far from being complete. A more in-depth scenario is provided in a more extended volume, but still cannot give top-down conclusions.[2] As one of the most striking facets it is very clear that microreactors give rise to a number of increases in selectivity and conversion, albeit the unsuccessful examples are not reported in open literature. It is also evident that by good mixing other parameters can be improved, such as the molecular weight of a polymer or the size, morphology, and distribution of a powder. There could be more "facets" added to this list; this information was largely given in the main section of this article and does not need to be repeated. In this sense, it is intended for this article to give the general information and to provide an overall impression of the field.

Finally, all this information must be used to build plants with microflow devices and to profit from the new technology. Otherwise the technology will stay at a level of an "innovation", "plaything", or whatever. Since the learning curve is large, the market is conservative, and the tool is not the solution to anything, it becomes increasingly apparent that "micro" should be only placed where it is needed and not where it may be technically feasible. To determine the "need", benchmarking with documentation and analysis is the proper way. Finally, a market has to be served and the tool has to be brought into application.

Acknowledgment