

**Total system failure/cooling liquid not being pumped**

[OS 82] [R 28] [P 62] Even when the cooling liquid is not being pumped (e.g. for reasons of pump failure), the high surface-to-volume ratio of the micro reactor still guarantees sufficient heat removal so that undesired heat generation or even explosions can be intrinsically avoided [64]. This is due to the high heat transfer coefficient ( $2000 \text{ W m}^{-2} \text{ K}^{-1}$ ) resulting from the large specific surface area of the reaction channel ( $10\,000 \text{ m}^2 \text{ m}^{-3}$ ).

**4.12****Oxidations and Reductions**

## 4.12.1

**C,O-Dihydro Elimination –  $\text{Br}(\text{OAc})_2^-$  Oxidations of Alcohols to Ketones**

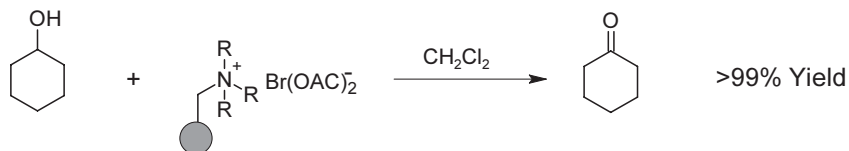
Proceedings: [3].

4.12.1.2 **Drivers for Performing  $\text{Br}(\text{OAc})_2^-$  Oxidations of Alcohols in Micro Reactors**

The carrying out of this reaction served to demonstrate organic synthesis on a newly developed porous-polymer-rod micro reactor [3].

4.12.1.2 **Beneficial Micro Reactor Properties for  $\text{Br}(\text{OAc})_2^-$  Oxidations of Alcohols**

A detailed study on velocity profiles, pressure drop and mass transport effects has been described [3]. This, in quantitative terms, precisely underlines the advantages (and limits) of the micro reactor concept.

4.12.1.3  **$\text{Br}(\text{OAc})_2^-$  Oxidations of Alcohols Investigated in Micro Reactors****Organic synthesis 83 [OS 83]:  $\text{Br}(\text{OAc})_2^-$  Oxidation of cyclohexanol**

Cyclohexanol is reduced to cyclohexanone at  $20^\circ \text{C}$  (6 h) by  $\text{Br}(\text{OAc})_2^-$  moieties [3].

4.12.1.4 **Experimental Protocols**

[P 63] Cyclohexanol was reduced in dichloromethane to cyclohexanone at  $20^\circ \text{C}$  (6 h) by  $\text{Br}(\text{OAc})_2^-$  moieties coupled to a porous polymer resin [3]. The polystyrene polymer was cross-linked by reacting divinylbenzene moieties in the main chain with each other. Initially, the polymer contained benzylchloride groups, which were converted to quaternary ammonium groups. By means of ion-exchange, functional anionic groups such as the reductive  $\text{Br}(\text{OAc})_2^-$  moiety can be introduced. Typical ion exchange capabilities of the micro reactor were about 0.1–1.0 mmol, depending on the polymer load.

## 4.12.1.5 Typical Results

**Conversion/selectivity/yield**

[OS 83] [R 3] [P 63] A > 99% yield was obtained after 6 h of processing [3].

## 4.12.2

**Oxodihydro Bisubstitution – Catalyzed Oxidation of Ethanol with H<sub>2</sub>O<sub>2</sub> to Acetic Acid**

Proceedings: [51].

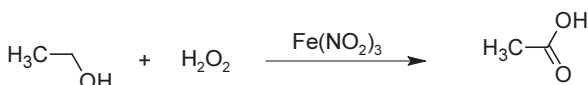
4.12.2.1 Drivers for Performing Catalyzed Oxidations with H<sub>2</sub>O<sub>2</sub> in Micro Reactors

Catalyzed oxidations of organic compounds such as ethanol with hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) are highly exothermic processes releasing large heat power [51]. At high conversion, there may be technical difficulties in removing the reaction heat so that the temperature may rise in an uncontrolled manner. For this reason, these reactions are typically carried out at low conversion, e.g. by dilution with solvent or by operation in differential reactors.

The catalyzed oxidation of ethanol to acetic acid is a well-studied reaction, carried out in continuous stirred tank reactors (CSTR) [51]. Hence it is a good test reaction for benchmarking micro reactor results.

4.12.2.2 Beneficial Micro Reactor Properties for Catalyzed Oxidations with H<sub>2</sub>O<sub>2</sub>

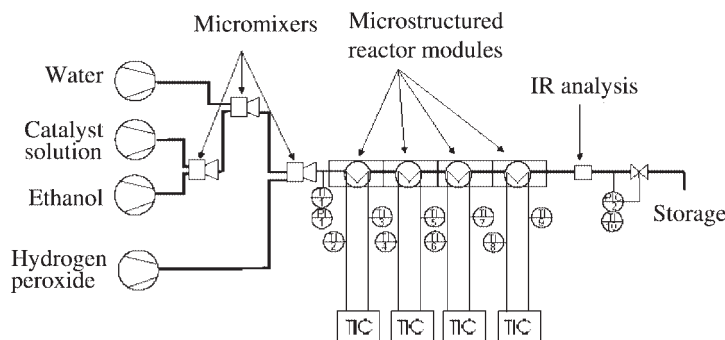
Micro reaction channels can be operated in tight contact with cooling channels so that large reaction heats can be removed. By this means, formerly uncontrollable reaction conditions may be realized.

4.12.2.3 Catalyzed Oxidations with H<sub>2</sub>O<sub>2</sub> Investigated in Micro Reactors**Organic synthesis 84 [OS 84]: Catalyzed oxidations of ethanol with hydrogen peroxide to acetic acid**

## 4.12.2.4 Experimental Protocols

[P 64] Flows of 0.2–0.9 kg h<sup>-1</sup> ethanol (98%) and 0.015–0.050 kg h<sup>-1</sup> of a 1 mol l<sup>-1</sup> aqueous solution of Fe(NO<sub>3</sub>)<sub>3</sub> and acetic acid were fed by pumps and mixed in a micro mixer; then this solution was mixed with 0.3–4.0 kg h<sup>-1</sup> hydrogen peroxide (35%) solution in a second micro mixer [51]. Such a mixed flow was passed through a series of four reaction modules with cross-flow guided thermofluids (Figure 4.90). The inlet temperatures of the modules were set to 70–115 °C. The modules had different temperatures, creating a temperature profile along the flow axis. In terms of process operations, this refers to the series ignition/reaction/quenching, with modules performing reaction. The temperatures were monitored at the inlets and outlets of each module. Pressure was held constant at 3–5 bar to avoid boiling. Analysis was performed by in-line NIR flow-cell measurement.

The range of flow rates is not given for the heat transfer fluids in [51]. However, for one typical experiment this was specified (0.71 kg h<sup>-1</sup> ethanol; 3.025 kg h<sup>-1</sup> hy-



**Figure 4.90** Scheme of test facility for ethanol oxidation by hydrogen peroxide [51].

drogen peroxide; 70 °C for ignition; 105 °C for reaction; 20 °C for quenching); 43 and 54 kg h<sup>-1</sup> water were pumped through the ignition and quenching modules, respectively. The two inner reactor modules were each fed by 300 kg h<sup>-1</sup> Marlotherm™ SH thermofluid.

Water could additionally be injected via a third micro mixer in the ethanol/catalyst solution mixture [51]. This served for heat transfer characterization, adjustment of temperature before reaction and most prominently dilution of the reaction mixture. By the last step, runaway situations occurring during the reaction can be managed.

#### 4.12.2.5 Typical Results

##### Conversion/selectivity/yield – benchmarking to batch processing

[OS 84] [R 24] [P 64] Near-complete conversion (> 99%) at near-complete selectivity (> 99%) was found in a micro reaction system [0.71 kg h<sup>-1</sup> ethanol, 98%; 3.025 kg h<sup>-1</sup> hydrogen peroxide, 30%; 1 mol l<sup>-1</sup> Fe(NO<sub>3</sub>)<sub>3</sub> and 1 mol l<sup>-1</sup> acetic acid; 70 °C for ignition; 105 °C for reaction; 20 °C for quenching] [51]. Processing in a continuous stirred tank reactor (CSTR) resulted in 30–95% conversion at > 99% selectivity (Table 4.13).

**Table 4.13** Comparison of reaction conditions and results obtained in a micro reactor set-up with results obtained in a continuous stirred tank reactor [51].

	<b>CSTR</b>	<b>Micro structured plug flow reactor</b>
Residence time (s)	1760	3
Pressure (bar)	Atmospheric	3–5
Conversion (%)	30–99, oscillating	> 99
Selectivity (%)	> 99	> 99
Reaction volume (cm <sup>3</sup> ) <sup>a</sup>	2900	3
Throughput (cm <sup>3</sup> h <sup>-1</sup> )	5930	4300
Space–time yield (h <sup>-1</sup> )	0.7–2.0, oscillating	500

**a** Reaction volume is defined as the volume in which the reaction took place, not the volume of the reaction system.

**Reaction time**

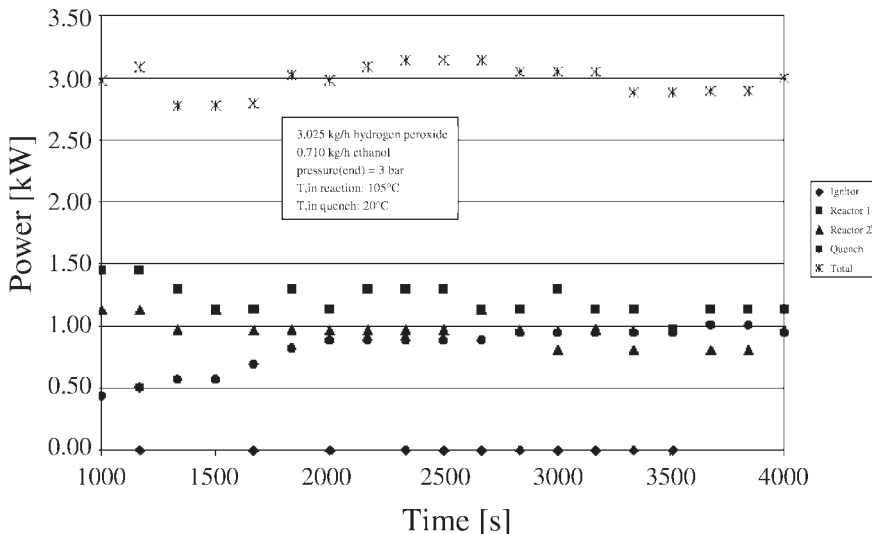
[OS 84] [R 24] [P 64] Micro-reactor operation was completed within 3 s, whereas processing in a CSTR takes nearly 30 min (exactly 1760 s) [0.71 kg h<sup>-1</sup> ethanol, 98%; 3.025 kg h<sup>-1</sup> hydrogen peroxide, 30%; 1 mol l<sup>-1</sup> Fe(NO<sub>3</sub>)<sub>3</sub> and 1 mol l<sup>-1</sup> acetic acid; 70 °C for ignition; 105 °C for reaction; 20 °C for quenching] [51].

**Space-Time yield**

[OS 84] [R 24] [P 64] The space-time yield of micro-reactor operation amounted to 500 h<sup>-1</sup>, while processing in a CSTR gives 0.7–2.0 h<sup>-1</sup> [0.71 kg h<sup>-1</sup> ethanol, 98%; 3.025 kg h<sup>-1</sup> hydrogen peroxide, 30%; 1 mol l<sup>-1</sup> Fe(NO<sub>3</sub>)<sub>3</sub> and 1 mol l<sup>-1</sup> acetic acid; 70 °C for ignition; 105 °C for reaction; 20 °C for quenching] [51]. As reaction volume, only the real processed volume was taken into account, i.e. not considering the complete outer volume. A comparison of the reaction volumes and throughputs of tank and micro reactors are also given [51].

**Power release**

[OS 84] [R 24] [P 64] Experimental power data ranged from 2.80 to 3.10 kW depending on reaction time, approaching the theoretical value of 3.13 kW [0.71 kg h<sup>-1</sup> ethanol, 98%; 3.025 kg h<sup>-1</sup> hydrogen peroxide, 30%; 1 mol l<sup>-1</sup> Fe(NO<sub>3</sub>)<sub>3</sub> and 1 mol l<sup>-1</sup> acetic acid; 70 °C for ignition; 105 °C for reaction; 20 °C for quenching] [51]. These power data were derived from a number of temperature measurements along the flow passage through the four reactor modules (Figure 4.91). The temperature data are also given [51].



**Figure 4.91** Power output calculated from measured temperature rise of the coolant fluid during oxidation reaction [51].

## 4.12.3

**Oxidation of Arylmethanes – Electrochemical Alternative Routes to the Étard Reaction**

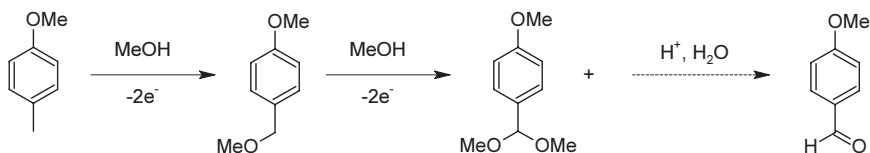
Proceedings: [69]; patents: [139]; sections in reviews: [42, 90, 105].

**4.12.3.1 Drivers for Performing the Electrochemical Oxidations of Arylmethanes in Micro Reactors**

The first study on the oxidation of arylmethanes used this reaction as a model to show the general advantages of electrochemical micro processing and to prove the feasibility of an at this time newly developed reactor concept [69]. Several limits of current electrochemical process technology hindered its widespread use in synthetic chemistry [69]. As one major drawback, electrochemical cells still suffer from inhomogeneities of the electric field. In addition, heat is released and large contents of electrolyte are needed that have to be separated from the product.

**4.12.3.2 Beneficial Micro Reactor Properties for Electrochemical Oxidations of Arylmethanes**

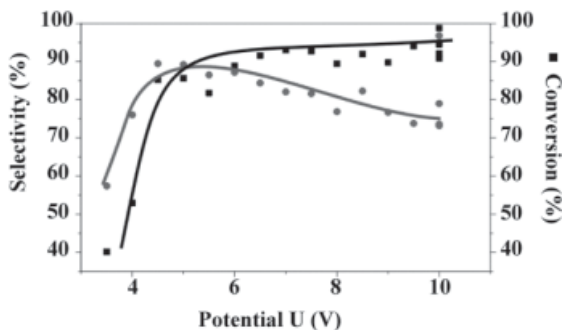
Micro reaction systems may help to overcome or at least reduce some of the above-mentioned limitations [69]. Electrochemical micro reactors with miniature flow cells where electrodes approach to micrometer distances should have much improved field homogeneity. As a second result of confined space processing, the addition of a conducting salt may be substantially reduced. In addition, benefits from a uniform flow distribution and efficient heat transfer may be utilized.

**4.12.3.3 Electrochemical Oxidations of Arylmethanes Investigated in Micro Reactors**  
**Organic synthesis 85 [OS 85]: Oxidation of 4-methoxy toluene to 4-methoxy benzaldehyde**

The electrosynthesis of 4-methoxybenzaldehyde (anisaldehyde) from 4-methoxytoluene by means of direct anodic oxidation is performed on an industrial scale [69]. Via an intermediate methyl ether derivative, the corresponding diacetal is obtained, which can be hydrolyzed to the target product. The different types of products – ether, diacetal, aldehyde – correspond to three distinct single oxidation steps.

**4.12.3.4 Experimental Protocols**

[P 65] Carrying out the oxidation of 4-methoxytoluene (20%,  $2.0 \text{ mol l}^{-1}$ ) in methanol, a constant current density of  $79 \text{ mA cm}^{-2}$  was employed using 0.1M KF as conducting salt [69]. A flow rate of  $0.1 \text{ ml min}^{-1}$  was applied, yielding a velocity of  $0.046 \text{ mm s}^{-1}$  ( $Re = 0.2$ ), at a pressure drop of 1.1 bar. This corresponds to a residence time of 21 s. A potentiostat/galvanostat was used in combination with a charge counter. For temperature control, the micro reactor was immersed in a thermostat.



**Figure 4.92** Conversion (■) and selectivity (●) diagram for the electrochemical reaction of 4-methoxytoluene with 0.1 M KF as conducting salt [69].

#### 4.12.3.5 Typical Results

##### Conversion/yield/selectivity

[OS 85] [R 33] [P 65] High conversion (> 85%) and selectivity (> 85%) were found at a potential of 4.5 V (0.1 M 4-methoxytoluene) [69]. At lower potential, a strong increase in both quantities is observed (Figure 4.92). At still higher potential, conversion increases slightly to 95% (at 10 V), whereas selectivity decreases to 75% (at 10 V).

##### Composition of product mixture

[OS 85] [R 33] [P 65] By means of HPLC analysis, it could be shown that all three types of products were formed during reaction in the micro reactor [69]. For a typical experiment, the main fraction was composed of 4-methoxybenzaldehyde dimethylacetal, the second largest fraction consisted of the aldehyde and 4-methoxybenzyl methyl ether was generated in a smaller amount.

The change of content of these three products was monitored as a function of temperature, in the presence of conducting salt (0.1 M KF) or in its absence [69]. In the first case, a near linear increase for the ether and acetal was found, but not for the aldehyde, which remained constant. The contents of the first two compounds were more than doubled. On adding no salt, the ether and acetal increased only slightly and the aldehyde decreased to some extent, probably due to oxidation.

##### Addition of conducting salt/temperature

[OS 85] [R 33] [P 65] Compared to the industrial process using 0.1–0.2 M KF, low contents of conducting salt (0.01 M) were used [69]. In some cases, even no salt at all was needed (Figure 4.93).

Without conducting salt, the yield and conversion increased with rising temperature (10–60 °C) owing to increased diffusion [69]. The yield approaches conversion so that selectivity is high. With conducting salt (0.01 M KF), conversion is much higher, close to 100%, and decreases slightly at higher temperature. increases up to 25 °C and then reaches a plateau at about 75%. The relative difference between yield and conversion is larger than for the no-salt experiment, hence selectivity is lower. The best selectivity for micro-reactor operation was determined to be 96%.

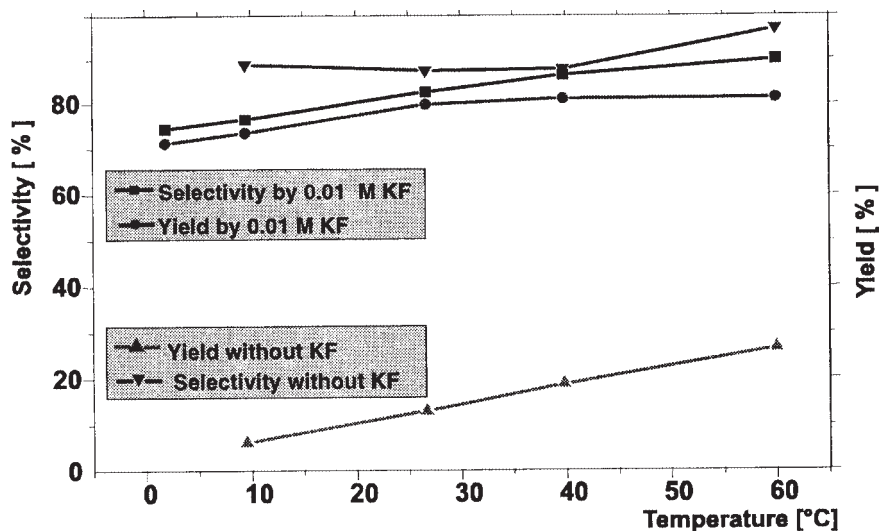


Figure 4.93 Comparison of selectivity and yield for the synthesis of 4-methoxybenzaldehyde depending on reaction temperature and amount of conducting salt [69].

#### Current efficiency

[OS 85] [R 33] [P 65] Using conducting salt (0.01 M) in a micro reactor yields a current efficiency of 60–65%, whereas operation without any salt has an efficiency of 96–98% [69]. For conventional electrochemical processing of 4-methoxybenzaldehyde, an efficiency of 49–54% is reported (Figure 4.94).

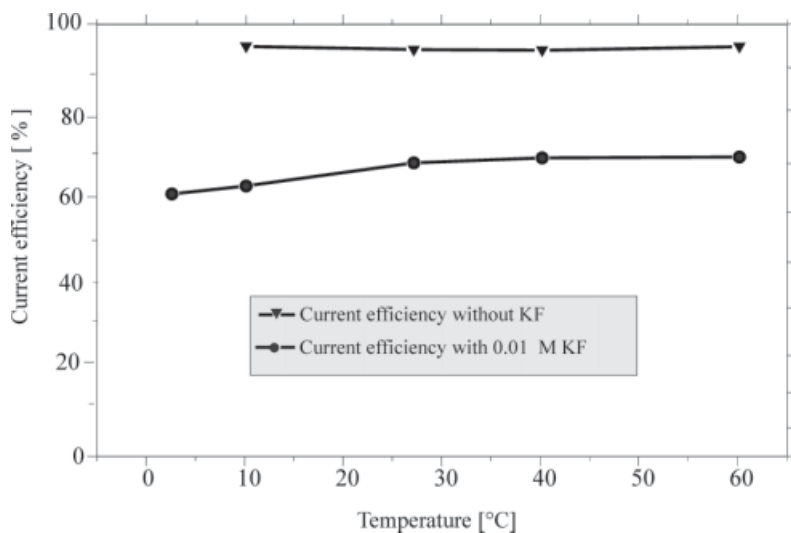


Figure 4.94 Comparison of current efficiency for the electrochemical process with 0.01 M KF and without conducting salt [69].

## 4.12.4

**Oxidative CO<sub>2</sub> Elimination – Electrochemical Decarboxylations**

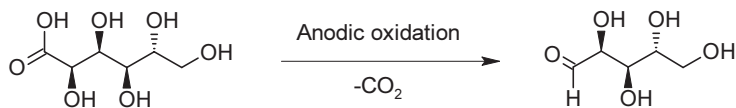
Proceedings: [65].

**4.12.4.1 Drivers for Performing Electrochemical Decarboxylations**

The drivers for performing decarboxylations come so far mainly from the general advantages of electrochemical processing which apply also to other reactions. They stem from using electrons instead of chemicals directly for chemical synthesis and refer to the ease of creating a suitable reaction environment simply by providing the right electrical potential. As large-scale electrochemical reactors cannot exploit this potential fully owing to field inhomogeneities and release of heat, micro reactors overcoming these limits are seen as a suitable alternative.

**4.12.4.2 Beneficial Micro Reactor Properties for Electrochemical Decarboxylations**

The micro reactor properties concern process control in the time domain and process refinement in the space domain [65]. As a result, uniform electrical fields are generated and efficiency is thought to be high. Furthermore, electrical potential and currents can be directly measured without needing transducer elements. The reactor fabrication methods for electrical connectors employ the same methods as used for microelectronics which have proven to satisfy mass-fabrication demands.

**4.12.4.3 Electrochemical Decarboxylations Investigated in Micro Reactors****Organic synthesis 86 [OS 86]: Electrochemical decarboxylation of D-gluconic acid**

D-Gluconic acid is decarboxylated to yield the five-carbon sugar D-arabinose, releasing carbon dioxide [65]. The reaction can be performed at a graphite electrocatalyst under conditions that do not imply further oxidation to low-order carbon sugars. Therefore, loss in selectivity does not come from consecutive reactions of arabinose, but rather from side reactions of the solvent or water giving oxygen. The side reactions should be reduced when having a more uniform electrical field, i.e. the potential distribution is equal.

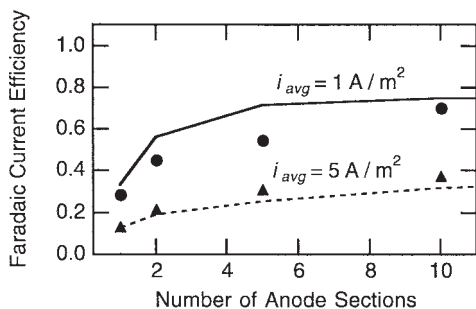
**4.12.4.4 Experimental Protocols**

[P 66] No details of the electrical field are given in [65] other than mentioning the average charge densities. These amount for two experiments to 1 and 5 A m<sup>-2</sup>.

**4.12.4.5 Typical Results****Faradaic current efficiency**

[OS 86] [R 29] [P 66] The Faradaic current efficiency, the electrical charge equivalent for conversion as a fraction of the total electrical charge, was measured for a





**Figure 4.95** Faradaic current efficiency as electrical charge equivalent for conversion of D-gluconic acid given for two values of average current density. The symbols represent measured conversion and the solid and dashed lines calculated results [65].

multi-sectioned electrode design in a micro reactor as a function of the number of electrode sections when conducting the electrochemical decarboxylation of D-gluconic acid [65]. As desired by the multi-sectioned concept, this current efficiency increases with increasing number of anode sections and approaches a constant value after 8–10 anodes.

#### Average electrical current

[OS 86] [R 29] [P 66] On increasing the average electrical current from 1 to 5 A m<sup>-2</sup> for the D-gluconic acid decarboxylation, the Faradaic current efficiency increases by a factor of 2–3 [65]. At best, a Faradaic current efficiency of about 75% is reached (Figure 4.95).

#### Modeling

[OS 86] [R 29] [P 66] A model is able to describe experimental results obtained for the electrochemical decarboxylation of D-gluconic acid (1 A m<sup>-2</sup>) [65]. At an average electrical current of 5 A m<sup>-2</sup> the model predicts better performance than is actually achieved.

#### 4.12.5

##### Photochemical Reductive Biradical Coupling – Pinacol Formation

Peer-reviewed journals: [72, 73]; proceedings: [74]; sections in reviews: [14, 83, 89, 90, 115]; additional information: [73]; general theoretical analysis on optical photocatalytic dissociation: [140].

##### 4.12.5.1 Drivers for Performing Photochemical Biradical Formation in Micro Reactors

The main driver here is not dedicated to the specific reaction, but rather stems from the general desire to establish photochemical paths for a wider range of reactions.

Photochemical reactions have the principal advantage of ‘clean chemistry’, as they use light of defined energy [72, 74]. Synthesis of vitamin D and photocleavage of protection groups, for example, are accepted organic synthesis routes. Nevertheless, no widespread use of photochemistry has been made so far as this technique

suffers from lack of scalability, efficiency and safety. As micro reactors are distinctively different here from other reactors, they may show completely different features with regard to such issues.

Large-scale reactors have low quantum yields as radiation does not penetrate deeply into the reaction vessel [72, 74]. As a consequence, high-power lamps have to be used causing a lot of excess heat and even posing safety constraints. These energy sources produce locally high quantities of radicals which may not mix thoroughly with the rest of the solution. Therefore, they may not find a second reaction partner, but instead react by themselves. This radical combination reduces selectivity and creates additional heat.

#### 4.12.5.2 Beneficial Micro Reactor Properties for Photochemical Biradical Formation

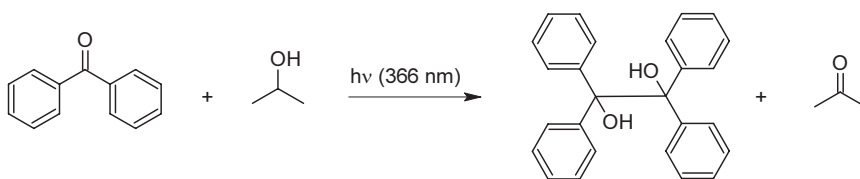
Micro reactors may favorably use thin liquid films to have high quantum yields [72, 74]. The energy of the light should be usable completely as the light can penetrate the full layer, having small length scale, and is not absorbed to a large extent before inducing reaction.

Diffusion of the highly reactive radicals is facile in micro reactors so that recombination, as one source of selectivity reduction, should be diminished strongly [72]. Heat generation, even if it occurs at all, is under control since heat transfer can be set high.

See also the theoretical description of a micro reactor for optical photocatalytic dissociation of non-linear molecules in [140]. Here, a mathematical model for a novel type of micro reactor is given. Rotating non-linear molecules at excitation of valent vibrations are considered, having a magnetic moment. Resonance decay of molecules can be utilized with comparatively weak external energy sources only.

#### 4.12.5.3 Photochemical Biradical Formation Investigated in Micro Reactors

##### Organic synthesis 87 [OS 87]: Benzopinacol formation by two-radical combination



The pinacol formation reaction follows a radical mechanism. Benzopinacol, benzophenone and the mixed pinacol are formed jointly with many radical species [72, 74]. In the course of the reaction, first a high-energy excited state is generated with the aid of photons. Thereafter, this excited-state species reacts with a solvent molecule 2-propanol to give two respective radicals. The 2-propanol radical reacts with one molecule of benzophenone (in the ground state, without photon aid) to lengthen the radical chain. By combination of radicals, adducts are formed, including the desired product benzopinacol. Chain termination reactions quench the radicals by other paths.

#### 4.12.5.4 Experimental Protocols

[P 67] A stock standard solution of benzophenone in 2-propanol (0.5 M) with a drop of glacial acetic acid was diluted to give further standard solutions of 0.1–0.4 M [72, 74]. These solutions were stored at room temperature, protected from exposure to light and were employed for a device having an optical path of 50  $\mu\text{m}$ . When using a second generation device with a 500  $\mu\text{m}$  path, the stock solution concentration was reduced to 0.05 M.

The reactor was first primed with a cleaning solution, then with the reacting solution, and fed by pumping for a longer period [72, 74]. Then, the liquid flow was set to 1 ml  $\text{min}^{-1}$ . The samples were analyzed typically after 48 h to ensure completion of 'dark' follow-up reactions.

A miniaturized UV lamp (120 V AC; 0.20 A) and a deuterium detection lamp were used during the experiments [72, 74]. They were turned on for at least 20 min prior to use. UV spectra were obtained in a spectrometer with a 10 s integration time. Absorbance was determined at 280, 310, 330 and 360 nm. The power output of the lamp was measured by using a digital power meter and a reference silicon chip with channels etched through, which hence allowed the light to pass through and to be measured after such passage.

Besides on-line UV analysis, off-line HPLC analysis was performed after about 48 h 'dark reaction' [72, 74]. In this period, the photoinduced reaction proceeds by radical paths in the dark.

Owing to the high concentration applied (0.5 M), the Lambert–Beer law is no longer valid [72, 74]. Therefore, absorption coefficients were derived experimentally as described in detail in [72]. These measurements took advantage of having the thin layers in the micro reactor, i.e. they would not have been feasible in conventional cuvettes.

#### 4.12.5.5 Typical Results

##### Conversion/selectivity/yield

[OS 87] [R 35] [P 67] Conversions of up to 20% of benzophenone were achieved [72, 74]. The conversion was measured by comparing the UV absorption spectra of reacted samples with those of standard solutions with defined degree of converted products.

##### Quality of first-generation on-line analysis

[OS 87] [R 35] [P 67] Generally, on-line analysis allows one to determine product concentrations, giving proper conversion [72, 74]. A limit is given by intermediates which also absorb in the same spectral range, also shifting the maximum of the absorption curve. It was assumed that the product pinacol does not contribute to the absorption, only the reactant and the intermediates. In addition, a delay arises between the end of irradiation and on-line analysis as the reaction mixture has to pass a conduit between the two locations. Hence the reaction proceeds further and this is dependent on the flow rate and residence time.

**Quality of improved, second-generation on-line analysis**

[OS 87] [R 35] [P 67] In a monolithic integrated device, the delay between the end of reaction and on-line analysis was reduced to only a few seconds [72, 74]. Consequently, higher absorbance, i.e. lower conversion, was found. In addition and surprisingly, this absorbance could be even higher than that of the unreacted solutions, indicating the identification of a short-living, strongly absorbing intermediate. This interference limited the quantitative judgement of the real performance of the second-generation analysis, but clearly its possibilities were improved.

**Residence time/flow rate**

[OS 87] [R 35] [P 67] The longer the residence time, the higher is the conversion, as expected [72, 74]. This trend is seen in the on-line UV- and off-line HPLC spectra. Whereas on-line UV absorption showed zero conversion at too short a residence time (flow rate  $10 \mu\text{l min}^{-1}$ ), a level of about 50% was found in the HPLC analysis. This clearly proves that the reaction proceeds by a radical path in the dark, if sufficient time is given.

**Overall quantum efficiency – benchmarking to photochemical set-ups**

[OS 87] [R 35] [P 67] Quantum efficiencies increase with flow rate and decrease with residence time [72, 74]. When the residence time is too long the light coming into the solution can no longer have a function. The quantum efficiencies, defined as moles reacted versus moles of photons, were of the order of 1–3.3, exceeding the performance of conventional photochemical set-ups at the higher end.

**4.13****Organic Synthesis Reactions of Undisclosed Mechanism****4.13.1****Vitamin Precursor Synthesis**

Peer-reviewed journals: [61, 62]; journals: [141]; proceedings: [127, 142, 143]; reactor description: [56, 58–60, 63]; sections in reviews: [42, 90, 105, 114, 115, 119, 144].

**4.13.1.1 Drivers for Performing Vitamin Precursor Synthesis in Micro Reactors**

The studies reported were mainly motivated by industrial investigations of process performance optimization [61, 62, 127, 142, 143]. For a known reaction which was part of a multi-step process finally yielding a vitamin, new process parameter data had to be analyzed, i.e. the micro reactor served to gather precise information. This concerned short-temperature processing ( $< 4 \text{ s}$ ), which simply was not possible using macroscopic bench-scale apparatus. In the latter case, almost 50% of the reaction heat was released already at the mixer unit, rather after entering the subsequent heat exchanger. The temperature rise led to side reactions, reducing the yield. Hence isothermal processing was the major issue of choosing micro-channel processing. Furthermore, the micro reactor has to allow short-time processing so

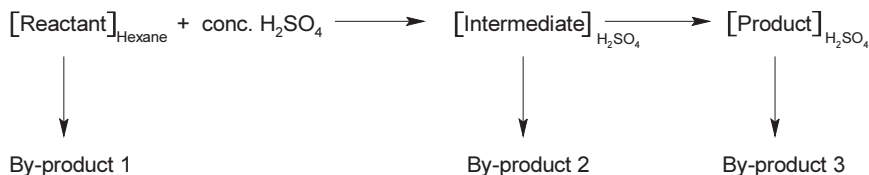
that residence time setting was another issue. The main reaction course and the side reactions were known to be very rapid. Therefore, avoiding back-mixing also had to be taken into account.

#### 4.13.1.2 Beneficial Micro Reactor Properties for Vitamin Precursor Synthesis

Regarding the issue of isothermal processing, the excellent heat exchange properties of special micro-channel geometries are of major interest for the drivers outlined above [61, 62, 127, 142, 143]. Concerning this and the second issue, residence time setting and the integration of a micro mixing and heat exchange unit were inevitable. Concerning the device actually used, the mixer was directly followed by heat exchange micro channels having large heat exchange surfaces. This combination allowed processing in the second range and below. Owing to the laminar-flow properties, back-mixing can be largely excluded for micro-channel processing.

#### 4.13.1.3 Vitamin Precursor Synthesis Investigated in Micro Reactors

##### Organic synthesis 88 [OS 88]: Synthesis of a vitamin precursor



The reactants and the product were not disclosed in the open literature as the industrial process is proprietary [61, 62, 127, 142, 143]. The reactant is dissolved in hexane and the reaction is catalyzed by concentrated sulfuric acid which is present in quantitative amounts. Thus, the reaction is carried out as a liquid/liquid process. A reaction scheme is given in [61, 62]. The reactant quickly forms an intermediate which again quickly reacts to give the product. Thermally induced side reactions occur.

On an industrial level, the reaction is carried out in semi-batch mode with a yield of 70% [61, 62, 127]. First steps towards continuous production with a mixer and a cooler increased the yield to 80–85%; however, the reaction occurred partly in the mixer, thereby increasing the temperature in this unit. The reaction is quenched by dilution with water, also having a cooling function.

#### 4.13.1.3 Experimental Protocols

[P 68] No detailed experimental protocol was given [61, 62, 142, 143]. Two reactant streams, the solution of the reactant in hexane and concentrated sulfuric acid, were fed separately in a specially designed micro reactor by pumping action. There, a bilayer was formed initially, potentially decomposed to a dispersion, and led to rapid mass transfer between the phases. From this point, temperature was controlled by counter-flow heat exchange between the reaction channel and surrounding heat-transfer channel. The reaction was typically carried out at temperatures from 0 to 50 °C and using residence times of only a few seconds. If needed, a delay loop of

larger internal dimensions served to prolong the reaction path and residence time. In a subsequent mini mixing unit, water was introduced and quenched the reaction.

#### 4.13.1.4 Typical Results

##### **Conversion/selectivity/yield – benchmarking to industrial process and laboratory-scale processing**

[OS 88] [R 27] [P 68] A maximum yield of 80–85% was obtained at 4 s residence time and a temperature of 50 °C by micro reaction system processing [61, 62, 127, 142, 143]. Using ordinary laboratory-processing with standard laboratory glassware yielded only 25%. The continuous industrial process had a yield of 80–85%; the previously employed semi-batch industrial process gave a 70% yield. The temperature and the residence time of industrial and micro reactor continuous processing were identical.

##### **Simultaneous residence time and temperature variation – benchmarking to industrial process**

[OS 88] [R 27] [P 68] On increasing the residence time from 4 to 30 s and decreasing the reaction temperature from 50 to 20 °C, a yield of 90–95% was obtained [61, 62, 127, 142, 143]. This is a considerable improvement over the yield of the continuous industrial process of 80–85% (see also above).

##### **Fouling – channel blockage**

[OS 88] [R 27] [P 68] During extended laboratory studies of a micro reaction system, no blockage of the tiny micro channels (60 μm width) was found, although the use of reactants (viscous concentrated sulfuric acid) and the product mixtures known from industrial processing would have one led to such a conclusion [61, 62, 127, 142, 143]. As an explanation, the absence of temperature gradients and of averaged-velocity gradients between the individual flows was put forward.

#### 4.13.2

##### **Methylation of Aromatics**

Proceedings: [127].

##### **4.13.2.1 Drivers for Performing Methylation of Aromatics in Micro Reactors**

To achieve excellent thermal control, to use short residence times and to have no back-mixing were the main drivers for an industrial investigation of the methylation of an aromatic. The target molecule yielded thereby, a precursor for a crop-protection product, is temperature sensitive [127]. Accordingly, cryo-processing has to be applied to avoid decomposition when the reaction is conventionally performed. A driver for micro reactor processing would be to enable room-temperature processing or, at least, to increase the reaction temperature closer to ambient.

##### **4.13.2.2 Beneficial Micro Reactor Properties for Methylation of Aromatics**

The above-mentioned research targets generally address the good heat transfer properties achieved by micro-channel processing, in particular referring to isother-

mal processing. Also, short average residence times can be realized largely avoiding back-mixing.

#### 4.13.2.3 Methylation of Aromatics Investigated in Micro Reactors

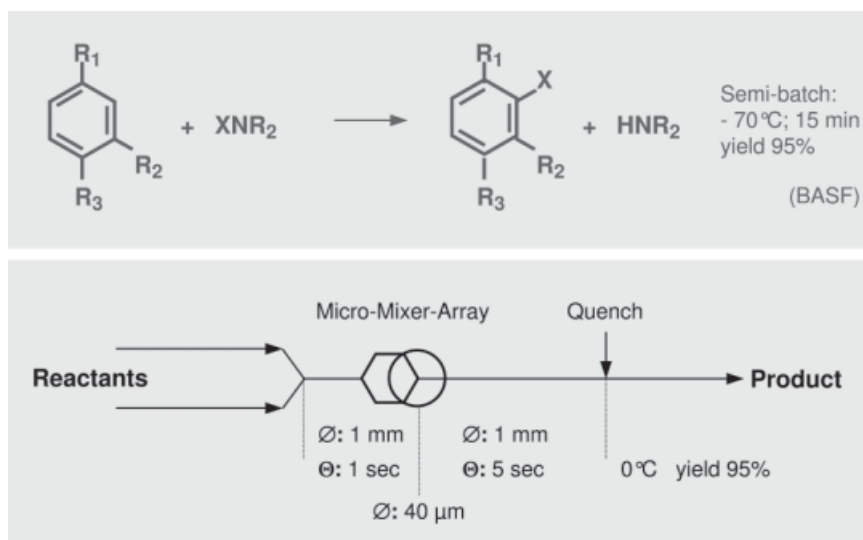
##### Organic synthesis 89 [OS 89]: Methylation of a 1,3,4-substituted benzene



The 1,3,4-substituted benzene is reacted with an *N,N*-disubstituted-*N'*-methylamine resulting in transfer of the methyl group to the 2-position of the aromatic ring, thereby creating a crowded 1,2,3,4-substituted aromatic [127]. No details on the nature of the substituents and the presence of a solvent are given, as the process is proprietary. The temperature in the micro reactor was set to 0 °C.

#### 4.13.2.4 Experimental Protocols

[P 69] No details on the solvent used and concentrations are given in [127], as the process most likely is proprietary (Figure 4.96). Probably the process is solvent-free as obviously one of the reactants has also the function of dissolving the other. The temperature for micro-channel processing was set to 0 °C. The residence time between the pre-reactor and micro mixer was 1 s and between the micro mixer and quench 5 s, totalling 6 s.



**Figure 4.96** Flow sheet of the micro reactor set-up used for methylation of a 1,3,4-trisubstituted benzene [127].

#### 4.13.2.5 Typical Results

##### **Blockage – use of pre-reactor**

[OS 89] [R 19] [P 69] Without a pre-reactor, blockage occurred owing to only partial solubility of one reactant in the other [127]. Processing was therefore not possible. With a tubular pre-reactor, having Y-shaped mixing guidance of the streams upstream the micro mixer, no blockage occurred for 0 °C processing. Probably, reaction was initiated, yielding some product which acted in a solution-enhancing manner.

##### **Conversion/selectivity/yield – benchmarking to industrial process**

[OS 89] [R 19] [P 69] Using a special reactor configuration with an interdigital micro-mixer array with pre-reactor, subsequent tubing and a quench, a yield of 95% at 0 °C was obtained [127]. The industrial semi-batch process had the same yield at –70 °C.

##### **Increase of reaction temperature close to ambient**

[OS 89] [R 19] [P 69] Using the special reactor configuration outlined above, processing could be done at 0 °C, which is energetically much more favorable than the previous –70 °C industrial semi-batch processing [127].

## 4.14

### **Inorganic Reactions**

#### 4.14.1

##### **Halogenation of Acids – The Belousov–Zhabotinskii Reaction**

Proceedings: [68].

##### **4.14.1.1 Drivers for Performing Halogenation of Acids in Micro Reactors**

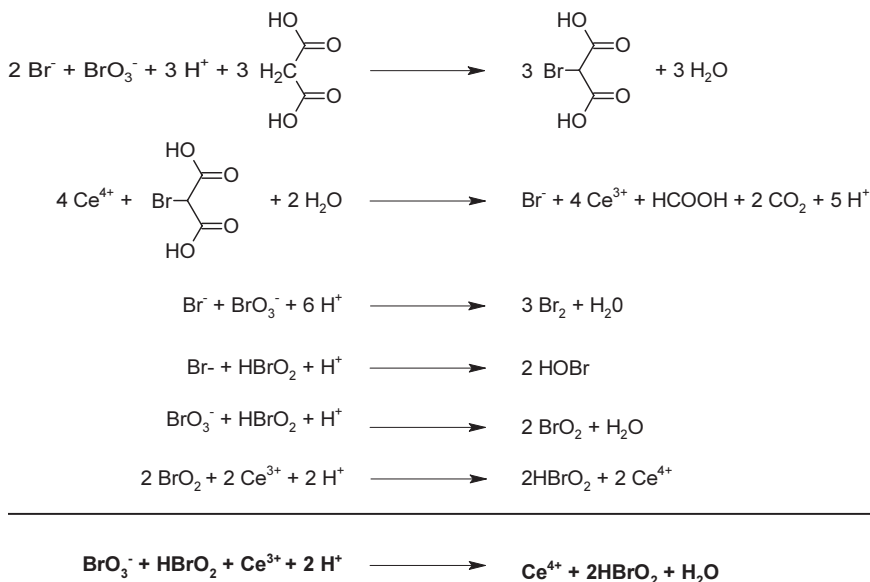
For the catalytic oxidation of malonic acid by bromate (the Belousov–Zhabotinskii reaction), fundamental studies on the interplay of flow and reaction were made. By means of capillary-flow investigations, spatio-temporal concentration patterns were monitored which stem from the interaction of a specific complex reaction and transport of reaction species by molecular diffusion [68]. One prominent class of these patterns is propagating reaction fronts. By external electrical stimulus, electromigration of ionic species can be investigated.

##### **4.14.1.2 Beneficial Micro Reactor Properties for Halogenation of Acids**

To study the effects of molecular diffusion and formation/destabilization of reaction fronts it is advised to rely on small flow-through chambers such as capillaries or cells of sheet-type cross-section [68]. These micro reactors simply provide the small-scale environment needed for such laboratory investigations.



## 4.14.1.3 Halogenation of Acids Investigated in Micro Reactors

**Organic synthesis 90 [OS 90]: Catalytic oxidation of malonic acid by bromate**

This reaction, widely known as the Belousov–Zhabotinskii reaction, can proceed in an oscillatory fashion [68]. For overall slow conversion, the concentrations of intermediates and the catalyst undergo cyclic changes. By this means, many pulse-like reaction zones propagate in a spatially distributed system. Ferriin/ferrin can be applied as an optically detectable catalyst.

## 4.14.1.4 Experimental Protocols

[P 70] No details on the protocol are given in [68].

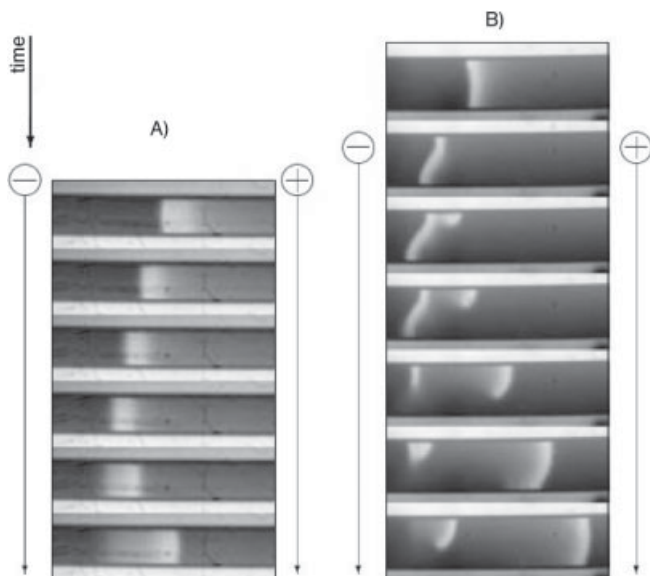
## 4.14.1.5 Typical Results

**Weak electrical field stimulus**

[OS 90] [R 31] [P 70] At weak electrical field, the propagation velocity of a reaction front in a capillary-flow reactor was increased or decreased depending on the mutual orientation of the electrical field and the reaction zone propagation [68]. The movement of two reaction fronts was given by optical images in [68].

**Strong electrical field stimulus**

[OS 90] [R 31] [P 70] At strong electrical field, global changes of the reaction in a capillary-flow reactor were induced which depend on the features of the reaction mechanism [68]. For fields of different strength, experimental findings showed that this involves the formation of several new reaction zones out off the original one, the reversal of the direction of the reaction zone propagation and termination of the reaction (Figure 4.97).



**Figure 4.97** Global changes of the Belousov–Zhabotinskii reaction behavior in the capillary reactor under electrical field. (A) Reversal of the direction of the reaction zone (white stripe) propagation (0.5 mm capillary reactor);  $E = 12 \text{ V cm}^{-1}$ ; monitored length of the capillary  $L = 3 \text{ mm}$ ;  $\Delta t$  between snapshots is 20 s. (B) Break of the planar reaction zone in a 1 mm capillary reactor;  $E = 6 \text{ V cm}^{-1}$ ;  $L = 4.4 \text{ mm}$ ;  $\Delta t = 40 \text{ s}$  [68].

#### Stability of reaction front

[OS 90] [R 31] [P 70] Capillary micro flow reactors of various inner cross-sections were used to study the stability of the reaction front and the homogeneity of the concentration profiles [68]. By concentration changes, hydrodynamic flow may be created which affects the reaction front stability. As expected, stronger influences were found for capillaries of larger cross-section. It was further found that the reaction front is perpendicular to the flow axis of the capillary for positive fields or when no field is applied (spatially one-dimensional case). For negative fields, bent or otherwise modified, reaction zones were found so that two- or three-dimensional propagation was induced. Splitting-off of zones and gradual spreading resulted from such geometry changes.

#### 4.14.2

##### Redox Reaction Iodide/Iodate – Dushman Reaction

Proceedings: [22].

#### 4.14.2.1 Drivers for Performing the Dushman Reaction

The Dushman reaction was chosen for its changes in UV–visible properties to demonstrate the capability of such in-line monitoring in a micro reactor [22].

#### 4.14.2.2 Beneficial Micro Reactor Properties for the Dushman Reaction

The aim given above refers to the possibility of integration of multiple functions in a micro device; here, this refers to the combination of flow processing and sensing [22].

#### 4.14.2.3 Dushman Reaction Investigated in Micro Reactors

**Organic synthesis 91 [OS 91]: Redox reaction of iodate and iodide**



This reaction is the reverse hydrolysis of iodine [22]. In a further reaction, the product iodine reacts with iodide to give triiodide. Both iodine and triiodide absorb in the visible region, hence the reaction can be monitored optically.

#### 4.14.2.4 Experimental Protocols

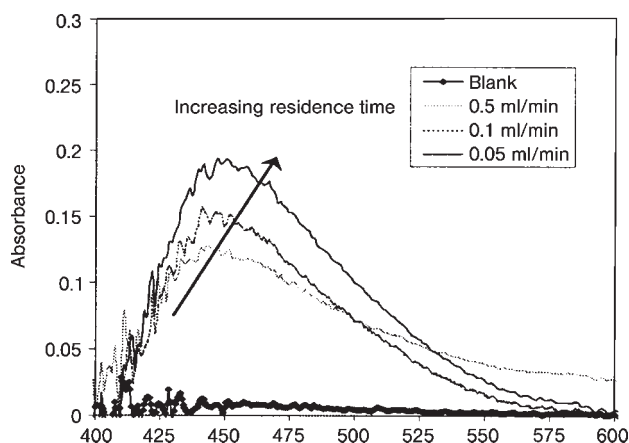
[P 71] Only flow rates were given; no further details on process parameters were revealed [22]. The reactants were filtered and fed by syringe pumps.

Processing in the micro reactor was analyzed by a CCD camera with a long working distance magnifying lens [22]. Visible spectrometry was applied for in-line sensing. The change in product concentration was determined at 450 nm. The light was collected via an optical fiber and sent to the spectrometer.

#### 4.14.2.5 Typical Results

##### Flow rate/residence time

[OS 91] [R 9] [P 71] By in-line spectrometry, the course of the reaction can be directly followed when changing the residence time (Figure 4.98). For decreasing reaction times, increasing flow rate, a decrease in absorption of the product was monitored, as expected [22].



**Figure 4.98** With decreasing of residence time a lower Dushman reaction product is observable, indicated by in-line spectrometry [22].

## 4.14.3

**Oxidation of Arsenous Acid – Combined Dushman/Roebuck Reaction**

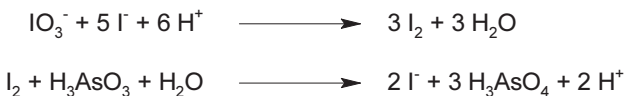
Proceedings: [68, 145].

**4.14.3.1 Drivers for Performing Arsenous Acid Oxidation in Micro Reactors**

For arsenous acid oxidation, fundamental studies on the interplay of flow and reaction were made. By means of capillary-flow investigations, spatio-temporal concentration patterns were monitored which stem from the interaction of a specific complex reaction and transport of reaction species by molecular diffusion [68]. One prominent class of these patterns is propagating reaction fronts. By external electrical stimulus, electromigration of ionic species can be investigated.

**4.14.3.2 Beneficial Micro Reactor Properties for Arsenous Acid Oxidation**

To study effects of molecular diffusion and formation/destabilization of reaction fronts, it is advised to rely on small flow-through chambers such as capillaries or cells of sheet-type cross-section [68]. These micro reactors simply provide the small-scale environment needed for such laboratory investigations.

**4.14.3.3 Arsenous Acid Oxidation Investigated in Micro Reactors****Organic synthesis 92 [OS 92]: Oxidation of arsenous acid by iodate**

The arsenous acid–iodate reaction is a combination of the Dushman and Roebuck reactions [145]. These reactions compete for iodine and iodide as intermediate products. A complete mathematical description has to include 14 species in the electrolyte, seven partial differential equations, six algebraic equations for acid–base equilibria and one linear equation for the local electroneutrality.

This reaction undergoes conversion in one sequence of consecutive elementary reaction steps and so only one propagating front is formed in a spatially distributed system [68]. Depending on the initial ratio of reactants, iodine as colored and iodide as uncolored product, or both, are formed [145].

**4.14.3.4 Experimental Protocols**

[P 72] No details on the protocol are given in [68] or [145].

**4.14.3.5 Typical Results****Weak electrical field stimulus**

[OS 92] [R 32] [P 72] At weak electrical field, the propagation velocity of a reaction front in a capillary-flow reactor could be increased or decreased depending on the mutual orientation of the electrical field and the reaction zone propagation [68]. The movement of two reaction fronts was given by optical images in [68].



**Figure 4.99** Images of radial movement of reaction zones [68].

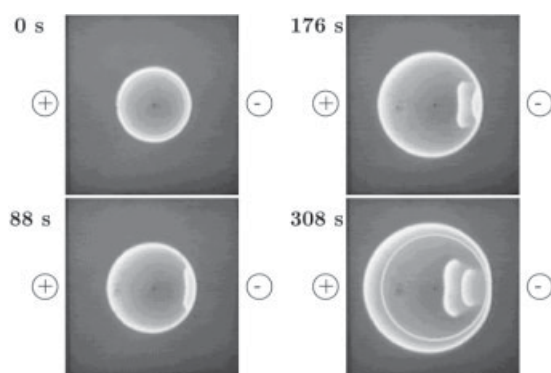
[OS 92] [R 32] [P 72] At weak electrical field, the propagation velocity of a reaction front in a capillary-flow reactor could be increased or decreased depending on the mutual orientation of the electrical field and the reaction zone propagation [68]. The movement of two reaction fronts (Figure 4.99) was given by optical images in [68].

#### Strong electrical field stimulus

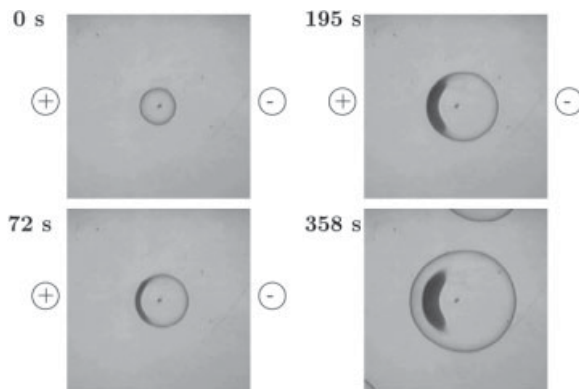
[OS 92] [R 32] [P 72] The iodate–arsenous acid reaction proceeds to one of two stationary states in different parts of the capillary when an electrical field of specific strength is applied [68]. Accordingly, a spatially inhomogeneous distribution of reaction products is generated along the capillary.

#### Wave splitting by electrical stimulus

[OS 92] [R 32] [P 72] For radial movement from a center position, wave splitting was found [68]. Two new reaction zones were formed from a part of the circular reaction zone (Figure 4.100).



**Figure 4.100** Wave splitting of the reaction zone (white circle) in an electric field. Top view of the monitored area ( $3 \times 3$  cm). Numbers show the time intervals after the electric field was switched on ( $E = 4.06 \text{ V cm}^{-1}$ ) [68].



**Figure 4.101** Formation of zones due to the change of reaction mechanism by applying an electrical field during the oxidation of arsenous acid by iodate ( $E = 2.0 \text{ V cm}^{-1}$ ). Numbers show the time intervals after the electric field was switched on. Intermediate product iodine (dark) and iodide (white) [68].

#### Electric field-induced switching between iodide and iodine

[OS 92] [R 32] [P 72] Iodide and iodine are autocatalysts. When an electrical field is applied, iodide moves to the positive electrode and, by this means, the propagation of the reaction is accelerated [145]. As a net result, more iodide is generated for fronts which approach the positive electrode; in turn, iodine is formed favorably for fronts propagating to the negative electrode. On switching the field off, the system comes back to the prior state.

#### Electric field-induced switching between iodide and iodine

[OS 92] [R 32] [P 72] A mathematical model based on transport and reaction was able to reproduce the experimental findings described above [145].

#### Changes of reaction mechanism by electrical stimulus

[OS 92] [R 32] [P 72] When switching on an electrical field, the reaction mechanism changes [68]. At zero field, iodine is formed as intermediate and converted to iodide. At non-vanishing field, iodine is the product, as evidenced by large colored zones. On switching off the field, uncolored iodide is formed again (Figure 4.101).

#### 4.14.4

##### Landolt Reaction

Proceedings: [145].

##### 4.14.4.1 Drivers for Performing Landolt Reactions in Micro Reactors

See Section 4.14.3.1.

#### 4.14.4.2 Beneficial Micro Reactor Properties for Landolt Reactions

See Section 4.14.3.2.

#### 4.14.4.3 Landolt Reactions Investigated in Micro Reactors

##### Organic synthesis 93 [OS 93]: Modified Landolt reaction



This reaction is autocatalytic concerning the H<sup>+</sup> ions [145]. The concentration of H<sup>+</sup> ions increases within the reaction front. For this reason, acid–base indicators can monitor the front propagation.

#### 4.14.4.4 Experimental Protocols

[P 73] No details on the protocol are given in [145].

#### 4.14.4.5 Typical Results

##### Change of homogeneous radial front propagation by unidirectional electrical field

[OS 93] [R 31] [P 73] When applying a uni-directional electrical field, migration of H<sup>+</sup> ions induces propagation of the reaction front towards the negative electrode and suppresses the propagation towards the positive electrode [145]. Accordingly, the speed of the reaction front depends on the orientation to the electrode axis. As a result, the formerly homogeneously radial moving front is distorted towards the positive electrode.

##### Modeling the effect of axial dispersion

[OS 93] [R 31] [P 73] Using a simplified modeling approach, it was shown that axial dispersion changes the direction and shape of moving reaction fronts and also affects the interplay between dispersion and migration in an electrical field [145].

#### 4.14.5

##### Transition Metal–Ligand Complex Formation – Co(II) Complexes

Peer-reviewed journals: [28].

#### 4.14.5.1 Drivers for Performing Co(II) Complex Formations in Micro Reactors

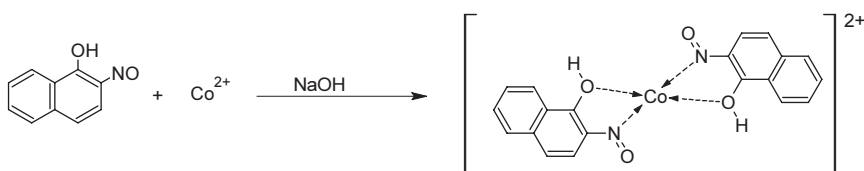
Co(II) complex formation is the essential part of copper wet analysis. The latter involves several chemical unit operations. In a concrete example, eight such operations were combined – two-phase formation, mixing, chelating reaction, solvent extraction, phase separation, three-phase formation, decomposition of co-existing metal chelates and removal of these chelates and reagents [28]. Accordingly, Co(II) complex formation serves as a test reaction to perform multiple unit operations on one chip, i.e. as a chemical investigation to validate the Lab-on-a-Chip concept.

#### 4.14.5.2 Beneficial Micro Reactor Properties for Co(II) Complex Formations

Micro reactors, in particular chip-based systems, offer a high degree of integration of diverse processing units in a confined space, typically not exceeding a few centimeters length scale (for width and length of chip). By flow-through operation, diverse unit operations can be performed on a time scale just long enough for completion of performance and be directly combined with the next operational step. As a result, operations that may require many manual steps at the macro-scale may here be carried out at once just by using pumping or electrical action for feeding.

#### 4.14.5.3 Co(II) Complex Formations Investigated in Micro Reactors

##### Organic synthesis 94 [OS 94]: Complex formation between Co(II) and 2-nitroso-1-naphthol



#### 4.14.5.4 Experimental Protocols

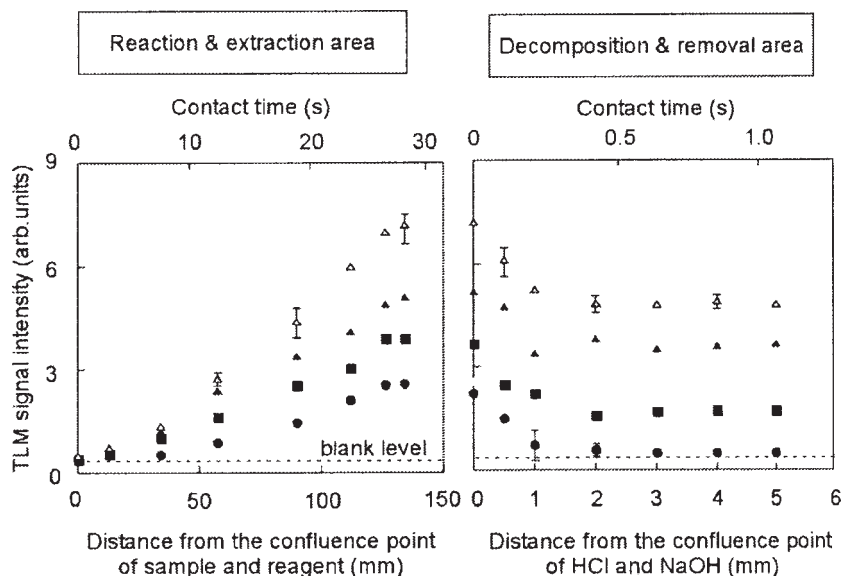
[P 74] Aqueous solutions of Co(II) with concentrations of  $0\text{--}1.5 \times 10^{-7}$  M in the presence of  $1.0 \times 10^{-6}$  M Cu(II) were introduced into a three-feed contactor [28]. One other feed was charged with an aqueous mixture solution of 2-nitroso-1-naphthol and NaOH. The two aqueous phases merged, induced the chelating reaction to give a colored complex, and were contacted with *m*-xylene fed via the third line. The aqueous and xylene phases formed a bi-layer in one micro channel with special structuring of the channel bottom supporting flow guidance of continuous streams and avoiding intermixing of phases. After such extraction of the metal ions, the xylene stream was encompassed by two aqueous streams. One stream contained NaOH and cleaved the copper complex, while not affecting the cobalt complex. Thereby, copper ions were released and moved to the second organic phase containing HCl. Analysis of concentration was done optically with a thermal lens microscope (TLM).

#### 4.14.5.5 Typical Results

##### Conversion/selectivity/yield

[OS 94] [R 13] [P 74] For admixture of samples with varying concentrations of Co(II) and Cu(II), the respective changes in the Co(II) chelate complex concentration as a function of contact time were optically derived [28]. Analysis was performed in the reaction/extraction area and also in the decomposition/removal area (Figure 4.102). As expected, more complex is formed in the reaction/extraction area with increasing contact time. Also, more complex results when increasing the Co(II) concentration at constant Cu(II) concentration. This proves that mass transfer is efficient (as high concentrations can also be handled) and that no interference from other analytes falsifies the measurement. As a result, calibration curves were derived.





**Figure 4.102** Dynamic evolution of Co chelate formation in the reaction/extraction and decomposition/removal areas at various concentrations: ( $\Delta$ )  $1.5 \times 10^{-7}$ ; ( $\blacktriangle$ )  $1.0 \times 10^{-7}$ ; ( $\blacksquare$ )  $5.0 \times 10^{-8}$ ; ( $\bullet$ ) 0 M Co(II) [28].

#### Analysis time

[OS 94] [R 13] [P 74] The analysis time for one sample, less than 1 min, is considerably faster than that of a conventional system, which needs about 2 h [28].

#### 4.14.6

#### Transition Metal–Ligand Complex Formation – Nickel–Pyridine Complexes

##### 4.14.6.1 Drivers for Performing Ni–Pyridine Complex Formations in Micro Reactors

The reversible formation of a complex by  $\text{Ni}^{2+}$  ions and the bidentate ligand pyridine-2-azo-*p*-dimethylaniline is a simple and thus reliable reaction, not accompanied by side reactions [17]. Kinetic rate law and rate constants for the reaction are known. The time demand of the reaction fits the short time scales typical for micro reactors. The strong absorption and the strong changes by reaction facilitate analysis of dynamic and spatial concentration profiles.

Accordingly, the above-mentioned complex formation was used as a test reaction to gather physico-chemical parameters and to validate quantitatively predictions of the spatial and temporal evolutions of concentrations [17].

##### 4.14.6.2 Beneficial Micro Reactor Properties for Ni–Pyridine Complex Formations

Owing to its nature as a test reaction, not the reaction itself but rather the micro-channel flow was the focus of the investigations. Hence nothing is to be said here on the beneficial micro reactor properties for the reaction applied.



#### 4.14.6.5 Typical Results

##### Flow mode

[OS 95] [R 5] [P 75] Plugs of pyridine-2-azo-*p*-dimethylaniline were inserted in a continuous  $\text{Ni}^{2+}$  ion stream. Thereafter, spatial concentration profiles were monitored in the micro channels as a result of interpenetrating flow fronts due to varying mobility of the species in an electrical field [17].

Depending on what species port was 'activated', i.e. which reactant stream was moved, different flow modes were available, deliberately changing the concentration profiles in a predetermined manner [17]. These flow modes were termed 'flow mode', 'inject mode' and 'restarted flow mode', corresponding to  $\text{Ni}^{2+}$  ion channel filling, ligand slug injection and  $\text{Ni}^{2+}$  ion movement after slug insertion, respectively.

At the  $\text{Ni}^{2+}$  ion solution/ligand slug interface, the complex is formed, as evidenced by the color change [17]. Since the formation is reversible, decomposition of the complex can also be observed, on reducing the content of pyridine-2-azo-*p*-dimethylaniline.

##### Comparison with modeling

[OS 95] [R 5] [P 75] Numerical calculations were performed which were based on electroosmotic flow, electrophoresis, diffusion and chemical reaction [17]. The concentrations of  $\text{Ni}^{2+}$  ions, pyridine-2-azo-*p*-dimethylaniline and the respective complex as functions of both time and channel position were determined, describing mixing and reaction in a slug-insertion mode governed by electrophoretic mobility (see also [14]). The calculations were mainly in accordance with the experimental results. In particular, this refers to the formation of a relatively narrow peak of the complex. In turn, the concentration profiles at the edges of the ligand slug were not adequately described.

#### 4.14.7

##### Diverse Inorganic Reactions

###### 4.14.7.1 Ionic Chemical Systems for Electrolyte Diode and Transistors

Simple chemical systems with several components (HCl, KOH, KCl in hydrogel) were used for modeling mass and charge balances coupled with equations for electric field, transport processes and equilibrium reactions [146]. This served for demonstrating the chemical systems' function as electrolyte diodes and transistors, so-called 'electrolyte-microelectronics'.

## References

- 1 NIELSEN, C. A., CHRISMAN, R. W., LAPOINTE, E., MILLER, T. E., *Novel tubing microreactor for monitoring chemical reactions*, *Anal. Chem.* **74**, 13 (2002) 3112–3117.
- 2 HASWELL, S. J., O'SULLIVAN, B., STYRING, P., *Kumada–Corriu reactions in a pressure-driven microflow reactor*, *Lab. Chip* **1** (2001) 164–166.
- 3 KUNZ, U., KIRSCHNING, A., *A new microreactor for the solution-phase synthesis of potential drugs*, in MATLOSZ, M., EHRFELD, W., BASELT, J. P. (Eds.), *Microreaction Technology – IMRET 5: Proc. 5th International Conference on Microreaction Technology*, pp. 424–445, Springer-Verlag, Berlin (2001).
- 4 WOOTTON, R. C. R., FORTT, R., DE MELLO, A. J., *On-chip generation and reaction of unstable intermediates – monolithic nanoreactors for diazonium chemistry: azo dyes*, *Lab. Chip* **2** (2002) 14N–21N.
- 5 WATTS, P., WILES, C., HASWELL, S. J., POMBO-VILLAR, E., *Solution phase synthesis of  $\beta$ -peptides using micro reactors*, *Tetrahedron* **58**, 27 (2002) 5427–5439.
- 6 SKELTON, V., GREENWAY, G. M., HASWELL, S. J., STYRING, P., MORGAN, D. O., *Micro-reactor synthesis: synthesis of cyanobiphenyls using a modified Suzuki coupling of an aryl halide and aryl boronic acid*, in EHRFELD, W. (Ed.), *Microreaction Technology: 3rd International Conference on Microreaction Technology, Proc. of IMRET 3*, pp. 235–242, Springer-Verlag, Berlin (2000).
- 7 GREENWAY, G. M., HASWELL, S. J., MORGAN, D. O., SKELTON, V., STYRING, P., *The use of a novel microreactor for high throughput continuous flow organic synthesis*, *Sens. Actuators B: Chemical* **63**, 3 (2000) 153–158.
- 8 WILES, C., WATTS, P., HASWELL, S. J., POMBO-VILLAR, E., *1,4-Addition of enolates to  $\alpha,\beta$ -unsaturated ketones within a micro reactor*, *Lab. Chip* **2** (2002) 62–64.
- 9 GARCIA-EGIDO, E., WONG, S. Y. F., *A Hantzsch synthesis of 2-aminothiazoles performed in a microreactor system*, in RAMSEY, J. M., VAN DEN BERG, A. (Eds.), *Micro Total Analysis Systems*, pp. 517–518, Kluwer Academic Publishers, Dordrecht (2001).
- 10 GARCIA-EGIDO, E., WONG, S. Y. F., WARRINGTON, B. H., *A Hantzsch synthesis of 2-aminothiazoles performed in a heated microreactor system*, *Lab. Chip* **2** (2002) 31–33.
- 11 SANDS, M., HASWELL, S. J., KELLY, S. M., SKELTON, V., MORGAN, D., STYRING, P., WARRINGTON, B., *The investigation of an equilibrium dependent reaction for the formation of enamines in a microchemical system*, *Lab. Chip* **1** (2001) 64–65.
- 12 HASWELL, S. J., *Miniaturization – what's in it for chemistry*, in VAN DEN BERG, A., RAMSAY, J. M. (Eds.), *Micro Total Analysis System*, pp. 637–639, Kluwer Academic Publishers, Dordrecht (2001).
- 13 SKELTON, V., GREENWAY, G. M., HASWELL, S. J., STYRING, P., MORGAN, D. O., H., WARRINGTON, B. H., WONG, S., *Micro reaction technology: synthetic chemical optimisation methodology of Wittig synthesis enabling a semi-automated micro reactor for combinatorial screening*, in *Proceedings of the 4th International Conference on Microreaction Technology, IMRET 4*, 5–9 March 2000, pp. 78–88, AIChE Topical Conf. Proc., Atlanta, GA (2000).
- 14 FLETCHER, P. D. I., HASWELL, S. J., POMBO-VILLAR, E., WARRINGTON, B. H., WATTS, P., WONG, S. Y. F., ZHANG, X., *Micro reactors: principle and applications in organic synthesis*, *Tetrahedron* **58**, 24 (2002) 4735–4757.
- 15 WILES, C., WATTS, P., HASWELL, S. J., POMBO-VILLAR, E., *The aldol reaction of silyl enol ethers within a micro reactor*, *Lab. Chip* **1** (2001) 100–101.
- 16 SKELTON, V., HASWELL, S. J., STYRING, P., WARRINGTON, B., WONG, S., *A micro-reactor device for the Ugi four component condensation (4CC) reaction*, in RAMSEY, J. M., VAN DEN BERG, A. (Eds.), *Micro Total Analysis Systems*, pp. 589–590, Kluwer Academic Publishers, Dordrecht (2001).
- 17 FLETCHER, P. D. I., HASWELL, S. J., ZHANG, X., *Electrokinetic control of a chemical reaction in a lab-on-a-chip micro-*

- reactor: measurement and qualitative modeling, *Lab. Chip* 2 (2002) 102–112.
- 18 FERNANDEZ-SUAREZ, M., WONG, S. Y. F., WARRINGTON, B. H., *Synthesis of a three-member array of cycloadducts in a glass microchip under pressure driven flow*, *Lab. Chip* 2 (2002) 170–174.
  - 19 WILSON, N. G., MCCREEDY, T., *On-chip catalysis using a lithographically fabricated glass microreactor – the dehydration of alcohols using sulfated zirconia*, *Chem. Commun.* 9 (2000) 733–734.
  - 20 GARCIA-EGIDO, E., SPIKMANS, V., WONG, S. Y. F., WARRINGTON, B. H., *Synthesis and analysis of combinatorial libraries performed in an automated micro-reactor system*, *Lab. Chip* 3 (2003) 67–72.
  - 21 FLOYD, T. M., JENSEN, K. F., SCHMIDT, M. A., *Towards integration of chemical detection for liquid phase microchannel reactors*, in *Proceedings of the 4th International Conference on Microreaction Technology*, IMRET 4, 5–9 March 2000, pp. 461–466, AIChE Topical Conf. Proc., Atlanta, GA (2000).
  - 22 FLOYD, T. M., LOSEY, M. W., FIREBAUGH, S. L., JENSEN, K. F., SCHMIDT, M. A., *Novel liquid phase microreactors for safe production of hazardous specialty chemicals*, in EHRFELD, W. (Ed.), *Micro-reaction Technology: 3rd International Conference on Microreaction Technology*, Proc. of IMRET 3, pp. 171–180, Springer-Verlag, Berlin (2000).
  - 23 KIKUTANI, Y., HORIUCHI, T., UCHIYAMA, K., HISAMOTO, H., TOKESHI, M., KITAMORI, T., *Glass microchip with three-dimensional microchannel network for 2 × 2 parallel synthesis*, *Lab. Chip* 2 (2002) 188–192.
  - 24 KIKUTANI, Y., HISAMOTO, H., TOKESHI, M., KITAMORI, T., *Fabrication of a glass microchip with three-dimensional channel network and its application to a single-chip combinatorial synthetic reactor*, in RAMSEY, J. M., VAN DEN BERG, A. (Eds.), *Micro Total Analysis Systems*, pp. 161–162, Kluwer Academic Publishers, Dordrecht (2001).
  - 25 MITCHELL, M. C., SPIKMANS, V., BESSOTH, F., MANZ, A., DE MELLO, A., *Towards organic synthesis in microfluidic devices: multicomponent reactions for the construction of compound libraries*, in VAN DEN BERG, A., OLTHUIS, W., BERGVELD, P. (Eds.), *Micro Total Analysis Systems*, pp. 463–465, Kluwer Academic Publishers, Dordrecht (2000).
  - 26 KANNO, K., MAEDA, H., IZUMO, S., IKUMO, M., TAKESHITA, K., TASHIRO, A., FUJII, M., *Rapid enzymatic transglycosylation and oligosaccharide synthesis in a microchip reactor*, *Lab. Chip* 2 (2002) 15–18.
  - 27 KANNO, K., FUJII, M., *Microreactor: new device for organic and enzymatic synthesis*, *Yuki-Gosei-Kagaku-Kyokai-shi* 60, 7 (2002) 701–707 (in Japanese).
  - 28 TOKESHI, M., MINAGAWA, T., UCHIYAMA, K., HIBARA, A., SATO, K., HISAMOTO, H., KITAMORI, T., *Integration of chemical process in on a microchip*, in RAMSEY, J. M., VAN DEN BERG, A. (Eds.), *Micro Total Analysis Systems*, pp. 533–534, Kluwer Academic Publishers, Dordrecht (2001).
  - 29 UENO, K., KITAGAWA, F., KITAMURA, N., *Photocyanation of pyrene across an oil/water interface in a polymer microchannel chip*, *Lab. Chip* 2 (2002) 231–234.
  - 30 WAN, Y. S. S., CHAU, J. L. H., GAVRIILIDIS, A., YEUNG, K. L., *Design and fabrication of zeolite-based microreactors and membrane microseparators*, *Micropor. Mesopor. Mater.* 42 (2001) 157–175.
  - 31 BURNS, J. R., RAMSHAW, C., *Development of a microreactor for chemical production*, *Trans. Inst. Chem. Eng.* 77, 5/A (1998) 206–211.
  - 32 SCHWESINGER, K., FRANK, T., *A modular microfluid system with an integrated micromixer*, in *Proceedings of the MME '95*, pp. 144–147, Copenhagen (1995).
  - 33 SCHWESINGER, W., FRANK, T., *A static micromixer built up in silicon*, in *Proceedings of Micromachining and Microfabrication*, pp. 150–155, SPIE, Austin TX (1995).
  - 34 SCHWESINGER, N., FRANK, T., *Device for mixing small quantities of liquids*, WO 96/30113, Merck Patent GmbH, Darmstadt (1995).
  - 35 SCHWESINGER, N., FRANK, T., WURMUS, H., *A modular microfluid system with an integrated micromixer*, *J. Micromech. Microeng.* 6 (1996) 99–102.
  - 36 SCHWESINGER, N., *Mikrostrukturierte modulare Reaktionssysteme für die*

- chemische Industrie, F & M, Feinwerktechnik, Mikrotechnik, Meßtechnik **110**, 4 (2002) 17–21.
- 37 ANTES, J., TÜERCKE, T., MARIOTH, E., SCHMID, K., KRAUSE, H., LOEBBECKE, S., *Use of microreactors for nitration processes, in Proceedings of the 4th International Conference on Microreaction Technology, IMRET 4*, 5–9 March 2000, pp. 194–200, AIChE Topical Conf. Proc., Atlanta, GA (2000).
- 38 ANTES, J., TÜRCKE, T., MARIOTH, E., LECHNER, F., SCHOLZ, M., SCHNÜRER, F., KRAUSE, H. H., LÖBBECKE, S., *Investigation, analysis and optimization of exothermic nitrations in microreactor processes*, in MATLOSZ, M., EHRFELD, W., BASELT, J. P. (Eds.), *Microreaction Technology – IMRET 5: Proc. 5th International Conference on Microreaction Technology*, pp. 446–454, Springer-Verlag, Berlin (2001).
- 39 EHRFELD, W., GOLBIG, K., HESSEL, V., LÖWE, H., RICHTER, T., *Characterization of mixing in micromixers by a test reaction: single mixing units and mixer arrays*, *Ind. Eng. Chem. Res.* **38**, 3 (1999) 1075–1082.
- 40 HESSEL, V., HARDT, S., LÖWE, H., SCHÖNFELD, F., *Laminar mixing in different interdigital micromixers – Part I: experimental characterization*, *AIChE J.* **49**, 3 (2003) 566–577.
- 41 LÖWE, H., EHRFELD, W., HESSEL, V., RICHTER, T., SCHIEWE, J., *Micromixing technology, in Proceedings of the 4th International Conference on Microreaction Technology, IMRET 4*, 5–9 March 2000, pp. 31–47, AIChE Topical Conf. Proc., Atlanta, GA (2000).
- 42 EHRFELD, W., HESSEL, V., LÖWE, H., *Microreactors*, Wiley-VCH, Weinheim (2000).
- 43 LÖWE, H., SCHIEWE, J., HESSEL, V., DIETRICH, T., FREITAG, A., *Verfahren und statischer Mikrovermischer zum Mischen mindestens zweier Fluide*, DE 10041823, IMM Institut für Mikrotechnik Mainz GmbH, mgt mikroglas technik AG (2000).
- 44 FREITAG, A., DIETRICH, T. R., *Glass as a material for microreaction technology, in Proceedings of the 4th International Conference on Microreaction Technology, IMRET 4*, 5–9 March 2000, pp. 48–54, AIChE Topical Conf. Proc., Atlanta, GA (2000).
- 45 FREITAG, A., DIETRICH, T. R., SCHOLZ, R., *Glass as a material for microreaction technology, in Proceedings of the VDE World Microtechnologies Congress, MICRO.tec 2000*, 25–27 September 2000, pp. 355–359, VDE Verlag, Berlin, EXPO Hannover (2000).
- 46 HERWECK, T., HARDT, S., HESSEL, V., LÖWE, H., HOFMANN, C., WEISE, F., DIETRICH, T., FREITAG, A., *Visualization of flow patterns and chemical synthesis in transparent micromixers*, in MATLOSZ, M., EHRFELD, W., BASELT, J. P. (Eds.), *Microreaction Technology – IMRET 5: Proc. 5th International Conference on Microreaction Technology*, pp. 215–229, Springer-Verlag, Berlin (2001).
- 47 DIETRICH, T. R., EHRFELD, W., LACHER, M., KRÄMER, M., SPEIT, B., *Fabrication technologies for microsystems utilizing photoetchable glass*, *Micron. Eng.* **30** (1996) 497–504.
- 48 HESSEL, V., LÖWE, H., HOFMANN, C., SCHÖNFELD, F., WEHLE, D., WERNER, B., *Process development of fast reaction of industrial importance using a caterpillar micromixer/tubular reactor set-up, in Proceedings of the 6th International Conference on Microreaction Technology, IMRET 6*, 11–14 March 2002, pp. 39–54, AIChE Pub. No. 164, New Orleans (2002).
- 49 EHRFELD, W., HESSEL, V., KIESEWALTER, S., LÖWE, H., RICHTER, T., SCHIEWE, J., *Implementation of microreaction technology in process engineering, in EHRFELD, W. (Ed.), Microreaction Technology: 3rd International Conference on Microreaction Technology, Proc. of IMRET 3*, pp. 14–34, Springer-Verlag, Berlin (2000).
- 50 IMM, unpublished results.
- 51 KRAUT, M., NAGEL, A., SCHUBERT, K., *Oxidation of ethanol by hydrogen peroxide, in Proceedings of the 6th International Conference on Microreaction Technology, IMRET 6*, 11–14 March 2002, pp. 352–356, AIChE Pub. No. 164, New Orleans (2002).
- 52 TAGHAVI-MOGHADAM, S., KLEEMANN, A., GOLBIG, K. G., *Microreaction technology as a novel approach to drug design, process de-*

- velopment and reliability, *Organic Process Res. Dev.* **5** (2001) 652–658.
- 53 GOLBIG, K., TAGHAVI-MOGHADAM, S., BORN, P., *CYTOS<sup>TM</sup>-technology – microreaction technology in practical sense*, in *Proceedings of the 6th International Conference on Microreaction Technology*, IMRET 6, 11–14 March 2002, pp. 131–134, AIChE Pub. No. 164, New Orleans (2002).
- 54 TAGHAVI-MOGHADAM, S., GOLBIG, K., *Microreactors: application of CYTOS<sup>TM</sup>-technology from laboratory to production scale*, *MST News* **3** (2002) 36–38.
- 55 WILLE, C., AUTZE, V., KIM, H., NICKEL, U., OBERBECK, S., SCHWALBE, T., UNVERDORBEN, L., *Progress in transferring microreactors from lab into production – an example in the field of pigments technology*, in *Proceedings of the 6th International Conference on Microreaction Technology*, IMRET 6, 11–14 March 2002, pp. 7–17, AIChE Pub. No. 164, New Orleans (2002).
- 56 RICHTER, T., EHRFELD, W., HESSEL, V., LÖWE, H., STORZ, M., WOLF, A., *A flexible multi component microreaction system for liquid phase reactions*, in EHRFELD, W. (Ed.), *Microreaction Technology: 3rd International Conference on Microreaction Technology*, Proc. of IMRET 3, pp. 636–644, Springer-Verlag, Berlin (2000).
- 57 RICHTER, T., EHRFELD, W., WOLF, A., GRUBER, H. P., WÖRZ, O., *Microreactors in highly corrosion- and heat-resistant materials fabricated by various micro-EDM techniques*, in *Proceedings of Microreaction Technology, 1st International Conference on Microreaction Technology*, IMRET 1, 23–25 February 1997, Frankfurt/M. (1997).
- 58 RICHTER, T., EHRFELD, W., GEBAUER, K., GOLBIG, K., HESSEL, V., LÖWE, H., WOLF, A., *Metallic microreactors: components and integrated systems*, in EHRFELD, W., RINARD, I. H., WEGENG, R. S. (Eds.), *Process Miniaturization: 2nd International Conference on Microreaction Technology*, IMRET 2, *Topical Conf. Preprints*, pp. 146–151, AIChE, New Orleans (1998).
- 59 RICHTER, T., EHRFELD, W., WOLF, A., GRUBER, H. P., WÖRZ, O., *Fabrication of microreactor components by electro discharge machining*, in EHRFELD, W. (Ed.), *Microreaction Technology – Proc. of the 1st International Conference on Microreaction Technology*, IMRET 1, pp. 158–168, Springer-Verlag, Berlin (1997).
- 60 WOLF, A., EHRFELD, W., LEHR, H., MICHEL, F., RICHTER, T., GRUBER, H., WÖRZ, O., *Mikroreaktorfertigung mittels Funkenerosion*, F & M, *Feinwerktechnik, Mikrotechnik, Meßtechnik* **105**, 6 (1997) 436–439.
- 61 WÖRZ, O., JÄCKEL, K.-P., RICHTER, T., WOLF, A., *Microreactors – a new efficient tool for reactor development*, *Chem. Eng. Technol.* **24**, 2 (2001) 138–143.
- 62 WÖRZ, O., JÄCKEL, K.-P., RICHTER, T., WOLF, A., *Mikroreaktoren – Ein neues wirksames Werkzeug für die Reaktorentwicklung*, *Chem. Ing. Tech.* **72**, 5 (2000) 460–463.
- 63 RICHTER, T., WOLF, A., JÄCKEL, J.-P., WÖRZ, O., *Mikroreaktoren, ein neues wirksames Werkzeug für die Reaktorentwicklung*, *Chem. Ing. Tech.* **71** (1999) 973–974.
- 64 WEBER, M., TANGER, U., KLEINLOH, W., *Method and device for production of phenol and acetone by means of acid-catalyzed, homogeneous decoposition of cumenehydroperoxid*, WO 01/30732, Phenolchemie GmbH (1999).
- 65 MATLOSZ, M., VALLIERES, C., *Micro-sectioned electrochemical reactors for selective partial oxidation*, in EHRFELD, W., RINARD, I. H., WEGENG, R. S. (Eds.), *Process Miniaturization: 2nd International Conference on Microreaction Technology*, IMRET 2, *Topical Conf. Preprints*, pp. 54–59, AIChE, New Orleans (1998).
- 66 SUGA, S., OKAJIMA, M., FUJIWARA, K., YOSHIDA, J.-I., *Cation Flow method: a new approach to conventional and combinatorial organic syntheses using electrochemical microflow systems*, *J. Am. Chem. Soc.* **123**, 32 (2001) 7941–7942.
- 67 SUGA, S., OKAJIMA, M., FUJIWARA, K., YOSHIDA, J., *New electrochemical micro flow sytem for CationFlow method*, in *Proceedings of the 6th International Conference on Microreaction Technology*, IMRET 6, 11–14 March 2002, pp. 29–31,

- AIChE Pub. No. 164, New Orleans (2002).
- 68 SEVCIKOVA, H., SNITA, D., MAREK, M., *Reactions in microreactors in electric fields*, in EHRFELD, W. (Ed.), *Microreaction Technology – Proceedings of the 1st International Conference on Microreaction Technology, IMRET 1*, pp. 47–54, Springer-Verlag, Berlin (1997).
- 69 ZIOGAS, A., LÖWE, H., KÜPPER, M., EHRFELD, W., *Electrochemical microreactor: a new approach in microreaction technology*, in EHRFELD, W. (Ed.), *Microreaction Technology: 3rd International Conference on Microreaction Technology, Proc. of IMRET 3*, pp. 136–156, Springer-Verlag, Berlin (2000).
- 70 MENEGAUD, V., BAGEL, O., FERRIGNO, R., GIRAULT, H. H., HAIDER, A., *A ceramic electrochemical microreactor for the methoxylation of methyl-2-furoate with direct mass spectrometry coupling*, *Lab. Chip* **2** (2002) 39–44.
- 71 FERRIGNO, R., REID, V., GIRAULT, H. H., *Single flow electrochemical microreactor application to furan methoxylation*, in EHRFELD, W. (Ed.), *Microreaction Technology: 3rd International Conference on Microreaction Technology, Proc. of IMRET 3*, pp. 294–301, Springer-Verlag, Berlin (2000).
- 72 LU, H., SCHMIDT, M. A., JENSEN, K. F., *Photochemical reactions and on-line UV detection in microfabricated reactors*, *Lab. Chip* **1** (2001) 22–28.
- 73 JACKMAN, R. J., FLOYD, T. M., GHODSSI, R., SCHMIDT, M. A., JENSEN, K. F., *Microfluidic systems with on-line UV detection fabricated in photodefinable epoxy*, *J. Micromech. Microeng.* **11** (2001) 263–269.
- 74 LU, H., SCHMIDT, M. A., JENSEN, K. F., *Photochemical reactions and online product detection in microfabricated reactors*, in MATLOSZ, M., EHRFELD, W., BASELT, J. P. (Eds.), *Microreaction Technology – IMRET 5: Proc. 5th International Conference on Microreaction Technology*, pp. 175–184, Springer-Verlag, Berlin (2001).
- 75 BREMUS-KÖBBERLING, E., GILLNER, A., KÖBBERLING, J., ENDERS, D., BRANDTNER, S., *Development of a microreactor for solid phase synthesis*, in MATLOSZ, M., EHRFELD, W., BASELT, J. P. (Eds.), *Microreaction Technology – IMRET 5: Proc. 5th International Conference on Microreaction Technology*, pp. 455–463, Springer-Verlag, Berlin (2001).
- 76 BREMUS-KÖBBERLING, E., GILLNER, A., KÖBBERLING, J., *Microreactor design for solid phase applications*, in *Proceedings of the VDE World Microtechnologies Congress, MICRO.tec 2000*, 25–27 September 2000, pp. 769–773, VDE Verlag, Berlin, EXPO Hannover (2000).
- 77 BREMUS, E., GILLNER, A., HELLRUNG, D., HÖCKER, H., LEGEWIE, F., POPRAWA, R., WEHNER, M., WILD, M., *Laser processing for manufacturing microfluidic devices*, in EHRFELD, W. (Ed.), *Microreaction Technology: 3rd International Conference on Microreaction Technology, Proc. of IMRET 3*, pp. 80–89, Springer-Verlag, Berlin (2000).
- 78 WERNER, B., DONNET, M., HESSEL, V., HOFMANN, C., JONGEN, N., LÖWE, H., SCHENK, R., ZIOGAS, A., *Specially suited micromixers for processes involving strong fouling*, in *Proceedings of the 6th International Conference on Microreaction Technology, IMRET 6*, 11–14 March 2002, pp. 168–183, AIChE Pub. No. 164, New Orleans (2002).
- 79 HESSEL, V., LÖWE, H., *Mikroverfahrenstechnik: Komponenten – Anlagenkonzeption – Anwenderakzeptanz – Teil 3*, *Chem. Ing. Tech.* **74**, 4 (2002) 381–400.
- 80 HESSEL, V., LÖWE, H., *Micro chemical engineering: components – plant concepts – user acceptance: Part III*, *Chem. Eng. Technol.* **26**, 5 (2003) 531–544.
- 81 SCHENK, R., HESSEL, V., WERNER, B., ZIOGAS, A., HOFMANN, C., DONNET, M., JONGEN, N., *Micromixers as a tool for powder production*, *Chem. Eng. Trans.* **1** (2002) 909–914.
- 82 HESSEL, V., personal communication (2002).
- 83 Schwalbe, T., Autze, V., Wille, G., *Chemical synthesis in microreactors*, *Chimia* **56**, 11 (2002) 636–646.
- 84 GARCIA, E., FERRARI, F., GARCIA, T., MARTINEZ, M., ARACIL, J., *Use of microreactors in biotransformation processes: study of the synthesis of diglycerol mono-laurate ester*, in *Proceedings of the 4th*



- International Conference on Microreaction Technology, IMRET 4*, 5–9 March 2000, pp. 201–214, AIChE Topical Conf. Proc., Atlanta, GA (2000).
- 85 SCHWESINGER, N., MARUFKE, O., QIAO, F., DEVANT, R., WURZIGER, H., *A full wafer silicon microreactor for combinatorial chemistry*, in EHRFELD, W., RINARD, I. H., WEGENG, R. S. (Eds.), *Process Miniaturization: 2nd International Conference on Microreaction Technology, IMRET 2, Topical Conf. Preprints*, pp. 124–126, AIChE, New Orleans (1998).
- 86 WATTS, P., WILES, C., HASWELL, S. J., POMBO-VILLAR, E., *Investigation of racemization in peptide synthesis within a micro reactor*, *Lab. Chip* **2** (2002) 141–144.
- 87 WATTS, P., WILES, C., HASWELL, S. J., POMBO-VILLAR, E., STYRING, P., *The synthesis of peptides using micro reactors*, *Chem. Commun.* (2001) 990–991.
- 88 WATTS, P., WILES, C., HASWELL, S. J., POMBO-VILLAR, E., STYRING, P., *The synthesis of peptides using micro reactors*, in MATLOSZ, M., EHRFELD, W., BASELT, J. P. (Eds.), *Microreaction Technology – IMRET 5: Proc. 5th International Conference on Microreaction Technology*, pp. 508–519, Springer-Verlag, Berlin (2001).
- 89 HASWELL, S. T., WATTS, P., *Green chemistry: synthesis in micro reactors*, *Green Chem.* **5** (2003) 240–249.
- 90 JÄHNISCH, K., HESSEL, V., LÖWE, H., BAERNS, M., *Chemie in Mikrostrukturreaktoren*, *Angew. Chem.* **44**, 4 (2003) in press.
- 91 BRIVIO, M., OOSTERBROEK, R. E., VERBOOM, W., GOEDBLOED, M. H., VAN DEN BERG, A., REINHOUDT, D. N., *Surface effects in the esterification of 9-pyrenebutyric acid within a glass micro reactor*, *Chem. Commun.* (2003) 1924–1925.
- 92 YOSHIDA, J.-I., NAGAKI, A., SUGA, S., *Highly selective reactions using micro-structured reactors*, in *Proceedings of the Micro Chemical Plant – International Workshop*, 4 February 2003, pp. L2 (3–9), Kyoto (2003).
- 93 BÖKENKAMP, D., DESAI, A., YANG, X., TAI, Y.-C., MARZLUFF, E. M., MAYO, S. L., *Microfabricated silicon mixers for sub-millisecond quench flow analysis*, *Anal. Chem.* **70** (1998) 232–236.
- 94 DUMMANN, G., QUITMANN, U., GRÖSCHEL, L., AGAR, D. W., WÖRZ, O., MORGENSCHWEIS, K., *The capillary-microreactor: A new reactor concept for the intensification of heat and mass transfer in liquid–liquid reactions*, *Catalysis Today*, Special edition – 4th International Symposium on Catalysis in Multiphase Reactors, CAMURE IV 78–79, **3** (2002) 433–439.
- 95 BURNS, J. R., RAMSHAW, C., BULL, A. J., HARSTON, P., *Development of a microreactor for chemical production*, in EHRFELD, W. (Ed.), *Microreaction Technology – Proc. of the 1st International Conference on Microreaction Technology, IMRET 1*, pp. 127–133, Springer-Verlag, Berlin (1997).
- 96 BURNS, J. R., RAMSHAW, C., HARSTON, P., *Development of a microreactor for chemical production*, in EHRFELD, W., RINARD, I. H., WEGENG, R. S. (Eds.), *Process Miniaturization: 2nd International Conference on Microreaction Technology, IMRET 2, Topical Conf. Preprints*, pp. 39–44, AIChE, New Orleans (1998).
- 97 BURNS, J. R., RAMSHAW, C., *A micro-reactor for the nitration of benzene and toluene*, in *Proceedings of the 4th International Conference on Microreaction Technology, IMRET 4*, 5–9 March 2000, pp. 133–140, AIChE Topical Conf. Proc., Atlanta, GA (2000).
- 98 LÖBBECKE, S., ANTES, J., TÜRCKE, T., MARIOTH, E., SCHMID, K., KRAUSE, H., *The potential of microreactors for the synthesis of energetic materials*, in *Proceedings of the 31st Int. Annu. Conf. ICT, Energetic Materials – Analysis, Diagnostics and Testing*, 27–30 June 2000, Karlsruhe (2000).
- 99 GAVRIILIDIS, A., ANGELI, P., CAO, E., YEONG, K. K., WAN, Y. S. S., *Technology and application of microengineered reactors*, *Trans. IChemE.* **80/A**, 1 (2002) 3–30.
- 100 HESSEL, V., LÖWE, H., *Micro chemical engineering: components – plant concepts – user acceptance: Part I*, *Chem. Eng. Technol.* **26**, 1 (2003) 13–24.

- 101 BURNS, J. R., RAMSHAW, C., *The intensification of rapid reactions in multiphase systems using slug flow in capillaries*, Lab. Chip **1** (2001) 10–15.
- 102 KASAREKAR, R. B., RAMAKRISHNA, M., JUVEKAR, V. A., *Effect of intensity of agitation on selectivity of aromatic nitration*, Chem. Eng. Technol. **20** (1997) 282–284.
- 103 DOKU, G. N., HASWELL, S. J., MCCREEDY, T., GREENWAY, G. M., *Electric field-induced mobilisation of multiphase solution systems based on the nitration of benzene in a micro reactor*, Analyst **126** (2001) 14–20.
- 104 HISAMOTO, H., SAITO, T., TOKESHI, M., HIBARA, A., KITAMORI, T., *Fast and high conversion phase-transfer synthesis exploiting the liquid–liquid interface formed in a microchannel chip*, Chem. Commun. (2001) 2662–2663.
- 105 DEWITT, S., *Microreactor for chemical synthesis*, Curr. Opin. Chem. Biol. **3** (1999) 350–356.
- 106 GEIPEL-KERN, A., *Vor dem Sprung in die Produktion – Trenbeitrag Mikroreaktionstechnik*, Chem. Produktion (2002) 28–30.
- 107 SALIMI-MOOSAVI, H., TANG, T., HARRISON, D. J., *Electroosmotic pumping of organic solvents and reagents in microfabricated reactor chips*, J. Am. Chem. Soc. **119** (1997) 8716.
- 108 KOCH, M., WEHLE, D., SCHERER, S., FORSTINGER, K., MEUDT, A., HESSEL, V., WERNER, B., LÖWE, H., *Verfahren zur Herstellung von Aryl- und Alkyl-Bor-Verbindungen in Mikroreaktoren*, DE 10140857, Clariant GmbH, Frankfurt (2001).
- 109 HESSEL, V., HARDT, S., LÖWE, H., *Chemical processing with microdevices: device/plant concepts, selected applications and state of scientific/commercial implementation*, in *Proceedings of the 6th Italian Conference on Chemical and Process Engineering, IChEAP-6*, 8–11 June 2003, Pisa, Chem. Engin. Trans. **3**, pp. 479–484 (2003).
- 110 DE BELLEFON, TANCHOUX, N., CARAVIEILHES, S., GRENOUILLET, P., HESSEL, V., *Microreactors for dynamic high throughput screening of fluid–liquid molecular catalysis*, Angew. Chem. **112**, 19 (2000) 3584–3587.
- 111 DE BELLEFON, C., ABDALLAH, R., LAMOUILLE, T., PESTRE, N., CARAVIEILHES, S., GRENOUILLET, P., *High-throughput screening of molecular catalysts using automated liquid handling, injection and microdevices*, Chimia **56**, 11 (2002) 621–626.
- 112 DE BELLEFON, C., CARAVIEILHES, S., GRENOUILLET, P., *Application of a micromixer for the high throughput screening of fluid–liquid molecular catalysts*, in MATLOSZ, M., EHRFELD, W., BASELT, J. P. (Eds.), *Microreaction Technology – IMRET 5: Proc. 5th International Conference on Microreaction Technology*, pp. 408–413, Springer-Verlag, Berlin (2001).
- 113 DE BELLEFON, C., *Application of micro-devices for the fast investigation of catalysis*, in *Proceedings of the Micro Chemical Plant International Workshop*, 4 February 2003, pp. L3 (9–17), Kyoto (2003).
- 114 HESSEL, V., LÖWE, H., *Micro chemical engineering: components – plant concepts – user acceptance: Part II*, Chem. Eng. Technol. **26**, 4 (2003) 391–408.
- 115 HESSEL, V., LÖWE, H., *Mikroverfahrenstechnik: Komponenten – Anlagenkonzeption – Anwenderakzeptanz – Teil 2*, Chem. Ing. Tech. **74**, 3 (2002) 185–207.
- 116 HAVERKAMP, V., EHRFELD, W., GEBAUER, K., HESSEL, V., LÖWE, H., RICHTER, T., WILLE, C., *The potential of micromixers for contacting of disperse liquid phases*, Fresenius' J. Anal. Chem. **364** (1999) 617–624.
- 117 CARAVIEILHES, S., DE BELLEFON, C., TANCHOUX, N., *Dynamic methods and new reactors for liquid phase molecular catalysis*, Catal. Today **66** (2001) 145–155.
- 118 TAGHAVI-MOGHADAM, S., KLEEMANN, A., OVERBECK, S., *Implications of microreactors on chemical synthesis*, in *Proceedings of the VDE World Microtechnologies Congress, MICRO.tec 2000*, 25–27 September 2000, pp. 489–491, VDE Verlag, Berlin, EXPO Hannover (2000).
- 119 EHRFELD, W., HESSEL, V., HAVERKAMP, V., *Microreactors*, in *Ullmann's Encyclopedia of Industrial Chemistry*, Wiley-VCH, Weinheim (1999).
- 120 FUKUYAMA, T., SHINMEN, M., NISHITANI, S., SATO, M., RYU, I., *A cop-*

- per-free Sonogashira coupling reaction in ionic liquids and its application to a microflow system for efficient catalyst recycling*, *Org. Lett.* **4**, 10 (2002) 1691–1694.
- 121 DE BELLEFON, C., PESTRE, N., LAMOUILLE, T., GRENOUILLET, P., *High-throughput kinetic investigations of asymmetric hydrogenations with micro-devices*, *Adv. Synth. Catal.* **345**, 1+2 (2003) 190–193.
- 122 WAN, Y. S. S., CHAU, J. L. H., GAVRIILIDIS, A., YEUNG, K. L., *TS-1 zeolite microengineered reactors for 1-pentene epoxidation*, *Chem. Commun.* (2002) 878–879.
- 123 WAN, Y. S. S., CHAU, J. L. H., GAVRIILIDIS, A., YEUNG, K. L., *Design and fabrication of zeolite-containing microstructures*, in MATLOSZ, M., EHRFELD, W., BASELT, J. P. (Eds.), *Microreaction Technology – IMRET 5: Proc. 5th International Conference on Microreaction Technology*, pp. 94–102, Springer-Verlag, Berlin (2001).
- 124 MENGEAUD, V., FERRIGNO, R., JOSSERAND, J., GIRAULT, H. H., *Towards a ‘plant-on-a-chip’ for the methoxylation of methyl-2-furoate: Electrochemical experiments and mixing simulations*, in MATLOSZ, M., EHRFELD, W., BASELT, J. P. (Eds.), *Microreaction Technology – IMRET 5: Proc. 5th International Conference on Microreaction Technology*, pp. 350–358, Springer-Verlag, Berlin (2001).
- 125 BAYER, T., PYSALL, D., WACHSEN, O., *Micro mixing effects in continuous radical polymerization*, in EHRFELD, W. (Ed.), *Microreaction Technology: 3rd International Conference on Microreaction Technology, Proc. of IMRET 3*, pp. 165–170, Springer-Verlag, Berlin (2000).
- 126 PYSALL, D., WACHSEN, O., BAYER, T., WULF, S., *Verfahren und Vorrichtung zur kontinuierlichen Herstellung von Polymerisaten*, DE 19816886, Aventis Research & Technologies GmbH (1998).
- 127 WÖRZ, O., *Microreactors as tools in chemical research*, in MATLOSZ, M., EHRFELD, W., BASELT, J. P. (Eds.), *Microreaction Technology – IMRET 5: Proc. 5th International Conference on Microreaction Technology*, pp. 377–386, Springer-Verlag, Berlin (2001).
- 128 HESSEL, V., LÖWE, H., *Mikroverfahrenstechnik: Komponenten – Anlagenkonzeption – Anwenderakzeptanz – Teil 1*, *Chem. Ing. Tech.* **74**, 2 (2002) 17–30.
- 129 UGI, I., ALMSTETTER, M., GRUBER, B., HEILINGBRUNNER, M., *MCR XII. Efficient development of new drugs by online-optimization of molecular libraries*, in EHRFELD, W. (Ed.), *Microreaction Technology – Proc. of the 1st International Conference on Microreaction Technology, IMRET 1*, pp. 190–194, Springer-Verlag, Berlin (1997).
- 130 UGI, I., ALMSTETTER, M., GRUBER, B., DÖMLING, A., *MCR X. Important aspects for automating preparative chemistry*, in EHRFELD, W. (Ed.), *Microreaction Technology – Proc. of the 1st International Conference on Microreaction Technology, IMRET 1*, pp. 184–189, Springer-Verlag, Berlin (1997).
- 131 GRUBER, B., ALMSTETTER, M., HEILINGBRUNNER, M., *MCR XI. Microreactors as processors for chemical computers*, in EHRFELD, W. (Ed.), *Microreaction Technology – Proc. of the 1st International Conference on Microreaction Technology, IMRET 1*, pp. 195–202, Springer-Verlag, Berlin (1997).
- 132 UGI, I. K., *New aspects of natural and preparative of one-pot multicomponent reactions and their libraries*, in EHRFELD, W., RINARD, I. H., WEGENG, R. S. (Eds.), *Process Miniaturization: 2nd International Conference on Microreaction Technology, IMRET 2, Topical Conf. Preprints*, pp. 111–117, AIChE, New Orleans (1998).
- 133 DÖMLING, A., UGI, I., *The seven component reaction*, *Angew. Chem. Int. Ed.* **32** (1993) 563–564.
- 134 KRUMMRADT, H., KOPP, U., STOLDT, J., *Experiences with the use of microreactors in organic synthesis*, in EHRFELD, W. (Ed.), *Microreaction Technology: 3rd International Conference on Microreaction Technology, Proc. of IMRET 3*, pp. 181–186, Springer-Verlag, Berlin (2000).
- 135 MARCH, J., *Advanced Organic Chemistry*, 4th ed., Wiley-Interscience, New York (1992).
- 136 SKELTON, V., GREENWAY, G., HASWELL, S., STYRING, P., MORGAN, D.,

- WARRINGTON, B., WONG, S., *The design of a continuous flow combinatorial screening micro-reactor system with on-chip detection*, in VAN DEN BERG, A., OLTUIS, W., BERGVELD, P. (Eds.), *Micro Total Analysis Systems*, pp. 59–62, Kluwer Academic Publishers, Dordrecht (2000).
- 137 MCCREEDY, T., WILSON, N. G., *Micro fabricated reactors for on-chip heterogeneous catalysis*, in *Proceedings of the Microreaction Technology – IMRET5: Proceedings of the 5th International Conference on Microreaction Technology*, 27–30 May 2001, Strasbourg (2001).
- 138 WILSON, N. G., MCCREEDY, T., *Microporous silica structures for the immobilization of catalysts and enhancement of electroosmotic flow (EOF) in micro reactors*, in EHRFELD, W. (Ed.), *Microreaction Technology: 3rd International Conference on Microreaction Technology, Proc. of IMRET 3*, pp. 346–352, Springer-Verlag, Berlin (2000).
- 139 LÖWE, H., KÜPPER, M., ZIOGAS, A., *Reaktor sowie Verfahren zur Durchführung elektrochemischer Umsetzungen*, DE 19841302, IMM Institut für Mikrotechnik Mainz GmbH (1998).
- 140 ANDREEV, V. V., *Microreactor for optical dissociation of non-linear molecules*, in *Proceedings of the VDE World Microtechnologies Congress, MICRO.tec 2000*, 25–27 September 2000, pp. 779–781, VDE Verlag, Berlin, EXPO Hannover (2000).
- 141 WÖRZ, O., JÄCKEL, K. P., *Winzlinge mit großer Zukunft – Mikroreaktoren für die Chemie*, *Chem. Techn.* **26**, 131 (1997) 130–134.
- 142 WÖRZ, O., JÄCKEL, K. P., RICHTER, T., WOLF, A., *Microreactors, a new efficient tool for optimum reactor design*, in EHRFELD, W., RINARD, I. H., WEGENG, R. S. (Eds.), *Process Miniaturization: 2nd International Conference on Microreaction Technology, IMRET 2, Topical Conf. Preprints*, pp. 183–185, AIChE, New Orleans (1998).
- 143 WÖRZ, O., JÄCKEL, K. P., RICHTER, T., WOLF, A., *Microreactors, new efficient tools for optimum reactor design*, in *Microtechnologies and Miniaturization, Tools, Techniques and Novel Applications for the BioPharmaceutical Industry*, IBC Global Conferences, London (1998).
- 144 WÖRZ, O., *Wozu Mikroreaktoren?* *Chem. Unserer Zeit* **34**, 1 (2000) 24–29.
- 145 SNITA, D., LINDNER, J., SEVCIKOVA, H., KOSEK, J., MAREK, M., *Microreactors for ionic reactions in liquids and gels in electric field*, in EHRFELD, W., RINARD, I. H., WEGENG, R. S. (Eds.), *Process Miniaturization: 2nd International Conference on Microreaction Technology, IMRET 2, Topical Conf. Preprints*, pp. 140–145, AIChE, New Orleans (1998).
- 146 PACES, M., HAVLICA, J., LINDNER, J., KOSEK, J., SNITA, D., MAREK, M., *Electrolyte microelectronics*, in *Proceedings of the VDE World Microtechnologies Congress, MICRO.tec 2000*, 25–27 September 2000, pp. 783–785, VDE Verlag, Berlin, EXPO Hannover (2000).