

The first two data sets were in good accordance, whereas a fit to the intrinsic kinetics without correction was only valid for short residence times and large flow rates. This is the consequence of achieving a low degree of liquid/liquid dispersion at low flow rates, i.e. the reaction becomes mass-transfer limited in this regime.

#### Setting micro mixing prior to reaction

[OS 63] [R 27] [R 18] [P 46] Using a slit-type interdigital micro mixer prior to a liquid/liquid reaction system improves the conversion to 80%, hence close to the kinetic limits [117]. This is an improvement over using a microgrid in front of the reactor (see the Section Conversion/selectivity/yield – benchmarking to batch processing/kinetics, above).

### 4.9

#### Addition to Carbon-Hetero Multiple Bonds

##### 4.9.1

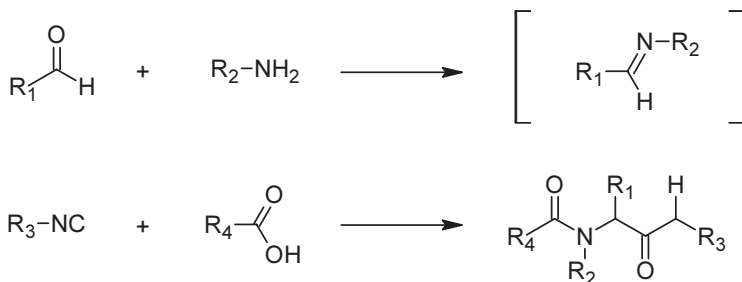
#### 1/*N*-Hydro-2/*C*-( $\alpha$ -Acyloxyalkyl),2/*C*-Oxo Biaddition – Ugi Four component Condensation (4CC)

Proceedings: [16, 25]; theoretical analysis: [129–131]; reviews on classical Ugi chemistry: [130, 132].

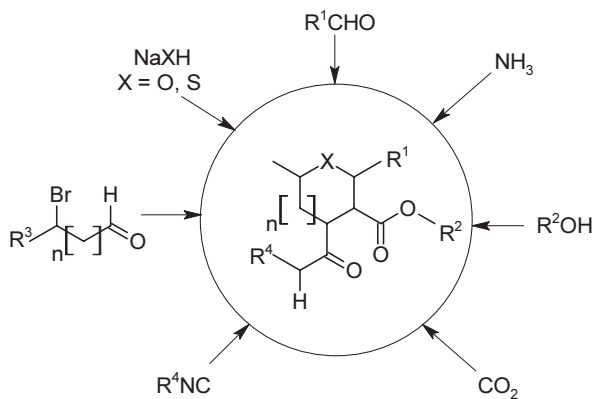
##### 4.9.1.1 Drivers for Performing Ugi reactions in Micro Reactors

The Ugi reaction is historically the first synthetic approach that truly can be termed combinatorial as in one step a multitude of reactants, typically four (but possibly up to seven, see Figure 4.79), react to give a complex compound [OS 64]. The Ugi reaction is carried out as a one-pot synthesis performing consecutive multiple reaction steps [16]. Accordingly, a general driver for performing Ugi reactions in micro reactors is oriented on the screening of pharmaceutical targets and on establishing a first methodology for using micro channel technologies for that purpose.

#### Organic synthesis 64 [OS 64]: General reaction scheme for Ugi reactions



Other drivers are low reagent consumption, the use of small volumes and rapid process optimization, especially with regard to combinatorial synthesis.



**Figure 4.79** The so-called 7CRs, a new principle of designing chemical reactions [130].

In another concrete example of use, the Ugi reaction served as a prominent example to test the performance of one micro mixer and to test specifically the effect of micro mixing on such a multi-stage reaction [25].

Some Ugi reactions are highly exothermic and therefore have to be performed at reduced temperature (e.g. at 0 °C) [25].

Ugi reactions as multi-component reactions are also for interest for creating molecular libraries by parallel means [129–131]. Such approaches so far have only been postulated in a generic way, mostly describing the mathematic tools for automated optimization of the Ugi reaction by micro-channel processing. In this context, a multi-parameter on-line optimization by means of a genetic algorithm or other heuristics was reported to give better yield or selectivity [129]. Micro channel arrays are seen to be central for such an approach. The computer-aided syntheses of molecular libraries under optimized conditions result in an automaton, achieved by choosing the molecular subunits of a multi-component reaction.

In further work, the achievement of well-controlled reaction conditions in micro reactors is highlighted to provide ‘chemical data’ yielding a highly parallel system of problem-solving functions [131]. This is used to approach a class of problems in computer science that is called NP-complete, for which algorithms are very difficult to solve. In summary, this mathematical approach is used to describe chemical reactions which are highly parallel systems as the parameter space and the related dependencies are virtually infinite (Figure 4.80).

In another report, aspects for automating preparative chemistry are described [130]. A comprehensive description of the Ugi reaction is given in [132] and the vision of a ‘micro multi-component reaction’ as automated parallel micro-channel synthesis is sketched. An interesting point is to convert aldehydes, chiral primary amines, carboxylic acids and isocyanates into corresponding  $\alpha$ -amino acids and peptides (U-4CR).

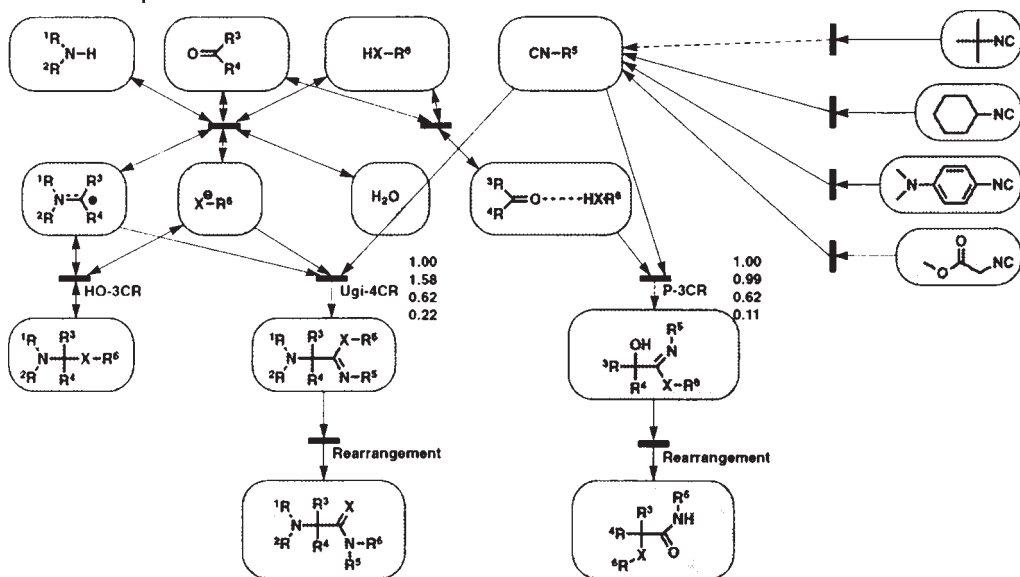


Figure 4.80 Multi-component synthesis for molecular libraries [131].

#### 4.9.1.2 Beneficial Micro Reactor Properties for Ugi Reactions

Concerning the information given above, the defined setting of residence times is an aspect making the use of micro reactors attractive [16]. This refers in particular to the individual residence times between the multiple injections. This allows an individual development of the single reactions one after the other.

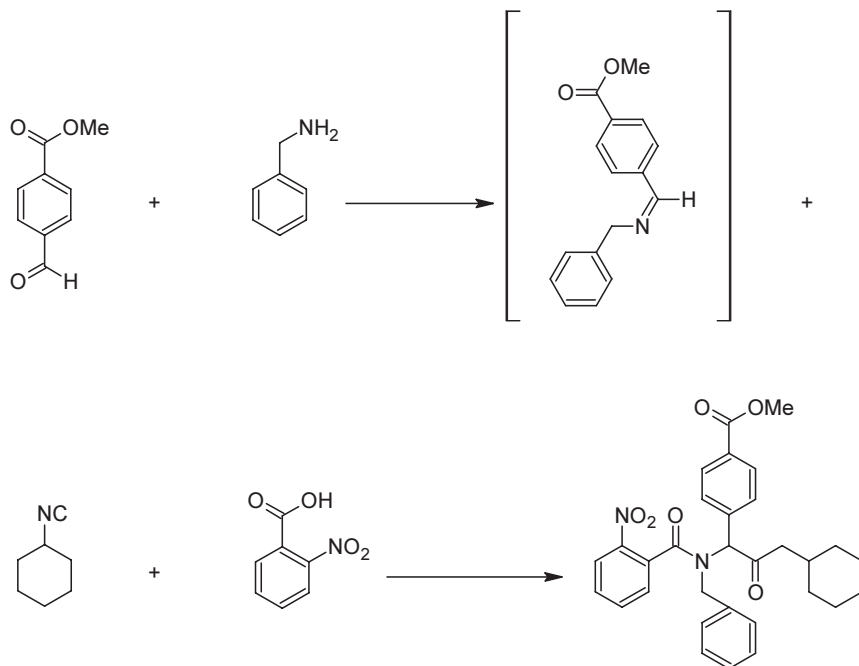
Micro reactors allow the sequential injection of the reaction partners, rather than introducing them in one step. By this means, the course of the reaction, in particular concerning the dynamic evolution of the concentration of reactants, may be changed. It is hoped that this may impact on selectivity.

Apart from such process optimization issues, it may be desired to conduct combinatorial screening in micro channels. Here, specific micro-channel geometries for both liquid serial [110] and parallel [23] screening in organic chemistry have already been described.

The possibility of isothermal processing in micro reactors may allow exothermic Ugi reactions to be conducted at room temperature rather than needing cooling much below ambient [25].

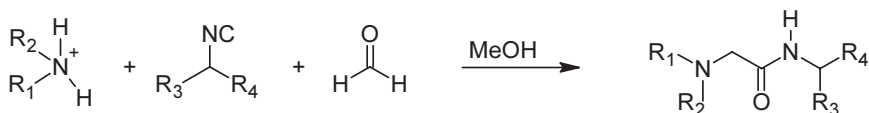
## 4.9.1.3 Ugi Reactions Investigated in Micro Reactors

Organic synthesis 65 [OS 65]: 4CC reaction between aldehyde, primary amine, acid and isocyanide



Methyl 4-formylbenzoate, benzylamine, 2-nitrobenzoic acid, and cyclohexyl isocyanide were converted to the corresponding 4CC Ugi adduct [16].

Organic synthesis [OS 66]: Ugi reaction between aldehyde, secondary amine salt and isocyanide



Formaldehyde was used; the exact nature of the secondary amine salt and isocyanide were not disclosed. The corresponding  $\alpha$ -dialkylacetamide was obtained [25].

A further summary of the many decades of achievement of the Ugi chemistry has been given [132].

## 4.9.1.4 Experimental Protocols

[P 47] Typically, a solution of 50  $\mu$ l of 0.03 M cyclohexyl isocyanide in methanol and 50  $\mu$ l of 0.075 M methyl 4-formylbenzoate in methanol were placed in corresponding reservoirs [16]. Benzylamine in methanol (50  $\mu$ l; 0.03 M) and 2-nitrobenzoic

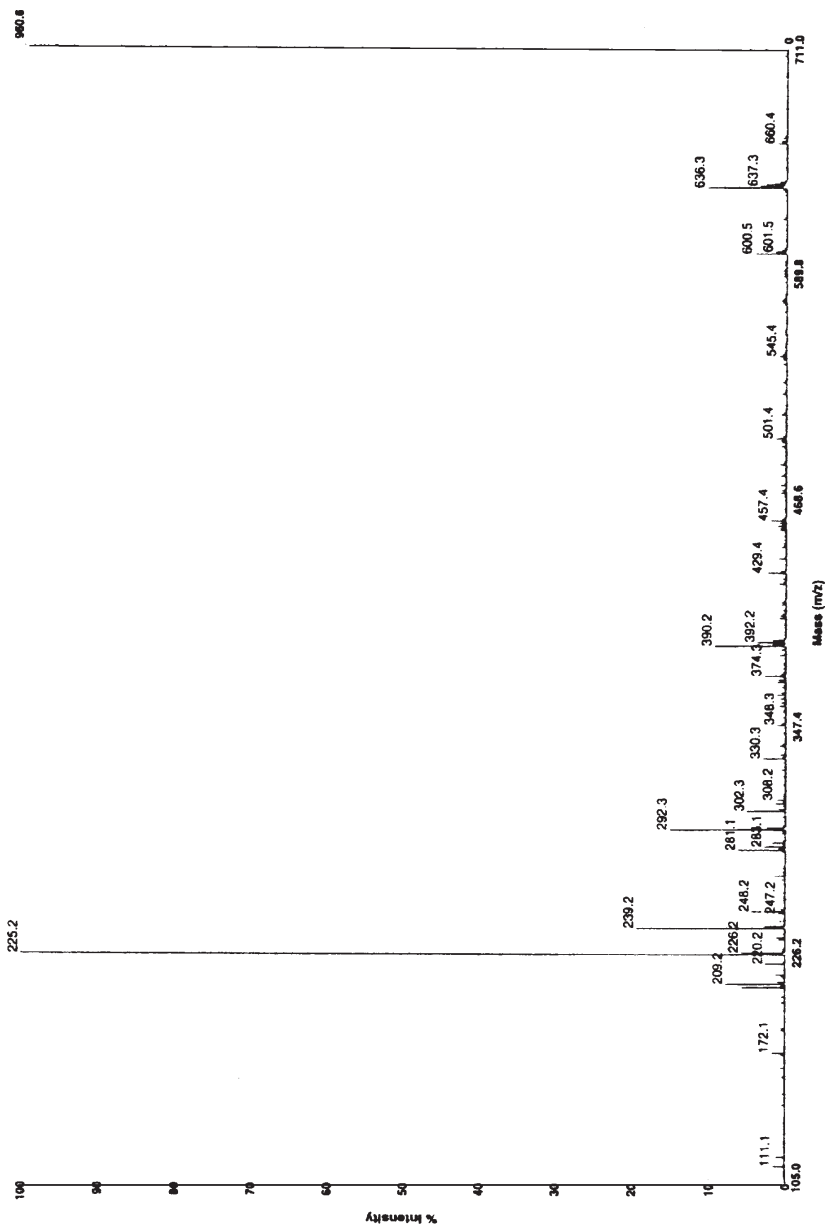


Figure 4.81 Proof of feasibility of performing Ugi MCR in a micro reactor by detecting the parent ion [25].

acid in methanol (50  $\mu\text{l}$ ; 0.03 M) were added to the other reservoir, methanol (30  $\mu\text{l}$ ) being placed in the collection reservoir. A field of 400 V  $\text{cm}^{-1}$ , a residence time of about 20 min and room temperature were applied.

[P 48] Initially, a solution of 2.0 mM formaldehyde in methanol (5  $\mu\text{l min}^{-1}$ ) and pure methanol (5  $\mu\text{l min}^{-1}$ ) were fed through a bifurcation-distributive chip micro mixer [25]. The methanol stream was replaced by a methanol solution of 2.0 mM isocyanide and 0.2 mM amine salt. The reaction was carried out at room temperature and no purification steps were applied.

#### 4.9.1.5 Typical Results

##### Conversion/selectivity/yield

[OS 65] [R 4c] [P 47] The imine intermediate was isolated in 94% yield. The final product can be obtained at yields ranging from 15 to 60%, depending on the reaction conditions [16].

##### Increase of reaction temperature to ambient

[OS 66] [R 11] [P 48] Despite the exothermic nature of a specific Ugi reaction, which in conventional batch processing demands cooling to 0 °C, room-temperature processing was accomplished in a chip micro mixer [25]. Although no active cooling was involved, this was explained by enhanced heat dissipation via the large specific surface areas of the micro channels. The product formation was only semi-quantitatively analyzed by mass spectra (Figure 4.81). A large parent peak of the product shows that a considerable yield was achieved; the exact quantity, however, is not given.

#### 4.9.2

##### Alkyliminodeoxo Bisubstitution – Hantzsch Synthesis

Peer-reviewed journals: [10]; proceedings: [9]; sections in reviews: [89, 90].

##### 4.9.2.1 Drivers for Performing Hantzsch Syntheses in Micro Reactors

The Hantzsch synthesis was primarily chosen to evaluate the potential of a micro-mixing-tee chip reactor for carrying out reactions above room temperature (e.g. 70 °C) [9, 10]. It is said to be the first example of a heated organic reaction performed in a glass chip reactor under electroosmotic flow (EOF) control [10] (for EOF see [14]). The performance of this reactor for room-temperature reactions such as the Wittig reaction and Suzuki coupling was demonstrated before.

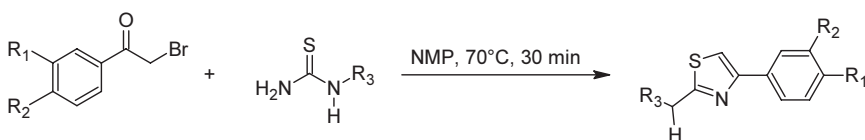
In a wider sense, the Hantzsch synthesis is a further example for evaluating the potential of microfluidic systems for high-throughput screening [9].

##### 4.9.2.2 Beneficial Micro Reactor Properties for Hantzsch Syntheses

Following the above-mentioned motivation, precise control over temperature can be exerted in micro reactors [9, 10]. Also, parallel or fast serial screening, handling small volumes distributed over compactly arranged reaction flow-through chambers, can be achieved in micro reactors.

## 4.9.2.3 Hantzsch Syntheses Investigated in Micro Reactors

**Organic synthesis 67 [OS 67]:** Hantzsch syntheses using diverse ring-substituted 2-bromoacetophenones and 1-substituted-2-thioureas



From the diverse examples on Hantzsch syntheses reported, the reaction of 2-bromo-4'-methylacetophenone and 1-acetyl-2-thiourea was exemplarily chosen to be represented here [10].

Other reactions with different reactants have been described [9, 10].

## 4.9.2.4 Experimental Protocols

[P 49] Typically, a voltage of 400 V was applied for 30 min [9]; alternatively [10], voltages of 300–700 V were favorably applied. As solvent *N*-methylpyrrolidone was used. The temperature was set to 70 °C.

## 4.9.2.5 Typical Results

**Conversion/selectivity/yield**

[OS 67] [R 4a2] [P 49] Initial micro reactor yields ranged from 58% to almost complete conversion (99%), depending on the voltages applied and the reaction considered [9]. In a later series of experiments, yields from 42 to 99% were reported, depending on the voltages applied and the reaction considered.

**Benchmarking to batch processing**

[OS 67] [R 4a2] [P 49] Comparative and better yields were achieved when using a micro-mixing tee chip reactor as compared with conventional laboratory batch technology (Table 4.9). In the case of improvement, the increase in yield amounted to about 10–20% [9, 10].

**Table 4.9** Benchmarking of mixing-tee chip micro-reactor operation to macro batch-scale synthesis for a series of 2-aminothiazoles [10].

Entry No.	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	Microreactor conversion (%)			Batch conversion (%)
				300 V	400 V	500 V	
1	Acetyl	H	H	42	63	14	44
2	Acetyl	H	OMe	53	58	14	53
3	Acetyl	H	Me	74	77	72	59
4	Acetyl	Br	H	91	95	99	83
5	Acetyl	NO <sub>2</sub>	H	99	99	99	96
6	Phenylethyl	H	H	99	99	99	99

**Electroosmotic parameters – voltage**

[OS 67] [R 4a2] [P 49] For a given reaction, the dependence of yield on voltage, ranging from 100 to 700 V, was exemplarily given in [10] (see also [9]). Up to 300 V an increase in yield was observed, and then a slight decrease up to 600 V was found, followed by an increase again to 700 V.

## 4.9.3

**O-Hydro, C-Alkyl Addition – Grignard Reaction (Mg Alkylation)**

Proceedings: [118, 134]; sections in reviews: [42, 90, 99, 100, 127, 128].

4.9.3.1 **Drivers for Performing Grignard Reactions in Micro Reactors**

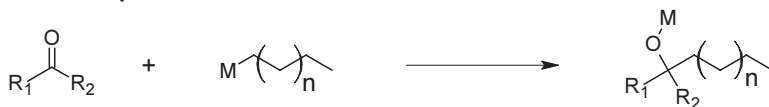
One investigation referred to using a Grignard reaction for industrial purposes [134]. It served as model reaction meeting the relevant criteria: highly exothermic, temperature sensitive, fast and difficult to handle in a stirred vessel. The reaction chosen had a reaction enthalpy of  $300 \text{ kJ mol}^{-1}$  and occurred in a time frame of about 10 s, as did most of the side reactions did. The avoidance of side reactions, i.e. an increase in selectivity, was the main motivation for the development of a micro-channel process.

4.9.3.2 **Beneficial Micro Reactor Properties for Grignard Reactions**

The above-mentioned research targets generally address the good mass and heat transfer properties achieved by micro channel processing, in particular referring to isothermal processing. Because the Grignard process is also very sensitive to the concentration profiles of the reactants, i.e. the actual ratio of reactants, the capability to have good micro mixing was essential.

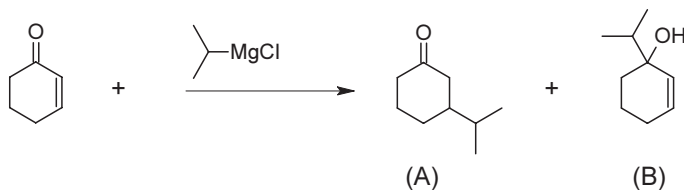
4.9.3.3 **Grignard Reactions Investigated in Micro Reactors**

**Organic synthesis 68 [OS 68]: Enolate formation by addition of the Grignard reactant to a carbonyl**



The Grignard reactant having a long alkyl chain was added to a keto compound; the substituents remain undisclosed [134]. Thereby, an enolate is formed which is further reacted in the framework of a multi-stage fine-chemical industrial process.

**Organic synthesis 69 [OS 69]: Grignard reaction between cyclohex-2-enone and diisopropylmagnesium chloride [118]**





#### 4.9.3.4 Experimental Protocols

[P 50] The temperature of the micro channel processing was set to  $-10\text{ }^{\circ}\text{C}$  at residence times  $< 10\text{ s}$  having volume flows e.g. in the range  $0.4\text{--}2.0\text{ l h}^{-1}$ . The reaction was carried out as a laboratory-scale process with three pumps (two reactants, one solvent) [134]. A slit-type interdigital micro mixer was used which was placed into a thermostatic bath. From this mixer, the reacting solution was transferred via tubing into a product vessel. No further information on the type of solvent and concentration are given in [134].

#### 4.9.3.5 Typical Results

##### Conversion/selectivity/yield – benchmarking to laboratory and industrial processes

[OS 68] [R 19] [P 50] A yield of 95% was obtained by a micro-mixer-based process ( $< 10\text{ s}$ , at  $-10\text{ }^{\circ}\text{C}$ ), while the industrial batch process ( $6\text{ m}^3$  stirred vessel) gave only 72% yield (5 h, at  $-20\text{ }^{\circ}\text{C}$ ) [134]. The laboratory-scale batch process ( $0.5\text{ l}$  flask;  $0.5\text{ h}$ , at  $-40\text{ }^{\circ}\text{C}$ ) gave an 88% yield.

[OS 69] [R 25] [no protocol] Software-supported process optimization (factorial design) in a micro reactor was carried out for a Grignard reaction [118]. In this context, 14 different reaction conditions were investigated in 14 h. By this means, the initial yield of 49% could be improved to 78% with a simultaneous increase in regioisomer ratio (A : B) from 65 : 35 to 95 : 5.

##### Transfer from laboratory to industrial process – numbering-up concept

[OS 68] [R 19] [P 50] Having a yield of 95% by a micro-mixer-based process ( $< 10\text{ s}$ , at  $-10\text{ }^{\circ}\text{C}$ ), it was decided to perform pilot-scale studies with a self-built mini mixer for reasons of clogging, which was not decisive at the laboratory scale [134]. With one mini mixer at the pilot scale a yield of 92% was obtained ( $< 10\text{ s}$ , at  $-10\text{ }^{\circ}\text{C}$ ). The validity of the numbering-up concept was proven by operating also five mini mixers of the same type at a yield of 92% ( $< 10\text{ s}$ , at  $-10\text{ }^{\circ}\text{C}$ ). This was the central part of the actual production process, running for more than 3 years until the life-cycle of the commercial product of the corresponding multi-stage process ran out (Table 4.10).

**Table 4.10** Comparison of residence time and yield for different reactor types [134].

Reactor type	Temperature ( $^{\circ}\text{C}$ )	Residence time	Yield (%)
Flask, $0.5\text{ l}$	$-40$	$0.5\text{ h}$	88
Production (stirred vessel, $6\text{ m}^3$ )	$-20$	$5\text{ h}$	72
Microreactor (laboratory set-up)	$-10$	$< 10\text{ s}$	95
Mini reactor (pilot scale)	$-10$	$< 10\text{ s}$	92
Five Mini reactors (production)	$-10$	$< 10\text{ s}$	92

##### Statistical experimentation design – flow rate

[OS 68] [R 19] [P 50] The experiments on micro-channel processing followed a statistical design [134]. The dependence of the yield on temperature and on the ratio

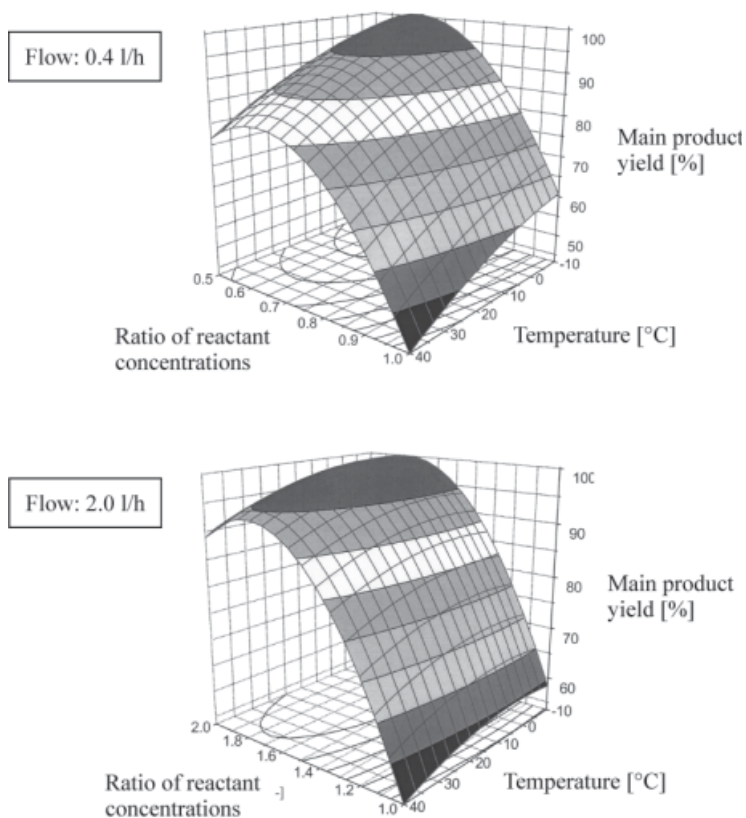


Figure 4.82 Results of trials according to the statistical design of experiments [134].

of the reactant concentrations for two flows ( $0.4 \text{ l h}^{-1}$ ;  $2.0 \text{ l h}^{-1}$ ) was given. This dependence was qualitatively the same; however, the highest yield exceeding 90% was only found at the higher flow rate ( $2.0 \text{ l h}^{-1}$ ), and also at higher temperatures as compared with the  $0.4 \text{ l h}^{-1}$  processing. This is in accordance with the need for flow equilibration in the array of the slit-type interdigital micro mixer (Figure 4.82).

By the statistical approach, the complete parameter set for processing at 95% yield was discovered very quickly.

#### Thermal control/energy expenditure

[OS 68] [R 19] [P 50] The lower yield of the industrial batch process ( $6 \text{ m}^3$  stirred vessel) of only 72% is due to limitations of the cooling system allowing processing only at  $-20 \text{ }^\circ\text{C}$ , and not at  $-40 \text{ }^\circ\text{C}$  as is possible for the better laboratory-scale batch process ( $0.5 \text{ l}$  flask;  $0.5 \text{ h}$ ; 88% yield) [134]. The industrial process had a surface-to-volume ratio of  $4 \text{ m}^2 \text{ m}^{-3}$ , the laboratory-scale process of  $80 \text{ m}^2 \text{ m}^{-3}$  and the micro reactor of  $10\,000 \text{ m}^2 \text{ m}^{-3}$ . Accordingly, the residence time had to be increased from  $0.5 \text{ h}$  to  $5 \text{ h}$  to allow less heat generation per unit time for the large-scale process.

As a consequence, the contribution of side and follow-up reactions is larger. In addition, micro-channel operation at  $-10\text{ }^{\circ}\text{C}$  causes less energy expenditure and costs than the former batch processing at  $-20\text{ }^{\circ}\text{C}$ .

#### Fouling/blockage

[OS 68] [R 19] [P 50] Fouling leading to blockage occurred by micro-mixer processing. Therefore, a new mixing element with wider channels was designed. The surface-to-volume ratio was  $4000\text{ m}^2\text{ m}^{-3}$  (micro mixer:  $10\,000\text{ m}^2\text{ m}^{-3}$ ). Using such a slight increase in internal dimensions and a more elaborate set-up, pilot-scale processing at 92% yield avoiding blockage could be achieved [134].

#### Production process – automation

[OS 68] [R 19] [P 50] A numbering-up of five mini mixers, tested at the pilot stage, was used [134]. Automation of the entire process was required; liquid-flow splitting to the single reactors was ‘... by no means trivial ...’ [134]. The capacity of one mini reactor was  $30\text{ ml s}^{-1}$ , i.e.  $108\text{ l h}^{-1}$ . The complete setup hence should be operated close to  $500\text{ l h}^{-1}$ . The micro-reactor plant was operated at intervals as the preceding step was carried out batchwise. The operation of the micro-reactor plant started in August 1998 after a period of only about 1.5 years for development.

#### 4.9.4

#### O-Hydro, C-Alkyl Addition – Li Alkylation of Ketones

Peer-reviewed journals: [83].

##### 4.9.4.1 Drivers for Performing Li Alkylations in Micro Reactors

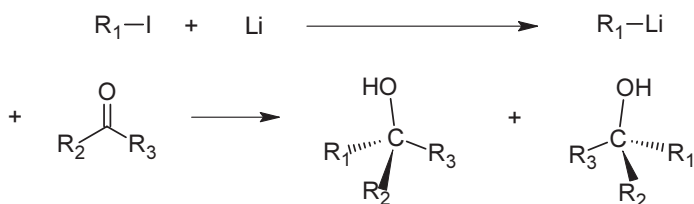
One main driver was to increase the processing temperature for this class of metallation reactions more towards ambient. Typically, Li alkylations are conducted under cryogenic conditions (e.g. at  $-60\text{ }^{\circ}\text{C}$ ) [83]. Further motivation came from aiming at increasing the yield reducing investment and operating costs.

##### 4.9.4.2 Beneficial Micro Reactor Properties for Li Alkylations

Improved control over heat and mass transfer as well as residence time by micro-channel processing often allows one to increase the reaction temperature of cryogenic processes without losing selectivity. It often leads to improved selectivity.

##### 4.9.4.3 Li Alkylations Investigated in Micro Reactors

#### Organic synthesis 70 [OS 70]: Li alkylation of ketones yielding chiral alcohols



In a first step, an alkyl iodide is converted by lithium to an unstable Li intermediate [83]. This reacts with the ketone to give a chiral alcohol.

This lithium process is the analogue of the magnesium-based Barbier reaction [135].

#### 4.9.4.4 Experimental Protocols

[P 51] No protocol is given in [83].

#### 4.9.4.5 Typical Results

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

[OS 70] [R 25] [P 51] The total yield of a combined lithiation and alkylation of a ketone to a chiral alcohol was increased to 93% by micro-reactor processing, whereas the batch process gave only an 83% yield [83]. This increase in yield is related to reduced  $\beta$ -elimination of the unstable Li intermediate.

##### Reaction temperature

[OS 70] [R 25] [P 51] The temperature of a lithiation step was raised from  $-78\text{ }^\circ\text{C}$  (batch) to  $-15\text{ }^\circ\text{C}$  (micro reactor) without losing selectivity [83]. The temperature of the subsequent alkylation of a ketone to a chiral alcohol could also be increased from  $-60\text{ }^\circ\text{C}$  (batch) to  $0\text{ }^\circ\text{C}$  (micro reactor).

#### 4.9.5

##### Alkyliminodeoxo Bisubstitution – Formation of Imines (Schiff Bases)

Proceedings: [127].

##### 4.9.5.1 Drivers for Performing Formation of Imines in Micro Reactors

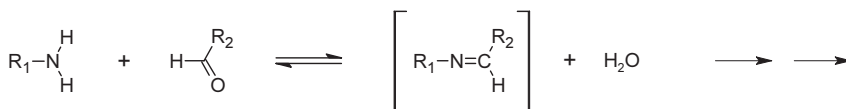
The motivation for an industrial investigation was to gather kinetic and mechanistic information for a very fast and highly exothermic reaction [127]. In particular, by-product formation was analyzed.

##### 4.9.5.2 Beneficial Micro Reactor Properties for Formation of Imines

Micro reactors can cope with situations as depicted above. They are excellent laboratory tools to gather such information.

##### 4.9.5.3 Formation of Imines Investigated in Micro Reactors

##### Organic synthesis 71 [OS 71]: Reaction of an aldehyde with a primary amine



Neither the substituents of the aldehyde nor of the amine were disclosed, as the reaction probably is a proprietary industrial process [127]. The Schiff base formed reacts further by decomposition.

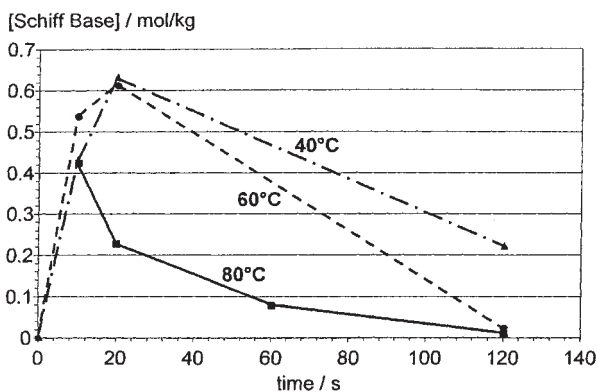


Figure 4.83 Formation and decomposition of a Schiff base at different temperatures [127].

#### 4.9.5.3 Experimental Protocols

[P 52] The reaction was carried out at 40–80 °C on a time-scale of 10–120 s. No further details are given in [127], as the reaction probably is a proprietary industrial process.

#### 4.9.5.4 Typical Results

##### Conversion/selectivity/yield

[OS 71] [no details on reactor] [P 52] The Schiff base is formed (Figure 4.83) with maximum yield at about a 20 s residence time at 40 and 60 °C [127]. At 80 °C, this decreases to less than 10 s.

##### Mechanistic information

[OS 71] [no details on reactor] [P 52] An intermediate, previously unknown, was discovered during micro-channel Schiff base formation [127].

##### Residence time

[OS 71] [no details on reactor] [P 52] A shift in the residence time needed for achieving maximum yield at a given temperature was observed [127].

##### Reaction temperature

[OS 71] [no details on reactor] [P 52] By micro-channel investigations, it was found that the decomposition of the Schiff base was much more pronounced at higher temperature [127].

#### 4.9.6

##### Dual Alkyliminodeoxo Bisubstitution and Ring Closure – Knorr Synthesis

Peer-reviewed journals: [20].

#### 4.9.6.1 Drivers for Performing Knorr Synthesis in Micro Reactors

Drug synthesis and industrial applications thereof were in the focus of recent investigations [20]. To achieve a high structural diversity, today the creation of combinatorial libraries is ultimately needed. Of particular importance is to achieve a close combination of synthesis and analysis. Performing organic syntheses in micro channels is seen as one important future technology for that purpose. By this means, a miniaturized screening variant of ultra-high throughput chemical synthesis should be achievable.

The Knorr synthesis was chosen as an example to demonstrate that with an automated micro-reactor system a further step was made over existing parallel micro flow processing techniques, providing a  $2 \times 2$  library in a chip micro reactor [20]. The new approach was designed for much higher diversity, aiming at a  $7 \times 32$  library.

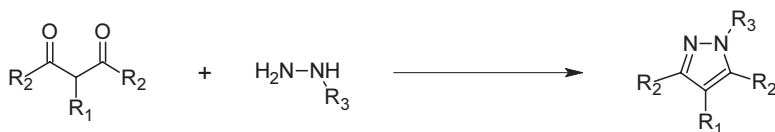
Hence the investigations made so far were aimed more at showing the capability of an automated micro-reactor system, using the Knorr synthesis as a model reaction; however, to a certain extent, information on this synthesis itself was also gained (see Section 4.9.6.5) [20]. The Knorr synthesis of pyrazoles chosen is of industrial interest since by this route compounds with a wide range of biological activity can be produced.

#### 4.9.6.2 Beneficial Micro Reactor Properties for Knorr Synthesis

From the time when it was shown that micro flow reactors can provide valuable contributions to organic chemistry, it was obvious to develop them further and their workflow towards modern screening techniques [20]. It was especially the finding of high reaction rates, the capability to transport and transform minute sample volumes and the first integration of analytics that paved the way to a parallelization of micro flow processing. These benefits were combined with the ease of automation of a micro flow system. By this means, the potential of on-line analysis of the reactions can be fully exploited.

#### 4.9.6.3 Knorr Synthesis Investigated in Micro Reactors

**Organic synthesis 72 [OS 72]: Pyrazole ring closure from 1,3-dicarbonyl compounds and hydrazines**

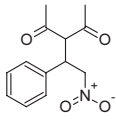
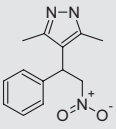
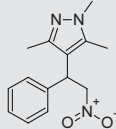
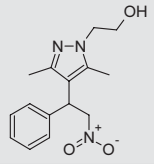
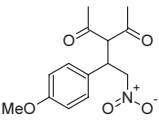
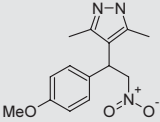
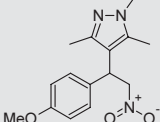
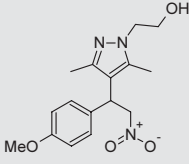
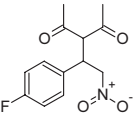
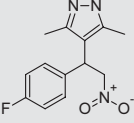
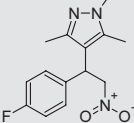
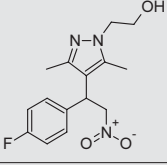
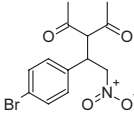
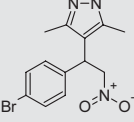
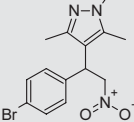
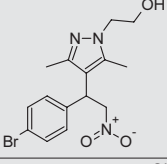
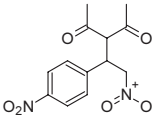
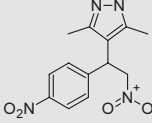
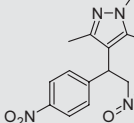
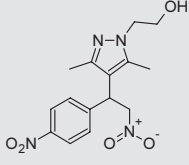
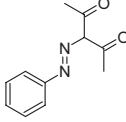
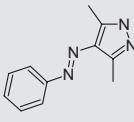
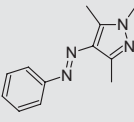
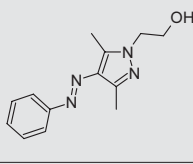
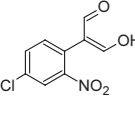
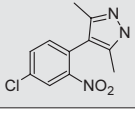
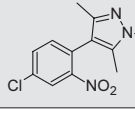
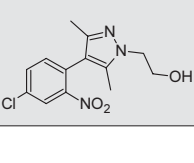


1,3-Dicarbonyl compounds react with the two nitrogen functionalities of hydrazines with ring closure to give pyrazoles [20]. The Knorr synthesis is of interest for drug applications as products with a wide range of biological activity can be generated in this way.

The reaction was also chosen for analytical reasons as the pyrazole ring is a good UV chromophore, facilitating analysis [20].

The  $3 \times 7$  library in Table 4.11, consisting of diverse 1,3-dicarbonyl compounds and hydrazines, was synthesized.

**Table 4.11** Synthesized  $3 \times 7$  library consisting of diverse 1,3-dicarbonyl compounds and hydrazines [20].

	$\text{H}_2\text{N-NH}_2$ B1	$\text{H}_2\text{N-NH}$ B2	$\text{HO-CH}_2\text{-CH}_2\text{-NH}_2$ B3
 A1			
 A2			
 A3			
 A4			
 A5			
 A6			
 A7			

#### 4.9.6.4 Experimental Protocols

[P 53] Before operation, a start-up time of about 10 min was applied to stabilize pressure in the chip micro reactor ([R 6]) [20]. As a result, a stable flow pattern was achieved. The reactant solutions were filled into vials. Slugs from the reactant solutions were introduced sequentially into the micro chip reactor with the autosampler and propelled through the chip with methanol as driving solvent. The flow rates were set to  $1 \mu\text{l min}^{-1}$ . The slug volume was reduced to  $2.5 \mu\text{l}$ .

The pyrazole library was created sequentially using 10 mM solutions of the 1,3-dicarbonyl compound and 0.8 M solutions of the hydrazines, each introduced as a  $2.5 \mu\text{l}$  slug [20]. This requires control of feeding of both reactant solutions so that the slugs enter the chip at the same time and mix thereafter. The residence time was 210 s. Thereafter, the reaction slugs were diluted on-chip by a 1 : 1 methanol–water stream at  $8 \mu\text{l min}^{-1}$  and detected. Analysis of the nature of the products and the degree of conversion was done using standards of reactant and product materials.

The chip micro reactor ([R 6]) was only one part of a complex serial-screening apparatus [20]. This automated system consists of an autosampler (CTC-HTS Pal system) which introduces the reactant solutions in the chip via capillaries. A pumping system ( $\mu$ -HPLC–CEC System) serves for fluid motion by hydrodynamic-driven flow. A dilution system [Jasco PU-15(5)] is used for slug dilution on-chip. The detection system was a Jasco UV-1575 and analysis was carried out by LC/MS (Agilent 1100 series capLC–Waters Micromass ZQ). All components were on-line and self-configured.

The UV intensity was recorded with the Lab-View program [20]. Such UV-decoded slug patterns were almost identical and near-rectangular with some axial dispersion at the slug edges (see the Section Slug dispersion, below, for more details on signal broadening).

#### 4.9.6.5 Typical Results

##### Conversion/selectivity/yield

[OS 72] [R 6] [P 53] Quantitative conversion was obtained for 16 out of 21 reactions for a  $3 \times 7$  library (Table 4.12) [20]. The other five reactions had conversions ranging from 35 to 85%.

**Table 4.12** Conversions for a  $3 \times 7$  library, the compounds in which (A1–A7; B1–B3) are depicted in Table 4.11 [20].

Reactant	Conversion (%)		
	B1	B2	B3
A1	99	99	99
A2	99	99	99
A3	99	99	99
A4	99	99	99
A5	99	99	99
A6	35	99	85
A7	57	56	49



In order to test the role of residence time for process performance, an experiment equal in process conditions to the one with the lowest performance (35 %) was conducted; the only exception being that residence time was doubled (420 instead of 210 s) [20]. A much improved conversion (52%) was obtained in this way (see also the Section Residence time, below).

#### **Slug dispersion**

[OS 72] [R 6] [P 53] Slug patterns, measured as UV absorption vs time, were almost identical for the various sequential slugs [20]. This proves that a regular and stable flow pattern was achieved for the micro flow in the chip. Although axial dispersion was evident from some broadening at the slug edges, over most of the slug length the same UV absorption was found, i.e. near-rectangular pulses were achieved. This shows that in the slug core-defined concentration profiles were maintained. Signal broadening increased with increasing residence time, as expected.

#### **Residence time**

[OS 72] [R 6] [P 53] For five reactions with non-quantitative conversions, processing was repeated at a doubled residence time (420 instead of 210 s). A control experiment with a reaction of quantitative conversion was also successfully made at the best residence times. Much higher conversions were obtained in this way for all five reactions, being about 20% in each case.

#### **Automated sequential preparation 3 × 7 library – feasibility**

[OS 72] [R 6] [P 53] A 3 × 7 library was made in a sequential and automated way with conversions of 35% (lowest) and 99% (quantitative; for 16 reactions) [20]. The results obtained were compared for consistency with single-reaction processing on the same chip.

#### **Cross-contamination of 3 × 7 library**

[OS 72] [R 6] [P 53] No cross-contamination was found during preparation of the 3 × 7 library [20]. Neither products, by-products nor the hydrazine in excess were intermixed.

### 4.9.7

#### **Alkyliminodeoxo Bisubstitution – Formation of Enamines**

Peer-Reviewed journals: [11]; sections in reviews: [14, 89].

##### **4.9.7.1 Drivers for Performing Formation of Enamines in Micro Reactors**

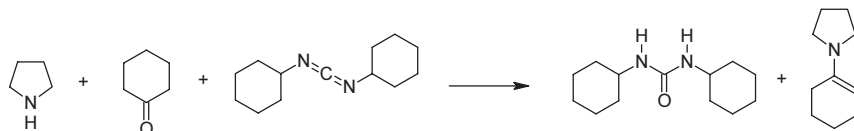
Research on enamine formation in micro reactors was focused on eliminating the need for using Lewis acid catalysts [11]. In addition, operation under mild conditions such as room-temperature processing was favored.

##### **4.9.7.2 Beneficial Micro Reactor Properties for Formation of Enamines**

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

## 4.9.7.3 Formation of Enamines Investigated in Micro Reactors

**Organic synthesis 73 [OS 73]:** Stork enamine formation from cyclohexanone and pyrrolidine



This carbon–carbon bond-generating reaction can be used extensively over a wide range of chemistries [11]. As the reaction is an equilibrium process, needing the removal of water to obtain high yields, chemical means have to be used to accomplish this task. 1,3-Dicyclohexylcarbodiimide (DCC) is a commonly used reagent for this purpose. Alternatively, molecular sieves find use for conventional processing, but are not so favorable for micro-reactor processing, because the sieve needs to be inserted into the micro channel (additional fabrication expenditure) and may disrupt the liquid transport if EOF is applied.

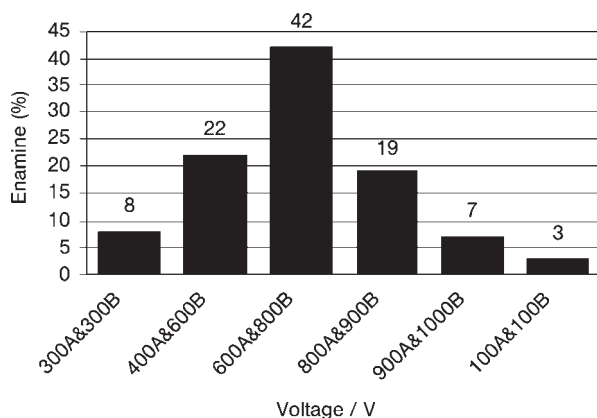
## 4.9.7.4 Experimental Protocols

[P 54] A 50  $\mu\text{l}$  volume of a 0.3 M solution of cyclohexanone in anhydrous methanol with about 1 mg of DCC is placed in one reservoir of a micro-mixing tee chip reactor [11]; 50  $\mu\text{l}$  of a 0.3 M solution of pyrrolidine is added to the other reservoir and anhydrous methanol is filled in the third, the collection reservoir. Voltages ranging from 300 to 1000 V are applied for a period of 40 min to transport the reaction species. The reaction is carried out at room temperature.

## 4.9.7.5 Typical Results

**Conversion/selectivity/yield**

[OS 73] [R 4a] [P 54] Depending on the voltages applied, enamine yields between 8 and 42% were achieved [11]. Using an external voltage combination of 600 V at one reservoir (cyclohexanone) and 800 V at the second reservoir (pyrrolidine) gives the highest yield without using a catalyst (Figure 4.84).



**Figure 4.84** Conversion of enamine depending on the voltages applied to the reservoirs [11].

**Benchmarking to batch synthesis/elimination of catalyst**

[OS 73] [R 4a] [P 54] The micro reactor yield (up to 42%) is comparable to that for batch Stork-enamine reactions using *p*-toluenesulfonic acid in methanol under Dean and Stark conditions [11].

**Reaction temperature**

[OS 73] [R 4a] [P 54] Reasonable micro reactor yields (up to 42%) can be obtained at room temperature [11].

## 4.9.8

**Bis(ethoxycarbonyl)methylenedexo Bisubstitution – Knoevenagel Condensation**

Peer-reviewed journals: [18]; sections in review: [89]. A Knoevenagel condensation is described under 4.8.2 Cycloadditions – The Diels–Alder Reaction, since both reactions were performed combined in a domino-type process.

## 4.9.9

**O-Hydro, C-(*α*-Acylalkyl) Addition – Aldol Reaction**

Peer-reviewed journals: [15]; sections in reviews: [14, 89, 90].

4.9.9.1 **Drivers for Performing Aldol Reactions in Micro Reactors**

The aldol reaction is one of the best known means of C–C-bond formation in organic chemistry. The reaction needs the formation of enolates, which themselves are one of the most extensive species permitting C–C-bond formation [15].

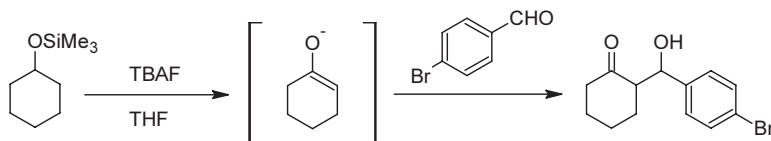
Reducing the processing time is a driver for micro channel processing of aldol reactions [15]. Using reactive reactants such silyl enol ethers, this can be accomplished.

4.9.9.2 **Beneficial Micro Reactor Properties for Aldol Reactions**

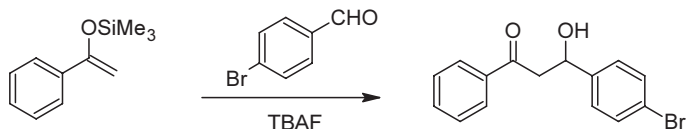
The above-mentioned research targets generally address the good mass and heat transfer properties achieved by micro channel processing, in particular referring to fast mixing.

4.9.9.3 **Aldol Reactions Investigated in Micro Reactors**

Silyl enol ethers are an elegant means to ‘protect’ the reactive and hence labile enolate moiety [15]. At the time of reaction, the enolate group is generated as an intermediate and reacts with the carbonyl-carrying compound.

**Organic synthesis 74 [OS 74]: Reaction between 4-bromobenzaldehyde and the silyl enol ether of cyclohexane [15]**

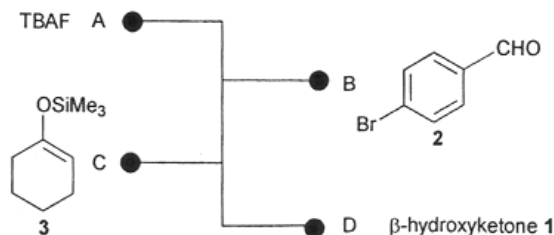
**Organic synthesis 75 [OS 75]: Reaction between 4-bromobenzaldehyde and the silyl enol ether of acetophenone [15]**



**4.9.9.4 Experimental Protocols**

[P 55] Before synthesis, a micro-mixing tee chip micro reactor (Figure 4.85) (with two mixing tees and four reservoirs) was primed with anhydrous tetrahydrofuran (THF). A 40  $\mu\text{l}$  volume of a 0.1 M solution of tetrabutylammonium fluoride trihydrate in anhydrous THF is filled into one reservoir of a micro-mixing tee chip reactor [15], 40  $\mu\text{l}$  of a 0.1 M solution of 4-bromobenzaldehyde in anhydrous THF is added to a second reservoir, 40  $\mu\text{l}$  of a 0.1 M solution of the silyl enol ether (masking the enolate of a carbonyl compound such as cyclohexanone) in anhydrous THF is added to a third reservoir and anhydrous THF is filled into the fourth collection reservoir. Electrical fields of 417, 455, 476 and 0  $\text{V cm}^{-1}$  are applied to transport the reaction species from the respective reservoirs. The reaction is carried out at room temperature.

See also [15] for a description of the corresponding batch syntheses.



**Figure 4.85** Flow configuration for the aldol reaction of silyl enol ethers in a mixing-tee chip micro reactor [15].

**4.9.9.5 Typical Results**

**Conversion/selectivity/yield**

[OS 74] [R 4b] [P 55] For the reaction of 4-bromobenzaldehyde with the silyl enol ether of cyclohexanone, only 1% conversion was achieved on applying protocol [P 55] [15]. Changing the set of electrical fields so that the concentration of tetrabutylammonium fluoride trihydrate was raised resulted in 100% conversion (417, 341, 333 and 0  $\text{V cm}^{-1}$ ).

**Reaction time**

[OS 75] [R 4b] [P 55] For the reaction of 4-bromobenzaldehyde with the silyl enol ether of acetophenone, 100% conversion with respect to the silyl enol ether was achieved in 20 min for a given set of electrical fields (375, 409, 381 and 0  $\text{V cm}^{-1}$ ) [15]. The corresponding batch synthesis time was about 1 day.

## 4.9.10

**C,O-Dihydro Addition – BH<sub>3</sub>-Carbonyl Hydrogenations**

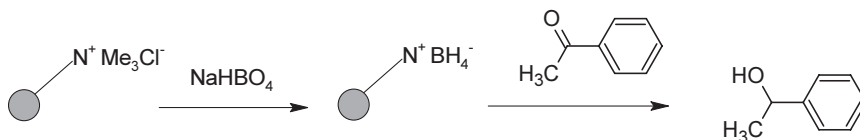
Proceedings: [3].

**4.9.10.1 Drivers for Performing BH<sub>3</sub>-Carbonyl Hydrogenations in Micro Reactors**

This reaction served to demonstrate organic synthesis on a newly developed porous-polymer-rod micro reactor [3].

**4.9.10.2 Beneficial Micro Reactor Properties for BH<sub>3</sub>-Carbonyl Hydrogenations**

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

**4.9.10.3 BH<sub>3</sub>-Carbonyl Hydrogenations Investigated in Micro Reactors****Organic synthesis 76 [OS 76]: Reduction of acetophenone**

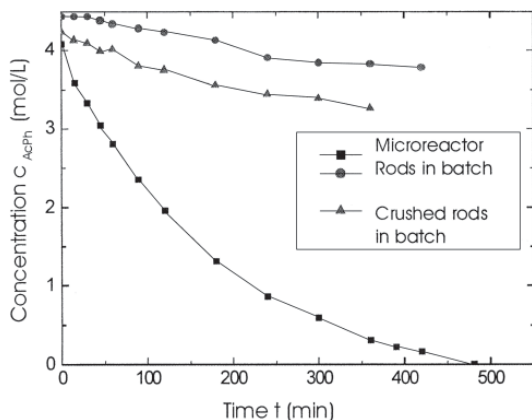
Acetophenone was reduced in methanol to 1-phenylethanol at 20 °C by borohydride moieties coupled to a porous polymer resin [3]. In principle, four hydrogen atoms can be released from the borohydride; the reactivity, however, decreases with each hydrogen atom lost. Experimentally it was shown that the first two atoms mainly contribute and to the reduction the other two remain on the polymer site.

**4.9.10.4 Experimental Protocols**

[P 56] A 1 mmol amount of acetophenone in methanol was reacted with borohydride moieties coupled to a porous polymer resin [3]. The reaction temperature was set to 40, 60 and 80 °C. The ratio of acetophenone to the solid borohydride was 0.90, 0.45 and 0.20. The polystyrene polymer was cross-linked by linking divinylbenzene moieties in the main chain. Originally, the polymer contained benzylchloride groups, which were converted to quaternary ammonium groups. By means of ion exchange, functional anionic groups such as the reductive cyanide moiety can be introduced. Typical ion-exchange capabilities of the micro reactor were about 0.1–1.0 mmol, depending on the polymer load.

**4.9.10.5 Typical Results****Conversion/selectivity/yield – benchmarking to batch processing**

[OS 76] [R 3] [P 56] After 500 h, total conversion was achieved for the micro reactor [3]. Polymer/glass rods and crushed rods were considerably less active, by a factor of 4–5 (Figure 4.86).



**Figure 4.86** Dynamic changes in conversion for a micro reactor and batches comprising rods and crushed rods [3].

#### Kinetic investigations – rate constants and activation energy

[OS 76] [R 3] [P 56] Two reaction rate constants at different temperature and reactant ratios were determined applying a set of four kinetic equations [3]. This mathematical model described the experimental results very well. Using an Arrhenius plot, frequency factors and activation energies were determined as well. For stage-one reduction, an activation energy of  $7.438 \text{ kcal mol}^{-1}$  resulted. For stage two, an activation energy of  $2.498 \text{ kcal mol}^{-1}$  was derived.

#### 4.9.11

##### Alkylidenedeoxy Bisubstitution – Wittig Reactions and Horner–Emmons Reactions

Peer-reviewed journals: [13]; proceedings: [12, 85, 136]; sections in reviews: [14, 42, 83, 89, 90].

##### 4.9.11.1 Drivers for Performing Wittig Reactions in Micro Reactors

The Wittig synthesis is a two-step reaction comprising first the formation of the ylide and then the double-bond closure [12]. The possibility of precisely setting the reaction times of these two steps in miniature continuous flow systems allows one a high level of chemical control, which is not possible by batch systems to the same extent. Another driver for Wittig syntheses is to control stereoselectivity [12]. Cis and trans isomers of the double bond are formed. Their ratio can be influenced generally by setting the flow and particularly by manipulating it by means of electroosmotic flow (EOF) (for EOF see [14]).

Another driver is doing screening and combinatorial syntheses in micro reactors [13].

##### 4.9.11.2 Beneficial Micro Reactor Properties for Wittig Reactions

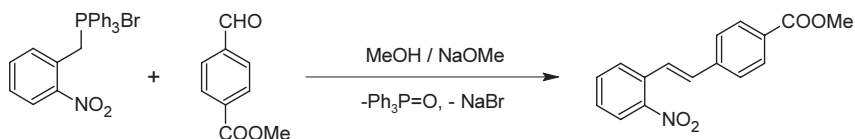
The precise definition of residence times for various stages of reactions by introducing reactants in a spatially confined manner in micro flow devices allows new ways

of chemical control [12]. Even properties such as the ratio of stereoisomers, although intuitively not evident, seem to be influenced by flow properties in micro channels.

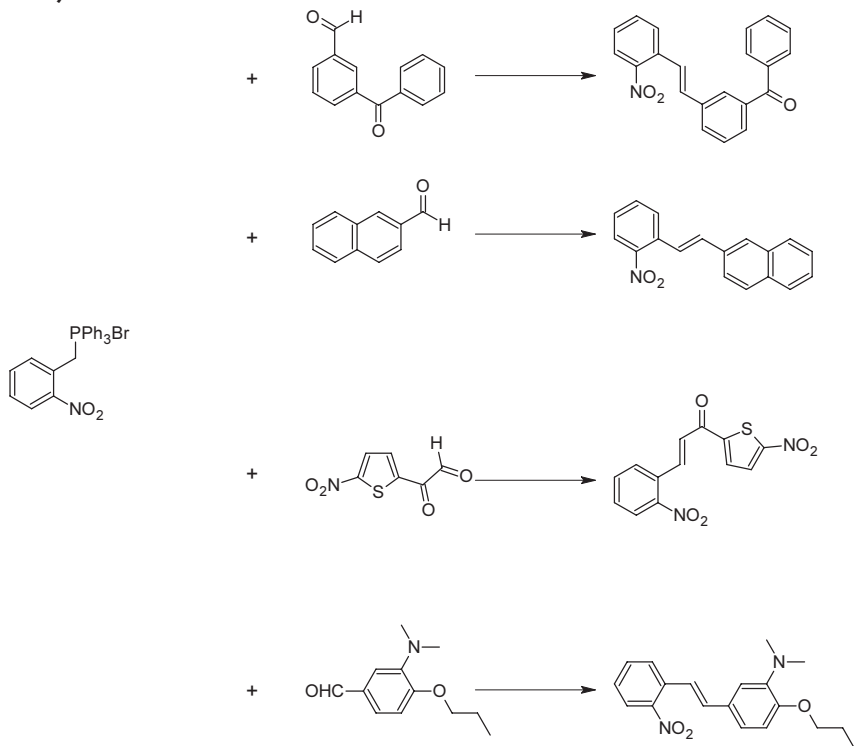
Mixing can be performed in a fast manner, so limiting residence time to the kinetic needs [12]. Particularly favorable is the application of EOF leading to plug-flow profiles, allowing one to set the residence time simply by changing voltages of the EOF, and also to perform mixing other than by diffusional means [12].

#### 4.9.11.3 Wittig Reactions Investigated in Micro Reactors

##### Organic synthesis 77 [OS 77]: 2-Nitrobenzyltriphenylphosphonium bromide and methyl 4-formylbenzoate [12]



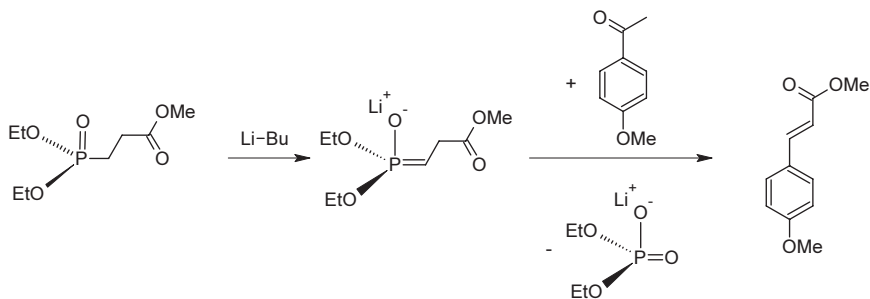
##### Organic synthesis 78 [OS 78]: 2-Nitrobenzyltriphenylphosphonium bromide and four aldehydes



The testing of 2-nitrobenzyltriphenylphosphonium bromide and methyl 4-formylbenzoate and four other aldehydes, 3-benzyloxybenzaldehyde, 2-naphthaldehyde, 5-nitrothiophene-2-carboxaldehyde and 4-[3-dimethylamino]propoxy]benzaldehyde, has been reported [13].

Wittig reactions generally occur in a two-stage manner. First, the triphenylphosphonium bromide reacts fast with sodium methoxide to give the corresponding ylide intermediate [12]. The coloration by ylide formation allows one to follow the course of the reaction visually. Then, a second-order reaction with the aldehyde compound follows to give the product containing the double-bond moiety. Here, *cis* and *trans* isomers may be formed. Side products refer to triphenylphosphine oxide and the derivatives of the non-conjugated reactants.

**Organic synthesis 79 [OS 79]: Methyl diethoxyphosphonoacetate and 4-methoxybenzaldehyde (Wittig–Horner–Emmons)**



4-Methoxybenzaldehyde and methyl diethoxyphosphonoacetate were reacted via the Wittig–Horner–Emmons route to give the corresponding alkene product [85] (see a more detailed description in [42]).

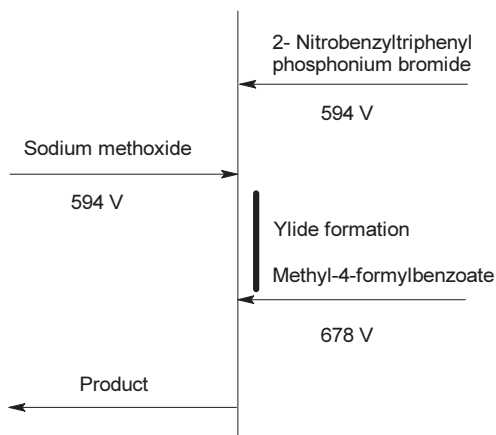
**4.9.11.4 Experimental Protocols**

[P 57] One early investigation focused on plug production (Figure 4.87), flow being fed by electroosmotic means [12]. Therefore, the voltages for moving the different reactants in the three reservoirs were set to 594 V for both 2-nitrobenzyltriphenylphosphonium bromide and sodium methoxide and to 678 V for methyl 4-formylbenzoate. The reaction was carried out at room temperature. No other details are given in [12].

[P 58] Another protocol focused on continuous contacting of the two reactant solutions. Again, flow was fed by electroosmotic means [13]. A 0.01 M methanol solution of 2-nitrobenzyltriphenylphosphonium bromide was used; a 0.02 M methanol solution for methyl 4-formylbenzoate with sodium methoxide (0.015 M) was used. Volumes of 80  $\mu\text{l}$  of both solutions were set in the respective reservoirs on the chip and 40  $\mu\text{l}$  of methanol in the collection reservoir. A voltage of 400 V was applied for both feed lines. The reactions were carried out at room temperature and run for 20 min.

[P 59] A third protocol differed from [P 57] and [P 58] by sequential insertion of all reactants instead of using a pre-mixed solution of nitrobenzyltriphenylphosphonium bromide and sodium methoxide. As above, flow was fed by electroosmotic means [13]. A 40  $\mu\text{l}$  volume of a methanol solution of 0.01 M 2-nitrobenzyltriphenylphosphonium bromide was filled into the first reservoir, 40  $\mu\text{l}$  of a methanol solution of 0.015 M sodium methoxide in the second, 40  $\mu\text{l}$  of a methanol solution





**Figure 4.87** Flow configuration for a Wittig synthesis in a chip micro reactor with three vertical injections [13].

of 0.01 M methyl 4-formylbenzoate in the third and 40  $\mu$ l of methanol in the collection reservoir. Following the sketched sequence of feeding, the voltages applied were: 594, 660 and 678 V. The reactions were carried out at room temperature and run for 20 min.

#### 4.9.11.5 Typical Results

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

[OS 77] [R 4b] [P 57] The migration of the base, sodium methoxide, was enhanced by electrophoretic force [12]. This led to faster mixing than by diffusion only. As a consequence, the conversion rate was increased.

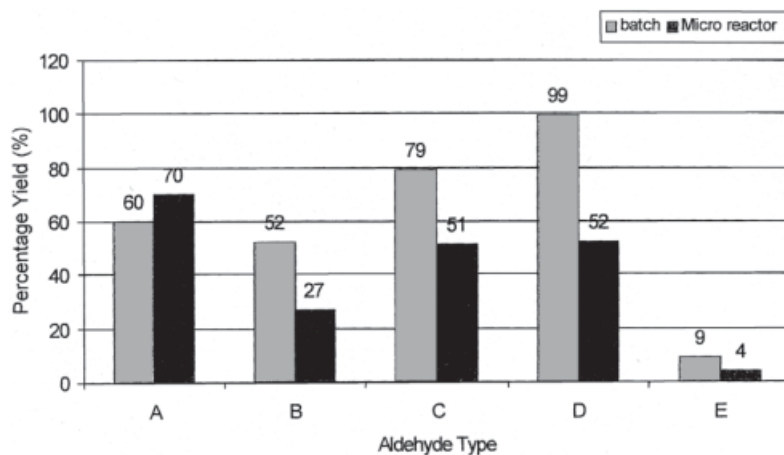
[OS 79] [R 17] [no protocol] 4-Methoxybenzaldehyde and methyl diethoxyphosphonoacetate were reacted by means of the Wittig–Horner–Emmons reaction [85] (see a more detailed description in [42]). A modified micro reaction system consisting of two mixers, for deprotonation of the phosphonates and introduction of the aldehyde, connected to an HPLC capillary of 0.8 m length and 0.25 mm diameter was employed. The micro reactor showed higher yields than laboratory batch synthesis.

##### Testing of different aldehydes at 2 : 1 ratio – benchmarking to batch synthesis

[OS 78] [R 4a] [P 58] The Wittig reactions of five aldehydes with 2-nitrobenzyltriphenylphosphonium bromide were investigated (using a 2-to-1 excess of the aldehyde) [13]: methyl 4-formylbenzoate, 3-benzyloxybenzaldehyde, 2-naphthaldehyde, 5-nitrothiophene-2-carboxaldehyde and 4-[3-dimethylamino]propoxy]benzaldehyde. Whereas the first reaction gave an improvement in yield compared with batch synthesis, the other four reactions did not. The different chemical natures of these species was not considered as a possible explanation for this finding, but it was rather suggested that the flow conditions were not set correctly (the voltages used, i.e., as the protocol was optimized for the first reaction and only applied to the



**Figure 4.88** Flow patterns, visualized by formation of the colored glide intermediate, allowing one to judge on mixing efficiency [13].



**Figure 4.89** Comparison between yields obtained by one mixing tee micro reactor and batch operation using five different aldehydes at 2 : 1 stoichiometry [13].

other). Flow monitoring of the ylide formation from the inlet section of the micro-mixing tee to the reaction channel demonstrates this (Figure 4.88).

Using optimized reaction conditions, the Wittig reactions with four of the five aldehydes resulted in an improvement in their yields (see Figure 4.89 below) [13].

#### Testing of different aldehydes at a 1 : 1 ratio

[OS 78] [R 4a] [P 58] The Wittig reactions of five aldehydes with 2-nitrobenzyltriphenylphosphonium bromide were investigated also at a 1 : 1 stoichiometric ratio [13]. Using optimized reaction conditions, improved yields were found for four of the five aldehydes.

For methyl 4-formylbenzoate, the yield decreased from 70% (2 : 1) to 59% (1 : 1) [13]. For batch processing, the yield decreased from 60% (2 : 1) to 48% (1 : 1), i.e. the reductions were similar. In both cases, micro channel processing was superior.

The 1 : 1 ratio was realized by plug insertion instead of continuous feed as in the 2 : 1 case. One injection per minute of 2-nitrobenzyltriphenylphosphonium bromide was made for a duration of 30 s into a continuous stream of the aldehyde solution at 400 V [13].

**Use of pre-mixed solutions versus sequential single-reactant injection**

[OS 78] [R 5] [P 59] Instead of using a premixed solution of nitrobenzyltriphenylphosphonium bromide and sodium methoxide, these two reactants were each feed into the reaction channel by single injection [136]. A total of three reactant streams were so inserted in a specially designed chip reactor for that purpose. Mixing was performed in the reaction channel and directly induced reaction. The yield obtained with fully single injection was 38%, whereas for the pre-mixed solution 59% was obtained. The reason for this is not really well understood; obviously the ylide formation was not completed under the conditions of protocol [P 59]. It was checked in advance that processing a pre-mixed solution in reactor [R 5] gave the same yield as for the originally used [R 4].

However, despite having a lower yield, sequential injection is seen to have the advantage of allowing more in-depth variation of process parameters, in particular concentration changes and performing individual stages of the reaction separately [136].

**Cis/trans- (Z/E) isomer ratio**

[OS 77] [R 4b] [P 57] By simply adjusting the voltages in an EOF driven chip, the ratio of cis and trans products (*Z/E* ratio) can be changed [12]. The *Z/E* ratio is also strongly influenced by moving the reactants separately or as a premixed solution. For a 1 : 1 ratio of the reactants, the *Z/E* ratio changed from 2.35–3.0 (premixed) to 0.82–1.09 (not pre-mixed, separate movement) [13].

These initial findings motivated a detailed analysis of the influence of flow properties, i.e. changing the voltage in an electroosmotic-driven experiment, on the *Z/E* ratio [13]. Voltages were varied between 300 and 700 V. It was shown that on decreasing the voltage, which is equivalent to increasing the residence time, the trans isomer is formed more predominately, but at the expense of a drastic reduction of the overall yield. This demonstrates that thermodynamic control is more effective here, as expected, for long residence times. For large changes in the *Z/E* ratio, relatively small voltage changes of the order of only 100 V were needed. For instance, changing the voltage from 694 to 494 V for one channel decreased the *Z/E* ratio from 2.3 to 0.57. The corresponding yields as outlined above, changed from 100 to 7%.

**4.10****Eliminations****4.10.1****Hydro-Hydroxy Elimination – Dehydrations of Alcohols**

Peer-reviewed journals: [19]; sections in reviews: [14, 89, 90]; microfabrication: [137, 138].

#### 4.10.1.1 Drivers for Performing Dehydrations of Alcohols in Micro Reactors

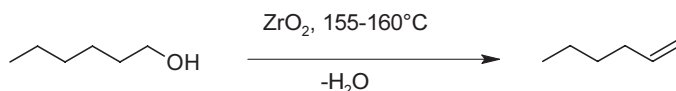
Performing this reaction primarily served as a model to show the feasibility of micro flow processing for solid/liquid reactions [19]. In a similar way as for catalyzed gas-phase reactions, micro-reactor processing was expected to show benefits in terms of mass and heat transfer. Particularly this relates to transfer enhancement when using porous media.

#### 4.10.1.2 Beneficial Micro Reactor Properties for Dehydrations of Alcohols

The benefits refer to the ability to achieve defined thin, highly porous coatings in micro reactors. In combination with the small length scales of the channels, diffusion to the active sites is facilitated. The residence time can be controlled, accurately minimizing consecutive reactions which may reduce selectivity.

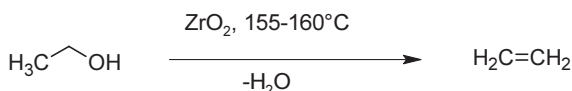
#### 4.10.1.3 Dehydrations of Alcohols Investigated in Micro Reactors

##### Organic synthesis 80 [OS 80]: Dehydration of 1-hexanol to hexene



The dehydration of 1-hexanol to hexene was conducted over heterogeneous sulfated zirconium oxide catalyst [19, 138]. The zirconia was treated with sulfuric acid and is known as super acid catalyst, having well documented performance for many reactions [19]. The reaction conditions are notably milder as for other acid catalysts, such as silica–alumina.

##### Organic synthesis 81 [OS 81]: Dehydration of ethanol to ethene



#### 4.10.1.4 Experimental Protocols

[P 60] The dehydration of 1-hexanol to hexene and of ethanol to ethene were conducted at 155 °C. Heating was accomplished by a heating wire inserted in the micro reactor's top plate. This wire was connected to a potentiostat (0–270 V); temperature was monitored by a digital thermometer with the probe close to the reaction channel. A syringe pump was applied for liquid transport [19]. A flow rate of 3  $\mu\text{l min}^{-1}$  was applied. The alcohols were purged with nitrogen directly prior to reaction to minimize coke formation.

After activation by heating, the catalyst was dusted over the surface of a thin polydimethylsiloxane (PDMS) layer, being coated on the PDMS top plate of the micro reactor [19]. Such a modified plate was baked for 1 h at 100 °C. A high surface area and firm immobilization of the catalyst resulted. Then, the micro reactor was assembled from the top and another bottom plate, having at one micro-channel wall the catalyst layer. Stable operation with the PDMS micro reactor up to 175 °C could be confirmed.

[P 61] For the dehydration of ethanol to ethane, electroosmotic pumping was applied for liquid transport [19]. A flow rate of 0.9–1.1  $\mu\text{l min}^{-1}$  was applied, giving longer residence times as in [P 60]. The other details of the protocol are identical with those for [P 60].

#### 4.10.1.5 Typical Results

##### Conversion/selectivity/yield – benchmarking to large-scale reactors

[OS 80] [R 7] [P 60] The acid-catalyzed dehydration of 1-hexanol to hexene was conducted in a micro reactor made of PDMS, which also contained a heating function [19, 138]. Sulfated zirconium oxide was coated as catalyst on the top plate of the micro reactor. A yield of 85–95% was obtained; by-products could not be detected. This performance exceeds those of conventional reactors (30%).

[OS 81] [R 7] [P 60] The acid-catalyzed dehydration of ethanol to ethene over sulfated zirconium oxide led to a mixture containing 68% ethene, 16% ethane, and 15% methane [19, 138].

##### Operational time

[OS 80] [R 7] [P 60] The micro reactor was used constantly for 3 days without any hint of losing performance [19, 138].

##### Residence time

[OS 81] [R 7] [P 61] An increase in residence time by a factor of about 3 was accomplished by changing the flow rate from 3.0 to 0.9–1.1  $\mu\text{l min}^{-1}$  [19]. By far the main reaction product detected was methane; otherwise only traces of methanol were present. Instead, at the shorter residence time a mixture containing 68% ethene, 16% ethane and 15% methane was obtained [19, 138]. Hence the presence of methane demonstrates that complete cracking occurred as a consecutive reaction to dehydration.

##### Electroosmotic pumping

[OS 81] [OS 80] [R 7] [P 60] [P 61] Whereas electroosmotic pumping can be achieved for ethanol, it is not feasible with hexanol, as the volume flow rate is inversely proportional to the carbon chain length [19, 138].

## 4.11

### Rearrangements

#### 4.11.1

##### Rearrangements of Hydroperoxides

Patents: [64].

##### 4.11.1.1 Drivers for Performing Rearrangements of Hydroperoxides in Micro Reactors

The only investigation so far refers to the second reaction of a two-step industrial process, the Hock process, which is used for phenol production world-wide [64].

Here, cumene hydroperoxide is rearranged to provide phenol and acetone via acid cleavage.

As this acid cleavage releases considerable heat, the apparatus used needs efficient heat exchange units [64]. Selectivity of the hydroperoxide cleavage is affected if temperature rises in an undesired manner. For this reason, not the technical 65–90 wt.-% solutions, but rather strongly diluted ones (e.g. below 10%) are employed. In the first case, a sudden loss of the heat exchange function could result in an temperature increase from 50 to 500 °C within seconds.

As a consequence, recycle processing is needed with high recycle ratios, e.g. 17 [64]. Depending on the acid/organic ratio, homogeneous or heterogeneous acid cleavage can be carried out. In the latter case, only a small portion of the acid is used. Accordingly, a mixture with very different ratios of the two solutions has to be prepared in a continuous-flow system which demands good mixing properties.

#### 4.11.1.2 Beneficial Micro Reactor Properties for Rearrangement of Hydroperoxides

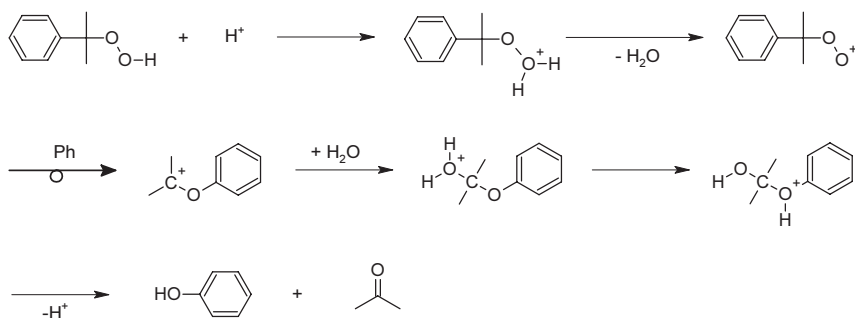
According to the above remarks, micro reactors have to provide efficient heat transfer and should be able to reduce the recycle ratios [64]. Further, they have to be able to mix streams at very different flow ratios.

The excellent heat transfer properties of micro reactors are a general feature that is not specifically related to the hydroperoxide rearrangement. Calculations on cumene hydroperoxide cleavage showed that even if the pumps stop working, i.e. the cooling fluid is no longer moving, no critical temperature increase has to be expected for micro-reactor processing [64]. This is a result of their extremely large surface-to-volume ratios. Thus, controllability of the hazardous substances used (peroxides) is notably improved.

The impact of micro reactor processing on the recycle ratio cannot be predicted in a straightforward manner. As this is somehow linked to mass transfer and mixing, improvements are possible; actually this was found experimentally, e.g. recycle ratios below 2 were used for micro flow processing (instead of 17 in the conventional industrial processing, see below) [64].

#### 4.11.1.3 Rearrangements of Hydroperoxides Investigated in Micro Reactors

##### Organic synthesis 82 [OS 82]: Rearrangement of cumene hydroperoxide



The Hock process includes the oxidation of cumene by air to hydroperoxides using large bubble columns and the cleavage of the hydroperoxide via acid catalysis, which is reaction [OS 82]. This process is used for the majority of world-wide phenol production and, as a secondary product, also produces large quantities of acetone [64]. Phenol is used, e.g., for large-scale polymer production when reacted in a polycondensation with formaldehyde.

The reaction mechanism is based on protonation of the hydroxyl moiety, rearrangement of the phenyl group and simultaneous cleavage of water, creating a carbocation as intermediate [135]. This cation is hydroxylated by water. Thereby, an unstable hemiacetal is formed that splits into two molecules, phenol and water.

#### 4.11.1.4 Experimental Protocols

[P 62] The acid cleavage was carried out at 45–75 °C at a pressure of 1–5 bar. Water may be added at levels of 0.3–1 wt.-% [64]. This addition was made upstream of the micro reactor or directly inside. The residence time was set in the range 0.5–5 min. Sulfuric acid was used as catalyst. By changing residence time and acid addition, the residual cumene hydroperoxide content was favorably reduced to 0.1–0.3 wt.-%. For this, an acid concentration of 50–500 ppm is typically required. Part of the so cleaved product stream may be recycled.

In a typical experiment in a micro reactor, 67 wt.-% technical cumene hydroperoxide was reduced to 1.0 wt.-% [64]. A recycle ratio of 2 was applied.

#### 4.11.1.5 Typical Results

##### **Conversion/selectivity/yield – benchmarking to conventional apparatus**

[OS 82] [R 28] [P 62] High-boiling substances are typical by-products of acid cleavage which need to be reduced to facilitate product purification. Using 67 wt.-% technical cumene hydroperoxide and a recycle ratio of 2 yields a content of high-boiling substances of 0.12 wt.-% [64]. Conventional processing at a recycle ratio of 17 results in 0.21 wt.-% high-boiling substances.

An increase in cumene yield by 0.5% was thus achieved in the micro reactor [64]. Considering an annual production of 7 million tons, this is a considerable improvement regarding economics.

##### **Recycle loop/recycle ratio**

[OS 82] [R 28] [P 62] The recycle ratio of acid cleavage was considerably reduced in micro reactors [64]. At better selectivity, a ratio of 2 or below was applied, whereas conventional processing relies on much larger ratios, e.g. 17. Even operation without recycling was possible in the micro reactor. In this case, 0.1 wt.-% high-boiling substances was achieved. This is a reduction by a factor of two compared with the state-of-the-art industrial processing.

For reducing the recycle ratio, the acid content had to be increased. Although this was detrimental in terms of selectivity, this effect was more than counterbalanced by the reduction of loop passages [64].

**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**

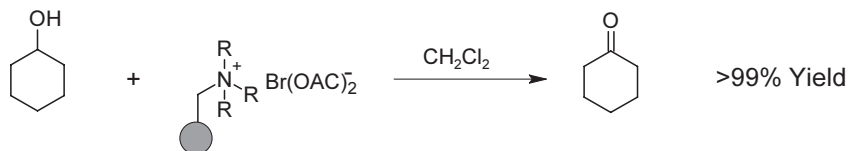
Proceedings: [3].

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  $20\text{ }^\circ\text{C}$  (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  $20\text{ }^\circ\text{C}$  (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.