Part III
Microreactor Plants: Case Studies

9
Industrial Microreactor Process Development up to Production

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This chapter is about industrial applications of microprocess technology. Industry is not very active in publishing not only because of confidentiality reasons but also because of the absence of direct need for a corresponding profile. Thus, one cannot expect that the ongoing developments can be shown with a similar degree of completeness, clarity and detailedness, as this is possible for reviewing scientific contributions from academy with a wealth of peer-reviewed papers. Especially, the information of major interest of what has been transferred to production and how do the companies make profit with the new technology is usually kept secret. Thus, it has to be accepted that some information is missing among the chapters and that this is only the tip of the iceberg. Also, the sources of information are not as validated as refereed literature because in some cases one has to rely on interviews and other information given in a magazine format.

Knowing these shortcomings, the contents were grouped in sections on industrial mission statements, laboratory process development, pilots and chemical production. For the process development part of this chapter, papers were also considered with industrial coauthors, assuming that the work was (partly) done under industrial perspective and reflects fields of interest and activity of industry.

9.1
Mission Statement from Industry on Impact and Hurdles

Fine chemistry is the present major application area of microprocess technology. Degussa in Hanau, Germany, a leading fine-chemical company, has tested the new approach for various liquid and gas processes including even transfer to plasma

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reactions [1]. Dominique Roberge, head of a project to evaluate microreactors at Lonza in Visp, Switzerland, states 'The question of whether microreactors are going to be used in the future, I think this is already answered "yes" [2]. The open question is what per cent of the market in fine chemicals they will take.' Lonza is a Swiss company that manufactures intermediates for the drug industry.

> "*The question of whether microreactors are going to be used in the future, I think this is already answered "yes".*" Dominique Roberge/Lonza

Georg Markowz, senior process engineer at Degussa, says 'At Degussa, we believe in the potential of microchannel process technology both as a development tool in the lab and for production technology.' Ralf Pfirmann from Clariant Pharmaceuticals, global pharmaceutical market management director, summarizes some of the primary effects of microreaction engineering and adds 'Use of microreactors in pharmaceutical synthesis ... much higher yields, with higher selectivities, and with economics therefore not possible.' [3]. Fabian Wahl, manager of R&D for Europe at Sigma–Aldrich, emphasizes the secondary effects and adds '... allowing far more precise reaction control and far better product quality control than can be achieved with conventional reactors' [4]. Wahl adds that about 800 from the 2000 reactions in Sigma–Aldrich's portfolio are suitable for microreactor processing, with or without minor process modifications. For the microreactor cases studied so far, reduction of reaction time and cost were major drivers. An application is especially seen in the Sigma–Aldrich's custom synthesis business with fast process development as the prime goal. Wahl expects a 40% reduction in process development time by using microreaction technology. Tony Wood, head of discovery chemistry for Pfizer in Sandwich, UK, adds 'What's interesting to me is the opportunity to pursue fields such as electrochemistry or photochemistry. That would enable us to functionalize molecules in a quite different way from mainstream transformations.' [2].

Besides the technical challenges one still has to take care of the soft factors, which is the human personnel that requires a change in the mindset. 'You are in a small, innovative team in an established company that has more than 100 years' experience in chemical production and you want to change things – there are some barriers beyond the technical', says Dominique Roberge from Lonza [2].

John Brophy, former general manager of corporate research of BP Chemicals in Sunbury-on-Thames, UK, states 'Microchannel process technology is being hailed as the next big thing for the process technologies.' He adds 'To date, industry has been sceptical, adopting a "show us" approach to such radical change in plant technology ... But now the pace is heating up with several companies developing and scaling up this brand-new technology' [1].

Concerning the potential of microprocess technology for large-scale and bulk chemicals production, Dow corporate leader Jon Siddall points out at the example of olefins production, which is the chemical produced in largest volume: 'Microchannel technology may allow us to reduce costs or otherwise improve the process for making an essential commodity of world commerce ... the irony of making large-volume chemicals in small-volume reactors is unmistakable.' [1].

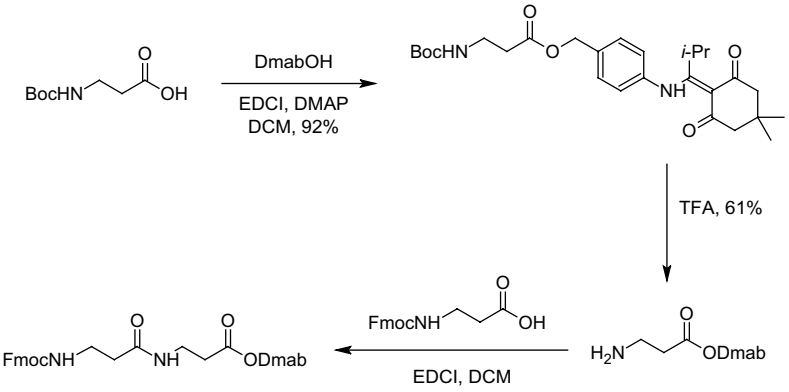
9.2
Screening Studies in Laboratory

9.2.1
Peptide Synthesis

The Nervous System Research branch of Novartis Pharma Ltd in Basel, Switzerland, and the University of Hull investigated peptide synthesis in chip-based microreactors [5]. β-Amino acids were chosen for demonstrating feasibility of microreactor processing, as there are no chiral centers that may complicate the analysis of the products [6].

Peptides are typically synthesized by solid-phase chemistry on polymer beads, a route discovered by and named after Merrifield [7, 8]. These polymer supports are expensive. Additional steps for linkage to and cleavage from the polymer are required. Hence, the motivation is to test solution chemistries as an alternative to the Merrifield approach.

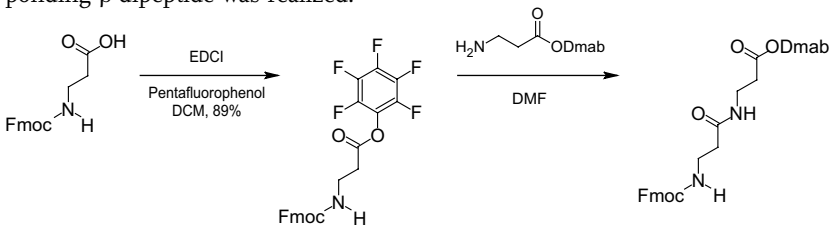
The impact of mixing in a microreactor was demonstrated through the experiment of β-dipeptide synthesis by carbodiimide coupling using Dmab *O*-protection. Boc-β-alanine was *O*-protected (carboxylic moiety) by DMAP (4-dimethylamino pyridine) coupling with DmabOH (4-{*N*-[1-(4,4-dimethyl-2,6-dioxocyclohexyliden)-3-methylbutyl]amino}benzyl alcohol) yielding Dmab-β-alanine, whereas the Fmoc group was used for *N*-protection of β-alanine [9]. Thereby, orthogonal protecting groups were established. By carbodiimide coupling, Dmab-β-alanine and Fmoc-β-alanine reacted and the synthesis of the corresponding β-dipeptide was realized.



Electroosmotic flow (EOF) conditions were applied and yielded only 10% conversion with constant reactant movement [9]. The use of stopped-flow techniques, which periodically push and mix the flow, led to a 50% increase in yield. A change in the coupling agent from 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (EDCI) to dicyclohexylcarbodiimide (DCC) for reasons of limited solubility resulted in a 93% yield of the dipeptide. Batch β-dipeptide synthesis using EDCI gave a yield of 50% [6].

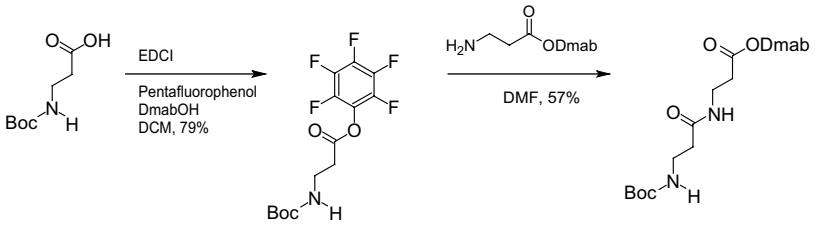
A reduction in reaction time by virtue of the improved transport properties in electroosmotic-driven microreactors was demonstrated for the β-dipeptide synthesis using pentafluorophenyl *O*-activation. Fmoc-β-alanine was preactivated by introducing the pentafluorophenyl function as ester group [9]. Dmab-β-alanine and the

pentafluorophenyl ester of Fmoc-β-alanine reacted, and the synthesis of the corresponding β-dipeptide was realized.



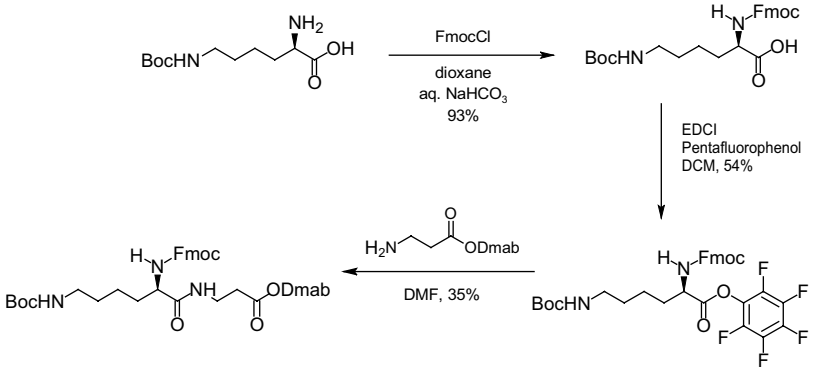
Quantitative yield of the dipeptide in only 20 min was achieved when using electroosmotic-driven microreactor, whereas batch synthesis under the same conditions gave only 46% yield needing 24 h [6, 9].

The same findings with respect to reaction time reduction were made for the β-dipeptide synthesis using pentafluorophenyl *O*-activation. Boc-β-alanine was preactivated by introducing the pentafluorophenyl function as ester group [9]. Dmab-β-alanine and the pentafluorophenyl ester of Boc-β-alanine reacted, and the synthesis of the corresponding β-dipeptide was realized.

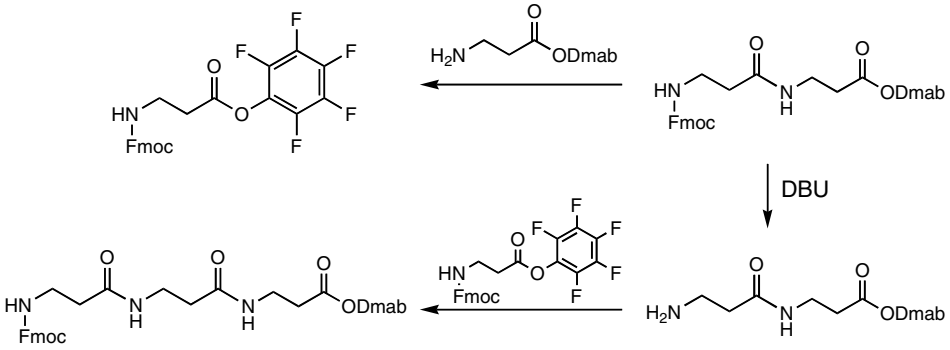


Electroosmotic-driven microreactor processing gave quantitative yield of the dipeptide in only 20 min, whereas batch synthesis under the same conditions gave only 57% yield needing 24 h [6, 9].

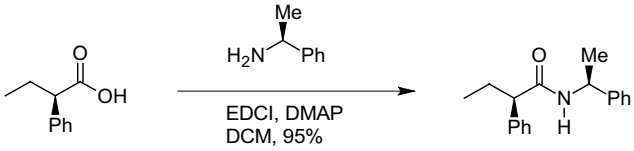
The formation of more complex dipeptides was also demonstrated by microchannel processing through the experiment of converting the amino acid *N*-ε-Boc-L-lysine with the additional amino function [5, 6]. Although the batch yield of only 9% is poor, microreactor synthesis is quantitative in 20 min.



In the next step, the preparation of longer chain peptides was done in electroosmotic microreactors. For this purpose, deprotection and peptide bond forming reactions had to be developed resulting in a yield of 30% [6, 9]. In this way, the formation of tripeptides was achieved. Dmab-β-alanine and Fmoc-β-alanine were reacted in the first step to a dipeptide [6]. After cleavage of the Fmoc function, Fmoc-β-alanine was added to such a dipeptide that resulted in tripeptide formation in 30% yield.

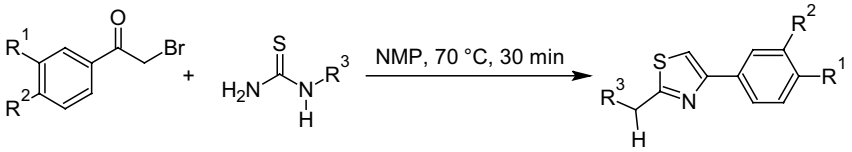


The degree of racemization was also monitored through the experiment of a simple carboxylic acid used in peptide synthesis, 2-phenylbutyric acid. The pentafluorophenyl ester of (*R*)-2-phenylbutyric acid and (*S*)-1-phenylethylamine reacts with the corresponding amino acid via an EDCI coupling [5]. In a control experiment, (*R*)-2-phenylbutyric acid and (*R*)-1-phenylethylamine were reacted as well. For the amino acid formation of (*R*)-2-phenylbutyric acid and (*S*)-1-phenylethylamine, a 4.2% racemization was found [6]. At higher concentration (0.5 M instead of 0.1 M), a higher degree of racemization was observed (7.8%).



9.2.2
Hantzsch Synthesis

GlaxoSmithKline Pharmaceuticals in Harlow, UK, performed the Hantzsch synthesis of 2-bromo-4′-methylacetophenone and 1-acetyl-2-thiourea in NMP (*N*-methyl-2-pyrrolidone) using a microchip reactor under EOF conditions [10] (for EOF see [11]) [10]. This is claimed to be the first example of a heated organic reaction performed on a glass chip reactor under electroosmotic flow control, whereas only room temperature reactions were made earlier. In a wider scope, the Hantzsch synthesis is a further example to evaluate the potential of microfluidic systems for high-throughput screening.

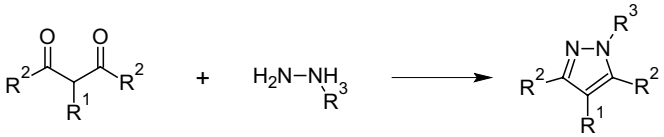


Yields from 42 to 99% were reported. Comparative and better yields were achieved when using a microchip reactor than the conventional lab batch technology. In case of improvement, the increase in yield amounted to about 10–20% [10, 12].

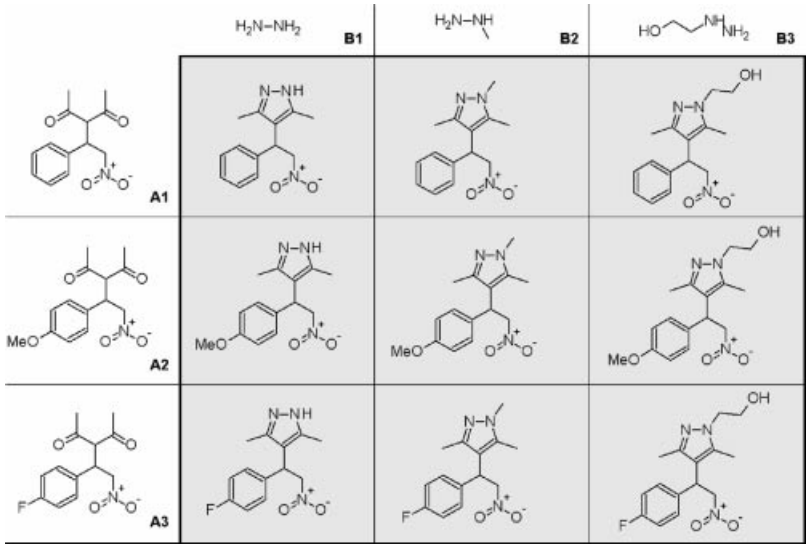
9.2.3
Knorr Synthesis

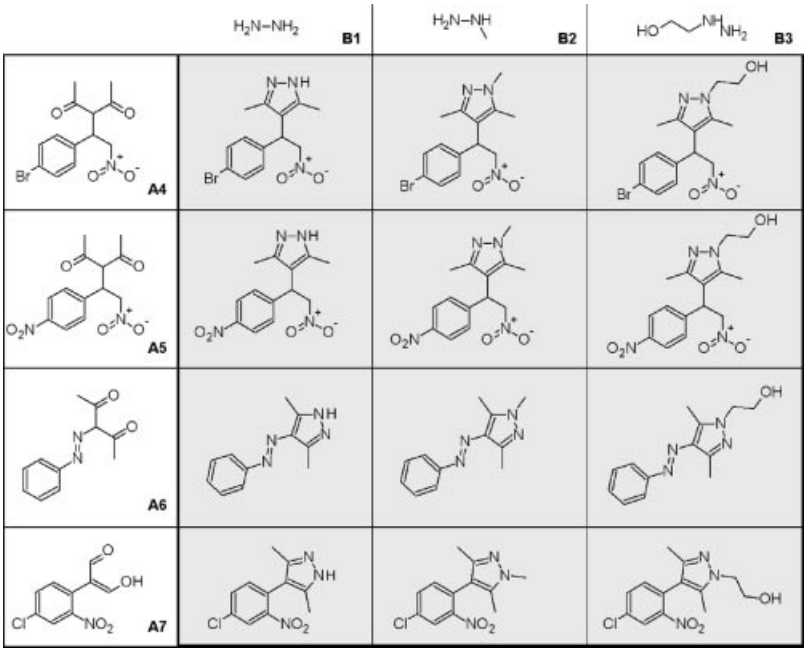
A Knorr synthesis of pyrazoles using a microchip reactor under electroosmotic flow conditions was developed by GlaxoSmithKline Pharmaceuticals in Harlow, UK [13]. The target was a high-diversity screening campaign (7×32 libraries in the long run) by parallel operation of microchannels after the feasibility of EOF processing had been demonstrated through the experiment of the Hantzsch synthesis. The Knorr synthesis is of interest for drug applications as products with a wide range of biological activity can be generated this way.

In the Knorr route, 1,3-dicarbonyl compounds react with hydrazines under ring closure to pyrazoles [13].



The following library consisting of seven (A1–A7) 1,3-dicarbonyl compounds and three hydrazines (B1–B3) was synthesized.





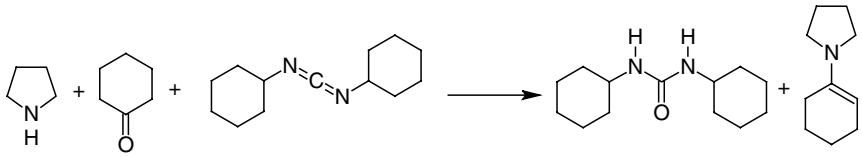
The 3×7 library was made in a sequential and automated way with conversions between 35 and 99% (quantitative; for 16 reactions). The corresponding chip is a commercial product of Caliper Technologies Company (110 Caliper chip), which was originally designated for μTAS applications. The chips were constructed from two glass plates by means of standard photolithography. The etched microchannels have different widths for more stable flow, for example, to avoid dependence of capillary forces in the reservoirs. The glass chip is glued to a polymer caddy for interfacing with a multiport control device, the Caliper 42 Workstation. This automated system consists of an autosampler (CTC-HTS Pal system) that introduces the reactant solutions in the chip via capillaries. A pumping system (μ-HPLC-CEC system) serves for fluid motion by hydrodynamic-driven flow. A dilution system (Jasco PU-15(5)) for slug dilution on-chip, a detection system (Jasco UV-1575) for detection and an analysis system (LC–MS, Agilent 1100 series capLC-Waters micromass ZQ) were used. All components were online and self-configured.

The results obtained were compared for consistency to those of single-reaction processing on the same chip. No cross-contamination was found during preparation of the library [13]. Neither products, by-products, nor the hydrazine in excess were intermixed.

9.2.4
Enamine Synthesis

GlaxoSmithKline Pharmaceuticals in Harlow, UK, performed an enamine synthesis using a microchip reactor under electroosmotic flow conditions [13]. The aim was on

eliminating the need of using Lewis acid catalysts for enamine formation by use of microreactors [14]. In addition, operation under mild conditions such as room temperature processing was favored.

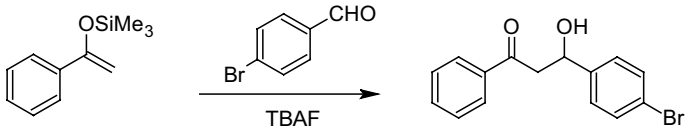


The microreactor yield (up to 42%) is comparable to that of batch Stork enamine reactions using *p*-toluene sulfonic acid in methanol under Dean and Stark conditions, that is, under water separation in a water trap (Dean–Stark apparatus).

9.2.5
Aldol Reaction

The Nervous Systems Research branch of Novartis Pharma Ltd in Basel, Switzerland, carried out the aldol reaction using a microchip reactor under electroosmotic flow conditions. Aldol reactions are well-established routes for C−C bond formation in organic chemistry.

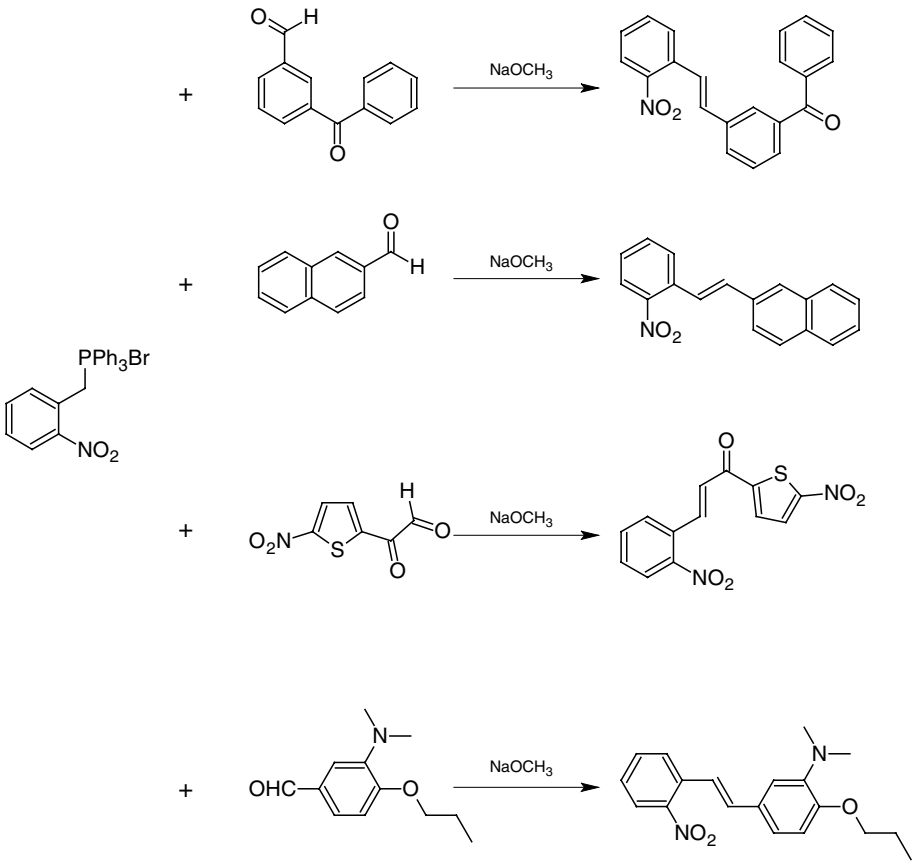
The reaction requires the formation of enolates that by themselves are one of the most profound species enabling C−C bond formation [15]. Reducing processing time is a driver for microchannel processing of aldol reactions [15] that can be accomplished using reactive reactants such as silyl enol ethers. For example, the reaction between 4-bromobenzaldehyde and the silyl enol ether of acetophenone was performed in a microreactor [15].



For this reaction, 100% conversion with respect to the silyl enol ether was achieved in 20 min [15]. The corresponding time for batch synthesis amounted to about 1 day.

9.2.6
Wittig Reaction

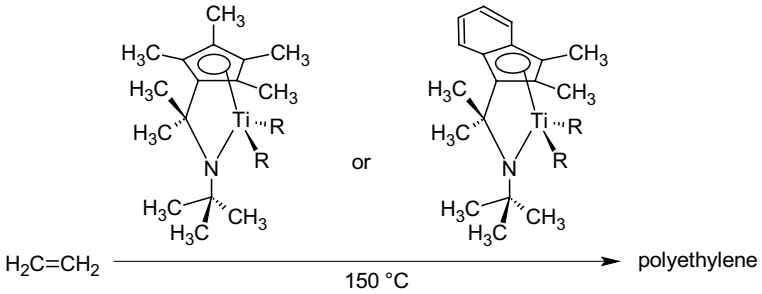
SmithKline Beecham Pharmaceuticals in Harlow, UK, carried out Wittig reactions using a microchip reactor under electroosmotic flow conditions. 2-Nitrobenzyltriphenylphosphonium bromide was reacted with methyl 4-formylbenzoate and four other aldehydes, 3-benzyloxybenzaldehyde, 2-naphthaldehyde, 5-nitrothiophene-2-carboxaldehyde and 3-dimethylamino-4-propoxybenzaldehyde [16, 17].



With the use of optimized reaction conditions, the Wittig reactions with four of the five aldehydes indeed resulted in improvement of their yields. The ratio of (*E*)- and (*Z*)-alkenes could be changed by simply adjusting the voltages in the electroosmotic-flow-driven chip [18]. 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 premixed, separate movement) [17].

9.2.7
Polyethylene Formation

DOW in Midland, USA, performed metallocene-catalyzed polymerization of ethylene using a homebuilt tube reactor setup with advanced microflow tailored plant peripherals for heating, temperature monitoring, pressure control and dosing via smart valves and injectors. Screening of process conditions was a driver [19]. Also, flexibility with regard to temperature and pressure at low sample consumption was an issue. Quality of the information is another motivation due to the advanced process control and sensing.



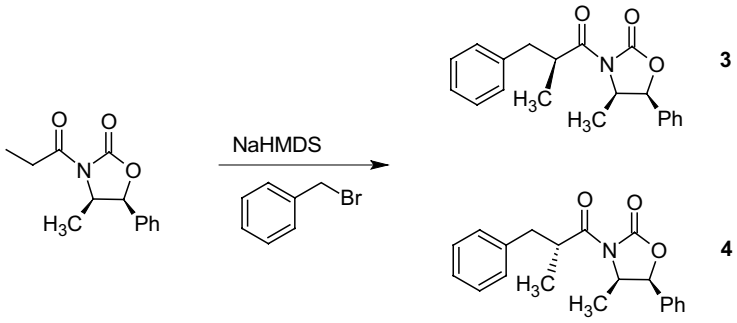
Ethylene is handled at 60 °C, well above the critical temperature [19]. Various combinations of precatalysts and activators were sampled and loaded by an autoinjector.

Temperature profiles versus time were taken for different positions at the reactor tube [19]. The maximum rise in temperature was about 23 °C. Improved pressure control was exerted by using advanced pressure control electronics [19]. In the regions of large temperature increase, pressure was slightly fluctuating; this effect diminished downstream. By deliberately changing pressure (in a loop), the temperature response followed immediately [19]. This proved that control of pressure is crucial for obtaining stable temperature baselines.

Catalyst-plug-induced microchannel ethylene polymerization allows to process about 10 runs per hour [19]. This is considerably more than achievable with conventional equipment (Parr reactors) processing only 4–6 runs per day.

9.2.8
Diastereoselective Alkylation

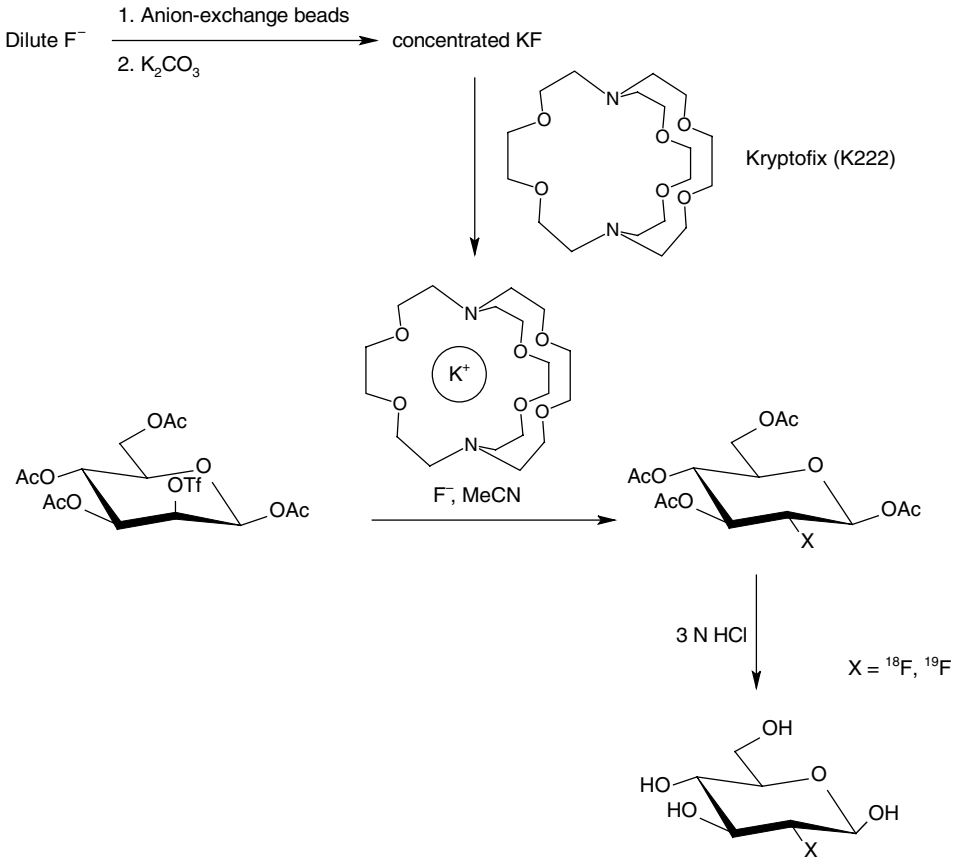
The Novartis Institute for BioMedical Research in Basel, Switzerland, and the University of Hull, UK, performed the diastereoselective alkylation of metal-stabilized enolates using a pressure-driven microreactor at −100 °C, whereby increased conversions and diastereoselectivity were observed compared to the batch process [20].



The diastereoselective synthesis of (2′*S*,4*R*,5*S*)-3-(2′-methyl-3′-phenylpropionyl)-4-methyl-5-phenyloxazolidin-2-one **3** was demonstrated in a chip microreactor, whereby diastereoselectivities of >91 : 9 (**3** : **4**) were obtained compared to 85 : 15 in the batch mode.

9.2.9
Multistep Synthesis of a Radiolabeled Imaging Probe

Several academic partners and Siemens Medical Solutions USA Inc. (Molecular Imaging) in Culver City, USA, made the synthesis of an [^{18}F]fluoride-radiolabeled molecular imaging probe, 2-deoxy-2-[^{18}F]fluoro-D-glucose in an integrated microfluidic device (see Figure 9.1) [21]. Five sequential processes were made, and they are [^{18}F]fluoride concentration, water evaporation, radiofluorination, solvent exchange and hydrolytic deprotection. The half-life of [^{18}F]fluorine ($t_{1/2} = 110$ min) makes rapid synthesis of doses essential. This is one of the first examples of an automated multistep synthesis in microflow fashion.



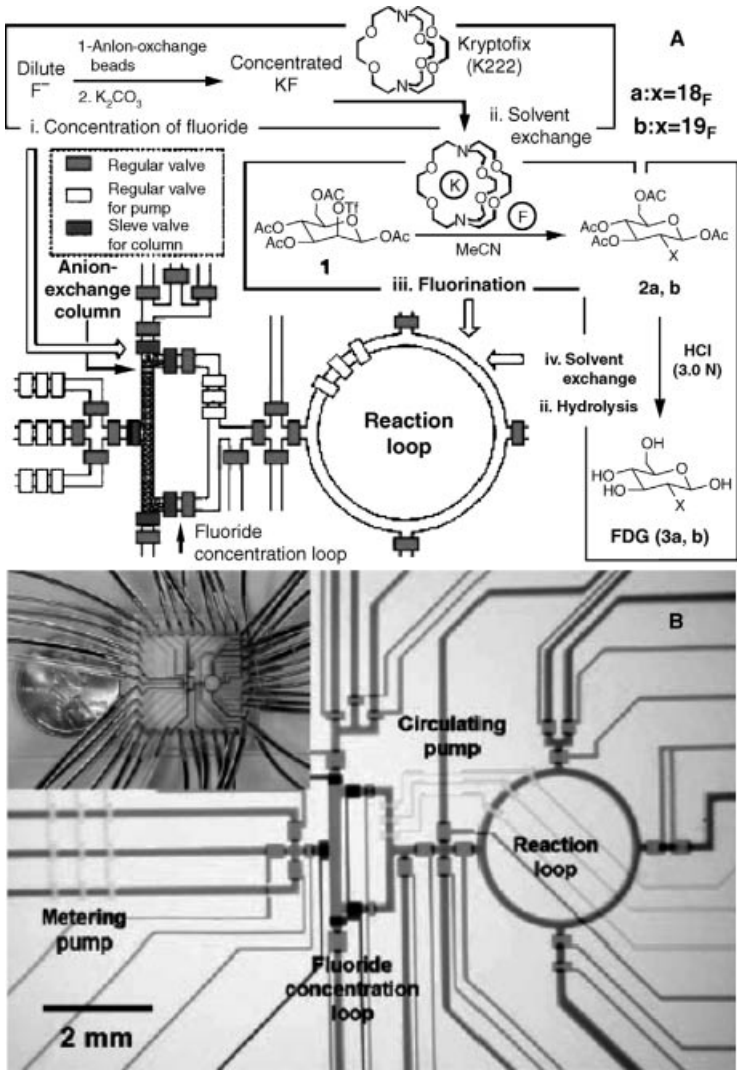


Figure 9.1 Top: a schematic of how to translate the chemical reaction steps of the synthesis of 2-deoxy-2-fluoro-D-glucose into a microfluidic design with microchannels and valves for consecutive fluid transport und manipulation (by courtesy of AAAS) [21]. Bottom: central area of the microfluidic circuit with channels filled with food dyes for visualization. Inset: photograph of the device (by courtesy of AAAS) [21].

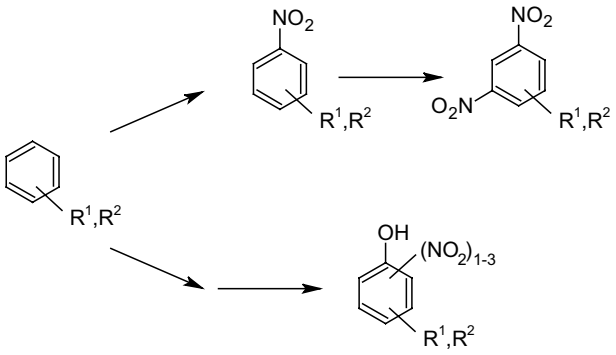
In comparison to the conventional automated synthesis, the radiochemical yield and purity of the compound obtained by microreactor processing was higher and also had shorter synthesis time [21]. Multiple doses of 2-deoxy-2-[^{18}F]fluoro-D-glucose for positron emission tomography imaging studies in mice were prepared. Today, 2-deoxy-2-[^{18}F]fluoro-D-glucose is routinely produced in about 50 min with the use of

expensive commercial synthesizers and the radiolabeled compound from ~10 to 100 doses is produced in a single run.

9.3
Process Development at Laboratory Scale

9.3.1
Nitration of Substituted Benzene Derivatives

BASF in Ludwigshafen, Germany, and university partners reported the nitration of several disubstituted benzene derivatives using a capillary-flow microreactor [22]. The exact nature of these species, however, was not disclosed.



Because the benzene derivative and nitric acid are immiscible, the impact of mixing/distribution on slug formation was investigated. Uniform slugs of the aromatic compound/nitric acid were formed in a Y-piece [22]. The capillary attached has a stabilizing effect on the slug flow. The deviation of slug size distribution is very small (about 5%). Hence, interfacial area is nearly constant for this type of capillary flow.

For the nitration of benzene derivatives, experiments were performed at two temperature levels, 60 and 120 °C [22]. For the 60 °C experiment, very small amounts of by-products such as phenol derivatives and dinitrated species were formed, not exceeding 50 ppm each. At 120 °C, high levels of by-products were found, with 300 ppm dinitrated species and 200 ppm phenol derivatives. The mechanism of by-product formation was also investigated [22]. Dinitrated products were generated by nitration of the mononitrated product. It was concluded that phenolic by-products were formed directly from the aromatic starting material rather than from the mononitrated product. This proposed reaction mechanism could be confirmed by performing selective nitration of the mononitrated product.

The influence of interphase mass transfer between liquid–liquid slugs was investigated for nitration of aromatic compounds in a capillary-flow reactor (see Figure 9.2) [22]. This was achieved by changing flow velocity via volume flow setting, while residence time was kept constant by increasing the capillary length.

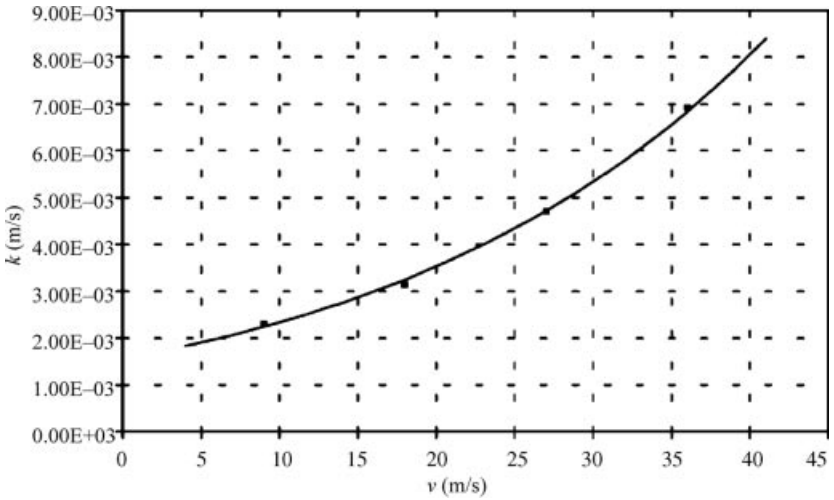


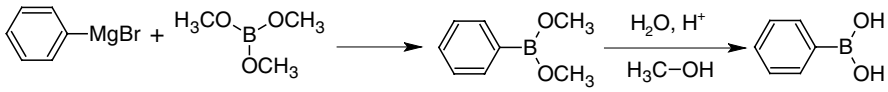
Figure 9.2 Interphase mass transfer coefficient obtained from reaction engineering model (by courtesy of Elsevier) [22].

Conversion to the mononitrated benzene derivative increased linearly with increasing flow velocity because of enhanced mass transfer. The formation of phenol by-products increased in the same manner for similar reasons. In turn, consecutive by-products, dinitrated aromatics, were formed in a linear decreasing fashion. This was explained by a mass-transfer-induced removal of the mononitrated product from the reacting slug.

In the last step, a reactor model was developed taking into account of both the mass transfer of organic components between the two phases and the homogeneous reaction within the aqueous phase, the latter relying on literature data [22]. From there, an extended kinetic model was developed and applied, considering the kinetics of the homogeneous side reactions as well [22]. With these efforts, the activation energies of these processes could be derived.

9.3.2
Phenyl Boronic Acid Synthesis

Clariant GmbH in Frankfurt, Germany, performed the synthesis of phenyl boronic acid from phenyl magnesium bromide and boronic acid trimethyl ester on a pilot-scale level [23].



This reaction suffers, like many organometallic reactions, from insufficient mixing because its reaction speed (at room temperature and below) is faster than the mixing times of many conventional mixer equipments. Thus, the reaction proceeds under nonstoichiometric conditions with timely and spatially changing concentration profiles, which promotes consecutive reactions. In addition, too long processing times, quite typical for batch reactions, favor side reactions such as oxidations and hydrolysis. This is solved in conventional processing by slowing down the reaction speed by virtue of cryogenic conditions, which reduces the impact of mixing and expands the mixing time scale so that selectivity is sufficient. For this purpose, cooling utilities that will add to the capital investment and make the process energy consumptive need to be installed.

For the microreactor process, a micromixer–tube rig was used with an interdigital mixer as a laboratory tool and a caterpillar mixer as a pilot tool [23]. The superior mixing of micromixers allows to perform the reaction at much higher reaction speed so that high selectivity of 90% could be demonstrated even at room temperature and above. This saves energy costs and also reduces the respective CAPEX (capital-related) investments. The crude yield was about 25% higher than that for the industrial batch production. The purity of the crude product was increased by about 10%. This had an impact downstream the reaction processing. Purification was simplified and could be achieved by means of crystallization only, whereas in the current industrial process energy-consumptive distillation is required (see Figure 9.3).

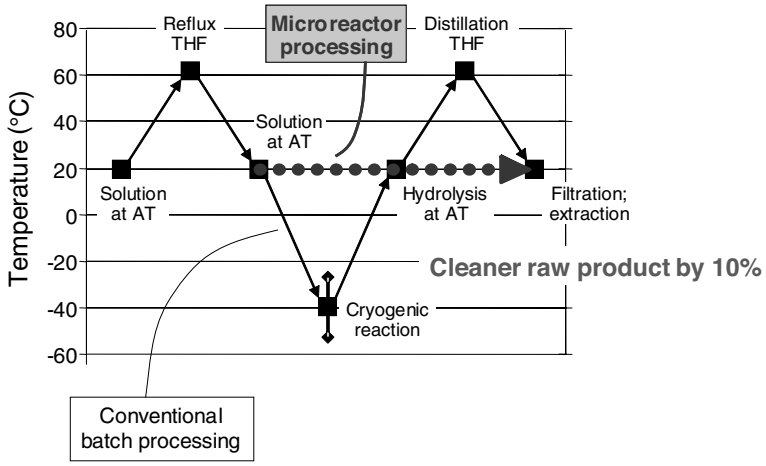
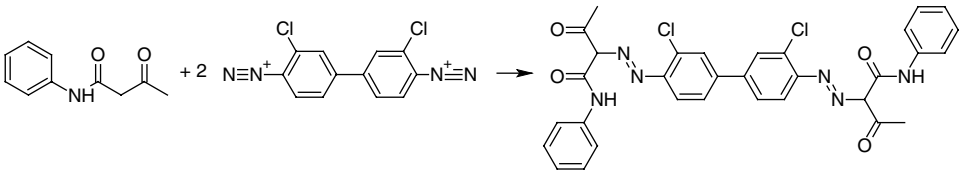


Figure 9.3 Temperature profile of the phenyl boronic acid synthesis along the major steps of the process flow scheme (AT: ambient temperature; THF: tetrahydrofuran). The difference in temperatures of the conventional batch and the microreactor processes stand for the reduction in energy consumption and respective heat transfer equipment when using the latter (by courtesy of ACS) [23].

9.3.3
Azo Pigment Yellow 12 Manufacture

Trust Chem Company in Hangzhou, China, was involved in the synthesis of the commercial azo pigment Yellow 12 [24].



Yellow 12

Particle synthesis, in general, forms products that differ in particle average size and distribution, shape, morphology, selectivity and many more properties. Mixing is the key step for particle seed formation and growth and can determine the above-mentioned product qualities. Owing to uniform concentration profiles and a good correlation between experiment and theory, product properties of particles made in microdevices are often superior and process development and upscaling can be faster and more predictable as compared to conventional technologies. In the ideal case of numbering up, the laboratory-scale performance is kept during piloting and production because the fluid dynamics are not changed or at least shift by analogy in a known manner.

The synthesis of the azo pigment Yellow 12 starts with a very fast precipitation and, consequently, is largely impacted by mixing in micromixers. Target of an investigation of the Trust Chem Company was to obtain narrow-sized crystals by microprocess technology. Using a laboratory-scale slit-type interdigital micromixer–reactor [24], smaller particles with a uniform size distribution were obtained for the commercial azo pigment Yellow 12 (see Figure 9.4) [24].

Related product properties are improved, for example, optical properties such as the glossiness and transparency (see Table 9.1). There are no negative consequences for dye manufacturing with the new microreactor made crystals, as the tinctorial power is the same as for conventional synthesis. Tinctorial power is a measure for the adhesion of the pigment to wool stuff or similar material. The intensification in coloration properties means that the same amount of material can be treated now with less amounts of the Yellow 12 azo pigment that reduces materials costs and increases the profitability of the pigment manufacture.

9.3.4
Desymmetrization of Thioureas

At the early stage of microreactor development, Merck AG in Darmstadt, Germany, and the University of Chemnitz, Germany, performed an industrial study on the general applicability of microreactors towards organic synthesis for pharmaceutical applications, aiming at performing combinatorial chemistry by microflow processing

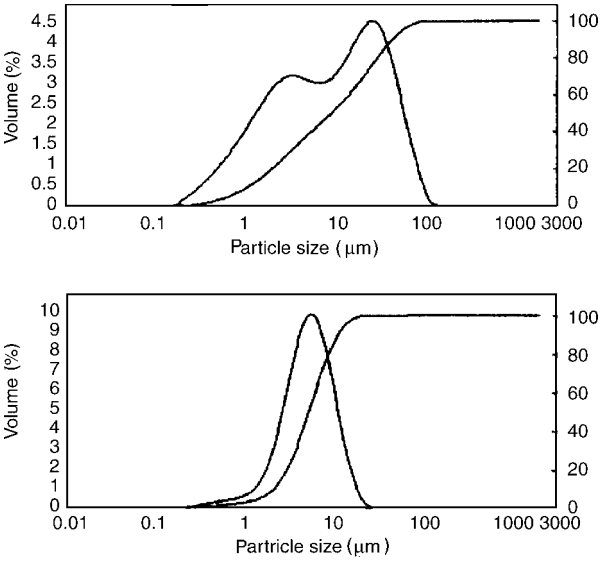


Figure 9.4 Particle size distribution of the batch (top) and the micromixer-based synthesis (bottom) of Yellow 12 (by courtesy of ACS) [24].

in the long run [25]. The scouting studies focused on determining suitable reaction parameters and to show basic feasibility, that is ability to reach yields similar to batch processes.

With the use of a micromixer/commercial tube reactor, the synthesis of a thiourea from phenyl isothiocyanate and cyclohexylamine at 0 °C was carried out [25].

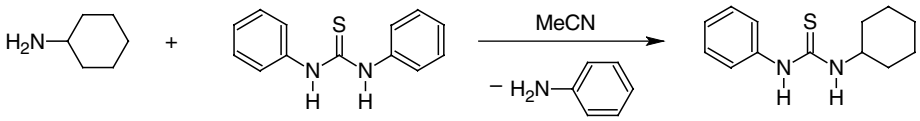
A single mixing device connected to a stainless steel tube of about 10 m length and 0.25 mm diameter was used [25]. The feasibility of performing a nearly spontaneous reaction could be shown. Further studies on the desymmetrization of thioureas showed that for the diphenyl thiourea/cyclohexylamine system reasonable reaction

Table 9.1 Glossiness of the imprinted color (GU = glossiness units) for micromixer-based and conventional Yellow 12 pigment manufacture.

No.	Micromixer (10 ml/min)/GU	Micromixer (30 ml/min)/GU	Micromixer (50 ml/min)/GU	Yellow 12 standard/GU
Mean	40.9	47.1	51.0	29.4
σ	1.8	1.4	1.3	1.8

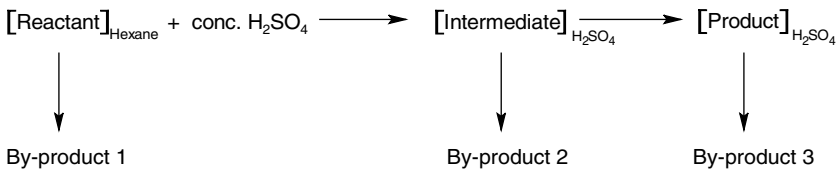
(From [24]). σ: standard deviation.

rates and conversions could be achieved [25, 26] as the short use of high-temperature operation up to 91 °C, exceeding the boiling point of the solvent (acetonitrile), was the key for this reaction that can be easily accomplished in microreactors.



9.3.5
Vitamin Precursor Synthesis

BASF in Ludwigshafen, Germany, carried out process development for a reaction as part of a multistep process finally yielding a vitamin [27, 28]. This concerned short-temperature processing (<4 s) that was simply 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 than after entering the subsequent heat exchanger. The temperature rise led to side reactions reducing the yield.



The reactants and the product were not disclosed in the open literature [27, 28]. Concentrated sulfuric acid is present in quantitative amounts besides the organic solvent so that a liquid/liquid process results. The reactant forms quickly an intermediate that again quickly reacts to the product. Thermally induced side reactions occur at each stage.

A maximum yield of 80–85% was obtained at 4 s residence time and a temperature of 50 °C by microreaction system processing [27, 28]. The use of ordinary lab processing with standard lab glassware yielded only 25%. The continuous industrial process had a yield of 80–85%; the former employed with semibatch industrial process gave 70% yield. The temperature and the residence time of industrial and microreactor continuous processing were identical.

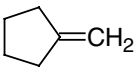
9.3.6
Ester Hydrolysis to Produce an Alcohol

Sigma–Aldrich in Buchs, Switzerland, performed an ester hydrolysis to produce an alcohol that decomposes quickly. None of these compounds could be disclosed [4]. Scale-up could not satisfy the commercial interest in the labile product, as the yield decreased strongly with batch vessel size. Seventy percent yield was found at 5 l scale, 35% at 20 l and 10% at 100 l.

The investigation in a microreactor was initially hampered by the presence of an insoluble compound for the ester process [4]. Because this reactant had to be changed, a process development study had to be carried out. A model reaction, an ester hydrolysis yielding a stable alcohol, was used instead of the real one in order to facile the process development. Twelve different conditions were run. Having acquired the process know-how, the same kind of process development was done for the real reaction in only 2 h with success.

9.3.7
Synthesis of Methylenecyclopentane

Methylenecyclopentane was synthesized by Sigma–Aldrich in Buchs, Switzerland, using an undisclosed route [4].



The reaction is highly exothermic, which makes scale-up difficult [4]. In addition, 30% of the yield is the thermodynamically stable side product 1-methylcyclopentene. Product and side product are difficult to separate. Both unsolved issues led to a stop in process development using conventional technology.

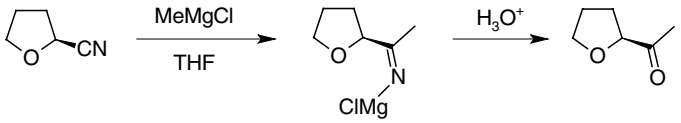
With the use of microreactor processing, 70% conversion was achieved that gave only product and no side product [4]. Actually, the microreactor conversion is lower than the conversion for batch, but the former is now the preferred route as the separation of the product from the reactant can be accomplished, whereas product, as mentioned, can be hardly purified from the side product. A throughput of 300 g/h was achieved.

9.3.8
Condensation of 2-Trimethylsilylethanol

Sigma–Aldrich in Buchs, Switzerland, performed the condensation of 2-trimethylsilylethanol and *p*-nitrophenyl chloroformate to give 2-(trimethylsilyl)ethyl 4-nitrophenyl carbonate [4]. Reduction of residence time is the issue to high selectivity, as the product degrades and side products also form. In contrast to the conventional technology that needs 14 h to accomplish the reaction, a microreactor that enhances selectivity accomplishes the same in about 18 min. The reason for the better microreactor performance is not detailed and if the process parameters (e.g. temperature) were changed.

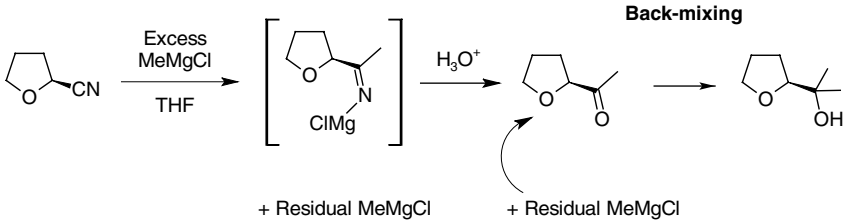
9.3.9
(*S*)-2-Acetyl Tetrahydrofuran Synthesis

SK Corporation in Daejeon, Korea, performed the synthesis of (*S*)-2-acetyl tetrahydrofuran with an alkylating step using a Grignard reaction and a hydrolysis step finally yielding a ketone moiety in the side chain starting with a cyano group [29].



The methylating agent MeMgCl is very reactive, even when compared to other Grignard reagents, and thus not easy to handle at large scale; this can also substantially cause safety and hazardous issues [29]. The microreactor allowed the minimization of moisture and oxidizing effects due to encased processing at low degree of contamination of decomposing species for Grignard reactants.

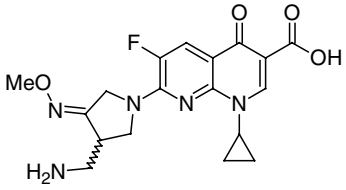
Overalkylation can lead to tertiary alcohol formation by consecutive reaction [29]. Product quality demands to keep this impurity level <0.2%. Microreactor operation yielded the overalkylated alcohol follow-up product at 0.18%, whereas level of impurity for the batch process was 1.56% [29]. The reason is probably the lower back-mixing in the microflow system, with concentration profiles being less deteriorated from ideal; that is, no excess of alkylating agent is generated locally to promote the follow-up reaction.



The α-hydrogen of the reactant is unstable under the basic reaction conditions applied, leading to a small degree of racemization [29]. Conservation of stereochemistry was largely achieved by microreactor operation; 98.4% enantiomeric excess (ee) was found as compared to 97.9% ee at batch level (see Table 9.2).

9.3.10
Synthesis of Intermediate for Quinolone Antibiotic Drug

LG Chem in Daejeon, Korea, performed the multistep synthesis of Gemifloxacin (FACTIVE), a quinolone antibiotic drug with enhanced activity against G(+) bacteria [30]. This drug has high activity against G(−) bacteria, atypical strains and major respiratory pathogens.

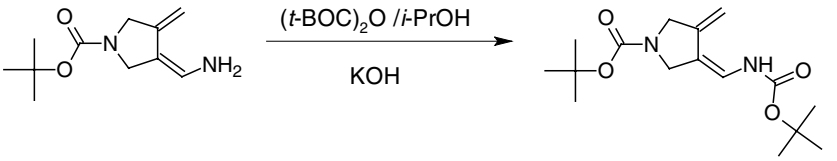


Gemifloxacin (FACTIVE)

Table 9.2 Impurity and optical purity of the batch and microreactor processes in the (*S*)-2-acetyl tetrahydrofuran synthesis [29].

	Impurity (%)	Optical purity (%)
Batch	1.56	97.7
Microreactor process	0.18	98.4

In one reaction step, the enamine moiety is protected by the *t*-Boc group in a fast and highly exothermic ($\Delta H = -213$ kJ/mol) reaction [30].



A consecutive reaction occurs with higher rate constant and higher activation energy, thus getting more dominant at higher temperatures [30]. The impurity level generated by the consecutive step becomes too high at temperatures >25 °C. This can be minimized by effective heat removal of the exothermic reaction. In addition, the product can react with KOH so that efficient mixing is required that avoids spatially strong varying concentrations of reactants. For similar reasons, it was speculated that narrower residence time distribution could increase selectivity.

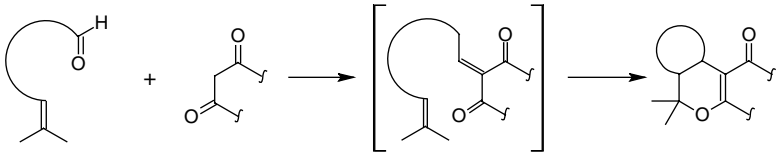
A slit-type interdigital micromixer was used for fast mixing [30] and compared to a tubular reactor and five Kenics mixers connected in series. Details on further components of the micromixer rig were not given, but most likely a capillary reactor was added for efficient heat exchange.

Mixing is essential to achieve dispersion of the two-phase mixture. For the tube reactor (without mixing function), the flow had to be very high to achieve turbulence ($Re > 2000$) and in this way to serve for dispersion [30]. As a result of the high flow rate, residence time was too short to complete reaction and only 27% conversion was achieved. At lower flow rate, phase separation occurs. An extrapolation of the reactor length for complete conversion comes to an impractical tube length of about 2 km. The combination of five Kenics static mixers guaranteed good mixing over an extended length so that a conversion of 97% was achieved as a result of the micromixer. The microreactor used has good mixing and was also able to remove the heat of reaction. No by-products were formed at conversions as high as 96%. Thus, although the microreactor performance in terms of selectivity is equal to that of the static mixers, it has the advantage of operation at ambient reaction temperature of 15 °C, whereas the latter need outside cooling of 0 or −20 °C because of the necessary heat removal.

9.3.11
Domino Cycloadditions in Parallel Fashion

GlaxoSmithKline Pharmaceuticals in Harlow, UK, investigated domino cycloadditions in a commercial chip and extended their process development by operation in

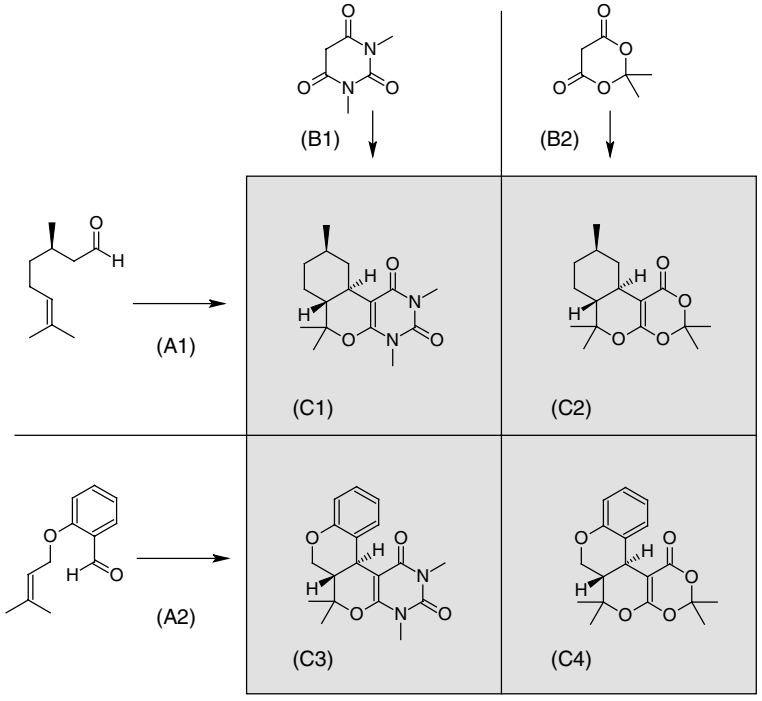
parallel fashion in a three-member array, which was one of the first examples of a parallel multireaction in microreactors [31].



(A) (B) (C)

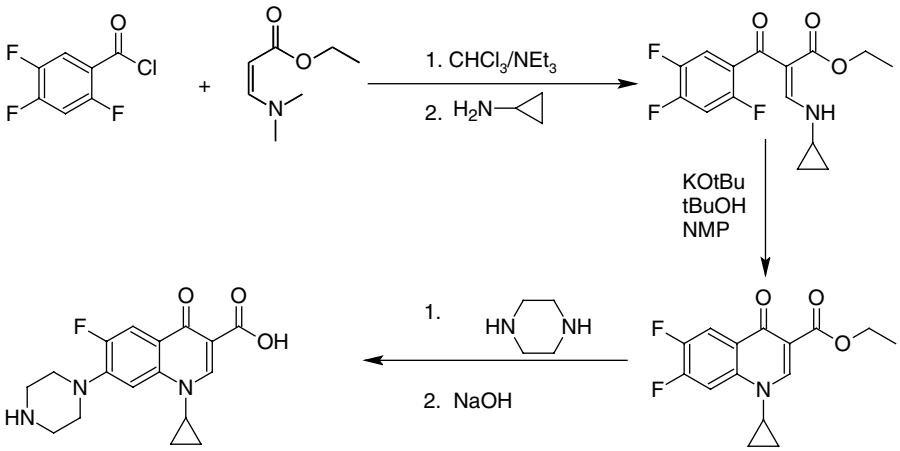
The domino reaction consists of a Knoevenagel condensation giving an intermediate that immediately undergoes an intramolecular hetero-Diels–Alder reaction with inverse electron demand [31]. As aldehydes, *rac*-citronellal, an aromatic aldehyde, and two commercially available 1,3-diketones, 1,3-dimethylbarbituric acid and Meldrum's acid, were selected. By combinations of these reactants, different cycloadducts were generated.

Process development was accomplished in single-run reactions [31]. The conversion of the microchannel processing typically amounted to about 50–75%, depending on the nature of cycloadduct and the residence time chosen, and was comparable to batch syntheses results [31]. By combinations of aldehydes and 1,3-diketones, different cycloadducts were generated simultaneously in one run on one chip, that is, an undesired transfer of solutions from one channel to another by imperfect sealing between these channels. The conversions were comparable to the single runs, with one exception. Also, cross-contamination was observed. It ranged from a few percent to about 50%.



9.3.12
Ciprofloxazin Multistep Synthesis

The synthesis of ciprofloxazin was one among several syntheses being performed in contract research by a microreactor developer for pharmaceutical industry and feasibility was demonstrated [32]. In this multistep synthesis, alkylamino-defluorinations were the essential part of the chemistry. Ciprofloxazin, the final product, is an antibiotic compound with a high sales volume.

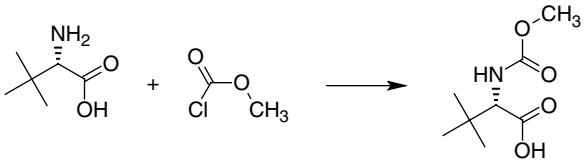


Ciprofloxazin

This reaction scheme involves two substitutions of fluorine moieties at the aromatic ring by amines, yielding the final product for pharmaceutical applications [32, 33]. All in all, five synthesis steps are actually required and performed subsequently in a microreactor system to get the target molecule.

9.3.13
Methyl Carbamate Synthesis

The Chemical Development & Drug Evaluation branch of Johnson & Johnson Pharmaceutical Research & Development LLC in Raritan, USA, performed the exothermic reaction of methyl chloroformate with amines to methyl carbamates [34]. Owing to large heat release, hot spots occur. For the reaction of *N*-methoxycarbonyl-L-*tert*-leucine with methyl chloroformate to the amino acid derivative, it is even observed at laboratory scale.



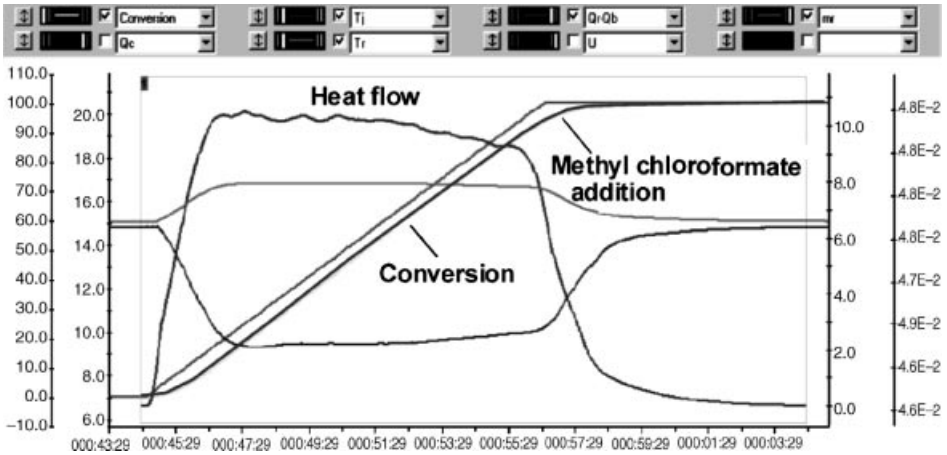
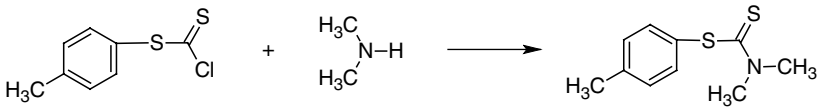


Figure 9.5 Reaction calorimetry results from the addition of methyl chloroformate (slight excess) to L-*tert*-leucine (by courtesy of ACS) [34].

Calorimetric measurements show that the addition is exothermic [34]. The heat release rate is mainly feed controlled, as the square shape of the heat flow curve demonstrates (see Figure 9.5). Whenever feed is added, the heat flow responds without delay.

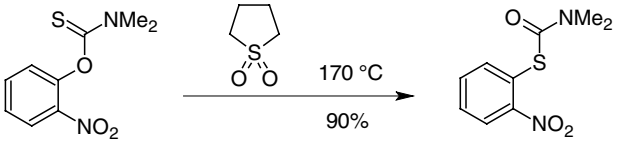
In case of complete malfunction of cooling and stirring systems, the temperature may exceed the solvent reflux temperature [34]. Accordingly, a slow dosing of the methyl chloroformate is necessary to have control over the heat release. After having determined the reaction parameters at 1 g scale, the reaction was carried out in a microreactor with 91% yield at 7 min residence time. More than 1 kg of *N*-methoxycarbonyl-L-*tert*-leucine was prepared within 12 h.

Scale-up by using a microreactor was also done for the amidation of *p*-tolyl chlorodithionoformate with dimethylamine to *p*-tolyl dimethyldithiocarbamate without further safety precautions at 96% yield that is comparable to the batch process [34]. At 1.4 min residence time, a capacity of 155 g/h was achieved.



9.3.14
Newman–Kuart Rearrangement

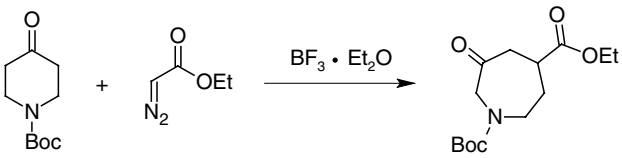
The Chemical Development & Drug Evaluation branch of Johnson & Johnson Pharmaceutical Research & Development LLC in Raritan, USA, tested microreactors for processes at elevated temperatures above the limit of most multipurpose conventional reactors, which is above ~140°C [34]. Operation above this limit is only possible by means of special reactors equipped with heat transfer units.



The Newman–Kuart rearrangement is an example of a high-temperature reaction [34]. With the use of a microreactor, the reaction temperature could be extended up to 200 °C. *O*-(2-Nitrophenyl)-*N*,*N*-dimethylthiocarbamate was converted to *S*-(2-nitrophenyl)-*N*,*N*-dimethylcarbamothioate at 170 °C in 14 min at 90% yield. Quantitative conversion with a throughput of 34 g/h was achieved with sulfolane as solvent at the same temperature and reaction time.

9.3.15
Ring-expansion Reaction of *N*-Boc-4-piperidone

The Chemical Development & Drug Evaluation branch of Johnson & Johnson Pharmaceutical Research & Development LLC in Raritan, USA, investigated the ring-expansion reaction of *N*-Boc-4-piperidone with ethyl diazoacetate in a microreactor system as an example of processing hazardous substances [34].



A crude yield of 90% was obtained in ether at −25 °C. When performed in a batch mode on 70 mg scale, no safety issues were taken and an 81% yield was obtained [34]. Reaction calorimetry reveals a very exothermic reaction after feeding and subsequent mixing with an initiation period; that is, the response of the heat flow curve is delayed by about 1 min as compared to that of the feed curve (see Figure 9.6). Therefore, the heat release rate with this mode of addition is not feed controlled. The reaction is very sluggish because the reaction occurs at a single blow as soon as 60% of the material has been added. Calculating the worst-case temperature rise shows that the reaction would rapidly increase with temperature and can approach the solvent reflux temperature, possibly throwing out the reaction mixture in case of cooling or stirring malfunction. This would particularly include the full accidental release of all the $BF_3{\cdot}Et_2O$.

The calculated worst-case temperature of 45.6 °C also approaches the reflux temperature of the solvent (diethyl ether) but does not reach the decomposition temperature of ethyl diazoacetate [34]. Furthermore, the evolution of large amounts of nitrogen gas during the reaction could lead to an overpressurization of the reaction vessel. All these reasons together prevented a scaling of the ring-expansion reaction to kilogram scales as a result of the related safety issues. Operating the microreactor

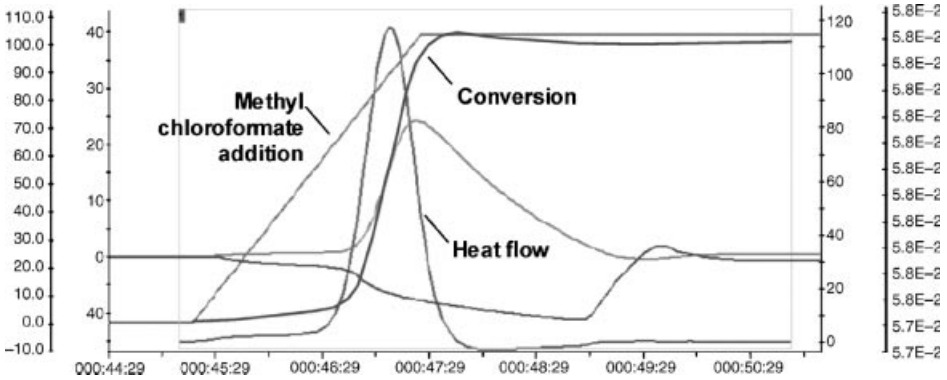
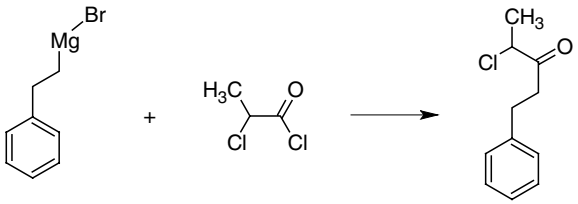


Figure 9.6 Addition of $BF_3{\cdot}Et_2O$ to *N*-Boc-4-piperidone and ethyl diazoacetate (by courtesy of ACS) [34].

system, however, allowed without any further optimization a precise control of the reaction, and 89% yield was obtained. Reaction time was only 1.8 min with a throughput of 91 g/h.

9.3.16
Grignard and Organolithium Reagents

Lonza in Visp, Switzerland, performed the reaction of an acid chloride with phenylethyl magnesium bromide in THF in a multiple-injection microreactor [35]. Many injection points were chosen to split and delocalize the reaction and heat release so that several small hot spots arise instead of having one large hot spot ($\Delta H = -260$ kJ/mol, $\Delta T_{\text{adiabatic}} =$ about 70 °C). The reaction is quenched at the reactor outlet with water.



The reaction performance was given for mixers with one to six injection points (see Figure 9.7) [35]. A considerable increase in yield from 21 to 38% can be seen.

In another process optimization step, the cooling was further improved (from 'sufficient' to 'efficient') by using a lower temperature of the cooling liquid, with 0 °C instead of 20 °C [35]. In this way, a yield of 39% was obtained with only three injection points, thus reducing the complexity of the microdevice and pressure drop (see Figure 9.8).

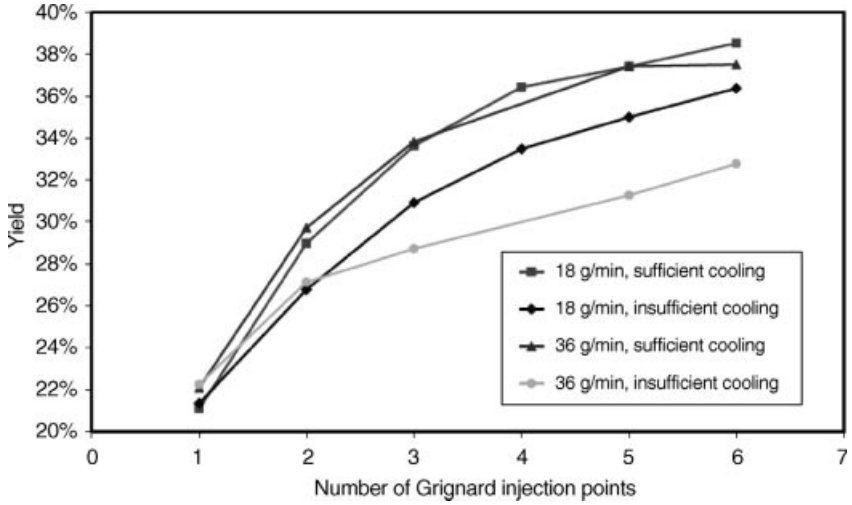


Figure 9.7 The impact of number of injection points and cooling on the yield of the reaction of an acid chloride with a phenylethyl Grignard reagent (by courtesy of D. Roberge/Lonza) [35].

The Chemical Development & Drug Evaluation branch of Johnson & Johnson Pharmaceutical Research & Development LLC in Raritan, USA, used the reaction of the Grignard reagent 3-methoxyphenylmagnesium bromide and a ketone to obtain the product Tramadol. *Cis*- and *trans*-isomers are formed in about 4 : 1 ratio [34]. The

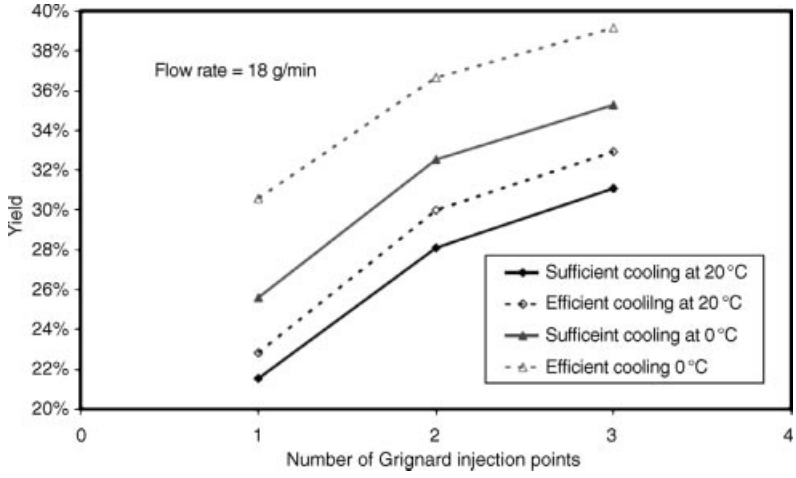
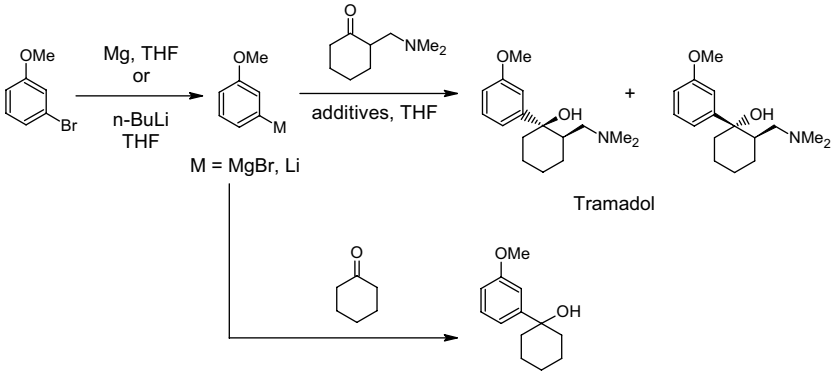


Figure 9.8 The impact of improved cooling on the yield of the reaction of an acid chloride with a phenylethyl Grignard reagent (by courtesy of D. Roberge/Lonza) [35].

organometallic compounds formed are unstable intermediates and are sensitive to moisture.



The use of aryllithium instead of the Grignard reagent resulted in a higher ratio of *cis*-isomer formation [34]. In reaction calorimetric studies, it was found that both steps, the formation of 3-methoxyphenyllithium and its addition to ketone, are pretty exothermic with worst-case temperature rises of up to 62 and 133 °C, respectively. The lithium intermediate has to be kept at very low reaction temperatures to prevent decomposition. We concluded that a continuous reaction may be a good alternative to batch synthesis to improve the reaction yield and to minimize the safety concerns because of the exothermicity of the reaction sequence.

3-Methoxyphenyllithium and cyclohexanone were reacted in a batch mode at −10 and −65 °C to give yields of 32 and 80%, the expected tertiary alcohol, respectively [34]. Such temperature effect was also planned to be used in the microreactor. The metal–halogen exchange step could be performed at −14 °C with 17 s residence time and the lithium intermediate further reacted with cyclohexanone in batch mode at −40 °C. Lower temperatures were not possible because of chiller limitations, and the availability of only one microreactor accounted for the combined continuous flow–batch processing. In this way, a yield of 87% yield at a throughput of 54 g/h was achieved.

9.4
Pilots Plants and Production

9.4.1
Hydrogen Peroxide Synthesis

$$H_2 + O_2 \rightarrow H_2O_2$$

The process developing Company UOP LLC in Des Plaines, USA, searched for direct routes for hydrogen peroxide manufacture from elementary hydrogen and oxygen by microprocess technology that almost under all process conditions inevitably involves processing in the explosive area [36, 37]. The better use of raw

materials and less technical expenditure owing to process simplification are the advantages of the direct over the indirect routes. The few process windows out of the explosive range need large dilution and/or multistep processing with the addition of intermediates as carriers for oxygen, such as the anthraquinone route.

On the contrary, operation in the explosive area ('New Process Windows') benefits from higher space–time yield because elevated temperatures, pressures and reactant concentrations are used [36, 37]. This is enabled by the higher safety potential of microreactors, which are less accident-prone by thermal runaway because of enhanced heat transfer and also do not allow uncontrolled, ever increasing radical chain propagation by providing an even high rate of radical quenching at the large surface area of the channel walls [38]. Owing to the latter flame-arrestor effect that is intrinsic to the devices, the term 'inherently safe' was assigned. However, this only refers to the device inner volume and is a theoretical term. For example, walls between microchannels may break under very high pressure shock waves or other similar incidents may occur so that a dimensional increase above the safety threshold may occur. Still, a practical safety evaluation needs to be done, and safety issues are different in the interconnections and fluid distributions to the device, which holds even more in the plant peripherals. Thus, although the intrinsic safety of the microchannel on a device level can be assumed in a theoretical manner, the same feature of the microprocess technology as a whole has to be verified and authorized for each chemical process. Despite these issues, advantages remain because of faster safety approval.

On the basis of this information, a process flow based on a mini-trickle-bed operation was developed where a premixed gas mixture of hydrogen and oxygen (without inert gas) was dispersed with an aqueous solution flowing through the interstices of a catalyst bed [36, 37]. Experimental investigations were first done at a laboratory level using slit-type high-pressure interdigital micromixer connected to a cartridge filled with catalyst. Special procedures and plant details were developed and added to have safety on a process level and to encounter typical failure situations such as total oxidation taking place outside the catalyst cartridge with water as heat absorbing medium.

The direct contact of hydrogen and oxygen offers other advantages besides having high concentrations and high reaction rates [36, 37]. Explosive regime mixing allows to generate hydrogen/oxygen mixtures in a stable and reliable manner. This will transfer the noble metal catalyst into a partially oxidized state that will then generate hydrogen peroxide with high selectivity. In the fully oxidized or fully reduced state of the catalyst, either only water is formed or no reaction is achieved, respectively.

Operation of this process at only 20 bar and the use of oxygen/hydrogen ratios close to 1 : 1 were considerably improved [36, 37] compared to processes from the patent literature [39, 40]. For oxygen/hydrogen ratios of 1.5–3, a selectivity as high as 85 at 90% conversion and a space–time yield of 2 g hydrogen peroxide per gram of catalyst per hour was achieved, exceeding industrial benchmarks from patent literature at that point of time. These laboratory experiments were followed by pilot tests that resulted in a basic engineering design for the production of about 150 000 t hydrogen peroxide per year.

FMC Corporation in Princeton, USA, one of the largest producers of hydrogen peroxide, works with Stevens Institute in Hoboken, USA, in a publicly funded project

for the on-demand production of hydrogen peroxide in a microreactor at end-user sites [1, 41]. Although today's hydrogen peroxide is mainly produced as a concentrated solution (70% in the anthraquinone process), many user applications demand solutions <15% so that dilution is common, and this overrides the efforts made by the energy-consumptive distillation to yield concentrated solutions. FMC summarizes the prospects of a direct microreactor route for on-site production to reduce transportation and storage costs as well as 'concentration–dilution' costs. To target the safe operation in the explosive regime, a low-pressure and energy-efficient process is designed. Solvent processing, gas recycling and treatment, and product purification are avoided as compared to the commercial anthraquinone process. The initial goal is to achieve the production of a 1% solution at laboratory scale and to transfer this to an on-site production scale within 5 years.

Hydrogen peroxide was generated in a microreactor in a gas–liquid–solid process with direct mixing of hydrogen and oxygen (using air), a liquid solvent and a solid catalyst [41], which included operation in the explosive regime. The particles of the self-developed platinum group catalyst supported on an oxide were packed in the microchannel. In addition, sol–gel wall coatings were adhered to the microchannels, and cellular structures were formed by different deposition routes involving closed-channel flow coating, open-channel surface-selective and dip coating methods. Using moderate pressure and temperature, the residence time could be decreased by almost two orders of magnitude as compared to the conventional reactors. The hydrogen peroxide concentrations were within the industrial relevant range. On the basis of the identification of the elemental reactions involved, a study of the reaction mechanism was done to determine the kinetics. Following the laboratory studies, an optimized process analysis, design and simulation was developed for a pilot plant comprising a multichannel, multilayered microreactor system built by Chart Energy and Chemicals in The Woodlands, USA (Figure 9.9). First runs proved the production of hydrogen peroxide in an industrial relevant range.

9.4.2
Diverse Case Studies at Lonza

Lonza Ltd in Visp, Switzerland, reported several further process developments [35]. For an organolithium exchange reaction up to 250 kg of product was obtained in a few weeks of operations using a Corning multi-injection reactor. At the end of the campaign, the reactor was cleaned by standard procedure and used again for a new project. For an organolithium coupling reaction, several kilograms of product were obtained by continuous operation for 1 week. The Corning multi-injection reactor as well as the Corning single-injection reactor was used for validation. In a nitration reaction, a few kilograms of product were obtained in 24 h operation using the Corning multi-injection reactor.

With the use of dedicated reactor technology, chlorination was carried out in a falling-film reactor that has a highly exothermic reaction ($\Delta T_{adiabatic} > 250\,^{\circ}C$) [35]. Dehydrogenations were done using a heterogeneous catalyst filled in a tubular packed bed at high temperatures above 500 °C. An organolithium coupling reaction was made in a small CSTR reactor to avoid reactor plugging.

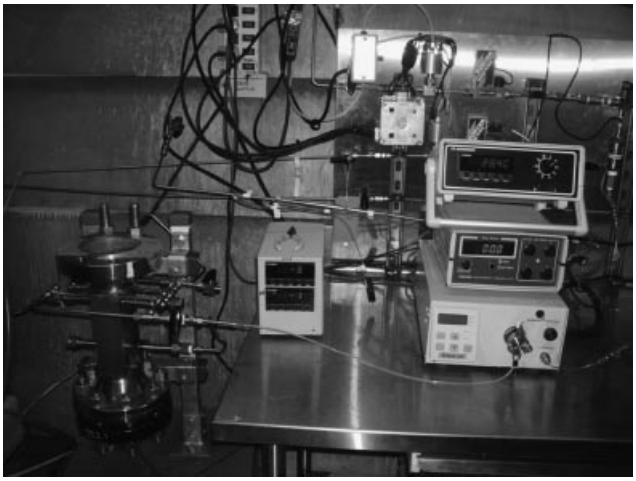


Figure 9.9 Hydrogen peroxide synthesis pilot microprocess plant by courtesy of FMC Corporation in Princeton, USA, and Niyi Lawal/Stevens Institute) [41].

A so-called continuous launch production unit R-01 was built with a capacity in the range of 150 kg/h and designed as a multipurpose system (see Figure 9.10) [35]. Conventional technology such as static mixers, mini-heat exchangers and so on was used following experience with microprocess technology. Such devices are the mesoscale extension of microdevices, albeit not always using the same mixing and heat exchange principles. Several campaigns were performed with in-between cleaning for the following reactions. Tons of products were made using the

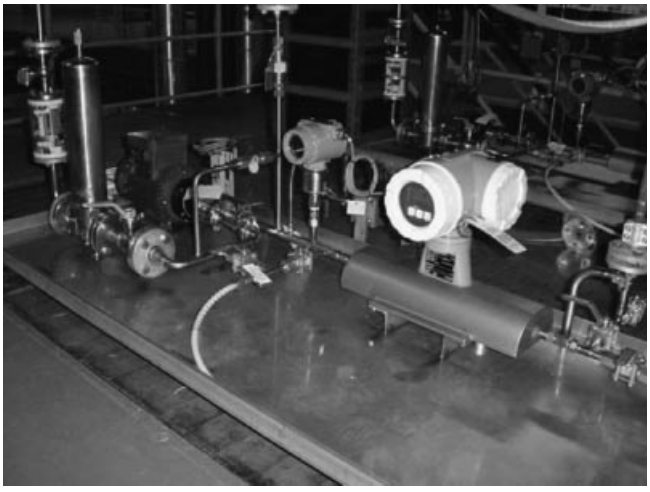
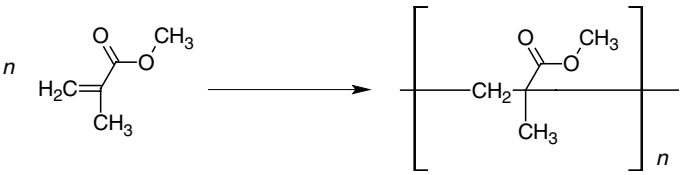


Figure 9.10 Continuous launch production unit R-01 at Lonza (by courtesy of D. Roberge/Lonza) [35].

Simmons–Smith reaction, and the production ran over weeks. A static mixer with conventional minitube heat exchangers was used. A similar amount of material was produced by an organolithium coupling reaction using a static mixer in an adiabatic regime.

9.4.3
Polyacrylate Formation

Axiva in Frankfurt, Germany (now Siemens-Axiva), performed the radical solution polymerization of acrylate resins using micromixer–tube reactors [42].



This reaction includes modified acrylates with or without the addition of styrene derivatives in combination with one or more initiators in a solent [43]. In the molecular weight distribution of the polymer obtained in the micromixer, no high molecular weights above a mass of $>10^5$ that are usually insoluble were found [42, 43]. As a result, no precipitates are formed on the surface of the microchannel despite the large surface-to-volume ratio (see Figure 9.11). In contrast to this result,

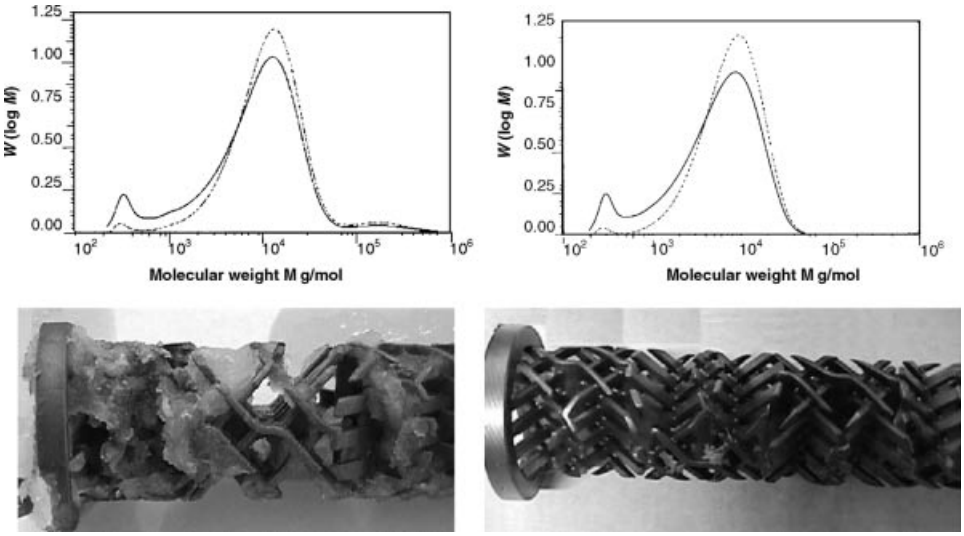


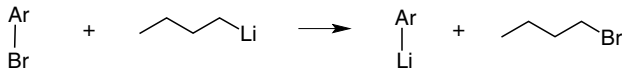
Figure 9.11 Radical polymerization of acrylates using a static mixer–reactor without (left) and with (right) a micromixer as premixer. Top: molecular weight distribution; down: appearance of the static mixer to illustrate the degree of fouling (by courtesy of Springer) [42].

polymer samples taken from conventional processes without micromixer displayed a small but significant fraction of high molecular weight polymer with a mass $>10^5$ (see Figure 9.11) [43]. Here, in some cases heavy precipitation occurred, resulting even in plugging of the static-mixer internals of the tube reactors [42].

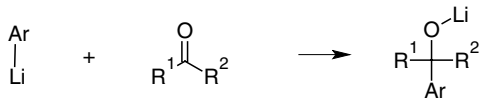
A micromixer-based laboratory plant would give 50 t/a, when assuming an annual operation time of 8000 h. On the basis of these laboratory experiments, a prebasic design comprising numbering up of 28 micromixers and 4 tube reactors was proposed [42]. Accordingly, the production of such plant was calculated to be in the order of 2000 t/a, when assuming 8000 h operation.

9.4.4
Butyl Lithium-based Alkylation Reactions

Lonza Ltd in Visp, Switzerland, developed at the beginning of the 1990s a process for the halogen exchange of a brominated aromatic compound with butyl lithium followed by the C−C coupling to a ketone [44].



Intermediate



Intermediate

The lithium intermediate is unstable, even at temperatures as low as −60 °C. Only a continuous process with a short residence time between the two reactions was allowed to avoid decomposition and have sufficient selectivity for an economical process [44]. Clogging is a major issue for the first process. Owing to heat release issues, high dilution is applied, and the recycling of the solvent was an important issue that needed to be considered.

The first reaction is highly exothermic with an adiabatic temperature rise >100 °C (classified as Type A in [45]), whereas the second reaction is only slightly exothermic with an adiabatic temperature rise <30 °C (this follows a classification given in [45]: Types A and B, respectively) [44]. Despite the latter, the second reaction is accompanied by the formation of large amounts of side products at long residence times >1 min, which almost excludes batch processing here. A conventional continuous system, a static mixer with much shorter residence times, was successfully used. The first reaction can be performed batchwise because the lithium intermediate is stable for a few hours. Still, a stop of production for several hours would lead to a significant loss of product.

Thus, it is more flexible to run both reactions continuously [44]. A microreactor is used for the more demanding, highly exothermic reaction, whereas a static mixer is sufficient for the second reaction. After laboratory process development, a pilot phase

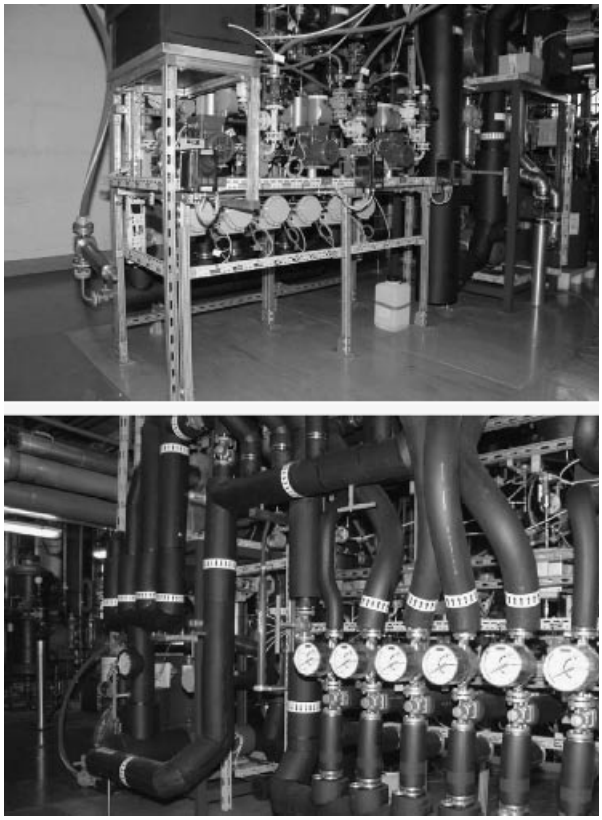


Figure 9.12 Lonza c-SSP with combined microreactor and conventional technologies (static mixers), process view (top) and service view (bottom) (by courtesy of PharmaChem/B5Srl) [44].

in the so-called continuous small-scale production (c-SSP) comprising microreactor technology followed (see Figure 9.12). The c-SSP plant is a multipurpose and modular approach and can operate from cryogenic to high temperature.

The c-SSP plant typically operates at a total flow rate of 100 g/min that relates to 70 kg product/week of product [44]. This gives sufficient material for preclinical studies or phase I clinical trials during a typical pilot campaign cycle time, which is 1–2 weeks (see Figure 9.13). The c-SSP plant qualified for c-GMP (GMP: Good Manufacturing Practice; guidelines for quality management for production processes and environment not only in the fields of pharmaceutical and medicinal products but also in food and animal feed industry) and meets the ATEX ('Atmosphère Explosible'; stands for two guidelines given by European Union in the field of explosion prevention) standards. The microreactor for cryogenic operation is insulated in the black box unit, as shown in the upper image of Figure 9.12. The alkyl lithium process was performed at multiple kilogram scale, was safe and led to a yield increase.

Methodologies for scale-out to phase II–III clinical trials are also given in Figure 9.12 [44]. One approach would be to scale up the c-SSP using static mixers and mini-heat exchangers, which are already in operation at Lonza. The possible

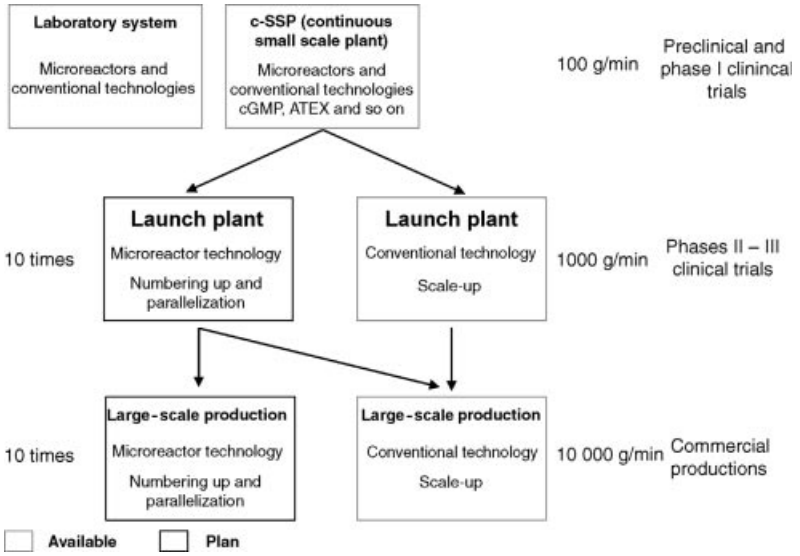


Figure 9.13 A schematic representation with typical process steps in the fine chemical and pharmaceutical industries and recommendation when to use microreactor technology or continuous processes based on a multipurpose approach (by courtesy of PharmaChem/B5Srl) [44].

flow rate of 1500 g/min is 10–15 higher than that of the c-SSP. Another approach is the replication of the laboratory system in a few number of identical base units (numbering up). A maximum of 10 base units is estimated for sufficient throughput to supply phase II–III clinical trials or quantities in the range of a few tons. The technical transfer would be more rapid than done conventionally, and scale-up issues would be avoided especially with exothermic reactions.

For commercial production, other issues arise [44]. Among these, the production cost is the key driver, as this last step in process development increasingly consumes large resources because of a number of additional tasks (scale-up, supply chain, waste management, ecology, location, etc.). The specific microreactor-related advantages such as speed in process R&D and avoidance of scale-up issues have not the same importance here as in the clinical productions. Thus, microprocess technology is here in competition to other technologies and one advantage may not be enough, as a highly complex scenario has to be considered.

9.4.5
German Project Cluster 2005

In 2004, the Federal Ministry of Education and Research (BMBF) gave microprocess engineering a research priority under its frame program 'Microsystems' [46]. In 2005, six industrial cooperation projects were launched, supervised by the funding agency VDI/VDE-IT, which are described in detail in the following. The target is the development of pilot plants for different reactions in several application fields for

demonstration of the technical and economic feasibility. A further comprehensive project was started to enable small- and medium-sized enterprises to judge if their processes are technically feasible and economic by microprocess engineering. This is done by means of compilation of a compendium. This research project cluster is accompanied by a similar education and training project cluster that aims to educate researchers with the specific skills and know-how necessary in the field. The education cluster is jointly initiated and funded by the Federation of the Chemical Industry (VCI), the German Federal Foundation for the Environment (DBU) and the Ministry of Education and Research (BMBF). Eight new projects have been started to develop educational courses and to equip universities and advanced technical institutes with educational devices.

9.4.6
Development for OLED Materials Production

Within the German public funded project POKOMI a microreactor-based pilot plant for the synthesis of polymeric, light-emitting semiconductors for use in displays (OLED materials) is developed [47]. COVION GmbH in Frankfurt, Germany, is a producer of these materials and the other partners are mikroglas chemtech GmbH, hte AG, IMM GmbH, Stiftung caesar and JUMO GmbH.

The microreactor plant will be equipped with the process control and online analysis [47]. The Suzuki coupling reaction is investigated as a common synthetic route for polymeric semiconductors. The transfer of the developed microflow process into chemical production is accompanied by economic and ecologic evaluations.

9.4.7
Development for Liquid/Liquid and Gas/Liquid Fine Chemicals Production

Within the German public funded project μ.PRO.CHEM, a concept for a continuously operated modularly assembled flexible pilot plants for highly exothermic two-phase liquid–liquid or gas–liquid reactions will be developed and validated [48]. The plant features process intensifying microprocess technologies. A goal of the project is the demonstration of the technical and economic feasibility of the plant concept on pilot scale with selected model processes.

The use of microprocess technology is to overcome limitations in mass transfer through large specific interfaces and in heat transfer that so far prevented using higher conversion rates and selectivity by process intensifying measures (e.g. higher temperatures or pressures). Retrofit of existing pilot plants and classical production plants with the newly developed microstructured reactors will be done, and rules for their numbering up are developed as 'scale-up free' methodologies. Process safety and reliability are issues beyond the demonstration of process advantages.

The new modular, decentralized plant concept for on-site production will be opposed to traditional chargewise processing in multiproduct and multipurpose plants. As potential process examples, the synthesis of organic peroxides (liquid–liquid) and the oxidation of cyclohexane with air (gas–liquid) were initially selected,

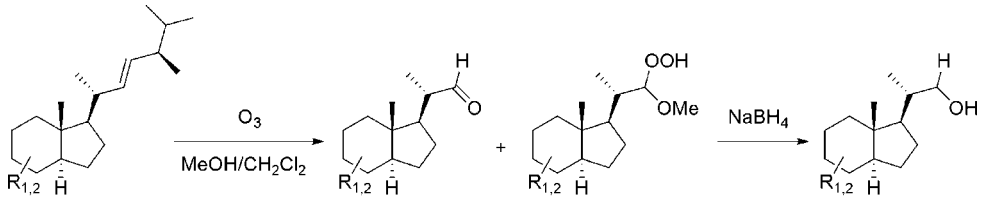
embracing fine- and bulk-chemical applications. Because this is an open collection, changes and additions in the chosen reactions during the project course are likely.

9.4.8
Development of Pharmaceutical Intermediates Production by Ozonolysis and Halogenation

Bayer Health Care (Bayer Schering Pharma) together with mikroglas chemtech GmbH, Mainz, and the Leibniz-Institut für Katalyse e. V. an der Universität Rostock (LIKAT), branch Berlin, develops the preparation of pharmaceutical intermediates by microprocess engineering in the German public funded project ZOHIR [49, 50]. These intermediates are required for the development of pharmaceuticals against skin diseases or for hormone replacement therapy and are typically produced at 1–10 t/a scale. The main focus of the work is the development and construction of equipment consisting of connectable components for safe and continuous ozonolysis, fluorination and bromination/hydrobromination, which are standard reactions in organic chemistry. Some of these reactions are highly exothermic so that heat transfer limitations are given that can be overcome by process intensifying measures. The heat may even be released in sudden bursts leading to explosions. As a result, large-scale synthesis in stirred batch reactors is here run under suboptimal synthesis efficiency conditions with large expenditure, and some syntheses are even totally excluded from scale-up. The reactants and products are also safety hazards, being either highly reactive or thermally instable. The goal is to achieve a productivity of 10–100 kg/week.

Miniaturized near-infrared sensors were developed and implemented for online analysis and automated process control to also meet the safety requirements for handling of ozone and halogenating agents [49, 50]. A target is to reduce the time from process idea to production (time-to-market) as well as development costs and costs for installation of the production unit. As pharmaceutical industry relies on the manufacture of many different products on smaller scale, and intermediates in quantities ranging from some kilograms to tons per year a modular approach toward a multipurpose microreactor plant is demanded.

A multistep gas–liquid process using a falling film microreactor was carried out for the ozonolysis of a steroid that is a fast and highly exothermic reaction [50].



Intermediate II | Aldehyde | Hydroperoxide | Alcohol

The ozonolytic cleavage of the double bond leads to the formation of hydroperoxide and aldehyde species, which are subsequently reduced to the alcohol [50]. Semibatch

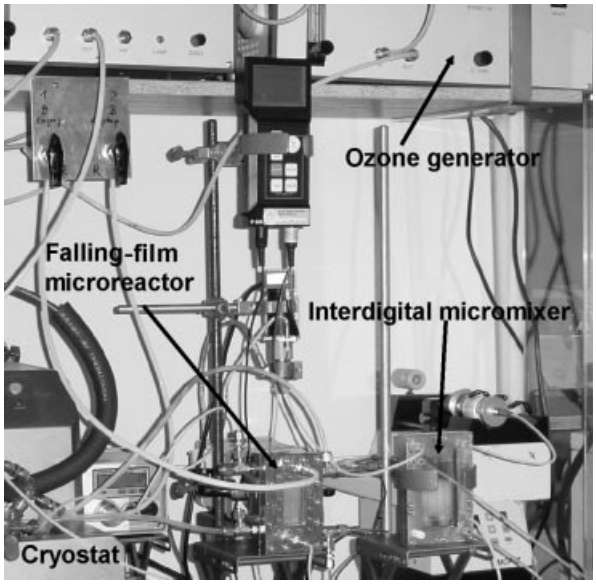


Figure 9.14 Microprocess laboratory plant for ozonolysis of steroids using a falling film microreactor (by courtesy of K. Jähnisch/LIKAT) [50].

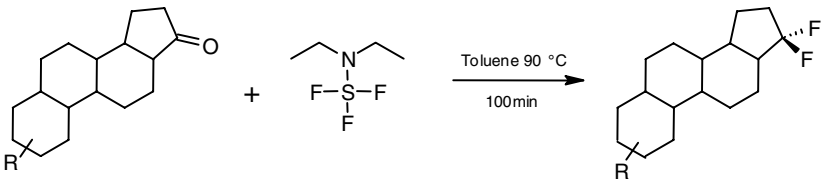
conditions are −60 °C, 7 h for dosing of ozone and 1 h for quenching. The processed volume is restricted to 10 l because of the danger of peroxide accumulation.

A laboratory-scale microprocess plant was built using a falling film microreactor for the first step and an interdigital mixer–microchannel reactor for the second one (see Figure 9.14) [50].

The aldehyde and the hydroperoxide concentrations were detected by means of FT-IR in self-made small online flow cells (see Figure 9.15) [50].

As a result of microreactor processing, the reaction temperature could be increased up to −20 °C at a residence time of only 15 s [50]. The reduction was done at 10–25 °C within several minutes. The quality of the product and the throughput were comparable to that derived from the minibatch processing. A throughput of about 100–200 g/day was achieved.

As another example, a continuous two-step liquid phase process was developed involving the geminal difluorination of a 17-keto steroid using diethyl amino sulfur trifluoride (DAST) and subsequent quenching in alkaline solution to consume the excess reactants [50].



DAST

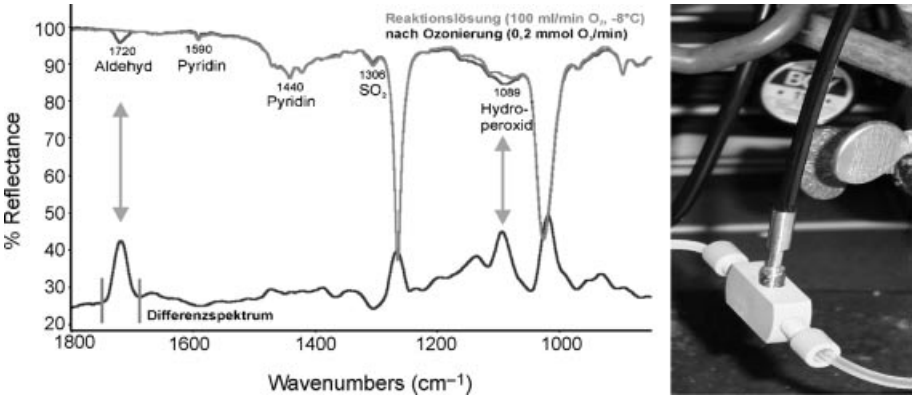


Figure 9.15 Online FT-IR monitoring of the microprocessing for the ozonolysis of steroids (left) and corresponding mini online flow cell (right) (by courtesy of K. Jähnisch/LIKAT) [50].

The corresponding semibatch process is a rather slow reaction at 90 °C with simultaneous exothermic decomposition of DAST. Thus, the processed volume is restricted to laboratory scale (<1 l) [50]. The transfer to production in a stirred tank is prohibited because of these safety reasons. A micromixer–tube reactor approach was chosen using the convective-flow-driven bas-relief caterpillar micromixer and tubes with diameters of 1–5 mm and lengths up to 20 m, respectively, and tube reactor volumes up to 500 ml (see Figure 9.16).

Again, process monitoring was made by means of FT-IR in self-made small online flow cells (see Figure 9.17) [50].

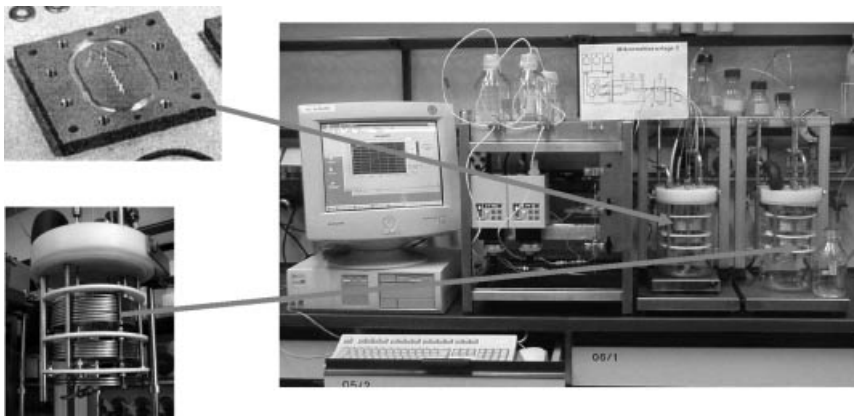


Figure 9.16 Microprocess laboratory plant for liquid phase fluorination of a 17-keto steroid with DAST (by courtesy of U. Budde/Bayer Schering Pharma) [50].

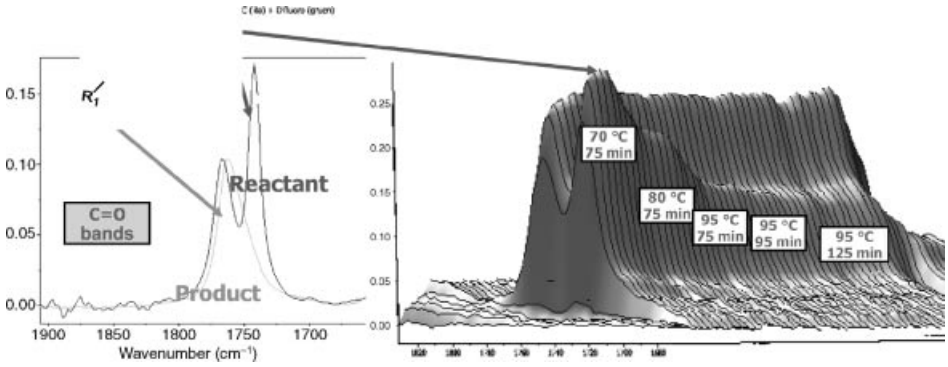


Figure 9.17 Online FT-IR monitoring of the microprocessing for the liquid-phase fluorination of a 17-keto steroid with DAST (by courtesy of U. Budde/Bayer Schering Pharma) [50].

With the use of microprocess technology, the fluorination with DAST can be performed under decomposition conditions in continuous-flow mode [50]. Temperatures of 90–100 °C and reaction times of 60–120 min are necessary for high conversions in order to compensate for the slow intrinsic reaction rate. A continuous quality control allows regulation of the process parameters (PAT, process analytical technology). A throughput of 5–10 kg/day using three parallel modules was achieved.

9.4.9 Industrial Photochemistry

The German public funded project μ-PR aims at the development, supply and testing of a microphotoreactor system in production experiments for chemical, pharmaceutical and biotechnological industry [51]. The reactor will be tested for exemplary applications of fine chemicals and photobiology.

Photoreactors are not largely used on industrial scale basically because the supply of light energy is not on the same standard or cannot be done with the same expenditure as for thermal energy. The radiation sources have high costs, emit wide-banded radiation, have limited lifetime and are energy consumptive, that is, produce large heats, which also decreases selectivity by thermal side reactions. Radiation sources have the largest share on capital costs for industrial photochemical plants. Standard Hg-based radiators have a lifetime of about 1000 operating hours, with recognizable deterioration right from the start. This aging changes the emitted radiation power and also lead to changes in the spectrum. Sensitizers are often needed to transfer the correct spectral energy to the molecules for reaction. An alternative here is the use of spectral filters; still this suffers from inefficient energy use. The main innovation of microreactors is to provide defined channel architectures that can be tailored so that the light energy can be homogeneously distributed

and optimally used. High-performance LED arrays offer a technological and economic perspective and have lifetimes of 10 000 to 50 000 operating hours. In this way, the big advantage of photochemical reactions as compared to thermally induced reactions can be used. The former principally can introduce energy in a sparing and selective manner. This is especially valid for natural product synthesis with large molecules and numerous functional groups that easily can lead to side reactions when treated thermally.

The applications investigated focus on two key market sectors with high added value, pharmaceutical industry with its high purity demands (cGMP) and biotechnological industry using microorganisms such as algae and bacteria. After the demonstration of feasibility, the photomicroreactors will be tested on-site by the partners.

9.4.10
Development of Ionic Liquid Production

The German public funded project NEMESIS focuses on the design and development of microreactors for the synthesis of ionic liquids at pilot scale [52]. Scientific objectives are to increase the yield of the corresponding ionic liquid as well as to decrease reaction time from hours up to days currently. Ionic liquids, a new innovative class of materials, are synthesized using microreaction technology. Possible application fields are their use as electrolytes for the elaborate deposition of metals. A concept for regeneration of the electrolyte is also considered.

In particular, the expectation is that by numbering up the same product quality can be assured for the production and laboratory level; obviously, this is not the case for the current practice, at least in a number of cases. Thus, increase in purity is one goal of the investigations. Online analysis with temporal and spatial resolution is used for process control. An economic and ecologic evaluation of the results is made. Applications are the sale of the ionic liquids as laboratory chemicals and a special use of these for electrochemical deposition for surface refinement of mass products.

9.4.11
Japanese Project Cluster 2002

The known industrial implementation of microprocess technology in Japan so far is done in a consorted action [53]. The Ministry of Economy, Trade and Industry (METI) launched the first project cluster in 2002, entitled 'High Efficiency Micro-Chemical Process Technology Project'. One year later, the focus of the associated works was more shifted into early industrial implementation, and the project cluster name was changed to 'Production, Analysis and Measurement System for Micro-Chemical Process Technologies'. The management of this project was done by the Association of Micro-Chemical Process Technology (MCPT), which is an umbrella for 30 chemical and instrument companies. The projects were organized in three groups

covering different facets, which are the development of microchemical plant technology, the development of microchip technology and systematization of microchemical process technology. In the following chapters, developments done under the first issue will be reported with focus on the transfer of process developments into pilot plants. It is mentioned that researchers from 7 companies and 11 research groups at Kyoto University and 4 other universities are engaged in the latter action. The schedule is to have 3-year fundamental development and then transfer to pilot plants. Another project cluster was started in July 2006, named 'Development of Microspace and Nanospace Reaction Environment Technology for Functional Materials'. This program is planned for 5 years and besides MCPT, the National Institute of Advanced Industrial Science and Technology (AIST) is involved. Furthermore, seven universities carry out research, with focal points at Kyoto University and the Tsukuba Intensive Research Center.

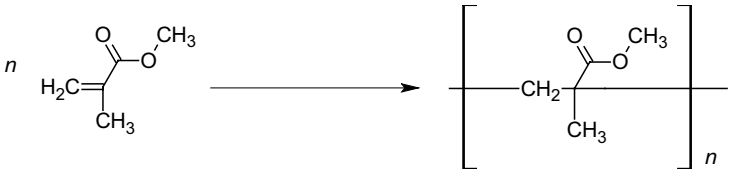
One major project refers to the isolation of activation and reaction spaces [53]. The idea is to create highly reactive intermediates in an 'activation space' by the use of energy and short reaction time and then to react these with another reactant in a 'reaction space' to the product. The conventional path is characterized by having activation and reaction space not separated and thus exposing all the reactants, intermediates and products to the harsh reaction conditions. The claim is that the new path is more selective and produces much less by-products. In addition, it allows to transfer multi-step synthesis to a one-step reaction, but now with several steps of activation that also saves purification steps. For this goal, a new type of hardware has to be developed that allows precisely to control the reaction conditions so that these activation and reaction steps can be carried really one after the other and do not partly merge. In particular, the setting of residence time is challenging.

The energy provision will not only be done conventionally, for example, by electrical heating. Alternative energy sources such as microwaves and light are tested as well [53]. The goal is to accelerate reaction rates by choosing much harsher reaction conditions, for example, in terms of temperature and pressure, than normal existing conditions in chemistry. The small spaces in microreactors help to conduct such extreme processing in a safe manner.

Because problems with fouling and erosion were encountered in previous projects, a fault detection and diagnosis system is developed as well [53]. This should detect blockage in an early stage. The aim is to also have new designs of microsystems with fewer blockages. Finally, a surface finishing method is one research target for protection of the microsystems from erosion. This is detected by an erosion monitoring method.

9.4.12
Pilot Plant for MMA Manufacture

Idemitsu Kosan in Chiba, Japan, operates a pilot plant for the free radical polymerization of methylmethacrylate (MMA) [54], following prior process development at Kyoto University [55].



The plant has a capacity of 10 t/a (see Figure 9.18) [54]. Eight microreactor blocks form the reactor core and each comprises three tube reactors with micron inner dimensions (500 μm internal diameter and 2 m length) in series. It could be shown that the numbering-up principle is valid; that is, relevant process figures such as the polydispersity index, yield and average number-based molecular weight were similar for single and parallel tube operation.

9.4.13
Grignard Exchange Reaction

Researchers at Kyoto University performed the Grignard exchange reaction of ethylmagnesium bromide and bromopentafluorobenzene to give pentafluorophenylmagnesium bromide [56]. Scale-out was made using small- and medium-scale microflow systems consisting of a micromixer and a micro heat exchanger. The shell and tube microheat exchanger used for the medium-scale microflow systems could be operated at a high flow rate of 6 l/h. The heat exchanger consists of 55 microtubes (i.d. 490 μm × 200 mm) embedded in a shell (i.d. 16.7 mm × 200 mm). Water as coolant is circulated through the shell.

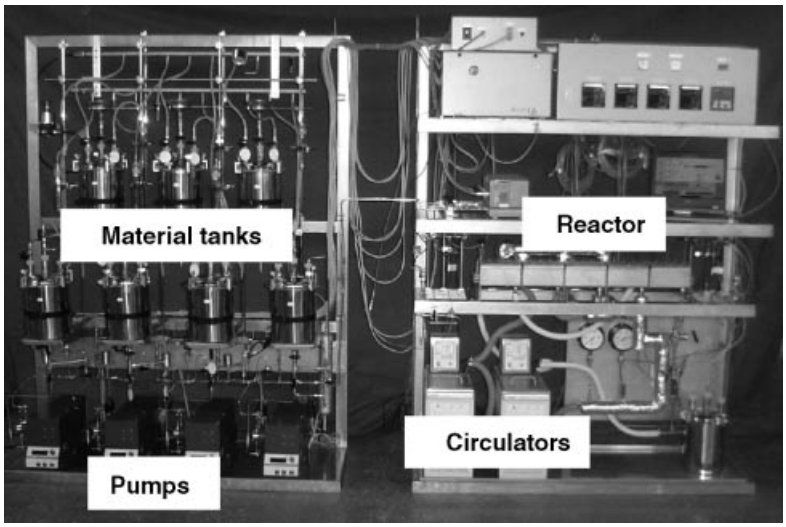
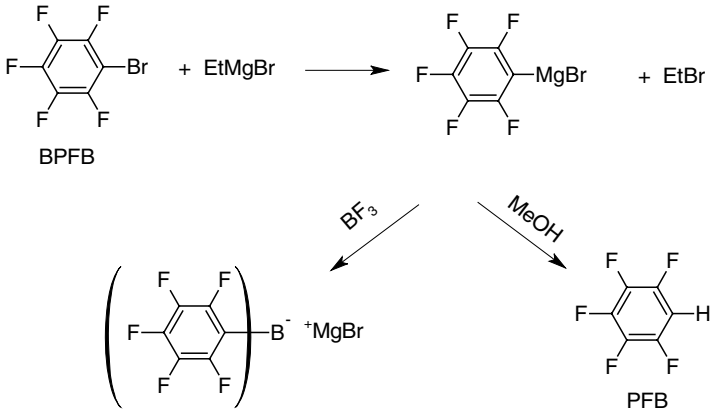


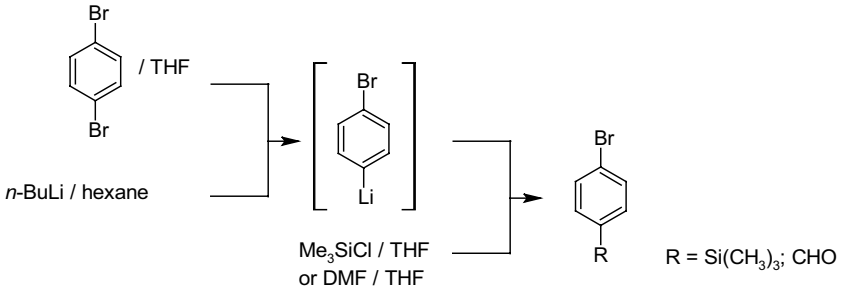
Figure 9.18 Microprocess pilot plant for radical polymerization reaction (by courtesy of ACS) [54].



In a detailed process optimization study, the impact of the type of micromixers and process parameters was determined [56]. As a result, a pilot with a Toray Hi-mixer connected to a shell and tube microheat exchanger was constructed. Continuous operation for 24 h was carried out to obtain pentafluorobenzene (PFB) after protonation (92% yield). In this time, 14.7 kg of the product was produced, that is, about 5 t/a. Thus, the industrial-scale production carried out using a batch reactor (10 m^3) can be replaced by adding only four microflow systems of the scale investigated. The pilot plant produces 0.5 kg in 6 h continuous operation, thus about 730 kg/a (see Figure 9.19). The name of the industrial company was not disclosed.

9.4.14
Halogen–Lithium Exchange Pilot Plant

The University of Kyoto, Japan, reports about a halogen–lithium exchange reaction of aryl bromides with butyl lithium (see Figure 9.20) [53, 57]. The intermediate was trapped with an electrophile. The whole process was done under noncryogenic conditions at 0 °C.



The pilot plant produces 0.5 kg in 6 h continuous operation, thus about 730 kg/a [53, 57]. The name of the industrial company was not disclosed (see Figure 9.21).

Figure 9.19 Microprocess pilot plant for Grignard exchange reaction (by courtesy of ACS) [56].

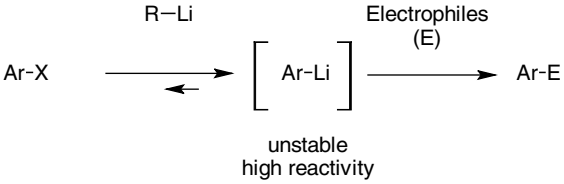


Figure 9.20 Halogen–lithium exchange reactions (by courtesy of Wiley-VCH Verlag GmbH) [57].

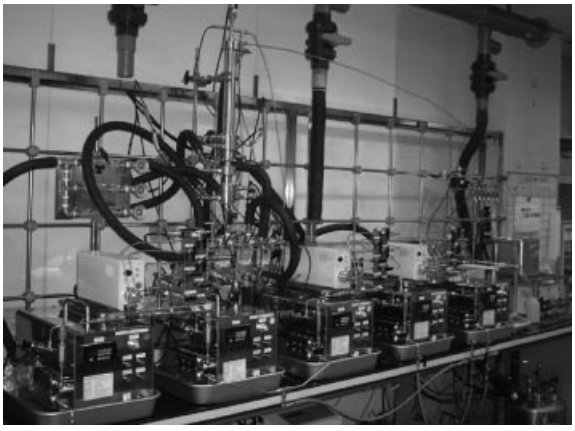
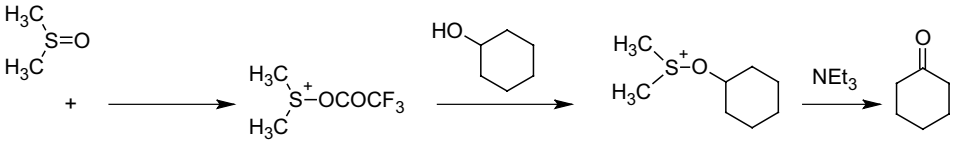


Figure 9.21 Microprocess pilot plant for halogen–lithium exchange process (by courtesy of Wiley-VCH Verlag GmbH) [57].

9.4.15
Swern–Moffat Oxidation Pilot Plant

Ube Industries in Yamaguchi, Japan, and Kyoto University investigated the Swern oxidation for pharmaceutical intermediates [57, 58]. In this reaction, alcohols are oxidized to carbonyl compounds using dimethyl sulfoxide. The reaction variant using dimethyl sulfoxide activated by trifluoroacetic anhydride (shown below) has found industrial application, but is limited to low-temperature operation (−50 °C or below) to avoid decomposition of an intermediate.



In a microscale tubular reactor, Swern oxidations were performed between −20 and 20 °C. Mixing was performed stagewise with a series of rapid mixing functions (see Figure 9.22) [57, 58]. First, dimethyl sulfoxide and trifluoroacetic anhydride were contacted in an interdigital micromixer followed by a stainless steel tube reactor R1. After addition of the alcohol and reaction in reactor R2, the mixture was then contacted with a triethylamine solution and passed through two more reactors (R3 and R4) to complete the reaction.

This microreactor system thus allows fast mixing, good temperature control and changing process parameters at short residence times – the overall time to pass all

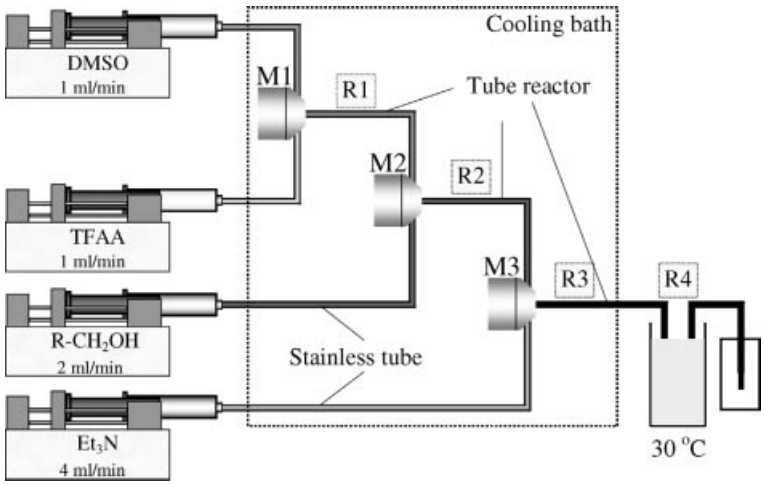


Figure 9.22 Schematic diagram of the microscale flow system for the Swern oxidation (by courtesy of Wiley-VCH Verlag GmbH) [58].

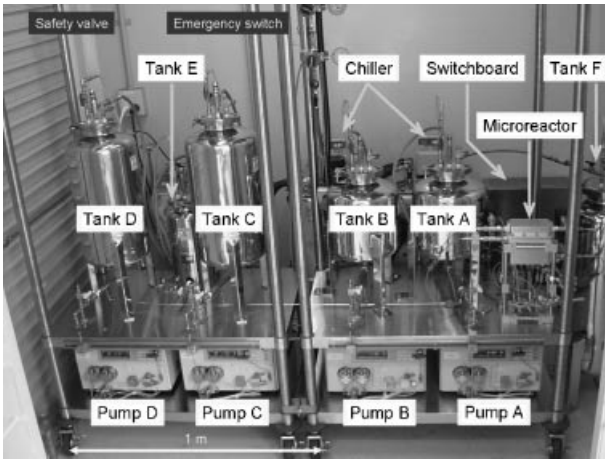


Figure 9.23 Microprocess pilot plant for Swern–Moffat reaction (by courtesy of J.-I. Yoshida/University of Kyoto).

reactors is between 8 and 11 s [57, 58]. The timescale between end and start of a new operation is 0.01 s in order to avoid significant decomposition. Thereby, conversions and yields were determined for primary, secondary, cyclic and benzylic alcohols in the temperature range of −20 and 20 °C, which were equal or better than lower temperature batch reactions. The oxidation of cyclohexanol was run for 3 h at 20 °C, and a stable process in terms of conversion and selectivity was observed.

Then, a pilot plant with a capacity of 10 t/a was build for the Swern–Moffat oxidation [57, 58]. The yield of the batch process is 83% at −70 °C, whereas the microchemical process achieved a yield of 88% at 20 °C. The pilot plant was operated under stable reaction conditions for a long run with similar product yields as in the laboratory experiment (see Figure 9.23).

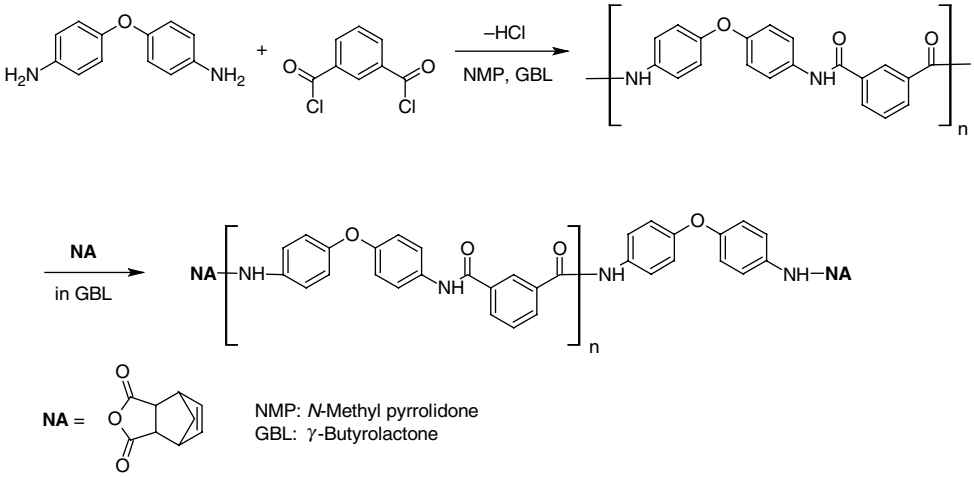
9.4.16
Yellow Nano Pigment Plant

The University of Kyoto, Japan, and Fuji in Tokyo, Japan, developed a pilot plant for the production of a yellow nano pigment with a capacity of 70 t/a, which was also developed and operated by Kyoto University and Fuji Company (see Figure 9.24) [59]. The particle size spectra show a clear impact of the flow conditions with smaller particles at higher flow rates.

9.4.17
Polycondensation

The MCPT research group investigated polycondensation reactions for the synthesis of highly thermal resistant polymers such as polyamide and polyimide [57]. These reactions are exothermic, which negatively impacts average molecular weights and the corresponding distributions when using conventional technology. A two-step

reaction with polycondensation and terminal modification with norbornene anhydride (NA) was conducted in a microreactor as shown in the following scheme.



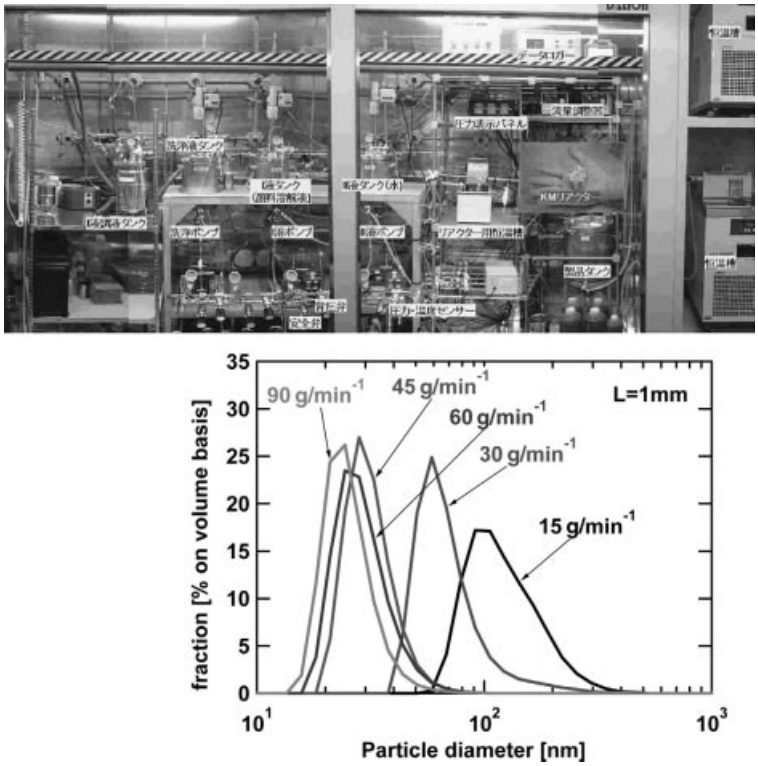
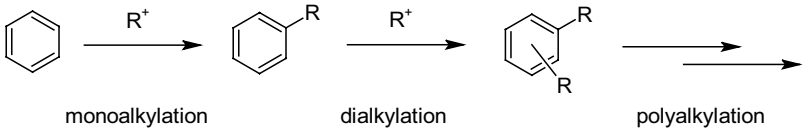


Figure 9.24 Top: yellow nano pigment pilot microprocess plant. Bottom: particle size spectra at various volume flows (by courtesy H. Maeta, Fuji) [59].

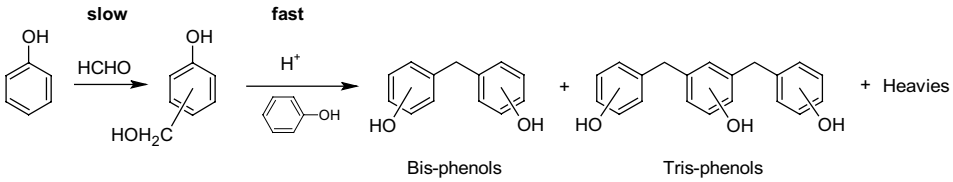
The reaction was faster in the microreactor than in the batch system, which is assigned to be a mixing effect [57]. The molecular weight distribution obtained in the microreactor is slightly narrower than that of the batch reactor, which is attributed to the good thermal management of the microreactor.

9.4.18
Friedel–Crafts Alkylation

The MCPT research group investigated Friedel–Crafts alkylations, a widely used reaction path in organic chemistry [57]. As an electron-donating substituent is introduced in the first reaction, the monoalkylated product is more reactive than the starting material and the second alkylation takes place more readily. This leads to by-products by dialkylation or even polyalkylation. This can be avoided by using a large excess of the starting material. However, a smart solution would be the achievement of a selective monoalkylation using only one equivalent of an aromatic compound. The key to this may be micromixing, as respective impact on selectivity has been found in earlier investigations.



As industrial relevant Friedel–Crafts reaction, the synthesis of Bisphenol-F, a material for epoxy resin, from phenol and formaldehyde was chosen [57]. This reaction involves formation of higher order condensates such as tris-phenols. To minimize the latter, the molar ratio of phenol to formaldehyde is set to a very high value (30–40), which is more than 15 times larger than the amount theoretically necessary. Three types of micromixers were used. These are a T-shaped mixer with 500 µm inner diameter, a multilaminating interdigital micromixer with 40 µm channels and a so-called self-made K-M micromixer with center collision mixing.



The selectivity increased with increasing phenol/hydroxybenzylalcohol ratio (see Figure 9.25) [57]. Best performance was given by the K-M mixer. The phenol/hydroxybenzylalcohol ratio was decreased to half in this way.

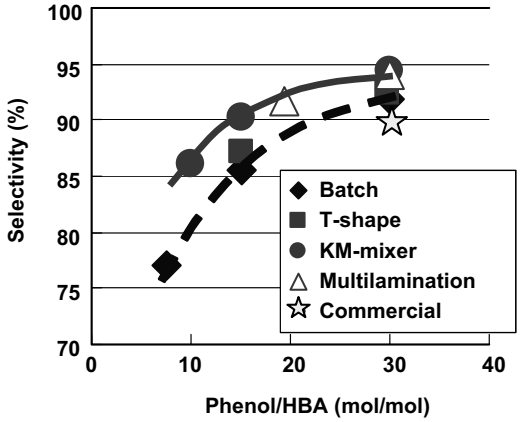
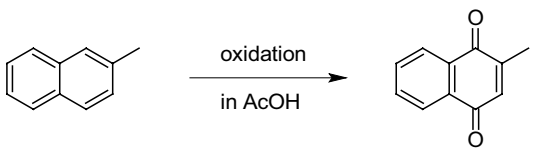


Figure 9.25 The impact of choice of micromixer on selectivity when varying the phenol/hydroxybenzylalcohol molar ratio (by courtesy of Wiley-VCH Verlag GmbH) [57].

9.4.19
H_2O_2 Based Oxidation to 2-Methyl-1,4-naphthoquinone

The MCPT research team investigated the synthesis of 2-methyl-1,4-naphthoquinone (vitamin K3) by the oxidation of 2-methylnaphthalene [57].



2MN (2-Methylnaphthalene) → VK3 (2-Methyl-1,4-naphthoquinone)

This is done in the commercial production with chromium trioxide, and the aim was to test for the possibility of substitution by using aqueous hydrogen peroxide (60%) as oxidant [57]. Hydrogen peroxide (H_2O_2) is a mild and environmentally friendly oxidant. For better performance, the oxidation could be made faster by using higher temperatures and higher concentrations of the oxidant. This, however, is prohibited by side reactions such as overoxidation, side-chain oxidation and decomposition of the oxidant. Therefore, dropwise addition of hydrogen peroxide is common to achieve high selectivities, usually at low temperatures. This results in long reaction times.

With the use of a microreactor and a feed comprising also palladium acetate and sulfuric acid, the reaction time was shortened to 10 min at 70 °C as compared to the

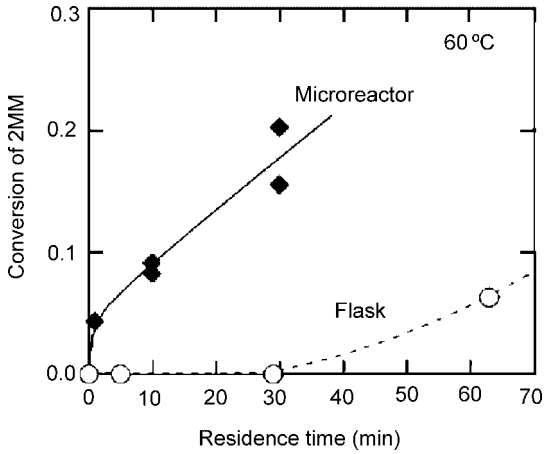
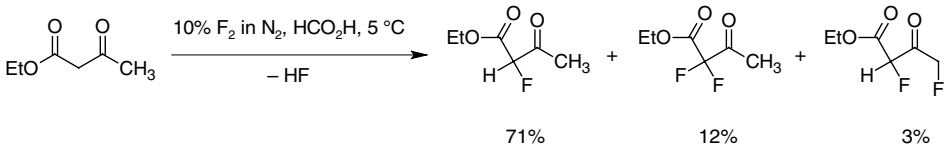


Figure 9.26 Speeding up the oxidation of 2-methylnaphthalene (2MN) in a microreactor by virtue of faster hydrogen peroxide addition and higher temperatures (by courtesy of Wiley-VCH Verlag GmbH) [57].

industrial semibatch process (see Figure 9.26) [57]. However, the selectivity was lower. This could be solved by process modification using peracetic acid, generated *in situ* from acetic acid and hydrogen peroxide.

9.4.20
Direct Fluorination of Ethyl 3-Oxobutanoate

Following extensive laboratory studies at the University of Durham, UK, on the direct fluorination of ethyl 3-oxobutanoate in formic acid, scale-out was made from a three- to a nine-channel microstructured reactor, in cooperation with Asahi Glass Co. in Yokohama, Japan [60].



The process was performed for many months yielding 700 g of monofluorinated product with a nine-channel microstructured reactor [60]. A continuous 150 h operation was performed without decline of yield or conversion. Even in the scale-out to a 30-channel reactor (see Figure 9.27), no loss in performance was noticed. A single feed system distributed the reactants and reagents to the various microchannels.

If the results of these first pilot studies are extrapolated to large-scale synthesis, a two-sided 30-channel device with 60 channels would be capable of synthesizing about

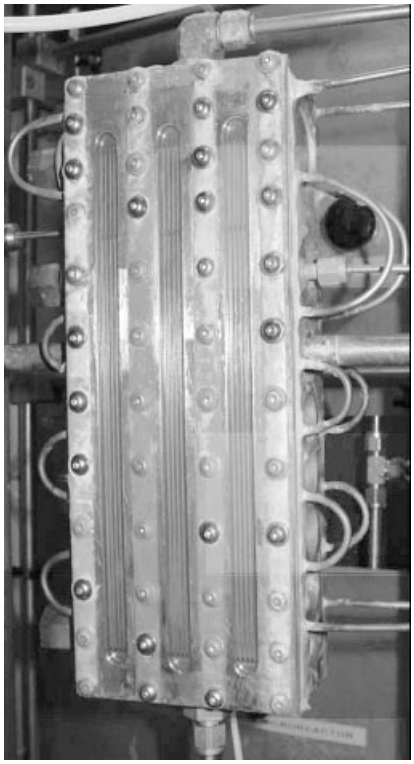
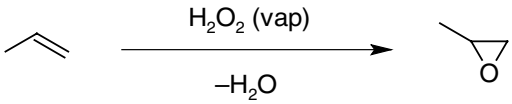


Figure 9.27 A 30-channel microstructured reactor for the direct fluorination of ethyl 3-oxobutanoate (by courtesy of the Royal Society of Chemistry) [60].

300 g product per day [60]. By external numbering to 10 reactors about 3 kg of product per day would result. Such pilot plant benefits from low expenditure and having exactly the same operating conditions as given for the laboratory processing. In addition, convenient maintenance and purification by distillation at improved safety features are predicted as major advantages.

9.4.21
Propene Oxide Formation

The propene oxidation process is globally conducted on a 5 million t/a scale. A new gas-phase oxidation process of propene to propene oxide using hydrogen peroxide would save the use of solvents and is expected to have high selectivity.



Microstructured reactors have the potential to perform a key step here to thermally treat concentrated hydrogen peroxide solutions for vaporization that would be otherwise dangerous when using conventional technology because of the handling of the combustible hydrogen peroxide. Thus, large microreactor units have to be built that are capable of safe operation of the hydrogen peroxide route. In addition, these units need to transfer the large reaction heats produced in the exothermic propylene oxide reaction.

Following these ideas, Degussa in Hanau, Germany, developed and built, together with the large-scale plant manufacturer Uhde in Dortmund, Germany, and other university and institute partners in a publicly funded project (DEMIS), a 6-m long, two-story high pilot-scale microstructured reactor by numbering up of meter-long and meter-wide plates brought to micron distance (see Figure 9.28) [61]. The lower part of the reactor comprises the vaporizer and in the longer upper part the reaction plates are positioned. The construction uses a simplified, robust approach with no real walls for laterally defining microchannels, but the few fins only have mechanical function, and the flow dimension in lateral direction is virtually infinite compared to that of typical microchannels. This simplification in reactor design has to be paid by the development of a catalyst coating technique for such extended dimensions. Typically, the small dimensions in microchannels help in having good mechanical adhesion to the substrate and also promote uniform coating because of surface

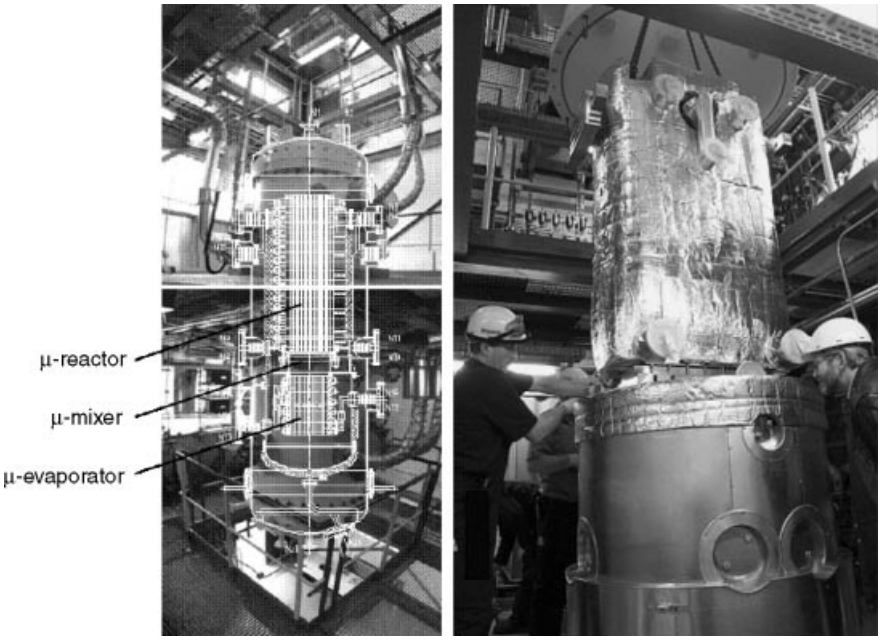
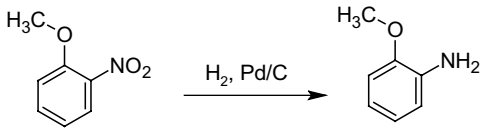


Figure 9.28 Left: DEMIS pilot reactor for propylene oxide formation at Degussa site, superposed by schematic on the reactor construction. Right: assembly of the reactor internals (by courtesy of Wiley-VCH Verlag GmbH) [61].

forces. Initial results are very stable and reproducible, and Degussa regards this as encouraging.

9.4.22
Diverse Industrial Pilot-oriented Involvements

Bayer operates several microprocess plants. Clariant has formed a competence center on microreaction technology in early 2004 to offer the technology in its custom synthesis business. Degussa started a new project house on Process Intensification encompassing the microreaction technology. Lonza has also used microreaction technology over years for pharmaceutical customers. The pharmaceutical company Brystol-Meyers-Squibb, Lucent Technologies and the Stevens Institute have a public funded project on hydrogenation reactions [62]. They started with a model reaction, the hydrogenation of *o*-nitroanisole to *o*-anisidine, and will move on to proprietary reactions.



The reaction engineering uses the innovative approach of fixing single Pd/C catalyst particles in thousands of small microstructured traps [62]. This is a mixed approach relying on traditional catalysts and using the innovative flow features in microchannels. In this way, higher specific surfaces between gas, liquid and catalyst are ensured than possible by using fixed beds. In comparison to wall coatings, it is expected that the trapped catalyst provides a more reliable and potentially higher catalyst coating.

Brystol-Meyers-Squibb has filed patents for making glycosides using noncryogenic processes that involve the lithiation of aromatic compounds [62]. These aryllithium derivatives react with carbonyl groups of other reactants to form a glycoside. Both steps are highly exothermic and rapid, which are tailored to reveal the advantages of microprocess technology in terms of selectivity and reduced cost of manufacture.

The Syrris Company, a system manufacturer, and GlaxoSmithKline developed an automated flow system AFRICA (Automated Flow Reaction Incubation and Control Apparatus) where a sequence of reactions can be run under several process conditions using the advantages of miniature-scale flow [62]. Attached to the system is an online high-pressure liquid chromatography for immediate product separation to analyze the performance of process optimization. As further scientific support, Syrris has entered into a cooperation with S.V. Ley at Cambridge University who studies flow-through liquid reactions with immobilized reagents. Pfizer has some high-throughput oriented research and development work with a microreactor combined to an automated multiple reactant feed upstream and UV detection downstream.

Dow Chemical in Midland, USA, the microprocess technologist Velocys in Plain City, USA, and PNNL in Richland, USA, as research institute in microreactor technology have a public funded project on high-intensity production of ethylene and other olefins by oxidation such as the formation of ethylene from ethane [1]. A two-step reactor engineering is performed, starting with a bench-scale reactor with microchannel dimensions equal to the latter commercial unit and followed by numbering to the latter. An economic analysis with focus on reactor costs and energy consumption completes the project.

9.4.23
Production of Polymer Intermediates

DSM Fine Chemicals, Linz, Austria, inserted a microstructured reactor into an existing production plant for the Ritter reaction in a retrofit manner (see Figure 9.29). A high-value intermediate, not disclosed by chemical formula, for the polymer industry is produced [63]. This approach, under involvement of the product team right from the start, stands for a plant philosophy which may best paraphrased by 'minimal invasive plant surgery', different from some holistic approaches on a total change in plant design. This enabled the replacement of a central reaction route in a very large reactor tank encasing several tons of explosive and corrosive chemicals. Design and fabrication of this reactor was done at the Institut für Mikroverfahrenstechnik (IMVT) in the Forschungszentrum Karlsruhe (FZK), Germany.

During a 10-week production campaign, over 300 t of the polymer product was produced [63]. The microstructured reactor (65 cm long, 290 kg heavy, special Nickel alloy, several ten thousands of microchannels) was operated at a throughput of 1700 kg liquid chemicals per hour. A crucial issue was the removal of the reaction heat

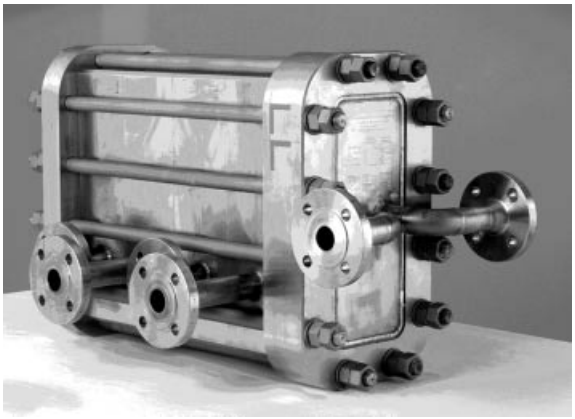
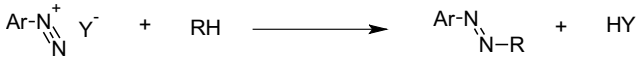


Figure 9.29 Production-type microstructured reactor for throughput at 1700 kg/h and transfer of a power of 100 kW. This apparatus was used for the manufacture of a high-value product for plastics industry at DSM in Linz, Austria (by courtesy of Wiley-VCH Verlag GmbH; from [64]).

that was accomplished within seconds. The yield exceeds that of the former route, albeit it was not detailed. It was also found that the process safety for handling the corrosive chemicals was higher for the microreactor process. The use of raw materials and the waste streams were reduced, improving the cost and efficiency of the process.

9.4.24
Synthesis of Diazo Pigments

Clariant carried out diazo-coupling for pigment synthesis. Laboratory developments were transferred to pilot scale, reported in the literature, and a further transfer to production scale was announced at conferences [65].



Particle synthesis is known to be highly sensitive to mixing, as this controls seed formation and crystal growth. With the Clariant and later works, it became evident that by the use of micromixing technology particles with more uniform size, defined morphology, or chemical selectivity can be prepared, that is with considerably improved product qualities, which is the main driver for such investigations. The motivation to use microreactors also stems from the benefits of developing a continuous process, for example, the production of flexible quantities and eliminating the need of refining, such as milling the pigment in the end of the production line, as typically given for batch processes. A further argument for microreaction technology in the case of diazonium salt-based synthesis comes from the hazardous potential of that intermediate. A major hurdle is to find processing solutions that allow to handle solids generated in microchannels.

Two commercial azo pigments, one yellow and one red colored, were made on the basis of azo coupling; the nature of the substituents was not disclosed [65]. Diazotation was performed in batchwise manner. A CPC microreactor with multilamination mixer (lamellae $<100\,\mu m$) was used. The two azo pigments had a color strength of 119 and 139%, a five and six times glossier brightness, and a five and six steps higher transparency, respectively, than the same products made by batch processing (see Table 9.3) [65]. This originated from the formation of smaller particles with more narrow size distribution (microreactor: $D_{50} = 250\,nm$, $s = 1.5$; batch: $D_{50} = 600\,nm$, $s = 2.0$).

The same features were found for pilot-size microreactor operation (see Figure 9.30). Brightness and transparency were the same, and the color strength could even be increased to 149% [65]. The mean particle size was even smaller than the lab-scale microreactor processing (microreactor: $D_{50} = 90\,nm$, $s = 1.5$; batch: $D_{50} = 600\,nm$, $s = 2.0$), probably because of process optimization.

Pilot-size microreactor operation was done using a flow of 500 ml/h, which is equivalent to a production in the range of 10 t/a that was estimated when accounting

Table 9.3 Coloristic properties of pigments synthesized in two different microreactors compared to the batch standard.

	Microreactor pigment 1	Microreactor pigment 2
Color strength	119%	139%
Brightness	Five steps glossier	Six steps glossier
Transparency	Five steps more transparent	Six steps more transparent

From [65].

for 8000 h annual running time [65]. The increase in throughput compared to laboratory-scale microreactors used prior (1 t/a; 20–80 ml/h) was achieved by both internal and external numbering up accompanied by a slight scale-up of internal dimensions. More reaction plates were assembled in parallel within one device; in addition, three such devices were connected in parallel. Furthermore, slightly larger microchannels were used, still ensuring laminar flow.

To test for fouling, a 24 h run of a pilot-scale microreactor for azo pigment production was performed using a diazo suspension [65]. At the end of this period, the pressure loss of the microreactor increased exponentially. Special means were developed to prevent clogging and instable operation. By partial removal of the deposits, the pressure loss was brought back to normal.

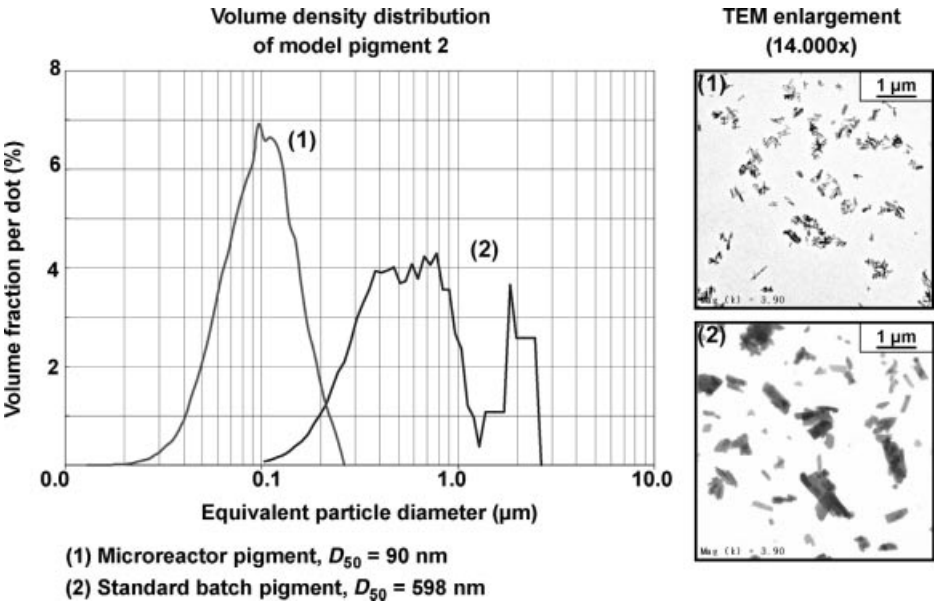
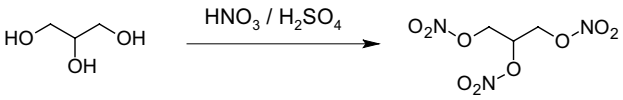


Figure 9.30 Size characterization of an azo pigment, yielded in the pilot plant microreactor, compared to the batch standard. Left: volume density distribution; right: TEM magnification (by courtesy of Wiley-VCH Verlag GmbH; from [66]).

9.4.25
Nitroglycerine Production



The Xi'an Huian Industrial Group in Xi'an, China, operates a nitroglycerine plant at 15 kg/h production that has been developed and installed by IMM (see Figure 9.31) [62].

The nitroglycerine is of pharmaceutical grade and used as medicine for acute cardiac infarction. This demands high selectivity and low levels of impurity. First manual plant start-up tests demonstrated that this can be achieved by performing the reaction in a microreactor. Safe operation was found during the first runs. In the second step, full automation of the plant is planned. The extension of the process chain is another future issue, adding a purification unit for washing and drying and finally a unit for formulation and packaging to encapsulate the nitroglycerine drug safely in tablets. Advanced wastewater treatment and a closed water cycle should lead to an environmentally clean process.

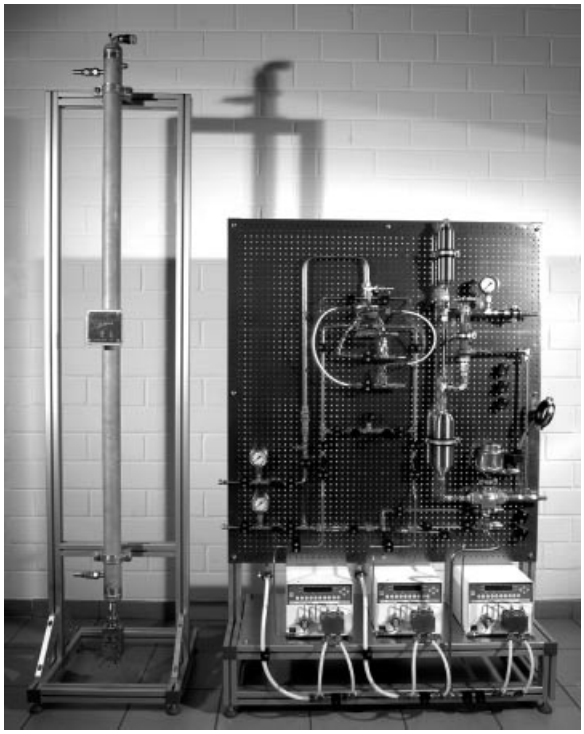


Figure 9.31 Microprocess production plant for pharmaceutical nitroglycerine (by courtesy of H. Löwe/IMM).

9.4.26
Fine Chemical Production Process

Microinnova KEG, Graz, Austria, made process development and the installation of a StarLam 3000 microstructured mixer in an existing production plant of an undisclosed customer and for an undisclosed chemical process (see Figure 9.32) [67]. The aim was to double the capacity of a running two-step batch process. This was achieved by installing the microreactor for the first reaction step. A higher reaction rate made it possible to reach overall throughputs of 3.6 t/h. Additionally energy savings were achieved. The microstructured mixer is running in production for more than a year now.

The application refers to the production of fine chemicals [67]. A 10 m^3 batch vessel was used to perform the two-step chemical process. The first strongly exothermic reaction step needed cooling because of the volatility of one of the starting materials. The reaction was finished when all of the volatile reactant had reacted. The second step was endothermic and the batch vessel had to be heated for some hours to complete the reaction. It took several hours to perform these two steps and a throughput of about 1800 kg/h was achieved.

In laboratory-scale investigations, the reactor and attached tube reactor were kept at temperatures of about 150 °C [67]. The experiments showed that in the microprocess lab plant the first reaction step can be finished in less then 60 s, whereas it takes about 4 h to perform it in the cooled batch vessel of the production plant.

Figure 9.32 StarLam 3000 microstructured mixer retrofitted to existing plant peripherals and tank reactor (by courtesy of Wiley-VCH Verlag GmbH) [67].

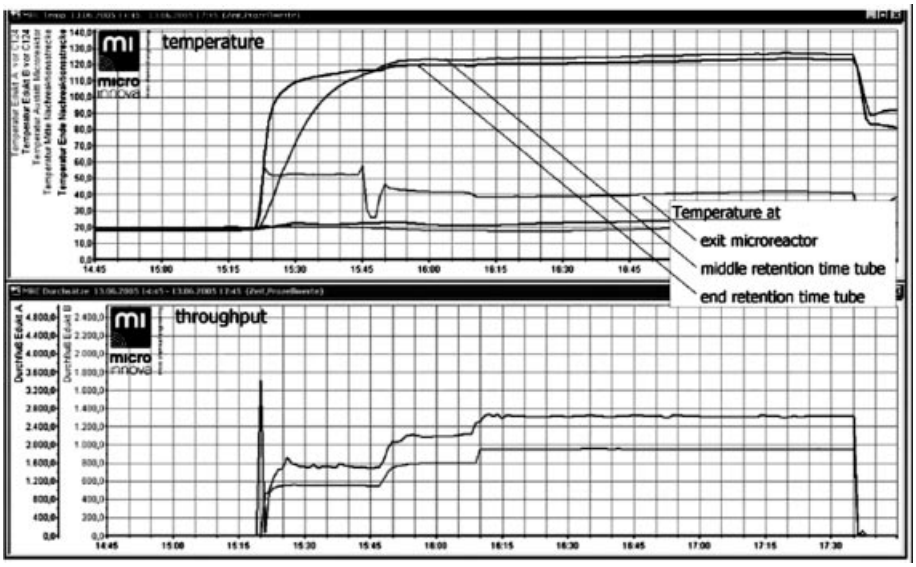


Figure 9.33 Temperature diagram of the microreactor assisted processing (by courtesy of Wiley-VCH Verlag GmbH) [67].

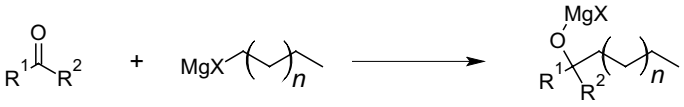
The inlet pipes of the two starting reactants to the batch vessel were simply connected to the StarLam mixer [67]. The only difference to the previous feed lines was the installation of filter cartridges before the entries to the microstructured mixer, necessary to avoid blocking of the reactor. The pressure drop in the lines was lower than 3 bar so that it was possible to keep the pumps used before in the plant. At the outlet of the reactor, a tube reactor was installed. During optimization it was found that it is sufficient to insulate this tube to reach the temperature needed to finish the reaction. The pipe ended directly in the batch vessel where the second endothermic reaction step was carried out as before.

The first start-up of the plant was in June 2005 [67]. A temperature diagram shows that most of the heat is released in the retention time tube (see Figure 9.33). The temperature measured directly at the outlet of the microstructured mixer–reactor StarLam 3000 was below 50 °C even at higher throughputs. During the retention time, tube temperatures up to about 130 °C were reached. The throughputs for this first test run were increased in three steps to up to 3600 kg/h.

9.4.27
Grignard-based Enolate Formation

Merck in Darmstadt, Germany, investigated a reaction of a Grignard reagent with a high reaction enthalpy of 300 kJ/mol and high reaction speed so that heat transfer limitations result for conventional technology [68]. The Grignard reagent having a long alkyl chain was added to a keto compound, the substituents remain disclosed.

Thereby, an enolate is formed that is further reacted in the frame of a multistage fine-chemical industrial process.



X = Br, Cl

A yield of 95% was obtained by a micromixer-based process (<10 s, at −10 °C), whereas the industrial batch process (6 m^3 stirred vessel) had only 72% yield (5 h, at −20 °C) [68]. The lab-scale batch process (0.5 l flask; 0.5 h, at −40 °C) had 88% yield (see Table 9.4). Pilot-scale studies followed with a homebuilt minimixer for reasons of clogging, which was not decisive at the lab scale. With one minimixer at the pilot scale, a yield of 92% was obtained (<10 s, at −10 °C). The validity of the numbering-up concept was proven by operating also five minimixers of the same type at a yield of 92% (<10 s, at −10 °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 multistage process run out (see Figure 9.34).

Meanwhile, Merck has reported to have 20 microreactor plants under operation for diverse reactions [65]. The production costs are typically reduced by 20% as compared to prior conventional technology. The throughputs range from 50 g/h to 4 kg/h, which corresponds to 146 kg/a and 11.7 t/a, respectively.

9.5 Challenges and Concerns

Concerns about an industrial use of microprocess technology are still existing [62]. Process chemists need to be familiarized with the new tool. Often it seems that these soft factors are even more relevant than the hard factors. Nonetheless, the performance of microprocess technology must show up a clear driver in the interplay of operating and capital costs of existing equipments and respective costs on the microflow processing side.

Processes that work best with microreactors are fast and generate high-value materials. This restricts the use currently to such niches [62]. However, it is also more

Table 9.4 Comparison of reaction time and yield for different reactor types.

Reactor type	Temperature (°C)	Residence time	Yield (%)
Flask 0.5 l	−40	0.5 h	88
Production (stirred vessel, 6 m^3)	−20	5 h	72
Microreactor (lab setup)	−10	<10 s	95
Minireactor (pilot scale)	−10	<10 s	92
Five minireactors (production)	−10	<10 s	92

From [68].

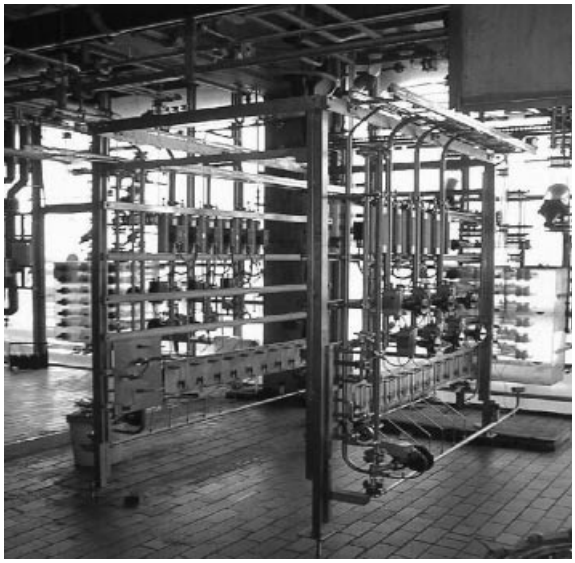


Figure 9.34 Merck production plant for Grignard-based enolate formation (by courtesy of Springer) [68].

and more recognized that speed-up of reactions can be achieved by changes in the chemical processing and synthesis in view of what is tailored for microreactors. This reorientation has now been started with an initiative on novel process windows (DBU project cluster in Germany, DBU German Environmental Agency), but will take many years though.

Microprocess technology is still regarded as rather radical change in chemical engineering. It will need probably another decade until it has become more routine business. On this way, intermediate solutions such as the use of mesoscale equipment, still of advanced nature, will complement the choice for smart continuous manufacturing. Also, other modern technologies such as microwave organic synthesis, ionic liquids and supercritical processing will probably be used jointly with microreactors in selected cases. In this way, some current limitations of microprocess technology may be overcome (e.g. concerning solubility, upper operating temperature and heat supply).

Microprocess technology is strongly knowledge driven. Education and training will have a major role [46].

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