Serial combinatorial synthesis

[OS 30] [R 30] [P 22] By simple flow switching, serial combinatorial synthesis for creating a cation pool from diverse carbamates and silyl enol ethers was accomplished (Figure 4.46) [66, 67]. The conversions and selectivities were comparable to continuous processing using three feed streams only (see Conversion/yield/selectivity, above).

4.3 Aromatic Electrophilic Substitution

4.3.1 Nitrodehydrogenation – Nitration of Aromatics

Peer-reviewed journal: [31, 94]; proceedings: [38, 95–98]; sections in reviews: [14, 83, 89, 99, 100]; additional information: [101, 102]. See also the information given on the nitration of aliphatics in Section 4.7.1.

4.3.1.1 Drivers for Performing Aromatic Nitrations in Micro Reactors

Most nitrations are highly exothermic and hence release a lot of reaction heat for most experimental protocols [37, 94]. This high exothermicity may even lead to explosions [37, 38]. Nitration agents frequently display acid corrosion [37]. For these reasons, nitrations generally are regarded as being hazardous [37, 38].

Owing to the heat release, nitrations often lack selectivity, i.e. many parallel, consecutive and decomposition processes are known to occur. As a result, product spectra are unusually wide and consequently yields and purity are low [37, 94].

The selectivity issue has been related to multi-phase processing [31]. Nitrations include both organic and aqueous phases. Oxidation to phenol as one side reaction takes places in the organic phase, whereas all other reactions occur in the aqueous phase and are limited by organic solubility. For this reason, enhancing mass transfer by large specific interfaces is a key to affecting product selectivity.

Having high mass transfer, in addition to good heat transfer, may change the product spectra, by increasing the conversion to product and decreasing the formation of some of the by-products [94]. Nitrations are well suited for two-phase capillary flow processing yielding uniform alternating slugs. In these slugs, internal circulation leads to high mass transfer. The defined setting of residence time can be achieved by establishing two-phase plug flow behavior in so-called capillary-flow reactors.

4.3.1.2 Beneficial Micro Reactor Properties for Aromatic Nitrations

The small reaction volumes in micro reactors and the large specific surface areas created are beneficial for coping with the problems caused by the release of the large heats, as mentioned above [37, 38]. Delicate temperature control is what is expected for micro-reactor operation; isothermal processing is said to be achiev-

Chemical Micro Process Engineering: Fundamentals, Modelling and Reactions
Volker Hessel, Steffen Hardt, Holger Löwe

ISBN: 3-527-30741-9

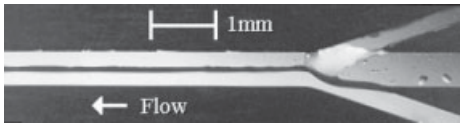


Figure 4.47 Image of parallel liquid/liquid flow through a micro channel [31].

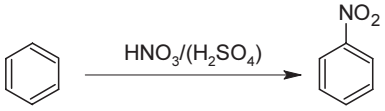
able even when large reaction heats are released [94]. Small size should so increase process safety and suppress unwanted secondary reactions [37, 38].

In micro reactors, very unique flow patterns can be established using proper contactors/mixers. This holds particularly for two-phase flow by capillary-flow processing yielding uniform alternating slugs (see Figure 4.51) [94] or parallel-flowing streams (Figure 4.47) [31]. Besides advantages in terms of improved mass transfer, they uniformly set residence time by plug-flow motion. Apart from increasing reaction to the kinetic limits, the flow patterns may directly affect selectivity, which depends on interfacial area [31].

4.3.1.3 Aromatic Nitration Reactions Investigated in Micro Reactors

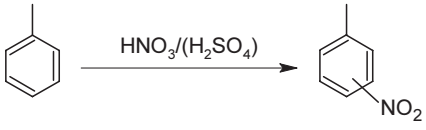
Nitration reactions are among the basic chemical pathways followed in organic synthesis. They are used for making pharmaceutical products, agricultural and pest control chemicals, pigments, precursors for polyurethane or polyamide production and explosives [37]. Typically, acidic nitration agents such as nitric acid are employed to insert the nitro function, using dehydrating agents such as sulfuric acid or anhydrous acetic acid. Dinitrogen pentoxide is usually more reactive and may be employed, if acid-sensitive substances have to be reacted.

Organic synthesis 31 [OS 31]: Mononitration of benzene



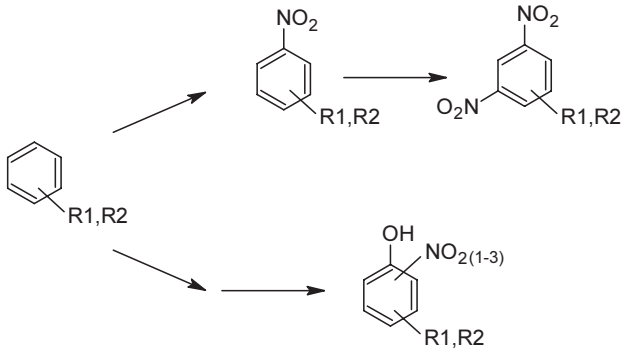
The nitration of benzene is a standard organic synthesis process, well described in the scientific and patent literature [31, 97].

Organic synthesis 32 [OS 32]: Mononitration of toluene



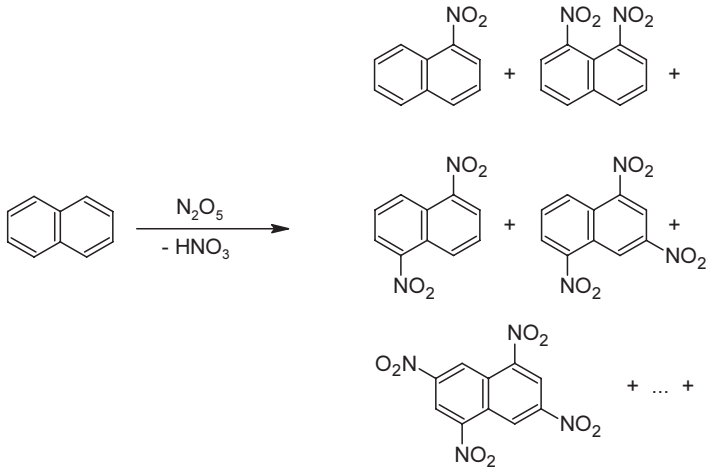
The nitration of toluene, similarly to the nitration of benzene, is a standard organic synthesis process, well described in the scientific and patent literature [31, 97].

Organic synthesis 33 [OS 33]: Nitration of substituted single-ring aromatics



The nitration of several single-ring aromatics with two substituents at various ring positions has been reported [94]. The exact nature of these species, however, was not disclosed, probably for intellectual property reasons, as the reactions were performed for an industrial company (BASF).

Organic synthesis 34 [OS 34]: Mononitration of naphthalene



The nitration of naphthalene was used as a test reaction [37]. As a consequence of having two aromatic rings, a particularly large variety of nitration products are in principle possible. This refers to multiplicity of nitration and to positional selectivity for each nitration step.

4.3.1.4 Experimental Nitration Protocols in Micro Reactors

[P 23] The nitration of two standard aromatic compounds, namely benzene and toluene, was performed utilizing nitric acid/sulfuric acid mixtures and the pure

organic reactant [31, 38, 97, 101, 103]. The sulfuric acid content in the mixture was set high, ranging from 70 to 85 mass-%, to achieve a high reaction rate, i.e. to test the mass transfer capabilities of the micro reactor when switching from kinetic to mass transfer control. Acid-to-organic ratios of flow rates were from 2 : 1 to 7 : 1; accordingly, the nitric acid : benzene molar ratios were about 0.3–2, depending on the afore mentioned flow ratios and sulfuric acid contents. The temperature was set from 60 to 90 °C. Residence times were several tens of seconds, typically 25 s.

[P 24] The nitration of naphthalene was carried out with dissolved or *in situ* generated N_2O_5 gas [37]. The temperature was set to –10 to 50 °C and residence times to 15–45 s. The reaction mixture processed in the micro reactor was quenched with water, extracted and analyzed by HPLC or GC with mass-selective detection.

[P 25] The nitration of various single-ring aromatics was performed in a capillary-flow micro reactor with capillary lengths of 1 to 8 m [94]. The aromatic and the pre-mixed nitration acid were fed by high-pressure piston pumps into a Y-piece contactor (0.5–1.0 mm inner diameter; 120°). The PTFE capillary of 0.5–1.0 mm inner diameter was inserted in a heating mantle, operated with silicone oil in counterflow mode. By this means, isothermal conditions were established. The reactor was operated at 4 bar. After having passed the capillary, the reaction was quenched to room temperature to slow the reaction. Further addition of cooled water completely stopped the reaction by cooling and dilution. A needle valve served for releasing pressure.

4.3.1.5 Typical Results

Conversion/selectivity/yield

[OS 31] [R 4] [P 23] Under electroosmotic flow conditions, the reactant benzene was mobilized as a microemulsion using sodium dodecyl sulfate (SDS) as surfactant [103] (see also [14]). The nitronium ions, generated *in situ* from sulfuric and nitric acid, were moved by electrophoretic forces. By this means, a 65% yield of a nitrobenzene was obtained; consecutive nitration products such as 1,3-dinitrobenzene (8% yield) and 1,3,5-trinitrobenzene (5% yield) were also produced.

[OS 34] [R 17] [R 19] [R 26] [P 23] By performing naphthalene nitration with fuming HNO_3 in micro reactors, the selectivity for mononitronaphthalenes can be significantly enhanced (Figure 4.48) [98]. The selectivity could be raised to more than 95%, independent of the microreactor used.

In addition, the isomeric ratios are affected. Whereas in industrial processes the ratio of 1- to 2-mononitronaphthalene is about 20 : 1; this ratio is dramatically increased to more than 30 by using micro reactors [98].

[OS 34] [R 17] [R 19] [R 26] [P 24] During naphthalene nitration in micro reactors, 100% conversion was obtained for all experiments undertaken [37]. Mainly mono and dinitro products were obtained (Figure 4.49) [37]. For batch processing of naphthalene, a wider range of products are found containing many isomers of the above-mentioned species, but also tri- or tetranitrated products. In the micro reactor, even at 50 °C and using a excess of nitrating agent, high selectivity was maintained, as exhibited by the high degree of mononitronaphthalenes in the product mixture [37].

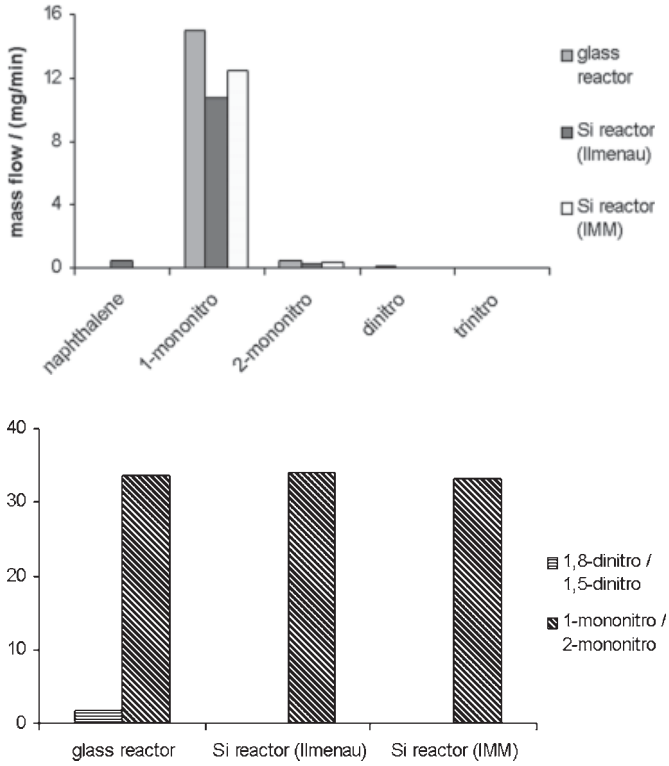


Figure 4.48 Product spectra and isomer ratios for the nitration of naphthalene with HNO_3 in micro reactors from different suppliers [98].

Ratio of regioisomers for aromatic substrates

[OS 34]] [R 17] [R 19] [R 26] [P 24] The isomeric ratio of two regioisomers, 1,5-dinitro- to 1,8-dinitronaphthalene, being constant at 1 : 3.5 for macroscopic batch reactors, changes to 1 : 2.8 in micro reactors [98]. The formation of the 1,5-dinitro product is, however, not favored (Figure 4.50, see also Figure 4.48 and Figure 4.49).

More detailed information concerning the characterization of micro mixers from different suppliers and of different mixing principles is given in [98] (this source may be difficult to obtain).

For conventional stirred tank processing of the nitration of benzene, see [102]. Here a description of regioisomer formation is given as a function of stirring intensity. Mechanistic analysis is also given there that may be applied to micro-reactor processing utilizing large specific interfaces.

Mixer/distributor impact on reaction

[OS 31] [R 16a] [R 26] [P 23] Reaction rates for the nitration of benzene increase strongly when the bore diameter is halved (from 127 to 254 µm) [31, 97]. In the temperature range investigated (60–90 °C), an increase in the reaction rate by a

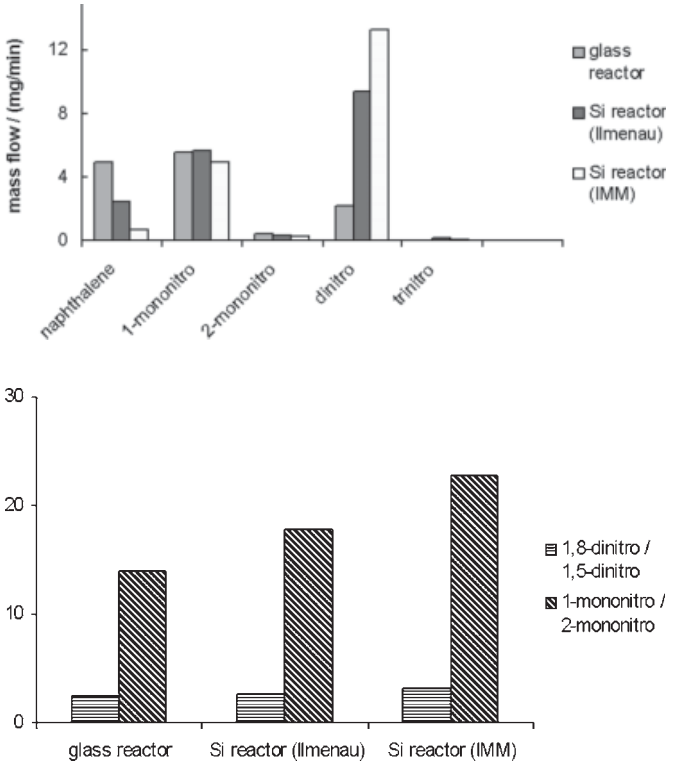


Figure 4.49 Product spectra and isomer ratios for the nitration of naphthalene with N_2O_5 in micro reactors of different types and from different suppliers [98].

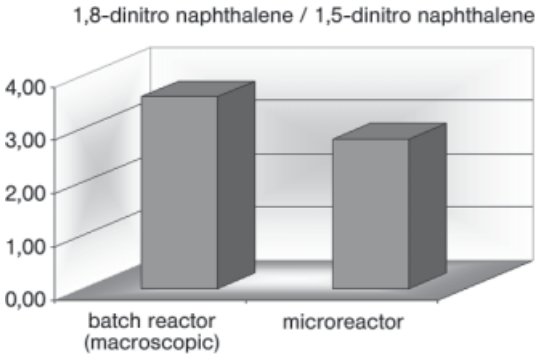


Figure 4.50 Comparison of isomeric ratios for 1,5- and 1,8-dinitronaphthalene. Reaction was performed in a macroscopic batch reactor and micro reactors of different types and from different suppliers [37].

factor of 3–4 was observed. The reaction rates (based on a shell-reaction model and a 1.5th-order assumption) achieved were in the range from 1 to 5.5 min^{-1}.

Smaller bore diameters naturally produce slugs of smaller diameter [31, 97]. Typically, a smaller length can also be generated thereby. As a consequence, internal circulation in the slug and specific interface between the slugs are increased. It is assumed that the impact of the increase in internal circulation on mass transfer/reaction processing is generally more dominant.

[OS 34] [R 17] [R 19] [R 26] [P 24] A detailed comparison of micro mixers from different suppliers and of different mixing principles, with regard to conversion, isomer formation and consecutive nitration, is given in [98].

For conventional stirred tank processing of the nitration of benzene, the dependence of conversion on impeller speed is given in [102].

Mixer/distributor impact on slug formation

[OS 33] [R 16b] [P 25] Uniform slugs of a single-ring aromatic/nitric acid were formed in a Y-piece having volumes according to the volumetric flows fed by piston pumps [94]. The volume of the individual slugs depends only on the internal diameter of the slugs. Thus, by decreasing the channel diameter, the interfacial area of the slugs can be increased. The capillary attached has a stabilizing effect on the slug flow and determines their length by setting the (fixed) internal diameter. The deviation of slug size distribution is very small and amounts only to about 5% from the average value. Hence the interfacial area is nearly constant for this type of capillary flow. A slug of the nitrating acid phase shown, for instance, has about a 0.75 mm diameter and 4 mm length; the slug of the organic phase is much smaller (Figure 4.51).

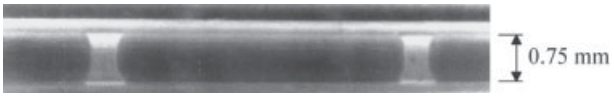


Figure 4.51 Liquid/liquid two-phase plug-flow with plugs of nitrating agent (dark) and organic phase (white) in a capillary micro reactor [94].

Mixer/distributor impact on phase contamination

[OS 33] [R 16c] [P 25] The amount of phase contamination, i.e. the undesired dispersion of one phase into the other as a consequence of unbalanced surface energies, of a parallel liquid/liquid flow through a 500 μm wide channel using a kerosene/propylene glycol/water mixture was studied to monitor a similar flow with benzene/nitric acid/sulfuric acid [31]. The study was performed at different aqueous/organic viscosity ratios (0.56–22.1). The contamination was analyzed as a function of the kerosene flow proportion, including ideal and non-ideal splitting (Figure 4.52). The experimental findings were compared with CFD results assuming laminar-flow properties. The two data sets were in agreement.

For optimum splitting, a contamination of less than 2% was found. By operating at slightly higher flow rates, one stream could be made contamination free. Thus, a clean product phase can be obtained when performing the nitration in the T-piece/tube reactor.

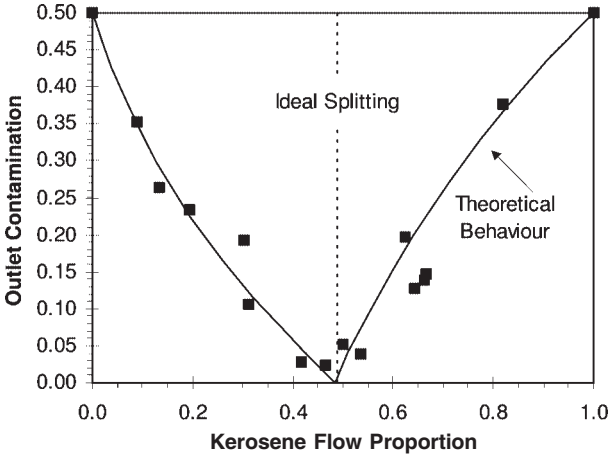


Figure 4.52 Observed flow splitting performance for a 1000 µm × 100 µm micro channel system [31].

Temperature impact

[OS 31] [R 16a] [P 23] On increasing the temperature, the reaction rate for nitration of benzene increases (Figure 4.53), as usually to be expected for most organic reactions [31]. For a capillary-flow micro reactor, more than doubling of the reaction rate was determined on increasing the temperature from 60 to 90 °C.

For toluene, a less significant impact of temperature (exceeding 70 °C) on reaction rates was observed than for benzene [31].

[OS 33] [R 16b] [P 25] For the nitration of a single-ring aromatic in a capillary-flow micro reactor, experiments were performed at two temperature levels, 60 and 120 °C [94]. Owing to the assumed increase in conversion rate with higher temperature, attempts were made to compensate for this by decreasing the capillary length at otherwise constant dimensions. For the 60 °C experiment, a very low

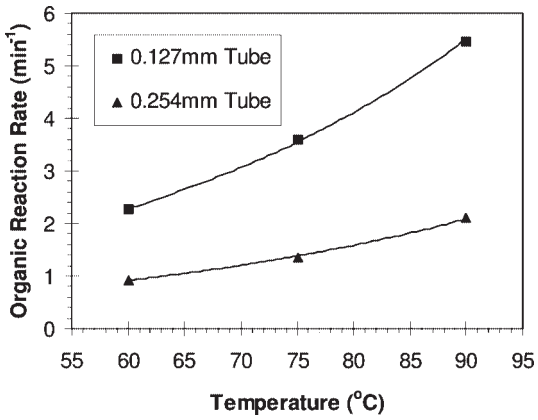


Figure 4.53 Increase of nitration performance as a function of temperature [31].

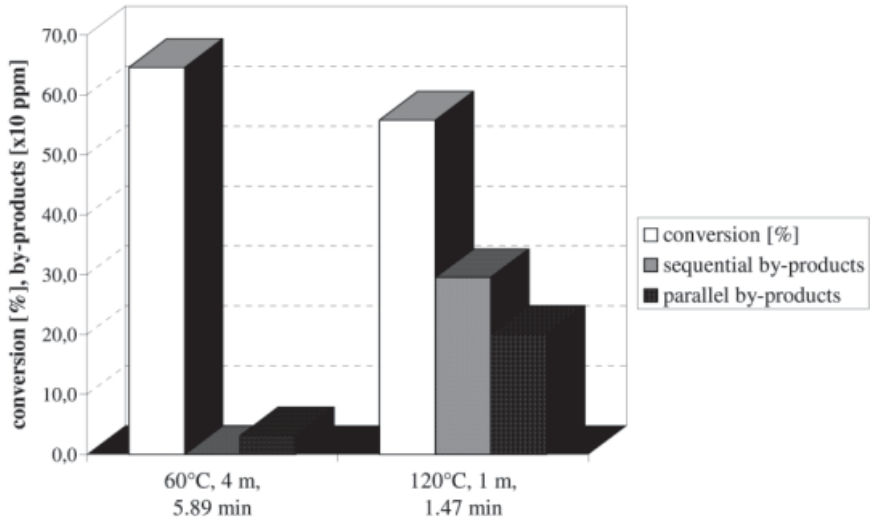


Figure 4.54 Comparison of conversion and by-product formation for two reaction temperatures [94].

level of parallel by-products (phenol derivatives) and consecutive by-products (dinitrated species) was found, not exceeding 50 ppm each (4 m capillary length; 0.75 mm diameter; 5.89 min). For the 120 °C experiment, high levels of parallel and consecutive by-products were found (1 m capillary length; 0.75 mm diameter; 1.47 min). Levels of 300 ppm dinitrated species and 200 ppm phenol derivative were detected (Figure 4.54). From 60 °C to 120 °C, the conversion decreased slightly from about 65 to about 56%. The increase in by-products with temperature shows that the activation energies of by-product formation are higher than for the product formation.

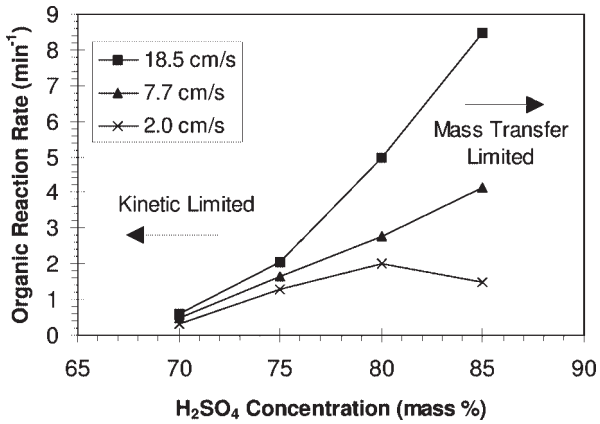


Figure 4.55 Varyiation of flow velocities to increase the nitration performance within the mass-transfer limited regime [31].

Flow velocity

[OS 31] [R 16c] [P 23] On increasing the flow velocity, the reaction rate for the nitration of benzene can be increased (Figure 4.55), provided that operation is performed in a mass-transfer limited regime [31, 97]. This was explained as being due to changing flow patterns which, in turn, affect the specific interface. Mass-transfer limited regimes were found at high sulfuric acid concentrations (> 75%). Reaction rates up to 8 min^{-1} were reached.

Sulfuric acid concentration/content of NO_2^+ ions

[OS 31] [R 16c] [P 23] By increasing the sulfuric acid content in the acid mixture, the acid strength is enhanced, i.e. more NO_2^+ ions are generated [31, 97]. This increases the reaction rate up to 8 min^{-1} (see Flow velocity, above).

Substrate reactivity

[OS 32] [R 16a] [P 23] Toluene nitration rates determined in the capillary-flow reactor were generally higher than benzene nitration rates [31, 97]. This is not surprising, as it stems from the higher reactivity of toluene towards electrophilic substitution owing to its more electron-rich aromatic core. For instance, at a reaction temperature of 60 °C, rates of 6 and 2 min^{-1} were found for toluene and benzene nitration, respectively. However, care has to be taken when quantitatively comparing these results, since experimental details and tube diameters vary to a certain extent or are not even listed completely.

Acid-to-organic flow ratio

[OS 32] [R 16a] [P 23] On increasing the ratio of flows in favor of the acid content, the toluene nitration reaction rate decreases, especially at low temperature (25 °C; 150 μm capillary tube) [31, 97]. The nitrotoluene concentration increases with increasing acid-to-organic flow ratio at a high temperature of 90 °C (178 μm capillary tube) [31, 97]. Mixtures having a ratio beyond 5 : 1 do not contribute any further to increasing nitrotoluene concentration as a consequence of the above mentioned decrease in the reaction rate. The concentration increases with increasing length of the capillary tube (450, 900, 1350 mm), which also shows that post-reaction in the collection vessel is of minor importance (Table 4.1).

Table 4.1 Influence of reaction temperature and acid-to-organic flow rate on the reaction rate of toluene nitration [31, 97].

to organic flow ratio	*Reaction rate at 25 °C (min^{-1})*	*Reaction rate at 60 °C (min^{-1})*
2 : 1	3.27	6.10
3 : 1	2.81	6.12
5 : 1	2.25	4.39
7 : 1	1.65	4.14

By-product formation

[OS 31] [R 16c] [P 23] The levels of dinitrobenzene, dinitrophenol and picric acid in the organic phase during benzene nitration in a micro reactor were monitored [31]. Picric acid levels were no higher than 100 ppm for all experiments conducted. Dinitrobenzene was the largest impurity fraction. A study revealed contents < 1000 ppm up to 34 mass-% on increasing the sulfuric acid content from 70 to 85%.

A more detailed and more accurate study showed the impact of temperature and tube inner diameter and took into account also the dinitrophenol impurity [31]. On increasing the temperature from 80 to 120 °C, the dinitrobenzene and dinitrophenol contents increase from 1640 and 340 ppm to 53 500 and 1233 ppm, respectively, for a 178 μm tube. For a 127 μm tube, the same temperature rise results in an increase in the dinitrobenzene and dinitrophenol contents from 970 and 90 ppm to 38 200 and 1281 ppm, respectively.

Tube diameter

[OS 31] [R 16c] [P 23] A decrease in tube diameter from 254 to 127 μm leads to an increased product yield for the nitration of benzene [31, 97]. At a temperature of 90 °C, the reaction rate increases by a factor of more than two.

Tube reactor length/residence time

[OS 32] [R 16a] [P 23] An increase in tube length from 45 to 135 cm leads to an increased product yield for the nitration of toluene [31, 97]. This is strongly dependent on the acid-to-organic flow ratio. The higher the latter, the larger is the difference in product yield (Figure 4.56).

The latter fact can be explained by the influence on the reaction time of varying the flow ratio [31, 97]. If the reaction time becomes longer than the residence time in any of the tubes investigated, differences in product yield result.

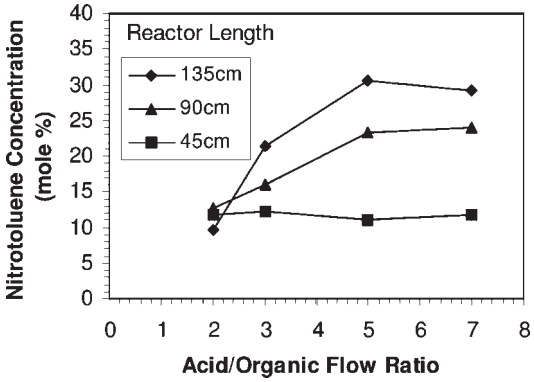


Figure 4.56 Nitrotoluene product formation at various acid-to-organic flow ratios using a reaction system with a liquid/liquid distributor and a tube at 90 °C [31].

Corrosion resistance

[R 16a] [R 19] [P 23] High sulfuric acid contents can lead to steel corrosion [37, 38, 97]. This may even lead to blockage owing to accumulation of corroded material in the tube. In [38] it is also claimed that steels are not suited for nitration; however, since the grade of the steel employed is not given, it cannot be excluded that high-alloy steels may behave better. Silicon, glass and titanium are recommended materials [38].

Benchmarking with patented literature

[OS 31] [R 16a] [P 23] For benzene nitration, the results achieved in the capillary-flow micro reactor were benchmarked against results claimed in the patent literature (see Table 4.2) [97]. An analysis of conversion, by-product level, reaction time and reaction rate showed that the results achieved in micro reactors and conventional equipment are competitive, i.e. were similar. As tendencies, it seemed that the micro reactor can lead to a lower by-product level owing to its better temperature guiding and that reaction times can be further shortened. However, the corresponding results are not absolutely comparable in terms of reaction conditions and hence further data are required here.

[OS 31] [R 16c] [P 23] In a further study, it is shown that about the same conversion (94%) can be achieved if the micro reactor is operated at lower temperature (90 °C instead of ~130 °C) and using higher sulfuric acid contents (78% instead of ~65%) [31]. The by-product level is, however, then much higher (4600 ppm instead of 1000–2000 ppm). The by-product level of the micro reactor can be decreased to commercial practice by decreasing the sulfuric acid content (to 72%), but at the expense of dramatically losing conversion (only 61%).

Table 4.2 Comparison of conversion and by-product formation for the nitration of benzene in conventional reactors and micro reactor set-ups [31].

Type of nitration process	*Inlet (°C)*	*Outlet (°C)*	*H_2SO_4 (mass-%)*	*Conversion (%)*	*By-product (ppm)*	*Time (s)*	*Rate (min^{-1})*
Conventional	80	128	60.6	89.5	1000	120	0.9
Conventional	80	134	65.2	99.9	2090	120	2.1
Conventional	95	120	69.5	90.0	1750	25.0	4.6
[97]	90	90	77.7	94.0 (178 µm capillary)	4600	24.4	5.9
[97]	90	90	72.2	60.7 (178 µm capillary)	< 1000	26.1	1.6

Mechanistic analysis of by-product formation

[OS 33] [R 16b] [P 25] For the nitration of a single-ring aromatic, the substituents of which were not disclosed, the mechanism of by-product formation was investigated in a capillary-flow micro reactor [94]. Dinitrated products were generated via consecutive nitration of the mononitrated product. It was concluded that phenolic by-products were formed directly from the aromatic, rather than from the mononitrated product. This proposed reaction mechanism could be confirmed by performing selective nitration of the mononitrated product. Here, even after relatively long residence times of about 20 min (at 120 °C), no phenolic moieties were detected in the product mixture. On the contrary, after less than 5 min phenols were formed using the single-ring aromatic (at 120 °C).

Interphase mass transfer between liquid–liquid slugs

[OS 33] [R 16b] [P 25] The influence of interphase mass transfer between liquid/liquid slugs was investigated for nitration of single-ring aromatics in a capillary-flow reactor [94]. This was achieved by changing flow velocity via volume flow setting. The residence time was kept constant by increasing the capillary length with respect to the flow change.

Conversion to the mono nitrated aromatic increased linearly with increasing flow velocity owing to enhanced mass transfer (120 °C; 2.95 min; 9.0–36.0 ml h^{-1}; 1.0–4.0 m capillary length; 0.75 mm capillary inner diameter) [94]. The formation of parallel by-products (phenols) increased in the same manner for similar reasons (Figure 4.57). 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.

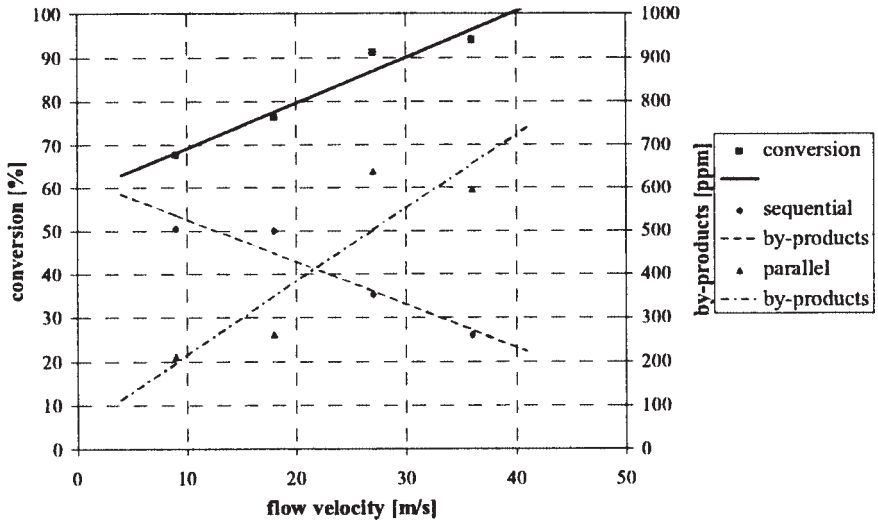


Figure 4.57 Dependence of conversion and the amounts of dinitrated and phenolic by-products on flow velocity (120 °C; 2.95 min) [94].

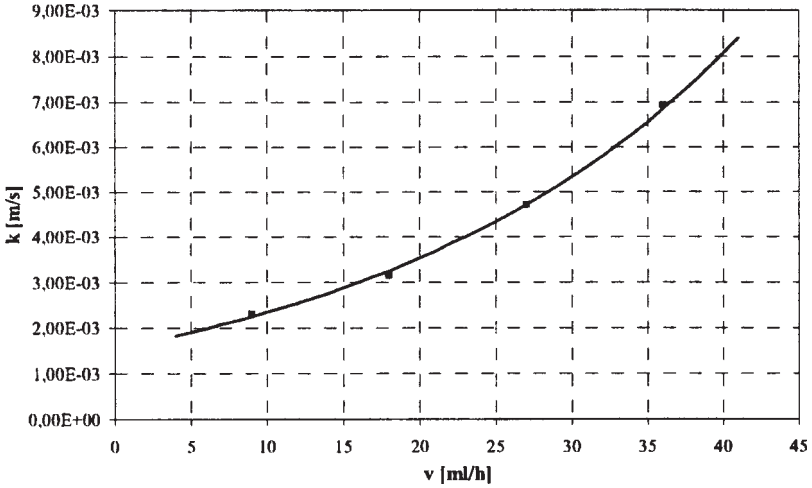


Figure 4.58 Interphase mass-transfer coefficient obtained for a reaction engineering model [94].

Reactor model

[OS 33] [R 16b] [P 25] For the nitration of single-ring aromatics in a capillary-flow reactor, a reactor model was developed, taking into account both mass transfer of organic components between the two phases and the homogeneous reaction within the aqueous phase, in the latter case relying on literature data [94]. For instance, results obtained at different flow velocities could be deduced in this way (Figure 4.58).

In a further step, an extended kinetic model was developed and applied, considering the kinetics of the homogeneous side reactions as well [94]. By this means, the activation energies of these processes could be derived.

Simulation of circulation zones

[OS 33] [R 16b] [P 25] For the nitration of single-ring aromatics in a capillary-flow reactor, internal circulation, exhibiting an inner downwards and an outer upwards flow, in the aqueous slug of a two-phase flow was simulated [94].

4.3.2 Diazotization + Arylazodehydrogenation – Diazonium Salt Formation + Diazo Coupling (Azo Chemistry)

Peer-reviewed journals: [4, 104] [107]; proceedings: [55]; sections in reviews: [14, 83, 89, 90, 105]; trade press: [106].

4.3.2.1 Drivers for Performing Azo Chemistry in Micro Reactors

Diazo coupling was used to demonstrate the feasibility of organic multi-step synthesis on a chip [4]. This involved showing the safe quenching of hazardous intermediates such as the diazonium salts needed as precursor for that synthesis. Especially, this involves the *in situ* generation and consumption of such species.

From an analytical point of view, azo coupling is easy to monitor as visual inspection of the color formation by reaction in transparent reactors can be performed.

As azo compounds are intensely colored, they find commercial use as pigments [55]. The motivation to use micro reactors here stems from the benefits of developing a continuous process – production of flexible quantities and eliminating the need for refining such as milling the pigment in the end of the production line, as typically given for batch processes. The new micro-reactor process with intensified mixing characteristics is also expected to provide pigments with improved features, as usually specified by color strength, transparency, brightness and purity.

Coupled with the latter investigations, it was shown that a diazo suspension can be fed through a micro device without leading to plugging [55]. This broadens the scope of micro processing applicability towards azo pigment formation.

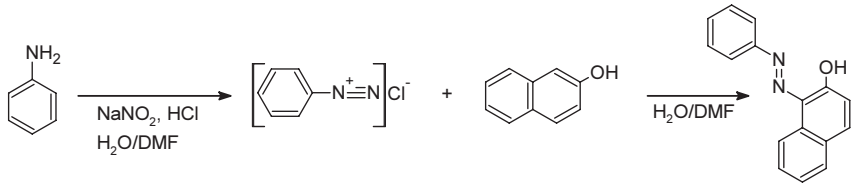
4.3.2.2 Beneficial Micro Reactor Properties for Azo Chemistry

When considering the thermal management of very exothermic reactions and the avoidance of corresponding explosions, it is the minute volume of micro reactors that is addressed [4].

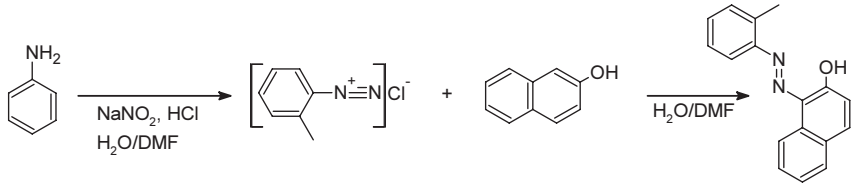
Micro mixers provide completely different and often improved mixing characteristics compared with conventional batch stirring. For this reason, it is very likely that the material properties of azo pigments produced by continuous micro chemical processing can be substantially changed [55]. By continuous processing using a simple micro mixer–tube reactor configuration, large throughputs can be realized, fulfilling the demands of pilot-scale processing.

4.3.2.3 Azo Chemistry Investigated in Micro Reactors

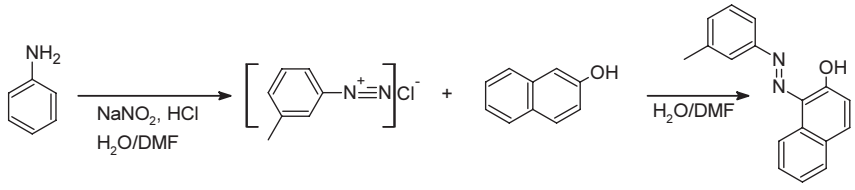
Organic synthesis 35 [OS 35]: Formation of 1-(phenylazo)-2-naphthol (Sudan I) [4]



Organic synthesis 36 [OS 36]: Formation of 1-(2-methylphenylazo)-2-naphthol [4]

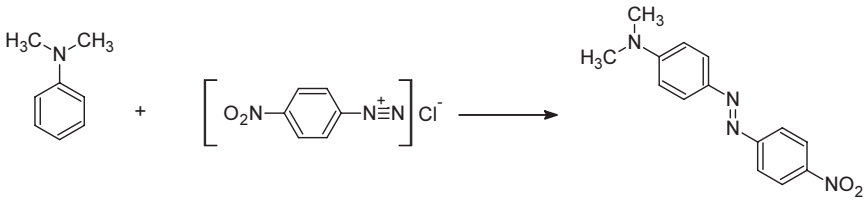


Organic synthesis 37 [OS 37]: Formation of 1-(3-methylphenylazo)-2-naphthol [4]



In addition to pigment applications, azo dyes are also used in medicinal chemistry. Sulfanilamide, the metabolite of an azo dye, has antibacterial properties [4]. The Sudan series of azo dyes, which have also been synthesized in micro reactors, are commonly used as microbial stains. The thermally unstable nature of the diazonium precursors and reported explosions often demand extensive safety procedures when going to an industrial scale, which limits the commercial applicability of the azo reaction.

Organic synthesis 38 [OS 38]: Formation of an azobenzene derivative from *N,N*-dimethylaniline with 4-nitrobenzenediazonium tetrafluoroborate



The synthesis of *N,N*-dimethylaniline with 4-nitrobenzenediazonium tetrafluoroborate yielded the corresponding azobenzene derivative [107] (see also [14]).

Organic synthesis 39 [OS 39]: Formation of azobenzene derivatives for pigment production

Two commercial azo pigments, one yellow and one red, were prepared following the scheme given above; the nature of the substituents was not disclosed [55].

4.3.2.4 Experimental Protocols

[P 26] A chip micro reactor with two consecutive micro-mixing tees, each attached to a serpentine channel section, was used [4]. In the first mixing tee, a solution of the following composition was fed: 0.1 ml of aniline, 0.35 ml of concentrated hydrochloric acid, 2 ml of water and 12 ml of *N,N*-dimethylformamide DMF. The second mixing tee was fed with a solution comprising 0.75 g of sodium nitrite in 4 ml of water and 20 ml DMF. Both solutions were fed at a flow rate of 3.5 µl min^{-1}. Thereafter, the mixed flow passed a serpentine channel section which acted as a delay loop. The length of this loop was set to guarantee at least complete diffusion mixing. Thereafter, a third solution was fed by a second mixing tee into the reacted solution, comprising 0.15 g of *β*-naphthol, 9 ml of 10% sodium hydroxide solution and 20 ml of water in 290 ml DMF. This solution was fed at a flow of 7 µl min^{-1} using a syringe pump. A second serpentine section was used to perform the azo coupling, which could be monitored by optical inspection.

[P 27] Diazotation was performed in batchwise manner [55]. A CPC micro reactor with multi-lamination mixer (lamellae < 100 µm) was embedded in a housing

and equipped with pumps, heating bath and vessels. No further details on the reactor were given. Into this micro reactor, the diazonium compound and the coupling agent were charged. The acid generated was buffered by an additional feed of 2–6% NaOH solution or by using internal buffer. No further details on the protocol were given. The pigment suspension formed was conventionally separated from the reaction solution, dried and milled.

4.3.2.5 Typical Results

Conversion/selectivity/yield

[OS 35] [R 4b] [P 26] A conversion of 52% was found [4].

[OS 36] [R 4b] [P 26] A conversion of 23% was found [4]. This result and that below, compared with the much higher value given above, show that the reaction is not optimized for azo chemistry. The large degrees in conversion do not stem from the different reactants applied solely.

[OS 37] [R 4b] [P 26] A conversion of 9% was found [4].

[OS 38] [reactor and protocol given in [107]] By reaction of *N,N*-dimethylaniline with 4-nitrobenzenediazonium tetrafluoroborate, the corresponding azobenzene derivative is obtained at a conversion of 37% using methanol (protic solvent) or acetonitrile (aprotic solvent) under electroosmotic flow conditions [107] (see also [14]).

Optical properties of pigments

[OS 39] [R 25] [P 27] The two azo pigments made in the micro reactor had a color strength of 119 and 139%, a 5 and 6 times glossier brightness and a 5 and 6 steps higher transparency compared with the same products made by batch-processing (Table 4.3) [55]. The beneficial product features were due to the formation of smaller particles with a narrower size distribution (micro reactor, $D_{50} = 250$ nm, $s = 1.5$; batch, $D_{50} = 600$ nm, $s = 2.0$).

Table 4.3 Color properties of pigments synthesized in two different micro reactors compared with the batch standard [55].

	Micro reactor pigment 1	*Micro reactor pigment 2*
Color strength (%)	119	139
Brightness	5 steps glossier	6 steps glossier
Transparency	5 steps more transparent	6 steps more transparent

The same features were found for pilot-size micro-reactor operation (Figure 4.59). Brightness and transparency were the same and color strength could be increased to 149% [55]. The mean particle size was even set to a lower value compared with the laboratory-scale processing (micro reactor, $D_{50} = 90$ nm, $s = 1.5$; batch, $D_{50} = 600$ nm, $s = 2.0$).

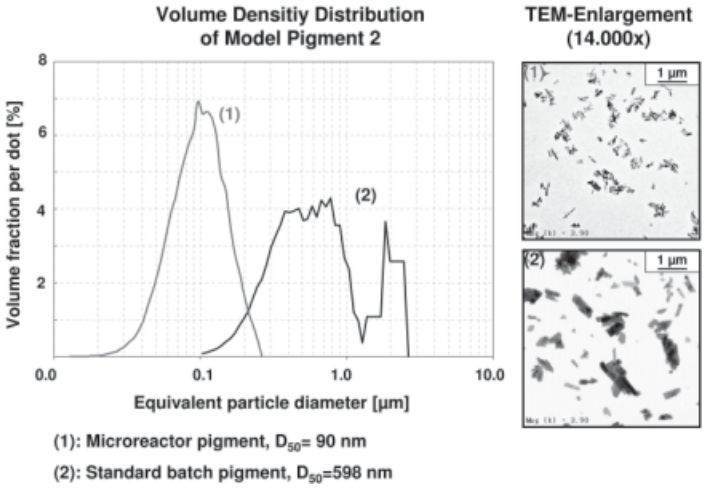


Figure 4.59 Properties of a model pigment (termed "2" in [55]) obtained in the pilot-plant micro reactor compared with the batch standard. Left: volume density distribution. Right: TEM enlargement [55].

Pilot-scale processing

[OS 39] [R 25] [P 27] Using a flow of 500 ml h^{-1}, a production of commercial azo pigments in the range of 10 t a^{-1} was estimated when accounting for 8000 h annual running time [55]. The increase in throughput compared to laboratory-scale micro reactors used previously (1 t a^{-1}; 20–80 ml h^{-1}) was achieved by both internal and external numbering-up accompanied by a slight scale-up of internal dimensions. More reaction plates were operated in parallel within one device; in addition, three such devices were operated in parallel. Furthermore, slightly larger micro channels were used, still ensuring laminar flow.

Fouling during suspension processing

[OS 39] [R 25] [P 27] A 24 h run of a pilot-scale micro reactor for azo pigment production was performed using a diazo suspension [55]. At the end of this period, the pressure loss of the micro reactor increased exponentially. Special means were developed to prevent clogging and unstable operation. By partial removal of the deposits, the pressure loss was brought back to normal.

4.3.3
Alkoxyborondehydro Substitution – Arylboron Formation

Proceedings: [48]; patents: [108]; sections in reviews: [79, 80, 90, 109].

4.3.3.1 Drivers for Performing Arylboron Formation in Micro Reactors

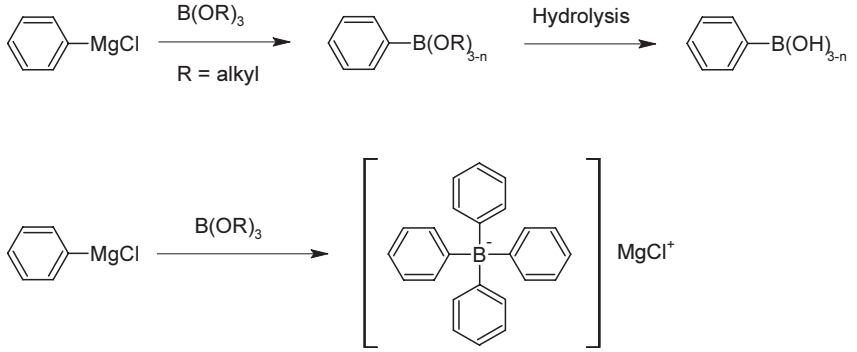
The main driver was to develop a laboratory-scale micro-channel process and transfer it to the pilot-scale, aiming at industrial fine-chemical production [48, 108]. This included fast mixing, efficient heat transfer in context with a fast exothermic reaction, prevention of fouling and scale-/numbering-up considerations. By this means, an industrial semi-batch process was transferred to continuous processing.

4.3.3.2 Beneficial Micro Reactor Properties for Arylboron Formation

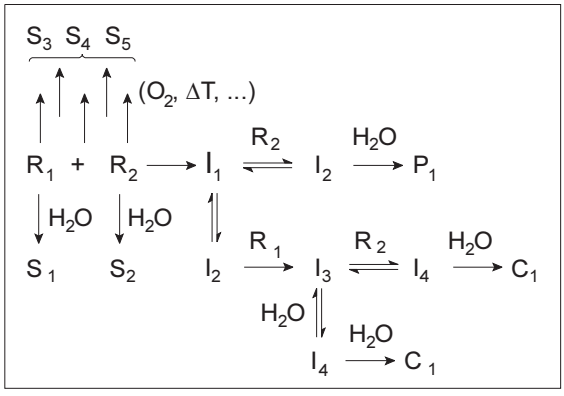
The above motivation refers to the general advantages of improving mass and heat transfer at reduced residence times. This particularly refers to micro mixing features. Also, the more facile scalability of micro-channel processing is targeted when going from laboratory-scale to pilot-scale processing.

4.3.3.3 Arylboron Formation Investigated in Micro Reactors

Organic synthesis 40 [OS 40]: Formation of phenyl esters of boronic acid



The formation of phenyl esters from boronic acid and phenylmagnesium bromide in THF is a fast liquid reaction involving contacting of two reactants, R_1 (boronic acid) and R_2 (phenylmagnesium bromide), dissolved in the same solvent to yield a liquid mixture [48, 108]. This mixture is post-processed by a fast hydrolysis. This step was performed conventionally in a batch mode.



The two reactants R_1 and R_2 form an intermediate I_1 which reacts to a second intermediate I_2 via two reaction pathways, one needing the presence of R_2 [48, 108]. A number of additional reactions decrease the selectivity and yield. First, the reactants R_1 and R_2 are labile to moisture. Hydrolysis results in the formation of the side product reactants S_1 and S_2. By more complex pathways, three other known

side products, S_3, S_4 and S_5, are generated. Second, a consecutive intermediate product I_3 is formed when I_2 reacts with R_1 (equivalent to R_2 reacting with two molecules of R_1). By addition of R_2 or by another process route, a further consecutive intermediate product I_4 is yielded. In the post-processing step, I_4 is converted to the final consecutive product C_1. A low content of this species is, in particular, important for a facilitated product separation. C_1 and all other side products remain in solution after finishing the process and cannot be separated simply by filtration.

The intermediates I_1 and I_3, however, precipitate in the course of the reaction [48, 108]. They are dissolved again by post-processing to the product P_1 and the consecutive product C_1.

4.3.3.4 Experimental Protocols

[P 28] A glass interdigital micro mixer was connected to PTFE tubes with an inner diameter of 2 mm which was immersed in an ice–water bath of appropriate temperature (laboratory set-up) [48, 108]. Operation was performed for 5–40 s at temperatures ranging from –12 to 50 °C.

Typically, 2 mol l^{-1} solutions of the reagents boronic acid and phenylmagnesium bromide were applied for the former semi-batch industrial process [48, 108]. However, operation with such highly concentrated solutions in a triangular interdigital mixer–tubular reactor resulted in intense fouling and even clogging. Therefore, it was attempted to dilute the solution to a concentration which can be properly handled. It turned out that a 0.5 mol l^{-1} reactant solution did fulfil this criterion. Thereby, it was possible to operate the set-up for about 15 min. Thereafter, fouling was clearly visible in the interdigital mixer by white stripes composed of precipitates along the interfaces between the liquid lamellae. A 15 min processing time turned out to be long enough to gather reliable data on process yield.

[P 29] A set-up comprising a steel caterpillar mini mixer and four steel tubes attached was used, being dipped into a cylinder completely filled with a cooling medium (scale-up set-up) [48, 108]. By means of a 5/2-way valve, it was possible to switch the reactants to either of the tubes acting as delay loops, differing in inner diameter and hence residence time.

Compared with the simple and flexible laboratory set-up, the scale-up set-up is said to be more robust and user-friendly [48, 108]. By selecting the proper delay tube via the 5/2-way valve, the residence time was varied 5, 10, 26 and 120 s at 10 and 20 °C, and 1, 5, 10 and 26 s at 30 and 40 °C. The stainless-steel tubes used had inner diameters of 0.7, 3.8, 4.8, 9.3 and 21.2 mm and a length of 1000 mm (four tubes were permanently mounted and one was exchanged, if needed).

4.3.3.5 Typical Results

Conversion/selectivity/yield

[OS 40] [R 20] [P 28] The best yield obtained in the interdigital micro-mixer laboratory-scale set-up was 83% (22 °C; 1000 ml h^{-1}; 8 s) [48]. Compared with the performance of the industrial production process (65%, batch), this is an improvement of nearly 20%. Most experiments done at widely different residence time and reaction temperature did not differ from this best yield by more than 5–10%.

Accordingly, for all these parameter sets, favorable mass and heat transfer could be achieved, which was explained as being mainly due to having the same flow patterns for all these sets and having large surface-to-volume ratios.

[OS 40] [R 21] [P 29] Using a caterpillar mini mixer inserted in the scale-up setup, a maximum yield of 89% was determined [48]. This is even slightly higher than for the laboratory-scale setup (83%, see above).

[OS 40] [R 20] [P 28] The above-mentioned clogging in the interdigital micro mixer [R 20] naturally was an exclusion criterion for being applied also to pilot-scale and production operation [48]. Hence a mixer with larger internals, the caterpillar mini mixer, was used, following a similar choice already made for another industrial process (see Section 4.9.3.5). By this, fouling and clogging could be largely avoided.

Residence time

[OS 40] [R 20] [P 28] Using an interdigital micro mixer, a nearly constant yield could be obtained for the full range of residence times at 22 and 50 °C (5–40 s) [48]. At lower temperature (–12 °C), a maximum yield at a flow rate of 1000 ml h^{-1} (5 s) is obtained. Still higher flow rates lead to a too low residence time (Figure 4.60).

[OS 40] [R 21] [P 29] Using a caterpillar mini mixer, the yield differed strongly on changing the flow rate (Figure 4.61) [48]. This was explained by the much stronger dependence of micro mixing of this split–recombine mixer as compared with a multi-lamination mixer (see above). A CFD simulation is also given, showing non-ideal flow patterns in the caterpillar mixer, deviating from ideal multi-lamellae arrangements.

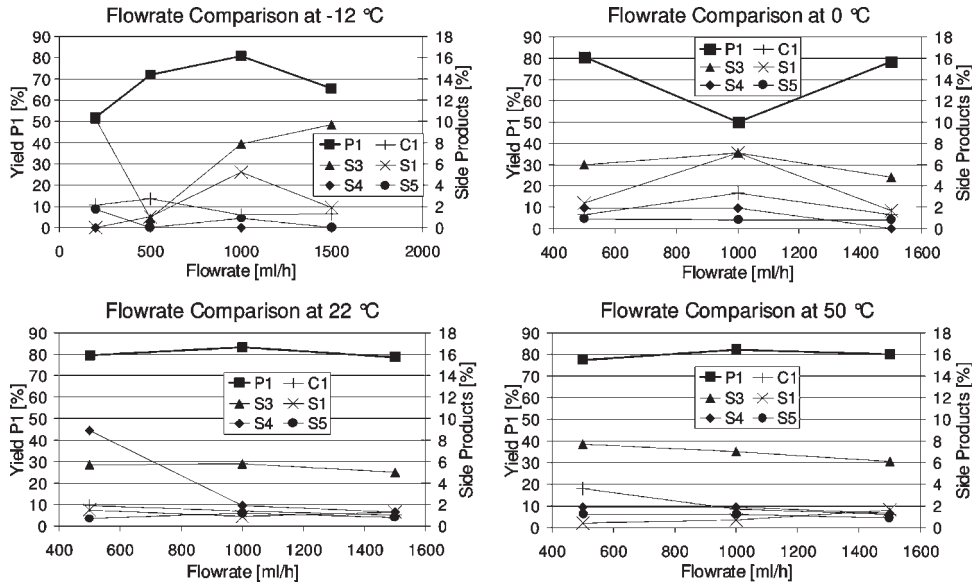


Figure 4.60 Yield of product and side/consecutive products as a function of flow rate, respectively residence time for the laboratory set-up with an interdigital micro mixer [48].

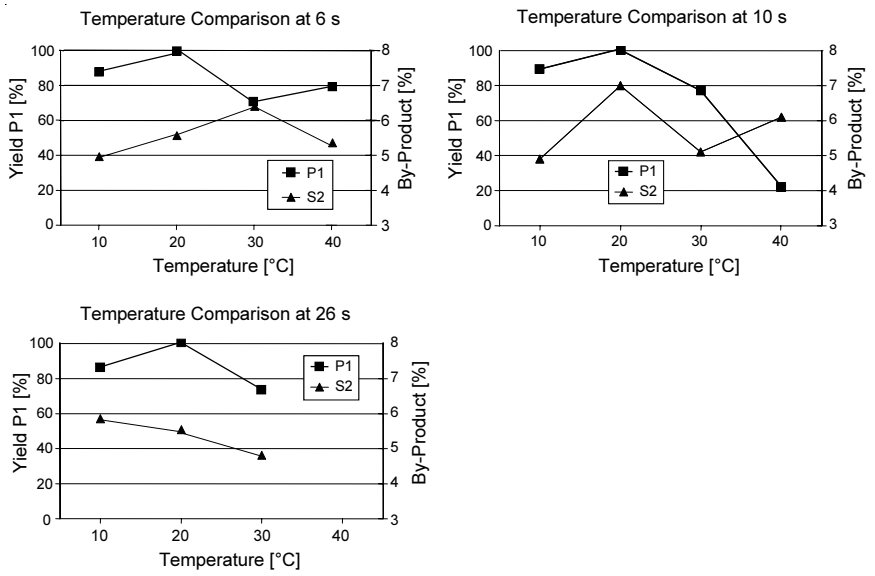


Figure 4.61 Yield of product and side/consecutive products as a function of temperature for the scale-up set-up with a caterpillar steel mini mixer [48].

This mixing-based explanation was confirmed by the finding that by changing the residence time at a constant flow rate, i.e. changing it by prolongation of delay-loop tubing, the yield was fairly constant [48]. Here, the same mixing quality is assured when the varying residence time.

Temperature

[OS 40] [R 20] [P 28] Similarly to residence time variation, fairly constant behavior was found on varying the temperature [48]. There is a slight increase in yield with a rise of temperature from –12 to 0 °C, then approaching a constant value. The fact that the yield does not decrease at high temperature is indicative of similar activation energies of the main and side reactions. It also confirms that the residence time was properly set, as a too long processing would enhance the contents of consecutive products.

[OS 40] [R 21] [P 29] A much larger dependence of yield on reaction temperature was observed for the caterpillar mixer–scale-up set-up than for the interdigital mixer–laboratory set-up [48]. At temperatures above ambient, significant decreases in yield of the order of several tens percent were determined.

Side and consecutive products

[OS 40] [R 20] [R 21] [P 28] Various side products were formed during the reactions, each typically not exceeding 5% [48]. The formation of side products decreases with increasing flow rate, i.e. providing a longer residence time than kinetically needed decreases selectivity (Table 4.4).

Table 4.4 Yields obtained for the target product and side/consecutive products using a laboratory-scale set-up with caterpillar steel micro mixer [48].

Temperature	*–12 °C*				*0 °C*			*30 °C*			*40 °C*		
Flow rate (ml h^{-1})	200	500	1000	1500	500	1000	1500	500	1000	1500	500	1000	1500
P_1	51.9	72.0	80.7	65.5	80.6	50.1	78.4	79.6	83.2	78.7	77.4	82.1	80.1
C_1	2.1	2.7	1.2	1.3	1.3	3.3	1.3	1.9	1.4	1.0	3.6	1.7	1.2
S_3	10.2	0.9	7.9	9.7	6.0	7.1	4.8	5.7	5.8	5.0	7.7	7.0	6.1
S_1	0.0	1.0	5.2	1.9	2.4	7.1	1.7	1.5	0.9	1.3	0.4	0.7	1.6
S_4	0.0	0.0	0.0	0.0	1.9	1.9	0.0	8.9	1.9	1.3	1.9	1.9	1.3
S_5	0.0	0.0	0.9	0.0	0.9	0.8	0.8	0.7	1.2	0.8	1.2	1.2	0.9

[OS 40] [R 21] [P 28] The amount of the various side/consecutive products for the scale-up set-up was of the same order (Table 4.5) as for the laboratory-scale investigations [48].

Table 4.5 Yields obtained for the target product and side/consecutive products using a laboratory-scale set-up with caterpillar steel micro mixer [48].

Flow rate (ml h^{-1})	*2000*	*10 000*
Mass of isolated crystals (g)	26.29	43.83
Yield (%)	65	81
P_1 content (%)	98.9	98.2
C_1 content (%)	~1.0	~1.7
Total content of S_1, S_3, S_4, S_5 (%)	< 0.1	< 0.1

Inner diameter

[OS 40] [R 21] [P 29] With the exception of one experiment, the choice of internal dimensions, i.e. the inner diameter of tubing attached to the micro mixer, did not greatly affect the yield [48]. Accordingly, heat transfer was probably not a major issue for micro-channel processing. Tubes as large as 4.8 mm could be employed successfully, provided that the temperature was not set too high. Processing in tubes of 9.3 mm inner diameter, however, resulted in clogging, probably owing to the extremely slow velocities applied, hence providing a high degree of back-mixing.

Preparative isolation

[OS 40] [R 21] [P 29] To corroborate HPLC results, obtained prior to yield analysis, preparative isolation of the product was achieved by precipitation and filtration of the crystals [48]. A crystal mass up to about 44 g was so isolated at a yield of up to 81%. The product was of high purity (> 98% of the total crystal mass).

4.4
Aliphatic Electrophilic Substitution

4.4.1
Keto–Enol Tautomerism – Isomerization of Allyl Alcohols

Peer-reviewed journals: [110, 111]; proceedings: [112, 113]; sections in reviews: [90, 99, 114, 115].

4.4.1.1 Drivers for Performing Isomerization of Allyl Alcohols in Micro Reactors

Allyl alcohol isomerization is typically conducted as a single-phase reaction, needing efforts for separation of the catalyst [110, 113]. One driver was to exploit a catalyzed liquid/liquid route with aqueous (catalytic) and organic phases as commonly employed in the chemical industry.

To establish a multi-phase process for isomerization requires high mass transfer between the phases to be conducted in a kinetically controlled manner [110, 112]. Despite affecting conversion, mass transfer is known to impact enantio- and regioselectivity for many reactions [110]. For this reason, also conventional micro-titration apparatus, typically employed in combinatorial chemistry of single-phase reactions, often suffers from insufficient mixing when dealing with multi-phases [110].

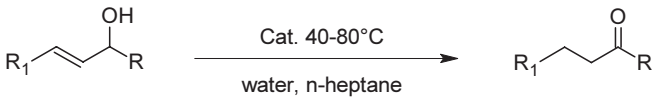
Furthermore, allyl alcohol isomerization is of interest for fine-chemical applications [112]. Owing to the large number of available allyl alcohol derivatives, by varying the two substituents, screening approaches are needed to exploit and investigate the full range of possible compounds.

4.4.1.2 Beneficial Micro Reactor Properties for Isomerization of Allyl Alcohols

Micro reactors are capable of generating large specific interfaces between two liquids, thereby enhancing mass transfer. For example, interdigital micro mixers are known to produce fine emulsions [116]. By using small samples, they also allow efficient screening. Besides parallel approaches, serial screening is increasingly recognized as an efficient way particularly for multi-phase micro-channel processing [110]. Detailed investigations concerning test-throughput frequency, sample consumption and significance of screening experiments have been reported, e.g. [111, 117].

4.4.1.3 Isomerization of Allyl Alcohols Investigated in Micro Reactors

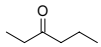
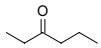
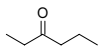
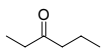
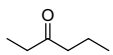
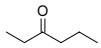
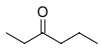
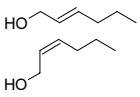
Organic synthesis 41 [OS 41]: Isomerization of diverse substituted allyl alcohols



The substrates and products of this reaction remain mainly in the organic layer, whereas the catalyst is soluble only in the water layer

(a) In one major study, 1-hexen-3-ol was used as substrate and reacted with diverse catalysts (Table 4.6). A restricted library consisting of eight catalytic systems from four transition-metal precursors (Rh, Ru, Pd, Ni) and four sulfonated phosphane or disphosphane ligands was described [110].

Table 4.6 Yield of 1-hexen-3-ol isomerization products when using different catalysts [110].

Catalyst	*Ligand : metal ratio*	*Product*	*Conversion (%)*
$RhCl_3$/TPPTS	4.6 : 1		53
Rh_2SO_4/TPPTS	4.1 : 1		34
$[Rh(cod)Cl]_2$/DPPBTS	1.1 : 1		36
$[Rh(cod)Cl]_2$/BDPPTS	1.1 : 1		1.5
$[Rh(cod)Cl]_2$/CBDTS	1.3 : 1		1
$RuCl_3$/TPPS	4.0 : 1		61
$PdCl_2$/DPPBTS	2.6 : 1		3.5
$Ni(cod)_2$/TPPS	4.0 : 1		9 3

(b) In a subsequent study, the substrate was also varied [112]. Five C_4–C_8 alcohols were employed.

4.4.1.4 Experimental Protocols

[P 30] The reaction was carried out at 40–80 °C using a catalyst in water/*n*-heptane. Organic pulses containing substrates (e.g. from a 1000 µl loop) were injected simultaneously with pulses containing catalyst solutions (e.g. from a 200 µl loop) and contacted in a slit-type interdigital micro mixer (Figure 4.62) [110]. Flow rates of the organic and aqueous phases were 60 and 300 ml h^{-1}, respectively, amounting to a residence time of 100 s. The mixer is part of a liquid/liquid HTS reaction system, comprising a reaction glass tube (4 mm inner diameter; 800 mm length),

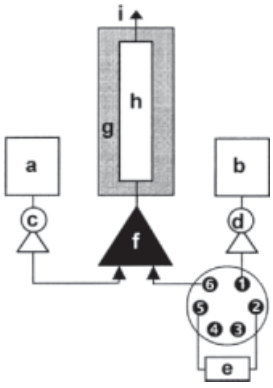


Figure 4.62 Experimental set-up for liquid/liquid experiments: (a) reservoir for the substrate in *n*-heptane; (b) water reservoir; (c, d) high-pressure liquid pumps; (e) HPLC injection valve with sample loop for catalyst injection; (f) micro mixer; (g) heating mantle; (h) tubular stainless-steel reactor; (i) outlet to analytics [112].

injection valves and high-pressure liquid pumps. By mixing, emulsification of the organic phase in water was achieved, creating a reacting segment (pulse) moving downstream the reactor tube. Such *n*-heptane-in-water emulsions were stable for more than 10 min.

4.4.1.5 Typical Results

Variation of transition metal used in the catalyst complex

[OS 41a] [R 19] [P 30] Palladium complexes were inactive with monophosphane ligands and only weakly active with diphosphane ligands (conversion 3.5%) [110]. Nickel complexes led to 1,3-transposition of the hydroxyl group. Ruthenium and rhodium complexes gave comparable conversions. Ruthenium had the highest activity of 61% conversion, but suffered from side reactions decreasing selectivity. Of various rhodium(I) complexes differing in the ligands, the ligand tris(*m*-sulfophenyl)phosphane gives the best result (conversion 53%). This catalyst also had activity for several other substrates than 1-hexen-3-ol.

Variation of alcohol substrate – benchmarking to conventional apparatus

[OS 41a] [R 19] [P 30] Ten different substrates (C_4–C_8 alcohols) were reacted with rhodium(I)–tris(*m*-sulfophenyl)phosphane [110]. The variance in conversions (ranging from about 1–62%) determined was explained by differences in the solubility of the alcohols in the aqueous catalytic layer and by their different intrinsic activities. Chain length and steric/electronic effects of the different alcohols affected their reactivity in a well-known pattern (Figure 4.63). The results obtained correspond to the conversions achieved in a well-mixed traditional batch reactor (40 cm^3). They further agreed with data from mono-phasic processing.

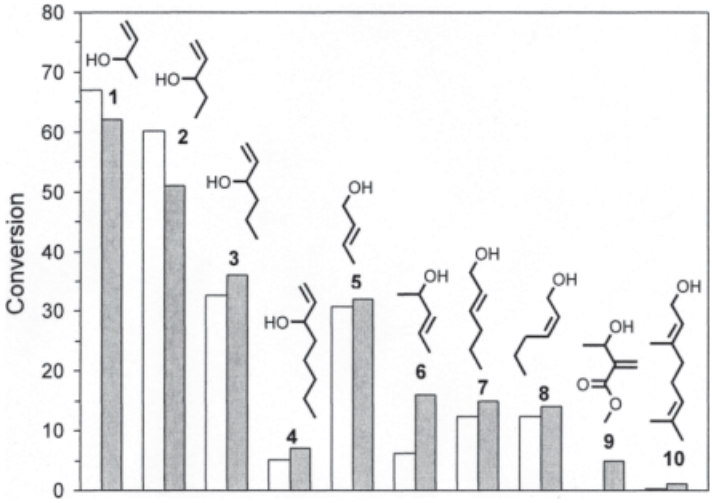


Figure 4.63 Comparison between the results of the screening of different substrates against one catalyst in a batch reactor (white columns) and micro reactor set-up (gray columns) [110].

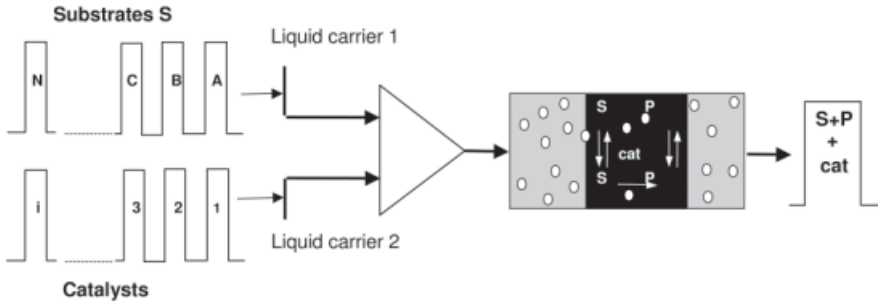


Figure 4.64 Schematic of a mixer–tube reactor set-up used for high-throughput sequential screening of (i) catalysts and (N) substrates. The substrate (S) is thus treated to form the product (P) [110].

Benchmarking to long-time small vial and short-time mini batch processing

[OS 41a] [R 19] [P 30] A study was undertaken to compare extended (1 h) processing in small vials (2 cm^3) with short-time (100 s) continuous micro reactor and mini-batch (10 cm^3) operation for 10 different substrates (C_4–C_8 alcohols) which were reacted with rhodium(I)–tris(*m*-sulfophenyl)phosphane [111]. The vials were either directly filled with the two phases yielding a bilayered fluid system with small specific interfaces or by interdigital micro mixer action yielding an emulsion with large specific interfaces.

Concerning the small-vial tests, it was evident that by introducing emulsions with small droplets, the conversion was generally increased [111]. An exception to this trend was a highly soluble substrate for which mass transfer was not an issue. The conversions found for the small vials, irrespective of whether a micro mixer was used or not, were generally high, reflecting the long reaction time provided. As a consequence, it was not possible to rank substrate reactivity, i.e. to perform kinetic studies. For this reason, a tool was needed providing shorter residence times such as continuous micro flow devices.

A micro mixer–tube reactor set-up, in which pulses of substrates and catalysts were injected (Figure 4.64), fulfilled that criterion [111]. By this means, a ranking of substrate reactivity was possible. It was shown that the different reactivities of the 10 substrates found were due to their varying solubility in the aqueous phase where the catalyst is provided.

By comparison with data from a vigorously stirred mini-batch reactor (10 cm^3), it could be shown that this micro-reactor operation gave intrinsic kinetic data [111]. This is demonstrated, e.g., by the lower conversion of the branched iso-alcohols respective to the normal-chain ones.

Parity plot – flow modeling

[OS 41b] [R 19] [P 30] A Parity plot (Figure 4.65) for five different substrates (C_4–C_8 alcohols) was derived, showing a comparison of experimental data with a plug and laminar flow model [112]. In the plug-flow case, much higher conversions were theoretically expected than actually measured. Laminar-flow modeling describes the results much better and is in line with visual inspections of the liquid/liquid flow.