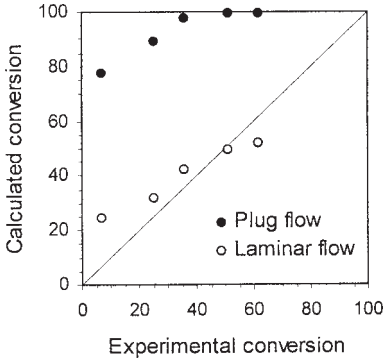


Figure 4.65 Parity plot comparing the conversion of a batch and laminar flow model for five different substrates made by allyl alcohol isomerization. For calculation, the same rate law was used for all substrates. The increase in conversion is due to increased substrate solubility [112].

4.5
Aromatic Nucleophilic Substitution

4.5.1
Aminodehalogenation – Alkylaminodefluorination in the Ciproflaxin® Multi-step Synthesis

Peer-reviewed journals: [83, 118].

4.5.1.1 Drivers for Performing Alkylaminodefluorinations in Micro Reactors

The synthesis of Ciproflaxin® was one among several syntheses being performed in contract research by a micro reactor developer for the pharmaceutical industry [83]. In this multi-step synthesis, alkylaminodefluorinations were an essential part of the chemistry.

The aims in performing the syntheses of functional molecules were manifold, but may be summarized by the term 'process intensification'. Syntheses should be carried out more rapidly and more reliably with more flexible quantities of better quality at higher yield [83]. Finally, improved economy was claimed.

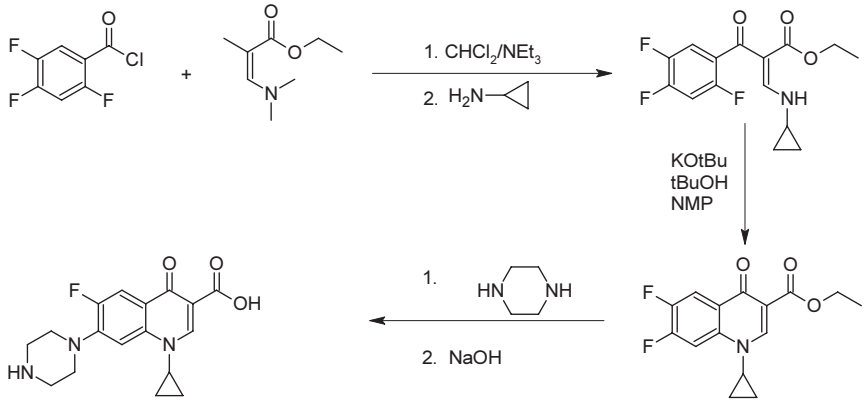
The selection of functional molecules was oriented at targeting blockbuster syntheses for pharmaceutical companies [83]. In this way, an already marketed blockbuster synthesis was applied to micro flow processing, with the aim of finally achieving production in micro reactors for the same synthesis.

4.5.1.2 Beneficial Micro Reactor Properties for Alkylaminodefluorinations

The above-mentioned targets refer to general advantages of micro reactors [42, 80, 100, 114, 119]. Enhanced transfer and better controlled residence time improve conversion and selectivity. The tools have small internal volumes, allowing one to generate flexibly a multitude of samples in serial or parallel fashion. Synthesis can be combined with a multi-step procedure. The economy of micro-reactor processes has not really been analyzed so far; however, it is clear that as laboratory tools they allow in a number of cases technical expenditure, personnel and costs to be reduced.

4.5.1.3 Alkylaminodefluorinations Investigated in Micro Reactors

Organic synthesis 42 [OS 42]: Ciproflaxin® synthesis



This reaction scheme involves two substitutions of fluorine moieties at the aromatic ring by amines, yielding the final product for pharmaceutical applications [83, 118]. In total, five synthesis steps are actually required to obtain the target molecule.

4.5.1.3 Experimental Protocols

[P 31] No protocol is given in [83, 118].

4.5.1.4 Typical Results

Demonstration of feasibility

[OS 42] [R 25] [P 31] The multi-step synthesis of the pharmaceutical agent Ciproflaxin® was carried out in a CPC micro reactor [83, 118].

4.5.2 Photocyanation of Aromatic Hydrocarbons

Peer-reviewed journals: [29].

4.5.2.1 Drivers for Performing the Photocyanation of Aromatic Hydrocarbons

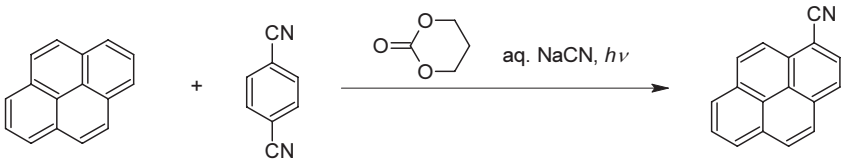
Photocyanations rely on photoinduced electron transfer [29]. This was demonstrated by monitoring cyanation yields as a function of the droplet size for oil-in-water emulsions. Hence increase in interfacial area is one driver for micro-channel processing. Typically, fluid systems with large specific interfacial areas tend to be difficult to separate and solutions for more facile separation are desired.

4.5.2.2 Beneficial Micro Reactor Properties for the Photocyanation of Aromatic Hydrocarbons

In micro reactors, large specific interfaces between immiscible phases can in general be achieved. In special laminating contactors, a stable two-phase flow with continuous phases can be obtained, while separation of the phases is facilitated when the two separate streams leave the micro reactor as there is no dispersion.

4.5.2.3 Photocyanation of Aromatic Hydrocarbons Investigated in Micro Reactors

Organic synthesis 43 [OS 43]: Photocyanation of pyrene



The pyrene molecule is transferred by irradiation to its cation radical [29]. This reacts at the oil/water interface by nucleophilic attack from the cyanide ion. Typically, the cyanated product remains in the organic phase.

4.5.2.4 Experimental Protocols

[P 32] Pyrene (20 mM), 1,4-dicyanobenzene (40 mM) and sodium cyanide (1 M) were reacted in propylene carbonate and water. A 100 µl solution of pyrene (20 mM), 1.4-dicyanobenzene (40 mM) in propylene carbonate and a 100 µl solution of sodium cyanide (1 M) in water were fed by programmable dual-syringe pumps via fused-silica capillary tubes into a micro-channel chip [29]. Both solutions were fed with equal flow velocity. A 300 W high-pressure mercury lamp was used as light source. After passing an optical filter made of a $CuSO_4$ solution, the whole chip was irradiated after formation of a stable oil/water interface inside. The oil phase was collected at the exit.

4.5.2.5 Typical Results

Conversion/Yield/Selectivity

[OS 43] [R 14] [P 32] A yield of 28% of the cyanated pyrene was obtained in a first run by two-liquid layer (oil/water) flow, using a residence time of 210 s and room-temperature processing (0.2 µl min^{-1}, 300 W, > 300 nm wavelength) [29]. Using a three-liquid layer (water/oil/water) flow resulted in a yield of 73%. The content of non-reacted pyrene was 8%. Thus, to close the balance, about 20% by-products had to be formed, i.e. conversion was high. The nature of these by-products was not identified (Figure 4.66).

Residence time

[OS 43] [R 14] [P 32] Changing the residence time from 70 to 210 s by varying the flow rates increases the yield of pyrene photocyanation from 7 to 28% [29].

Three-liquid layer processing – thinning of lamellae

[OS 43] [R 14] [P 32] Using a three-liquid layer (water/oil/water) flow instead of a two-liquid layer flow at constant channel dimensions decreases the liquid lamellae width and doubles the absolute value of the organic/aqueous interface. As a consequence, mass transport is facilitated compared with the two-flow configuration. Hence it was found that a much higher yield was obtained for the three-liquid layer flow when performing experiments of both flow configurations under the same experimental conditions (210 s, 0.2 µl min^{-1}, room temperature, 300 W, > 300 nm

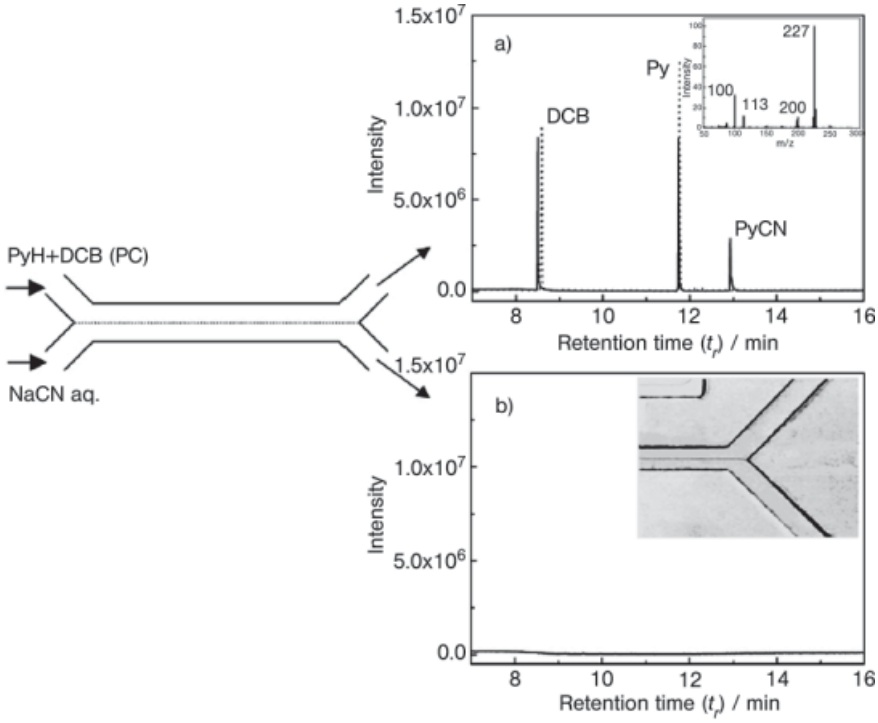


Figure 4.66 Photocyanation of pyrene (PyH) to the corresponding cyanated product (PyCN) in dicyanobenzene (DCB). Left: schematic of the flow inside the micro reactor and a microscope image of the chip micro channels. Right: GC and mass spectra of samples from micro flow processing [29].

wavelength) [29]. For the pyrene photocyanation, a yield of 73% was obtained (two-flow processing: 28%), hence an increase in reaction rate by a factor of about three.

Using a three-liquid layer (oil/water/oil) flow only gave a yield of about 35% (210 s, 0.2 µl min^{-1}, room temperature, 300 W, > 300 nm wavelength) [29]. This is explained by the fact that the specific interface here is not as large as for the water/oil/water flow. This is due to the larger volume of the oil phase compared with the water phase [29].

CN source

[OS 43] [R 14] [P 32] Experiments run without NaCN did not yield the cyanated photoproduct [29]. Therefore, NaCN and not 1,4-dicyanobenzene has to be considered as the source of the CN anion that is incorporated into the pyrene moiety.

Product extraction

[OS 43] [R 14] [P 32] The cyanated pyrene product leaves the reaction channel completely via the organic phase [29]. Since the reaction occurs with aqueous dissolved NaCN, one can draw the conclusion that complete extraction of the product was achieved.

4.6
Aromatic Substitution by Metal Catalysis or Other Complex Mechanisms

4.6.1
Aryldehalogenation – Suzuki Coupling using Pd(0)–Phosphine Catalysis

Peer-reviewed journals: [7]; proceedings: [6, 85]; sections in reviews: [14, 42, 83, 89, 90, 105].

4.6.1.1 Drivers for Performing Suzuki Couplings in Micro Reactors

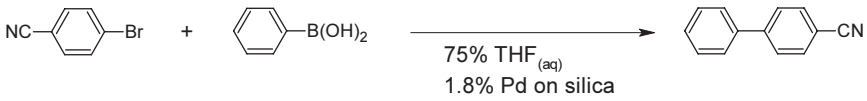
One driver for performing Suzuki couplings in micro reactors refers to enhancement of yield by increased mass transfer and especially by in-line generation of hydroxide ions that promote reaction [6]. By this means, modified Suzuki couplings are possible that no longer need addition of a base. A second driver refers to minimize the loss of colloidal catalyst when conducting the reaction heterogeneously. This contaminates the product, needing further separation. Achievement of this goal would also be an advantage over the homogeneously catalyzed reaction, used predominantly so far.

4.6.1.2 Beneficial Micro Reactor Properties for Suzuki Couplings

In addition to the general improvement of transfer in micro reactors, there is evidence that the voltage of electroosmotic flow (for EOF see [14]) in combination with the large internal surface area in glass chips can induce hydroxide ion formation [6]. Concerning catalyst loss, there is no obvious direct correlation; rather, micro reactors can act as mini fixed beds fixing heterogeneous catalyst particles.

4.6.1.3 Suzuki Couplings Investigated in Micro Reactors

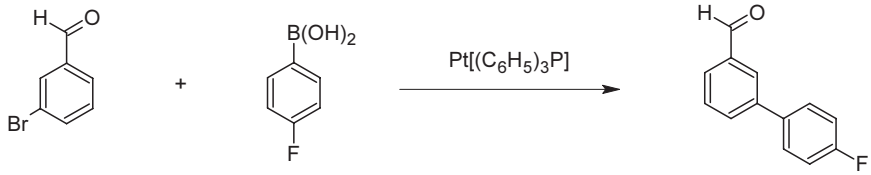
Organic synthesis 44 [OS 44]: C–C bond formation of 4-bromobenzonitrile and phenylboronic acid



A modified Suzuki coupling by Styring (see original citation in [6]) was applied in the micro reactor. Such Suzuki couplings usually have high selectivity for formation of carbon-to-carbon bonds; however, they suffer from the problem of catalyst degradation and loss into the product solution.

The Suzuki–Miyaura synthesis is one of the most commonly used methods for the formation of carbon-to-carbon bonds [7]. As a palladium catalyst typically tetrakis(triphenylphosphine)palladium(0) has been used, giving yields of 44–78%. Recently, Suzuki coupling between aryl halides and phenylboronic acid with efficient catalysis by palladacycles was reported to give yields of 83%.

Organic synthesis 45 [OS 45]: Suzuki coupling of 3-bromobenzaldehyde and 4-fluorophenylboronic acid



3-Bromobenzaldehyde and 4-fluorophenylboronic acid were coupled in DMF using tetrakis(triphenylphosphine)palladium(0) as catalyst [85] (see a more extended description in [42]).

The mechanism of the Suzuki coupling is known, although not in all details [6, 7]. The first step is an *oxidative addition* of the organohalide to Pd(0) (see a schematic of the mechanism below in Section 4.6.1.5, Addition of base). Pd(II) is generated and the organohalide splits into two moieties, serving as ligands for the central ion. The second step is a *transmetallation* with the organoboron compound. The aromatic moiety of the latter substitutes the halide group in the Pd(II) complex; boronic acid leaves as this step typically is assisted by base addition, usually as hydroxide ion. The exact nature of this hydroxide action is still under discussion. Not all proposed intermediates have been identified and different mechanisms have been proposed by various authors. The third step is a *reductive elimination* of Pd(II) to Pd(0); the starting catalytic material is obtained again. This is accompanied by cross coupling of the aromatic moieties, undergoing C–C bond formation at the position of the former halide and boron functionalities.

4.6.1.4 Experimental Protocols

[P 33] The catalyst bed was manually positioned in the micro channel (300 μm wide; 115 μm deep) at room temperature using a 10% (v/v) solution of formamide and potassium silicate [6, 7]. Micro reactor bottom and top plates were thermally bonded thereafter. Then, 75% THF (aqueous) solutions of 4-bromobenzonitrile and phenylboronic acid having equimolar concentrations were placed in the two reservoirs of a micro-mixing tee chip. In the collection reservoir, 30 μl of the THF solution was placed. Voltages ranging from 100 to 400 V were used, but kept constant only for one reservoir. The other one was switched on and off at 200 V for given time periods.

4.6.1.5 Typical Results

Conversion/selectivity/yield – benchmarking to batch processing

[OS 44] [R 4a] [P 33] A yield of 62% was found for micro flow processing, being about six times higher than for batch processing (10%) under comparable process conditions [6]. Furthermore, a base is required for the batch case, whereas the micro reactor gives a better performance without the need for any base.

[OS 45] [R 17] [no protocol] For the reaction of 3-bromobenzaldehyde and 4-fluorophenylboronic acid, improved conversion was found for a micro reactor, composed

of a mixer and reactor unit, compared with results obtained in a laboratory flask [42, 85]. This was explained by having temperature and concentration profiles within the flask, whereas both parameters are nearly uniform in the micro reactor.

Injection time/plug volume 4-bromobenzonitrile

[OS 44] [R 4a] [P 33] By switching on and off the electroosmotic-driven flow of one reactant, plugs can be inserted in the reaction channel [6]. 4-Bromobenzonitrile plugs (5 s) are inserted into a continuous phenylboronic acid stream. By this means, the effective concentration of the aryl halide in the micro channel can be increased. As expected, a maximum yield is found in this way.

An optimum injection length of 5 s was determined, corresponding to a yield of 14% [7].

Maximum frequency of 4-bromobenzonitrile injections/catalyst saturation

[OS 44] [R 4a] [P 33] 4-Bromobenzonitrile plugs (5 s) were inserted into a continuous phenylboronic acid stream for time intervals of 5, 15, 25, 30, 40 and 55 s (25 min reaction period) [6, 7]. For a 5–20 s delay, catalyst saturation occurs owing to the high injection rates rendering the phenylboronic acid concentration too low. In turn, for delay times of 30–55 s, the effective concentration of 4-bromobenzonitrile becomes too low. At 25 s, optimum performance with a yield of 62% was achieved (Figure 4.67).

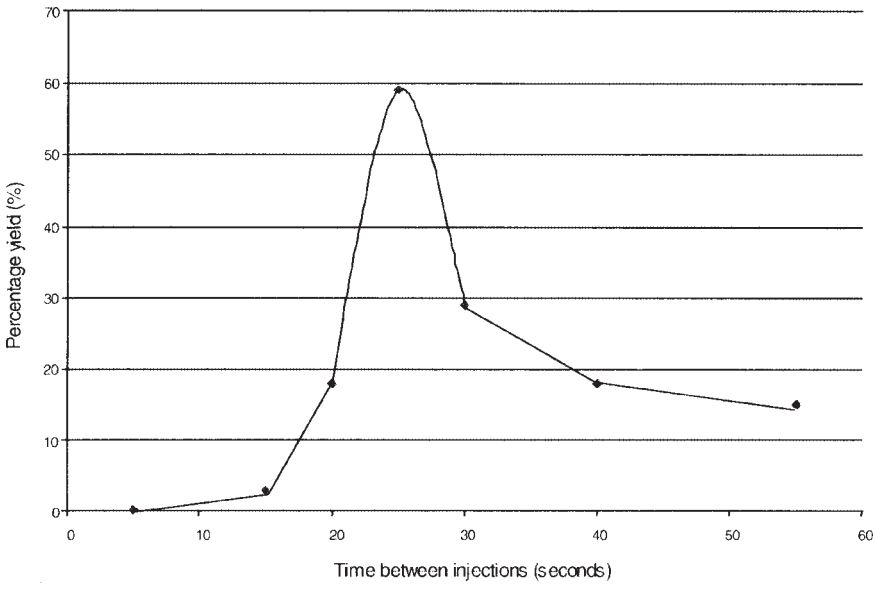


Figure 4.67 Periodic injection of 4-bromobenzonitrile into a continuous phenylboronic acid stream. Product yield is plotted as a function of injection interval [6, 7].

Flow rates/residence times/voltages

[OS 44] [R 4a] [P 33] On changing the voltages for electroosmotic flow and hence flow rates, the yield passes through a maximum (5 s injections with 25 s interval) [6, 7]. The best yields of 49–68% were obtained at 200 V (0.8 μl min^{-1}). At higher voltages (300–400 V), the flow rate (01.0–1.3 μl min^{-1}) is too high, thus residence time too low. At lower flow rate (0.65 μl min^{-1}), no effective transfer is observed.

Temperature

[OS 44] [R 4a] [P 33] At room temperature, no reaction is observed in the presence or absence of a base using a batch synthesis [7]. Using a base, sodium carbonate (aqueous, 0.2 M, 20 ml water), at 75–80 °C results in 10% conversion after 8 h. The best micro reactor conversion was 68%, using no base and operating at room temperature.

Addition of base

[OS 44] [R 4a] [P 33] Conventionally, base addition is needed for Suzuki couplings to activate the boronic acid group (Figure 4.68) [6, 7].

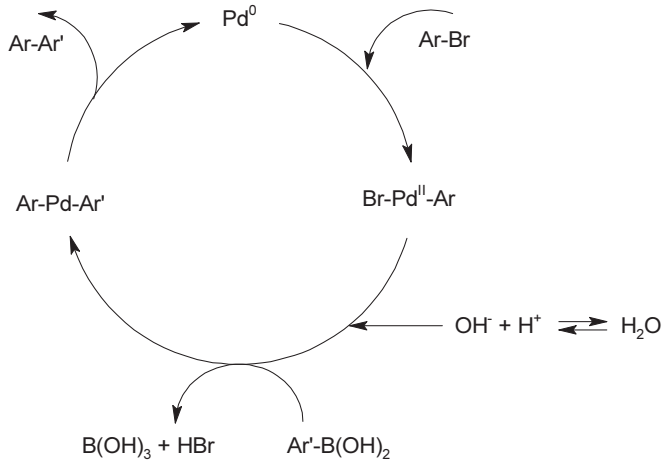


Figure 4.68 Proposed catalytic mechanism with addition of a base [6, 7].

Surprisingly, there is no need for addition of a base when performing Suzuki coupling in a glass chip micro reactor [6, 7]. This was explained as being due to local generation of a base at heterogeneous sites. Under the action of the voltage for electroosmotic micro flow processing, water can be converted to hydroxide ions. The high specific surface areas in the micro reactor probably accelerate this process. Although the corresponding hydroxide concentrations may be low in bulk, they potentially can be large at the catalyst surface where these species enrich. As a consequence, the Suzuki coupling can be performed without base in micro reactors. Testing with the same process parameters does not lead to any conversion in a batch reactor. Here, the addition of a base is essential.

Contamination of catalyst

[OS 44] [R 4a] [P 33] A residual content of the palladium catalyst of only 1.2–1.6 ppb in the outlet solution was found after micro-reactor processing using a heterogeneous catalyst [6, 7]. In turn, for batch processing with homogeneous catalysts, high catalyst impurities in the reacting solution are usually found.

Loss of catalyst activity

[OS 44] [R 4a] [P 33] For an operation of 35 h, performing many reactions, no loss of catalyst activity was detected [6, 7].

4.6.2 Alkinyldehydro Substitution – Sonogashira Coupling using Pd(II)–Phosphine Copper-free Catalysis

Peer-reviewed journals: [120].

4.6.2.1 Drivers for Performing Sonogashira Couplings in Micro Reactors

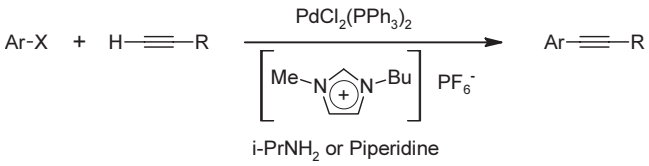
The performance of the Sonogashira reaction is claimed to be the first example of a homogeneously metal-catalyzed reaction conducted in a micro reactor [120]. Since the reaction involves multi-phase post-processing which is needed for the separation of products and catalysts, continuous recycling technology is of interest for an efficient production process. Micro flow systems with micro mixers are one way to realize such processing.

4.6.2.2 Beneficial Micro Reactor Properties for Sonogashira Couplings

Following the arguments given above, micro mixers are valuable tools for bench-scale continuous processing to fill the recycle loop. For first tests on feasibility, the total volume of the recycle loop has to be kept small, demanding also for small-scale processing units. Conventional devices would probably suffer here from too large internal volumes.

4.6.2.3 Sonogashira Couplings Investigated in Micro Reactors

Organic synthesis 46 [OS 46]: Copper-free Sonogashira reaction

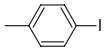
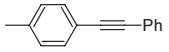
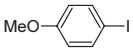
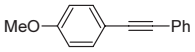
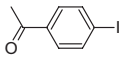
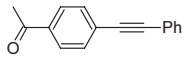
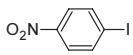
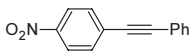
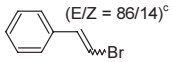
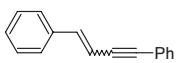
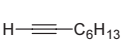
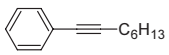
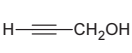
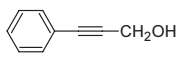
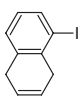
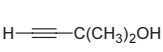
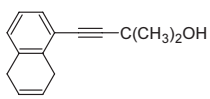
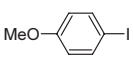
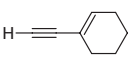
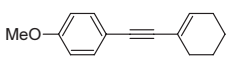
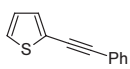


The reaction between iodobenzene and phenylacetylene was carried out in the presence of a catalytic amount of $PdCl_2(PPh_3)_2$ in an ionic liquid [120].

The Sonogashira reaction is a transition metal-catalyzed coupling reaction which is widely used for the preparation of alkyl-, aryl- and diaryl-substituted acetylenes (Table 4.7) [120]. This reaction is a key step in natural product synthesis and is also applied in optical and electronic applications. Sonogashira reactions involve the use of an organic solvent with a stoichiometric portion of a base for capturing the

acid produced in the reaction. Using ionic liquids facilitates catalyst separation since the organic products can be separated from the catalyst by extraction with organic solvents.

Table 4.7 Sonogashira coupling of aryl halides with terminal acetylenes in the presence of $PdCl_2(PPh_3)_2$ catalyst [120].

Ar-X	H—≡—Ph	Ar—≡—R	Yield (%)
			95
			91
			91
			97
			86 (E/Z = 93/7)[c]
			87
			88
			90
			97
			85

4.6.2.4 **Experimental Protocols**

[P 34] A mixture of phenylacetylene, iodobenzene and di-*n*-butylamine is fed into one inlet of the slit-shaped interdigital metal/steel micro mixer and the $PdCl_2(PPh_3)_2$ catalyst in the ionic liquid 1-butyl-3-methylimidazolium hexafluorophosphate is fed into the other inlet by means of a syringe pump [120]. The flow rate was set to 0.1 ml h^{-1} and the temperature to 119 °C. After being mixed in the micro mixer, the reactants pass through the flow-through chamber with about a 10 min residence time. From the outlet the product solution was sampled and the product was isolated by extraction with hexane/water (Figure 4.69).

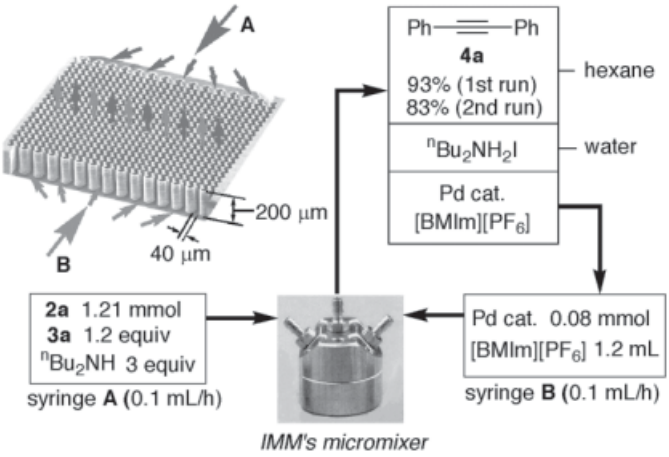


Figure 4.69 Flow scheme of a Sonogashira reaction performed in a micro flow system [120].

4.6.2.5 Typical Results

Conversion/selectivity/yield

[OS 46] [R 18] [P 34] In a recycling experiment, an initial yield of about 93% was found [120]. During the second recycle with recovered catalyst, a yield of 83% was determined.

Benchmarking to batch-recycle processing

[OS 46] [R 18] [P 34] The initial yield of batch-recycle processing was 96% (micro mixer: 93%) and the yield of the second recycle process was 80% (micro mixer: 83%) [120]. Hence the yields were comparable. For the batch recycling, the yields of the third and fourth runs were also determined, being 78 and 63% (no micro mixer data here).

4.6.3 Aryldehalogenation – Kumada–Corriu Reaction using Ni(II)–Phosphine Catalysis

Peer-reviewed journals: [2]; sections in reviews: [14, 90].

4.6.3.1 Drivers for Performing Kumada–Corriu Reactions in Micro Reactors

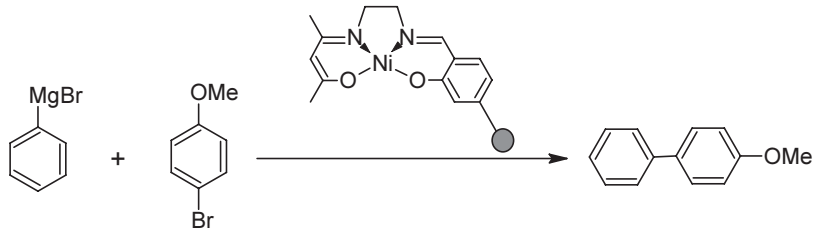
The Kumada–Corriu reaction is a metal-catalyzed reaction of great importance for the fine-chemical and pharmaceutical industries for making C–C bonds [2]. Owing to its mild conditions and clean conversion, this reaction is one of the most frequently applied processes for such chemistry. The motivation to use this reaction therefore was to demonstrate the feasibility of micro channel processing of quality comparable to standard processing [2]. Having done this, the 'normal' advantages of micro reactors, such as improved heat transfer and capability for numbering-up, were predicted to apply to the Kumada–Corriu reaction.

4.6.3.2 Beneficial Micro Reactor Properties for Kumada–Corriu Reactions

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

4.6.3.3 Kumada–Corriu Reactions Investigated in Micro Reactors

Organic synthesis 47 [OS 47]: Reaction between 4-bromoanisole and phenylmagnesium bromide [2]



In a Kumada–Corriu reaction, an aryl halide is oxidatively coupled with a homogeneous nickel(II)-phosphine catalyst [2]. This species reacts with a Grignard reagent to give biaryl or alkylaryl compounds. Later, palladium-phosphine complexes were also successfully applied. By this means, stereospecific transformations were achieved.

The Kumada–Corriu reaction is characterized by mild conditions and clean conversions [2]. A disadvantage of previous Kumada–Corriu reactions was due to the use of homogeneous catalysts, with more difficult product separation. Recently, an unsymmetrical salen-type nickel(II) complex was synthesized with a phenol functionality that allows this compound to be linked to Merrifield resin polymer beads (see original citation in [2]). By this means, heterogeneously catalyzed Kumada–Corriu reactions have become possible.

4.6.3.4 Experimental Protocols

[P 35] To test the feasibility of microfabricated reactor processing, first experiments were conducted in polypropylene or glass tubing of millimeter internal dimensions with flanged ends, so-called micro-flow reactors [2]. By use of syringe pumps, mixtures of equimolar (e.g. 1.0 M) solutions of 4-bromoanisole and phenylmagnesium bromide in THF were fed at room temperature through the tubing packed with catalyst beads. No reaction in the mixture occurred over 72 h in absence of catalyst. Flow rates of 13.3 μl min^{-1} or 33.3 μl min^{-1} were used, amounting to residence times of a few minutes. The output stream was passed directly into a flask with an aqueous solution containing sodium hydrogencarbonate to quench the reaction. This solution was extracted with diethyl ether.

See also [2] for a description of respective batch syntheses.

4.6.3.5 Typical Results

Conversion/selectivity/yield

[OS 47] [R 2] [P 35] A 60% conversion to the target compound was found, while 20% reacted to biphenyl as side product and 20% remained non-reacted [2].

Kinetics: rate constant/reaction time – benchmarking with batch processing

[OS 47] [R 2] [P 35] Observed rate constants have been determined [2]. For high-flow-rate processing (33.3 μl min^{-1}), an observed rate constant of 0.033 1 s^{-1} was obtained. This amounts to a rate enhancement of 3300-fold compared with the value for batch processing (Table 4.8). For a series of other reactants, less reactive iodoarenes, with Grignard reactants having two differing substituents, rate constants were also determined. The enhancement rates over batch processing are from about 16- up to 79-fold.

Table 4.8 Comparison of rate constants for a series of Kumada–Corriu coupling reactions in flow reactors with corresponding batch reaction [2].

R	*X*	*R′*	*Flow rate (μl min^{-1})*	*Rate constant k (10^{-3} s^{-1})*	*Rate constant k (10^{-3} s^{-1})*	*Rate enhancement (-fold)*
CH_3	I	Ph	25.0	2.67	3.50	76.3
OCH_3	I	Ph	25.0	1.59	3.50[a]	45.4
OCH_3	I	CH_3	25.0	2.67	3.35	79.3
CH_3	I	CH_3	25.0	1.05	6.73	15.6
OCH_3	Br	Ph	33.3	33.00	1.00	3300.0

a Rate constant estimated, since reaction complete (all of the 4-iodoanisole consumed) before first aliquot removed.

This was explained by having only the contribution of surface reaction in the case of batch processing, whereas micro reactors profit, in addition, from processing inside the pores of the catalyst beads. The penetration of the reaction solution into the pores is achieved here by applying pressure [2]. By this means, the number of available catalyst sites is increased.

Accordingly, Kumada–Corriu batch processes that need hours can be conducted in micro reactors in a few minutes [2]. 116 mg of product (0.62 mmol) was so produced in only 2 h. Numbering-up to 10 reactor units would give gram quantities.

4.7
Free-radical Substitution

4.7.1
Nitrodehydrogenation – Nitration of Aliphatics

Proceedings: [38, 97, 98]; sections in reviews: [89, 90, 100]. See also the information given on the nitration of aromatics in Section 4.3.1.

4.7.1.1 Drivers for Performing Aliphatics 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 are generally regarded as hazardous [37] [38].

Due to the heat release, nitrations are often lacking 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].

Having high mass transfer, in addition to good heat transfer, may change the product spectra, by increasing 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.

Multi-phase processing of nitrated aromatics is also described in [31], including both organic and aqueous phases. Side reaction take place in the organic phase, whereas all other reactions occur in the aqueous phase and are limited by organic solubility. For this reason, enabling mass transfer by large interfaces is a key to affect product selectivity.

4.7.1.2 Beneficial Micro Reactor Properties for Aliphatics Nitrations

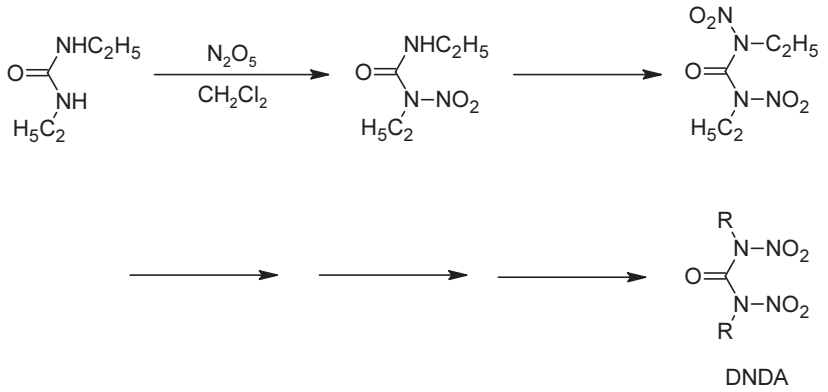
The small reaction volumes in micro reactors and the large specific surface areas created are seen as beneficial to cope with the problems caused by the release of the large amounts of heat, as mentioned above [37, 38]. Delicate temperature control is expected for micro-reactor operation; isothermal processing is said to be achievable even when high reaction heats are released [94]. Small size should 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 (Figure 4.51) [94] or parallel flowing streams (Figure 4.47) [31]. Besides demonstrating advantages in terms of improved mass transfer, the residence time was set in the latter two references uniformly by plug-flow motion. Apart from increasing reaction performance to the kinetic limits, the flow patterns may directly affect selectivity, which depends on interfacial area [31].

4.7.1.3 Aliphatic Nitration Reactions Investigated in Micro Reactors

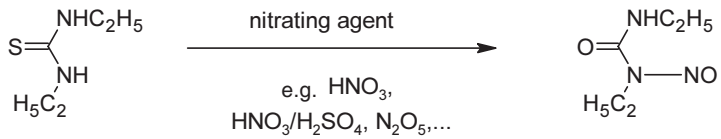
Nitration reactions are among the basic chemical pathways followed in organic synthesis. They are used for making pharmaceutical products, agricultural and pest control chemicals, pigments, precursors for polyurethane and polyamide production and for explosives [37]. Typically, acidic nitration agents 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 48 [OS 48]: Dinitration of *N,N′*-diethylurea



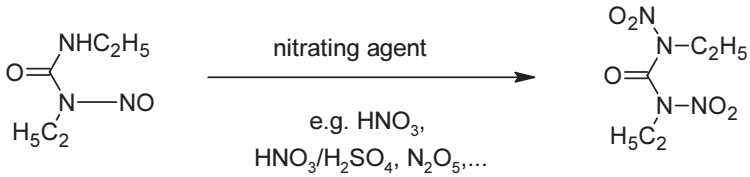
The nitration of *N,N′*-diethylurea gives nitrated products which are precursors for a new energetic plasticizer *N,N′*-dialkyl-*N,N′*-dinitrourea (DNDA). For macroscopic batch processing, this reaction is characterized by a lack of selectivity owing to mononitro derivative formation and thermal decomposition of the dinitro product due to increasing temperature during the course of reaction [37, 38].

Organic synthesis 49 [OS 49]: Mononitration/nitrosation of *N,N′*-diethylthiourea



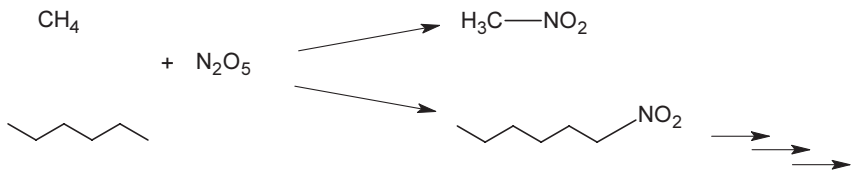
The derivatized thiourea is a much cheaper starting material than its oxygen analogue [38]. Basically it leads so the same product DNDA as described in [OS 48]. Although nitrating agents are used, nitroso compounds results. This stems from oxidation of the sulfur of the thiourea moiety by the nitrating agent, giving also HNO_2 as nitrosation agent, which, in turn, reacts with the nitrogen moiety. In excess of HNO_3, HNO_2 forms N_2O_4 that is completely ionized to NO^+ and NO_3^-.

Organic synthesis 50 [OS 50]: Nitration of *N*,*N*′-diethyl-*N*-nitrosourea



By this reaction, the nitroso moiety is replaced by a nitro group, in addition to the nitration of the –NH-ethyl group [38].

Organic synthesis 51 [OS 51]: Nitration of alkanes such as methane and hexane with N_2O_5



These reactions also have high exothermicity so that safe and reliable processing in technical processes still demands high technical expenditure [37].

4.7.1.4 Experimental Nitration Protocols in Micro Reactors

[P 36] For the synthesis of *N*,*N*′-diethylurea and *N*,*N*′-diethylthiourea, the respective ureas dissolved in dichloromethane were exposed to pure liquid or dissolved nitrating agents [38]. As nitrating agents were used concentrated HNO_3 (65%, fuming), mixed HNO_3/H_2SO_4 in ratios from 1 : 1 to 6 : 1 or N_2O_5 (dissolved in dichloromethane or *in situ* generated gas).

Nitrating agents were applied in up to 10-fold excess [38]. Residence times were set to 0.6–82 s by using tubes of different lengths. Temperatures were between 0 and 20 °C. Reaction mixtures were quenched with ice–water and/or cold dichloromethane and extracted. Analysis was made by NMR, MS, IR, HPLC or GC/MS. Analytical devices and sensors were used for temperature and flow monitoring/control. By FTIR microscopy, on-line monitoring of intermediates and final products for urea nitration in silicon micro reactors was performed, relying on the high spatial resolution (> 10 μm) of this technique. Thereby, the progress of the reaction was accessible on-line.

[P 37] Nitrations were carried out using dissolved or gaseous N_2O_5 at temperatures between –10 and 50 °C and residence times of 15–45 s [37]. The reaction stream was quenched with water, extracted and passed to analysis.

As micro devices, mixers from various suppliers ([R 19], [R 17]) were used [37]. These devices were each connected to a PTFE tube of length up to 150 cm. In addition, a tailor-made micro reaction system with parallel channels and integrated cooling was used ([R 26]).

4.7.1.5 Typical Results

Conversion/selectivity/yield

[OS 48] [R 17] [R 19] [R 26] [P 36] Yields of up to 75% were achieved for the nitration of *N,N′*-diethylurea concerning the dinitro product [38]. The dinitro product was obtained in a significantly larger ratio (to the mono product) in the micro reactor as compared with batch [37]. Other side products, e.g. stemming from thermal decomposition, were also formed to a much lower extent.

[OS 49] [R 17] [R 26] [P 36] At almost quantitative conversion, yields of 90% of two (in a first run) unidentified products and of 10% *N,N′*-diethylurea were reported, accompanied by small amounts of the mono-product [38]. All products no longer contained any C=S moiety, hence were somehow attacked via a nucleophilic route. By subsequent MS and IR analysis, the two main products were identified as *N,N′*-diethyl-*N*-nitrosourea and, probably, *N,N′*-diethyl-*N,N′*-dinitrosourea. By optimization of the [P 23] procedure, 100% selectivity for the nitration of *N,N′*-diethylurea to *N,N′*-diethylurea was achieved.

[OS 50] [R 17] [R 26] [P 36] By nitration of *N,N′*-diethyl-*N*-nitroso-urea the target compound for DNDA synthesis *N,N′*-diethyl-*N*-dinitro-urea was achieved with 100% selectivity [38].

[OS 48] [R 17] [R 26] [P 36] The selectivity achieved for the nitration of *N,N′*-diethylurea concerning the dinitro and mono-nitro products were almost similar to macroscopic batch processing, giving, if at all, a slight tendency for the di-nitro product [37, 38]. Isothermal operation and shortening of residence time being the major differences between micro-conti- and conventional-batch, these results accordingly showed that for this combination of reaction/reactor/processing parameters, no benefits could be gained.

[OS 51] [R 17] [R 19] [R 26] [P 37] Methane and hexane nitration were successfully performed under safe conditions in micro reactors [37]. The very preliminary character of these experiments did not allow any detailed process information to be derived apart from demonstrating feasibility and the fact that selectivity was low in the first runs. No significant improvement over the batch processing was obtained here. The formation of many undesired products was particularly high for nitration of hexane [37].

Step-by-step synthesis

[OS 48] [R 17] [R 19] [R 26] [P 36] For the nitration of urea and thiourea derivatives, a selective introduction of nitro and nitroso groups one after the other was demonstrated. Via monosubstituted nitroso groups, dinitro products were achieved [38]. Still other steps (reduction of keto moiety) are required to establish a fully ‘step-by-step mode’ for micro reactors to give the target compound DNDA. This would be a multi-step, highly selective micro reactor route for the synthesis of dangerous explosives that probably would be a safe route for on-demand production reducing waste. From the starting material until the final hazardous product, all would be done in one line.

Corrosion resistance

[R 16a] [R 17] [R 19] [P 36] High sulfuric acid contents can lead to steel corrosion [37, 38, 97]. This may even lead to blockage by accumulation of corroded material in the tube. It is also claimed [38] 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].

4.8 Addition to Carbon–Carbon Multiple Bonds

4.8.1 Hydrobis(ethoxycarbonyl)methyl Addition – Michael Addition

Peer-reviewed journals: [8]; sections in reviews: [14, 89].

4.8.1.1 Drivers for Performing Michael Additions in Micro Reactors

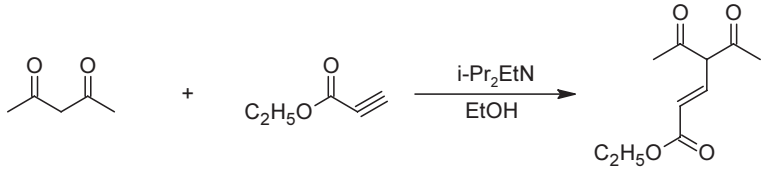
The reduction of reaction times by changing from batch processing to micro-reactor technology is a major driver [8]. Typical Michael batch additions require hours to be completed.

4.8.1.2 Beneficial Micro Reactor Properties for Michael Additions

Although no special information is given in [8], it is obvious that efficient mass and heat transfer serve for reduction of processing times by establishing kinetic control.

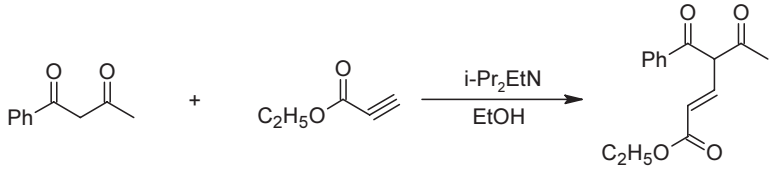
4.8.1.3 Michael Additions Investigated in Micro Reactors

Organic synthesis 52 [OS 52]: Addition of 2,4-pentanedione enolate to ethyl propiolate [8]

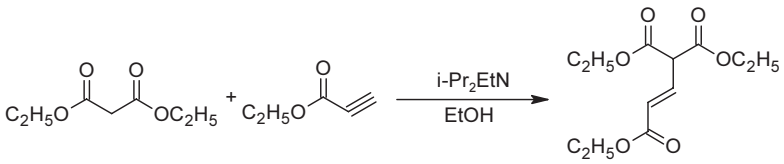


The reactions [OS 52], [OS 53], [OS 54] and [OS 55] were chosen as test reactions among a wide class of reagents employed for Michael additions. 1,3-Dicarbonyl compounds were chosen because of their relatively high acidity since they enable one to use weak bases instead of strong bases such as sodium ethoxide. The latter is labile to moisture and can react with the Michael acceptor [8]. Diisopropylethylamine was chosen as a weak base.

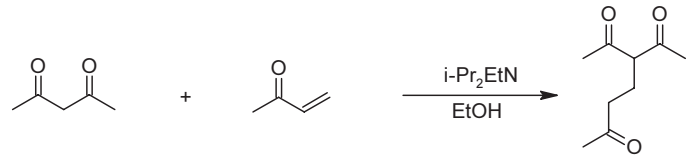
Organic synthesis 53 [OS 53]: Addition of benzoyl acetone to ethyl propiolate [8]



Organic synthesis 54 [OS 54]: Addition of diethyl malonate to ethyl propiolate [8]



Organic synthesis [OS 55]: Addition of 2,4-pentanedione enolate to methyl vinyl ketone [8]



4.8.1.4 **Experimental Protocols**

[P 38] Ethanol solutions of ethyl propiolate and diisopropylethylamine were pumped via electroosmotic flow through the micro channels of the reactor [8]. By mixing thereof the enolate was obtained. By subsequent contacting with the 1,3-dicarbonyl compound, the product was obtained. The temperature was set to room temperature. In a period of 20 min a volume sufficiently large for analysis was sampled. The reaction product spectra was analyzed by GC/MS via comparison with synthetic standards. The remaining amount of diketone was used for calculating conversions.

Typically, 40 µl of 5.0 M alkyne compound and 40 µl of 5.0 M alkyne of the diketo compound were placed in the corresponding reservoirs (Figure 4.70) [8]. The same holds for diisopropylethylamine (40 µl; 5.0 M). The electrical fields applied were:

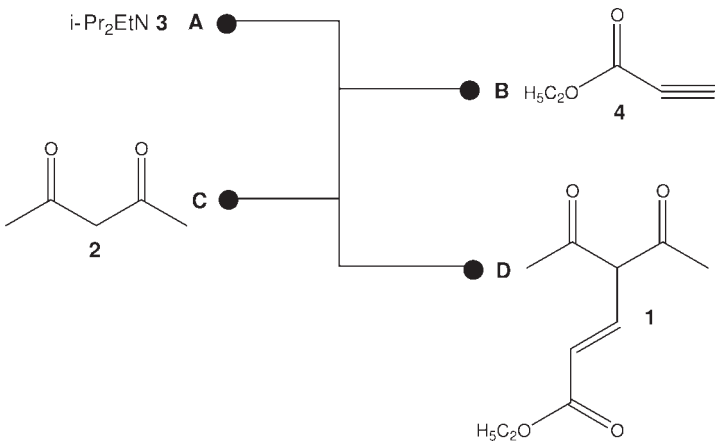


Figure 4.70 Flow configuration for the Michael addition using 2,4-pentanedione and ethyl propiolate in a two-mixing tee microreactor [8].

417, 318, 333 and 0 V cm^{-1}. The residence time was about 20 min and room temperature was applied.

The corresponding batch operation protocol refers to the following procedure [8]. The 1,3-dicarbonyl compound (0.25–0.50 g; 1.5–5.0 mmol) was added to a stirred solution of ethyl propiolate (0.15–0.49 g; 1.54–5.0 mmol) and diisopropylethylamine (0.40–1.29 g; 3.00–10.00 mmol) in ethanol (50 ml). After stirring overnight, the reaction mixture was concentrated and purified by silica gel chromatography.

4.8.1.5 Typical Results

Conversion/selectivity/yield

[OS 52 [R 4b] [P 38] Using a two-fold injection, the first for forming the enolate and the second for its addition to the triple bond, a conversion of 56% was achieved (batch synthesis: 89%) [8]. Using the stopped-flow technique (2.5 s with field applied; 5.0 s with field turned off) to enhance mixing, a conversion of 95% was determined.

Stopped-flow technique

[OS 52] [R 4b] [P 38] See discussions in the preceding and following sections [8].

Reactivity of different substrates with diketone moieties

[OS 52] [OS 53] [OS 54] [OS 55] [R 4b] [P 38] In a two-micro-mixing tee chip reactor, substrates with diketone moieties of known different reactivity, such as 2,4-pentanedione, benzoylacetone and diethyl malonate, were processed, each with the same acceptor ethyl propiolate [8]. Also, a reaction with the less alkynic Michael acceptor methyl vinyl ketone was carried out.

The conversions observed followed the sequence of reactivity known from batch experiments carried out in advance. For example, only 15% conversion was found for the less reactive reagent benzoylacetone in the micro reactor experiment, while 56% was determined when using the more reactive 2,4-pentanedione (batch syntheses: 78% and 89%, respectively) [8]. Using the stopped-flow technique (2.5 s with field applied; 5.0 s with field turned off) to enhance mixing, the conversions for both syntheses were increased to 34 and 95%, respectively. Using a further improved stopped-flow technique (5.0 s with field applied; 10.0 s with field turned off), the conversion could be further enhanced to 100% for the benzoylacetone case. For the other two substrates, diethyl malonate and methyl vinyl ketone, similar trends were observed.

Processing time

[OS 52] [R 4b] [P 38] To achieve comparable extents of conversion, 24 h operation was needed for batch synthesis, whereas micro-reactor operation needs only about 20 min [8].

Isomeric ratio

[OS 52] [R 4b] [P 38] The same isomeric ratio (99% trans; 1% cis) was observed for micro reactor and batch operations [8].

4.8.2 Cycloadditions – The Diels–Alder Reaction

Peer-reviewed journals: [18]; sections in reviews: [89, 90].

4.8.2.1 Drivers for Performing Cycloadditions in Micro Reactors

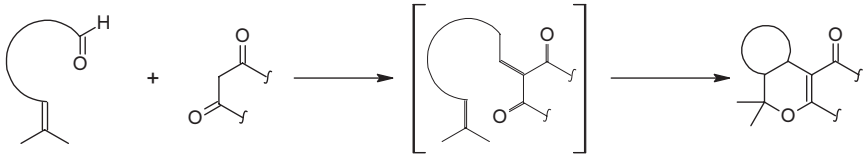
The aim of one study was to show that arrays of cycloadducts, from various precursors, can be made in a single run in one chip [18]. In addition, this study served more generally to demonstrate the feasibility and advantages of pressure-driven flow in micro chips exemplary of one prominent organic reaction. The advantages and drawbacks of pressure-driven flow as compared with electroosmotic flow (for EOF see [14]) were discussed [18].

4.8.2.2 Beneficial Micro Reactor Properties for Cycloadditions

The formation of arrays or libraries of compounds in microfluidic devices stems from the rapid changes of process parameters and reactants, mainly due to the small internal volumes allowing fast response. Furthermore, miniaturization offers a high degree of integration in a compact volume. Specifically, this allows one to introduce, mix and react many samples or reactants rapidly and in a confined area. As a further effect, the total processed volume is kept small. Especially when producing a large number of samples, this issue becomes relevant. Thus, micro channel processing saves time and resources. An estimation of test frequency and sample consumption concerning a library made by gas/liquid micro channel processing is given in [121].

4.8.2.3 Cycloadditions Investigated in Micro Reactors

[OS 56] Domino reactions

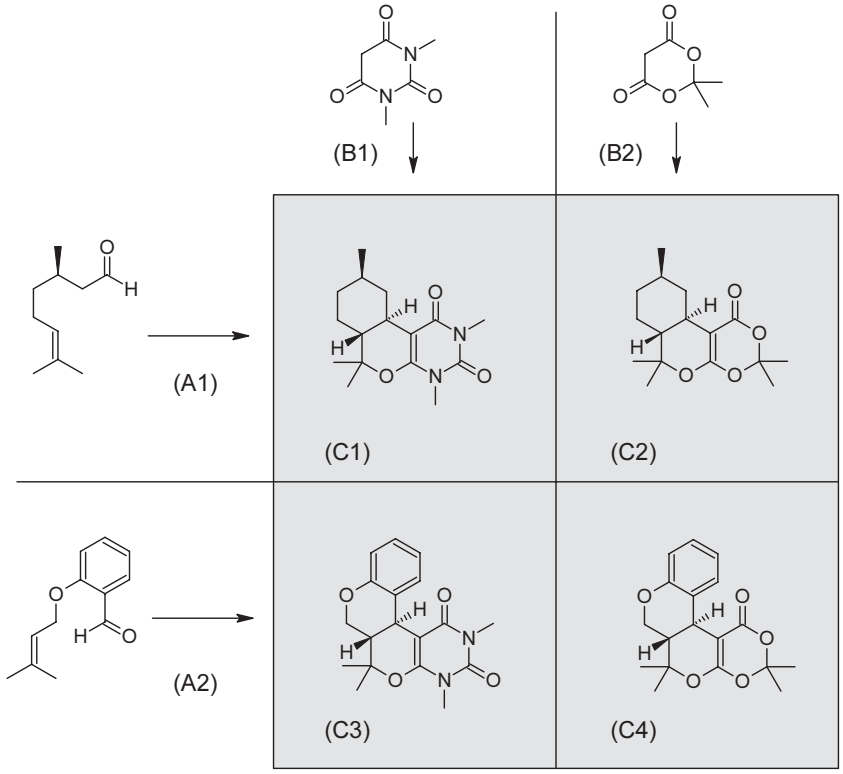


(A) (B) (C)

The domino reaction consists of a Knoevenagel condensation giving an intermediate which immediately undergoes an intramolecular hetero-Diels–Alder reaction with inverse electron demand [18].

As aldehydes, commercially available *rac*-citronellal and a synthesized aromatic aldehyde and also two commercially available 1,3-diketones, 1,3-dimethylbarbituric acid and Meldrum's acid, were selected [18]. By 2 × 2 combinations of these reactants, four different cycloadducts were generated ([OS 57]).

Organic synthesis [OS 57]: 2 × 2 combination of reactants to form four different cycloadducts



4.8.2.4 **Experimental Protocols**

[P 39] Protocol for single-run processing: reservoirs of the 110 Caliper chip™ were filled with the following solutions [18]: 0.10 M solutions of *rac*-citronellal and a synthesized aromatic aldehyde in methanol/water (80 : 20) and 0.12 M solutions of 1,3-dimethylbarbituric acid and Meldrum's acid in methanol/water (80 : 20) with 10% molar catalyst ethylenediamine diacetate (EDDA).

A 10 µl volume of the aldehyde was placed in three reservoirs and 10 µl of the 1,3-diketone in three other reservoirs [18]. The chip was inserted into the interfacing device and a script for defining pressures was set in the multiport control using a Caliper 42 Workstation™. A 30 min run was carried out. An eight-peristaltic pump system was used as pressure or vacuum source. No active quenching was performed, but it was assumed that by dilution in the collection reservoir reaction was stopped or at least notably slowed.

[P 40] A similar protocol was made for the 2 × 2 multi-reaction mode. Using a special script to guide flow over 700 or 1000 s, depending on the individual reaction, a residence time of 120 s was achieved for each reaction. The other features of the protocol are identical with [P 39].

See also [18] for references on corresponding batch syntheses.

4.8.2.5 Typical Results

Conversion/Selectivity/Yield

[OS 57] [R 6] [P 39] The conversion of the micro channel processing amounted typically to about 50–75%, depending on the nature of the cycloadduct and the residence time chosen [18].

Benchmarking to batch processing

[OS 57] [R 6] [P 39] The conversion using micro channel processing was comparable to that using batch syntheses [18].

Residence time

[OS 57] [R 6] [P 39] Increasing the residence time from 120 to 360 s results in an increase of about 6–10% in conversion for four chosen cycloadducts [18].

Parallel multi-reaction

[OS 57] [R 6] [P 40] One of the first examples of parallel multi-reaction was performed in a Caliper chip [18]. By 2×2 combinations of two aldehydes and two 1,3-diketones, four cycloadducts were generated simultaneously in one run on one chip (Figure 4.71). The conversions were comparable to those for the single runs, with one exception. Also, cross-contamination was observed. It ranged from a few percents to about 50%. It should be pointed out that despite these initial drawbacks the demonstration of multi-reaction feasibility is a further valuable step in micro channel processing.

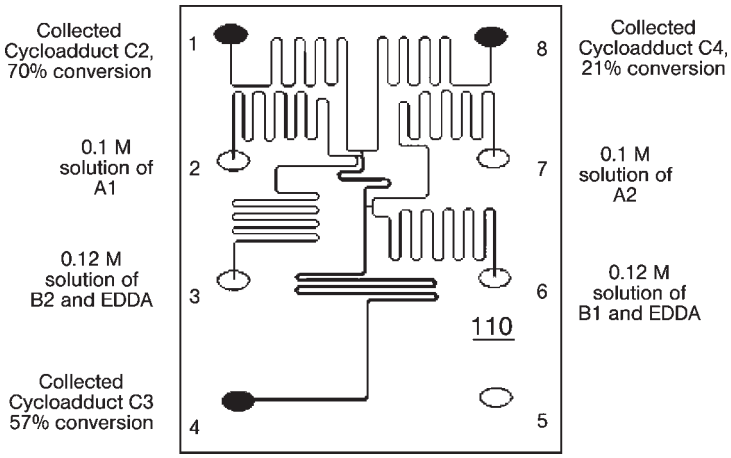


Figure 4.71 Design of a commercial Caliper chip and assignment of fluidic ports to reactant and product solutions used for carrying out (see [OS 57]) [18].

4.8.3 Addition of Oxygen – Epoxidations

Peer-reviewed journals: [30, 122]; sections in reviews: [90, 123]; literature for catalyst formation: [30, 123].

4.8.3.1 Drivers for Performing Epoxidations in Micro Reactors

1-Pentene oxidation over TS-1 catalyst is a fast reaction and hence fulfils a basic requirement for being suited to micro-channel processing [30]. Thus, it can serve as a model reaction to demonstrate the benefits of micro chemical engineering, particularly for zeolite-catalyzed reactions. Apart from this, epoxidations are an important class of organic reactions, also of industrial importance.

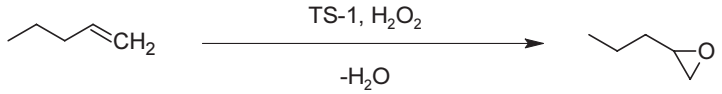
As the zeolite catalyst preparation is not trivial, a catalyzed epoxidation reaction serves to demonstrate the feasibility of gas/liquid/solid processing using this industrially well-applied catalyst class [30].

4.8.3.2 Beneficial Micro Reactor Properties for Epoxidations

The major attempts so far were to demonstrate the benefits of enhancing mass transport in micro channels, especially by decreasing the hydraulic diameter [30].

4.8.3.3 Epoxidations Investigated in Micro Reactors

Organic synthesis 58 [OS 58]: Epoxidation of *n*-pentene by hydrogen peroxide



The reaction is carried out using a titanium silicalite-1 (TS-1) zeolite catalyst [30, 122]. This type of catalyst is known to accelerate the selective oxidation of alcohols, epoxidation of alkenes and hydroxylation of aromatics. These reactions have importance for fine-chemical production.

4.8.3.4 Experimental Protocols

[P 41] Catalyst preparation: selective seeding on the micro channel wall surfaces was used to attach the TS-1catalyst [30]. Mercapto-3-propyltrimethoxysilane was used to modify the micro channel's surface for this purpose by forming a monolayer which provides better adhesion for the colloidal catalyst. After introducing a TS-1 seeding solution, the wafer containing the micro channels was calcined at 873 K. By hydrothermal synthesis using orthosilicates and titanates and an organic templating agent, a layer of TS-1 catalyst was grown on the seeded layer. By thermal treatment in air, organic residues were removed. A very homogeneous layer of 3 μm thickness was generated.

Reaction protocol: 0.9 M 1-pentene, 0.18 M hydrogen peroxide (30%) and 0.2 M *tert.*-butyl methyl ether were dissolved in methanol [30]. This mixture was passed over the catalyst at a rate of 30–120 μl h^{-1}. Reaction was carried out at room temperature. The product mixture was collected in an ice bath.

4.8.3.5 Typical Results

Conversion/selectivity/yield – benchmarking to conventional batch synthesis

[OS 58] [R 15] [P 41] The surface-to-volume ratio was varied by testing both 1000 and 500 μm wide micro channels [122]. By this comparably small increase in catalyst surface area, the yield of the epoxidation could be doubled.

Catalyst deactivation

[OS 58] [R 15] [P 41] When operating continuously for more than 100 h, deactivation of the catalyst occurs [122]. This seems not to be reversible, as calcinations by air do not bring back catalyst activity.

4.8.4 Dialkoxy Additions – Electrochemical Dialkoxylation of Heteroaromatics

Peer-reviewed journals: [70]; proceedings: [71, 124]; sections in reviews: [90].

4.8.4.1 Drivers for Performing Dialkoxylations

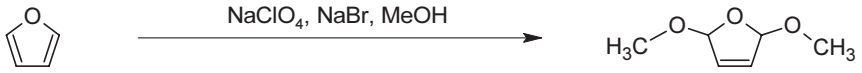
Electrochemical syntheses can be favorably performed at room temperature, thus saving economic resources [70, 71]. No additional reactants are required so that the reaction products are relatively pure. As the reaction occurs directly at the electrode surface, high regio- and stereoselectivity is achieved.

4.8.4.2 Beneficial Micro Reactor Properties for Dialkoxylations

Micro reactors are seen to have smaller inhomogeneities of the electrical field and less temperature rise in the reaction medium due to the Joule heating effect between the electrodes [70]. Submillimeter interelectrode gaps are expected to reduce the ohmic loss.

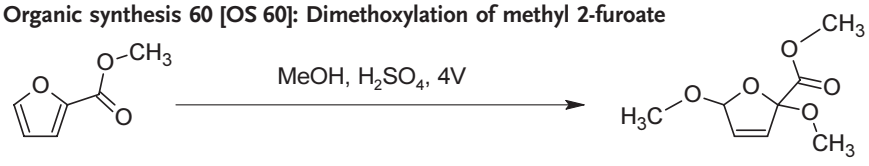
4.8.4.3 Dialkoxylations Investigated in Micro Reactors

Organic synthesis 59 [OS 59]: Di-methoxylation of furan



Furan was dimethoxylated to give 2,5-dihydro-2,5-dimethoxyfuran, using electrogenerated bromine molecules generated from bromide salts in electrolyte solutions [71]. This reaction was characterized in classical electrochemical reactors such as pump cells, packed bipolar cells and solid polymer electrolyte cells. In the last type of reactor, no bromide salt or electrolyte was used; rather, the furan was oxidized directly at the anode. However, high consumption of the order of 5–9 kWh kg^{-1} (at 8–20 V cell voltage) was needed to reach a current efficiency of 75%.

Organic synthesis 60 [OS 60]: Dimethoxylation of methyl 2-furoate



Methyl 2-furoate was dimethoxylated using methanol in sulfuric acid to give methyl-2,5-dihydro-2,5dimethoxy-2-furan carboxylate [70]. The reaction mechanism at the electrodes is not completely known. However, the anodic reaction is said to be the oxidation of methanol. A two-electron process is assumed and hydrogen production is observed at the cathode.

4.8.4.4 Experimental Protocols

[P 42] Typically, a flow rate of 150 µl min^{-1} was used [71]. A 0.1 M furan solution containing 0.1 M $NaClO_4$ and 5 mM NaBr was used as reaction medium. Reaction was carried out at room temperature. Interdigitated band electrodes with 100 µm wide gaps and 500 µm band widths were tested in a 800 µm deep Perspex micro reactor.

[P 43] Typically, a flow rate of 250 µl min^{-1} was established by use of syringe or peristaltic pumps [70]. A 0.1 M methanol solution in sulfuric acid was used as reaction medium. Reaction was carried out at room temperature at a voltage of 4 V.

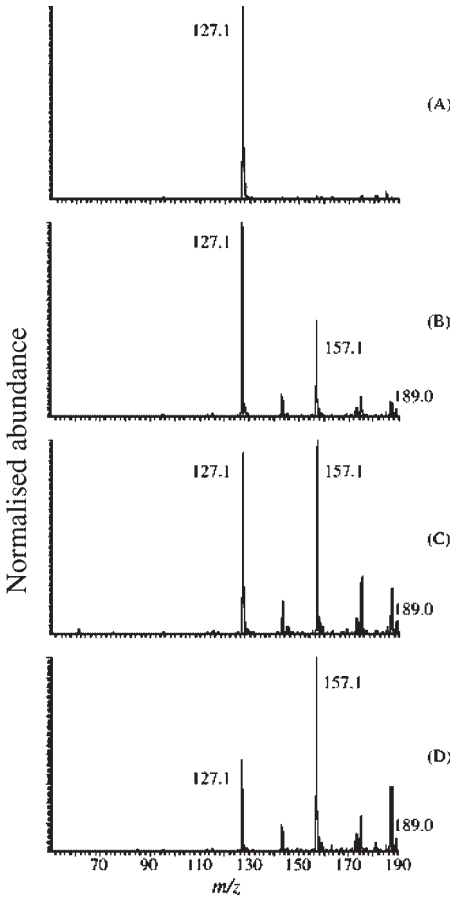


Figure 4.72 Mass spectrometric analysis of product formation of dimethoxylation of methyl 2-furoate for various flow rates. (A) Initial solution; (B) 250; (C) 150; (D) 50 µl min^{-1} [70].

4.8.4.5 Typical Results

Flow rate/residence time

[OS 60] [R 34] [P 43] Although no precise data on conversion and yield could be found, mass spectrometric analysis of the dimethoxylation reaction (Figure 4.72) allowed one to judge the impact when reducing the flow rate, respectively increasing residence time (250, 150, 50 μl min^{-1}) [70]. The peak assigned to the product increased relative to that of the reactant. Also, with increasing residence time, side reactions become evident, e.g. the formation of carboxylic moieties by saponification of the product.

Cell voltage/bromine production

[OS 59] [R 34] [P 42] The furan and dimethoxylated product concentrations were monitored as a function of the cell voltage [71]. The product concentration follows the sigmoidal shape of the bromide oxidation current. The furan concentration shows the inverse behavior. For a cell voltage of 3 V and a current of 30 mA, a concentration of 50% is approached. The product formation is limited by mass transfer of bromine generation.

Dimensions of inter-electrode gap

[OS 59] [R 34] [P 42] The furan dimethoxylation was conducted using interdigital electrodes with 100 and 500 μm inter-electrode gaps, for each case in the presence of electrolyte (0.1 M $NaClO_4$) and without [71]. Using 500 μm inter-electrode gaps, the conversion vs cell voltage curves differ considerably when using electrolyte and when not (150 μl min^{-1}). This is explained by the role of the electrolyte in maintaining the current for such a large electrode distance. Using a shorter distance (100 μm), this is obviously no longer needed. Here, the curves for operation with and without electrolyte are essentially the same (75 μl min^{-1}).

Bromide concentration/relation to energy consumption

[OS 59] [R 34] [P 42] Conversion was monitored versus cell voltage for four bromide concentrations, 5, 20, 100 and 200 mM NaBr (150 μl min^{-1}) [71]. Whereas a 50% conversion was achieved for the lowest salt content, the two highest concentrations led to 70% conversion. When the 5 and 100 mM operations were compared for the same conversion (70%), the energy consumption and the current efficiency were much worse when using the higher salt concentration (50 mM furan; 85 μl min^{-1}; 3 V).

Benchmarking to conventional reactors: current efficiency and energy consumption

[OS 59] [R 34] [P 42] Flow cells with interdigitated band electrode configurations provide a 50% energy saving when compared with conventional reactors such as packed-bed bipolar cells [71]. While 100 μm electrodes (no electrolyte) have an energy consumption of 1.5 kWh kg^{-1}, the bipolar cell needs double this amount. The current efficiency is 80 and 90% for the micro device and the bipolar cell, respectively. In view of the high selectivity of the micro flow process and the low contents of the electrolyte, successive purification steps are facilitated compared with conventional technology.

4.8.5 Polyalkenyl Addition – Polyacrylate Formation

Proceedings: [125]; patents: [126]; sections in reviews: [42, 90, 99, 100, 127, 128].

4.8.5.1 Drivers for Performing Polyacrylate Formation in Micro Reactors

Fouling is a major problem encountered during radical polymer formation [125]. High molecular-weight polymers, potentially of branched nature, form during polymerization and precipitate owing to their insolubility in the solvent.

Fouling is only one result stemming from the influence of mixing on establishing local concentration profiles and their impact on the course of reaction [125]. Hence, in a more comprehensive view, micro mixing can affect the local concentration of initiator, monomer and additives. This should have an impact on the molecular weight distribution of the polymer formed.

The mixing sensitivity of (fast) polymerizations is known and frequently described in literature. This is due to the fact that radical polymerizations typically take 1 s until chain termination [125]. However, typical mixing times of large-scale mixers, including conventional static mixers, are longer. Accordingly, the course of mixing has an effect on the product quality, i.e. the polymer-chain distribution.

4.8.5.2 Beneficial Micro Reactor Properties for Polyacrylate Formation

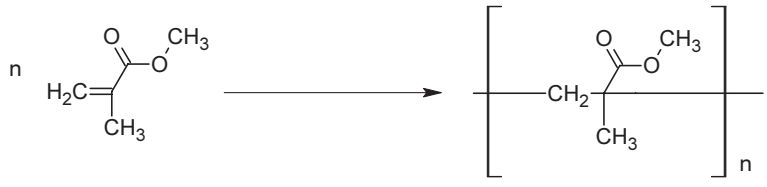
Micro mixers offer unique mixing physics by using different mixing mechanisms as compared with stirring and other conventional mixing means [125]. The range encompasses multi-lamination, distributive mixing (split–recombine) and chaotic mixing. By this means, more or less regular concentration profiles, with regard to time and space, are generated. If the reaction is faster than mixing (at least for conventional processing), mixing should have an influence on reaction.

Micro mixers permit mixing times much below 1 s. Some multi-lamination micro mixers even approach sub-millisecond mixing [40]. Therefore, mixing can performed faster than most known reactions, including fast radical polymerizations.

Potentially, the mixing physics in micro mixers may allow fouling-free processing, despite the use of tiny channels and nozzles, for cases which lead to plugging when using conventional equipment. Fast mixing in micro mixers may result in polymer molecular weight distributions having a ratio of the number average to the weight-average (M_n/M_w) of an ideally mixed radical polymerization [126].

4.8.5.3 Polyacrylate Formation Investigated in Micro Reactors

Organic synthesis 61 [OS 61]: Radical polymerization of acrylates



This reaction includes modified acrylates with or without addition of styrenes in combination with one or more initiators in a solvent [126]. In an example, tetrahydrofuran was used as solvent and the polymer concentrations amounted to about 5.6 g l^{-1}. Thus, the polymerization is carried out as solvent process.

4.8.5.4 Experimental Protocols

[P 44] The whole process was carried out in a pilot-scale plant (Figure 4.73) equipped with an interdigital micro mixer array and a tube reactor [126] (a shorter description of the set-up is also given in [125]). Monomer/solvent and initiator/solvent mixtures were taken from tanks and pre-heated in a heat exchanger, typically to a temperature below or approaching reaction temperature (50–180 °C). The pre-heated solutions entered the micro mixer array and left it either directly to a tube reactor or to a pre-mixer, set between the micro mixer and tube reactor. The tube reactor was actually composed of three tubes connected in series. The first two had an inner diameter of, e.g., 10 mm and contained commercial Kenics static mixers; the last one had an inner diameter of, e.g., 20 mm and contained a commercial Sulzer SMX static mixer. The tubes, however, can also be operated with the mixer internals. The diameters of the tubes were oriented on the throughput targeted. The total volume of all tubes was, for one reported type of equipment [126], about 0.5 l. The pre-mixer may be a Sulzer SMX with an internal diameter of 5 mm.

The ratio of monomer to initiator ranges from 1 : 1 to 10 : 1, and preferentially is set to 9 : 1 [126]. By setting initiator concentration, initiator type, residence time and temperature, the polymer molecular weight, conversion and solution viscosity are determined. The monomer is, e.g. acrylate-based with or without styrene. The pressure is regulated to be 2×10^5–5×10^6 Pa in order to avoid solvent and monomer boiling.

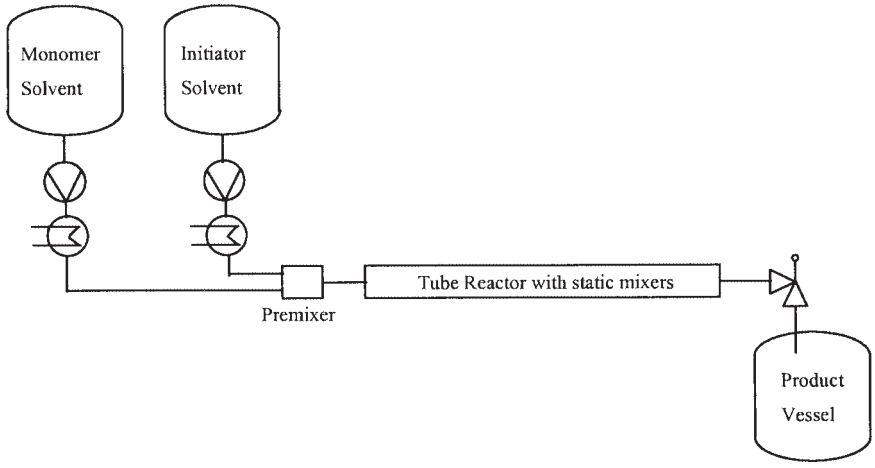


Figure 4.73 Schematic of laboratory-scale experimental set-up for polyacrylate formation. The Sulzer-type pre-mixer can be replaced by an interdigital micro mixer [125].

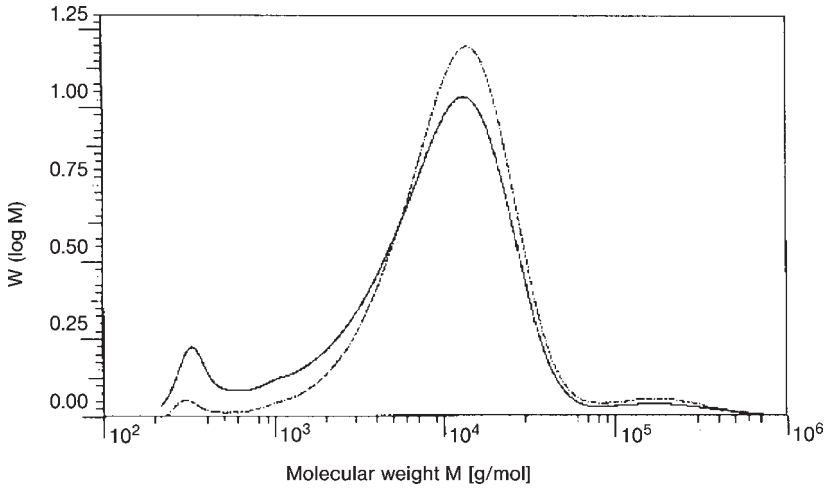


Figure 4.74 Radical polymerization of acrylates in a laboratory-scale experimental set-up with a Sulzer-type pre-mixer. Fouling at the feeding point of the static mixer (top) and molecular weight distribution (bottom) [125].

4.8.5.5 Typical Results

Molecular weight distribution – fouling – benchmarking to conventional processing

[OS 61] [R 20] [P 44] The polymer molecular-weight distribution of a micro-mixer based processing was given as the normalized frequency distribution $W(\log M)$, determined by both UV and refractive index analysis [126]. No high-molecular-weight contents above a mass of $> 10^5$ were found [125, 126]. As a result, no precipitates formed on the micro channels' surface, despite the large surface-to-volume ratio (Figure 4.74).

In contrast to this result, polymer samples taken from processing without a micro mixer displayed a small but significant fraction of high-molecular weight polymer with a mass $> 10^5$ [126]. Here, in some cases, heavy precipitation occurred, resulting even in plugging of the static-mixer internals of the tube reactors [125].

Micro mixing

[OS 61] [R 20] [P 44] The polymer molecular-weight distribution of a static mixer-based processing, which was determined both by UV and refractive index analysis,

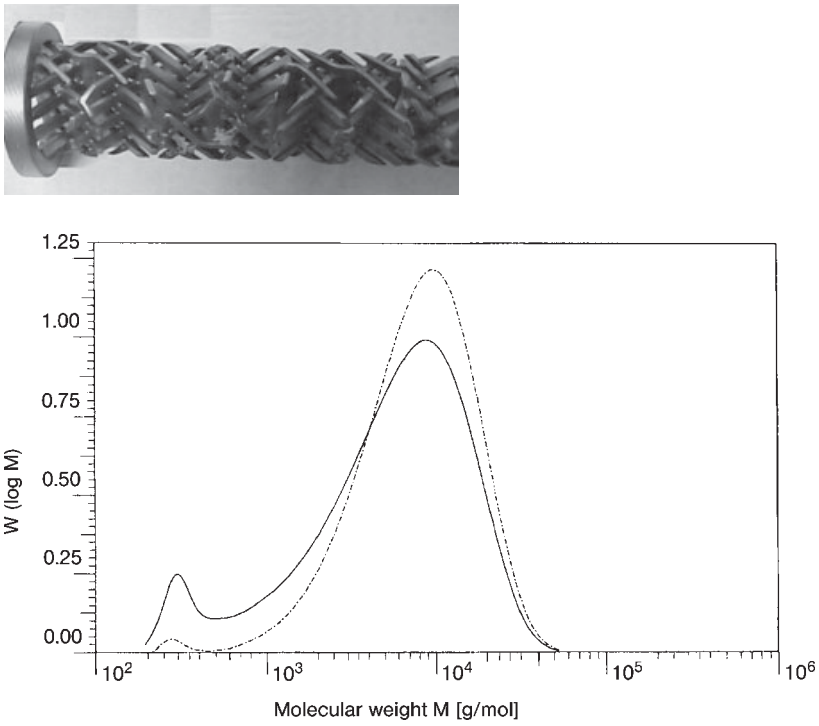


Figure 4.75 Radical polymerization of acrylates in a laboratory-scale experimental set-up with a micro mixer as premixer. Less fouling at the feeding point of the static mixer (compare with Figure 4.74) (top) and molecular weight distribution (bottom) [125].

showed a high-molecular-weight peak [125]. This was explained by the longer time needed for mixing than for reaction. Radical polymerizations are typically completed in about 1 s; mixing in static mixers may take longer. Hence reactions are conducted under segregated concentration profiles, partly promoting long-chain formation. Such high-molecular-weight polymers, especially when being branched, tend to be insoluble and cause fouling of the mixer (Figure 4.75).

In turn, the interdigital micro mixer mixes much faster, provides more unique concentration profiles before reaction takes place and consequently changes the course of the reaction [125]. As a result, no high-molecular-weight polymer fraction is observed by GPC measurement and no fouling occurs, although the specific wall surfaces of the micro device are expected to promote deposition.

Scale-up

[OS 61] [R 20] [P 44] A micro mixer-based laboratory plant would give 50 t a^{-1}, assuming an annual operation time of 8000 h. Based on these laboratory experiments, a pre-basic design comprising numbering-up of 28 micro mixers and four tube reactors was proposed [125]. Accordingly, the production of such plant was calculated to be in the order of 2000 t a^{-1}, assuming 8000 h operation.

4.8.6
Polyalkenyl Addition – Polyethylene Formation

Peer-reviewed journals: [1].

4.8.6.1 Drivers for Performing Polyethylene Formation in Micro Reactors

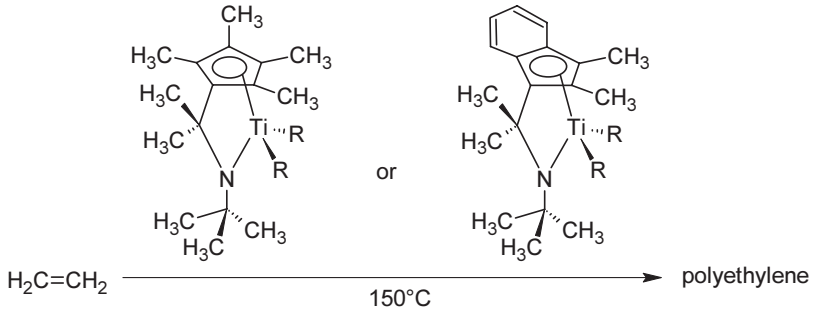
Screening of process conditions was one driver for performing polyethylene synthesis [1]. Thus, test-throughput frequency, the number of possible samples per day, is a target value. Also, flexibility with regard to temperature and pressure at low sample consumption is a major issue. In addition to fastness and flexibility, the quality of the information and the insight obtained is seen as a motivation for micro-channel studies.

4.8.6.2 Beneficial Micro Reactor Properties for Polyethylene Formation

The above-mentioned targets result from the build-up and operation of a complex apparatus rather than from the micro-channel device or the tubing itself [1]. It is the interplay between the use of advanced HPLC tools, delicate temperature monitoring, electronics (e.g. for pressure control), control system and modern software that allows high-level screening. The most striking micro-channel property here is the possibility of controlling temperature easily by ohmic self-heating and measuring the temperature evolution by voltage taps.

4.8.6.3 Polyethylene Formation Investigated in Micro Reactors

Organic synthesis 62 [OS 62]: Radical polymerization of ethylene



A stream of ethylene is fed into the reactor by use of quaternary LC pumps and subsequently dissolved in a 1.90 ml h^{-1} toluene stream [1]. Ethylene is handled at 60 °C, well above the critical temperature. Catalyst additions are fed via HPLC-type sample injection valves. Various combinations of precatalysts and activators were sampled and loaded by an autoinjector. Catalyst solutions typically were diluted 20-fold within the micro reactor.

4.8.6.4 Experimental Protocols

[P 45] The entire flow system was put in a glove-box in an oxygen-free environment (< 1 ppm, v/v) [1]. A quaternary feed system was used to provide different comonomer additives dissolved in toluene that are mixed with ethylene (25 h) in a mixer.

The total solvent flow rate was set to 2.0 ml min^{-1}. Separate streams of catalyst (0.02 M in toluene) and cocatalyst (0.02 M in toluene) formulations were fed to the tubing reactor in the microliter per minute range by use of special micro-pumps. The volume of the injection loops amounted to 20 µl; the catalyst stream was set to 50 µl min^{-1}. In an electrothermal pre-heat zone the ethylene/comonomer mixture in toluene was brought close to reaction temperature before adding catalyst. The reaction was carried out at 175 °C and a pressure of 2.8 MPa. In several subsequent zones each of 16 cm length (volume: 200 µl) along the reactor tubing, temperature was monitored by voltage pads.

4.8.6.5 Typical Results

Temperature profiles

[OS 62] [R 1] [P 45] Temperature profiles versus time for different positions along the reactor tubing were obtained for catalyst plug-induced ethylene polymerization [1]. The maximum rise in temperature was about 23 °C. With downstream flow passage, the profiles exhibit a decreasing maximum temperature and broaden in shape (Figure 4.76). This was explained by the laminar flow inducing increase in plug length by axial dispersion. Heat transfer effects are seen also to play a role.

Pressure monitoring – relationship to temperature increase

[OS 62] [R 1] [P 45] Improved pressure control was exerted for catalyst plug-induced ethylene polymerization by using advanced pressure control electronics [1]. In the regions of large temperature increase, the pressure fluctuated slightly; this effect diminished downstream.

By deliberately changing the pressure (in a loop), the temperature response followed immediately [1]. This proved that control of pressure is crucial for obtaining stable temperature baselines.

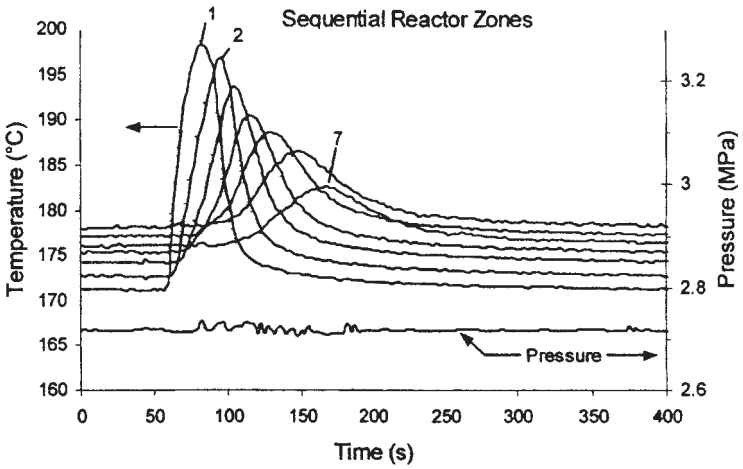


Figure 4.76 Temperature profiles during ethylene polymerization versus time for different positions along the reactor tubing [1].

Reliability of processing – statistics on temperature profiles

[OS 62] [R 1] [P 45] By monitoring temperature profiles, a high reproducibility for catalyst plug-induced ethylene polymerization could be demonstrated [1]. The standard deviation for the temperature peak area was found to be only 1.6%.

Variation in catalyst

[OS 62] [R 1] [P 45] The impact of the choice of catalyst on catalyst plug-induced ethylene polymerization was analyzed [1]. A constrained-geometry catalyst (CGC) with a cyclopentadienyl moiety was about 3.6 times more active than a CGC–indenyl catalyst.

Temperature

[OS 62] [R 1] [P 45] The impact of temperature on catalyst plug-induced ethylene polymerization was determined using a CGC–cyclopentadienyl catalyst [1]. Catalyst activity and polymer formation were higher at lower temperature (155 °C) than at higher temperature (175 °C). This was explained by thermally induced catalyst degradation (Figure 4.77).

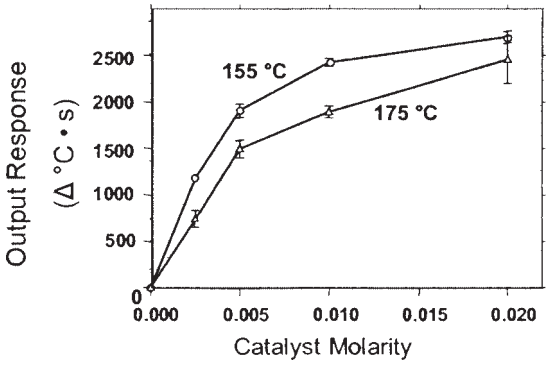


Figure 4.77 Effect of temperature and catalyst modularity on catalyst activity for ethylene polymerization [1].

Test-throughput frequency

[OS 62] [R 1] [P 45] Catalyst plug-induced micro-channel ethylene polymerization allows to process about 10 runs per hour [1]. This is considerably more than achievable with conventional equipment (Parr reactors) processing only 4 to 6 runs per day.

4.8.7
Dihydro Addition – Hydrogen-transfer Reduction

Peer-reviewed journals: [117].

4.8.7.1 Drivers for Performing H-transfer Reduction in Micro Reactors

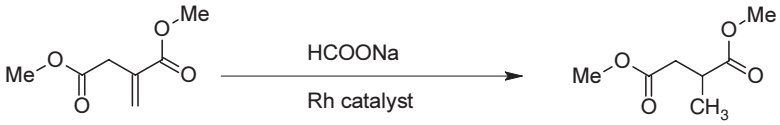
Short residence time and high heat transfer capabilities are demanded for the transfer hydrogenation of dimethyl itaconate, as in general for comparable liquid/liquid reactions [117].

4.8.7.2 Beneficial Micro Reactor Properties for H-Transfer Reduction

The above-mentioned criteria can be met by suitable micro-channel devices.

4.8.7.3 H-transfer reduction Investigated in Micro Reactors

Organic synthesis 63 [OS 63]: H-transfer reduction of dimethyl itaconate



This H-transfer reduction with sodium formate and employing catalysis by a water-soluble rhodium-phosphine catalyst yields dimethyl methylsuccinate [117].

4.8.7.4 Experimental Protocols

[P 46] Prior to the liquid/liquid micro reaction system used, a microgrid serves for dispersing the phases [117]. No other details on performing the reaction are given.

4.8.7.5 Typical Results

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

[OS 63] [R 27] [P 46] A 43% conversion was achieved by micro-channel processing, while both batch experiments and expectation from intrinsic kinetics indicated conversions close to 90% [117]; 80% was achieved by micro-channel processing with an additional micro mixer (see the Section Setting micro mixing prior to reaction, below).

Correction for liquid/liquid mass transfer resistance

[OS 63] [R 27] [P 46] Experimental results were compared with a kinetic model taking into account liquid/liquid mass transfer resistance [117]. Calculated and experimental conversions were plotted versus residence time; the corresponding dependence of the mass-transfer coefficient $k_l\acute{a}$ is also given as well (Figure 4.78).

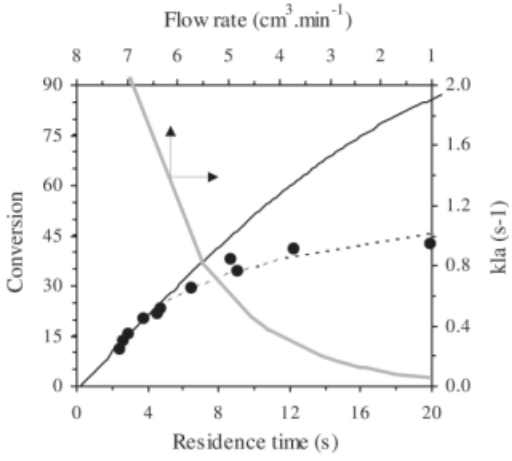


Figure 4.78 Liquid/liquid H-transfer reduction of dimethyl itaconate to dimethyl methylsuccinate: experimental results vs models. Main axis: experimental conversions (●); intrinsic kinetic model (solid line); kinetic model + mass transfer kinetics (dashed line). Secondary axis: variation of computed k_1a with flow rate. Further details are given in [117].

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

Setting micro mixing prior to reaction

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

4.9
Addition to Carbon-Hetero Multiple Bonds

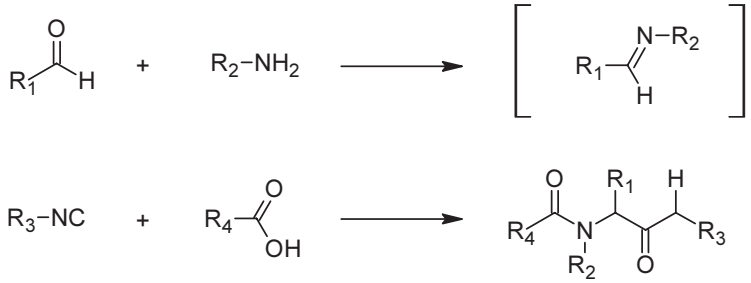
4.9.1
1/*N*-Hydro-2/*C*-(α-Acyloxyalkyl),2/*C*-Oxo Biaddition – Ugi Four component Condensation (4CC)

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

4.9.1.1 Drivers for Performing Ugi reactions in Micro Reactors

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

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



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

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