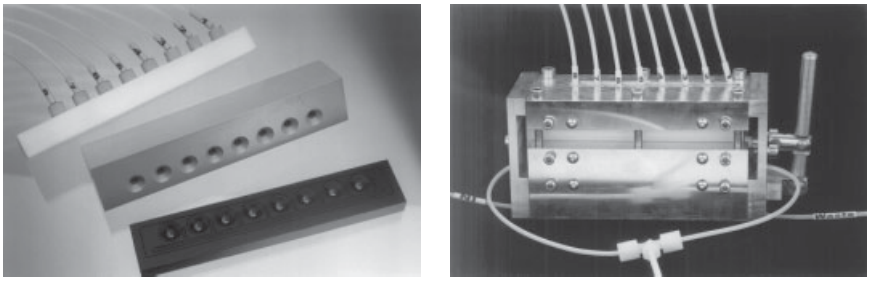


Figure 4.36 Solid-phase synthesis–pneumatic agitation–8-reactor system. Left: dismantled system. Right: same system, assembled [75].

4.2
Aliphatic Nucleophilic Substitution

4.2.1
Hydroxydehalogenation – Hydrolysis of Chlorides and Acid Chlorides

Proceedings: [46] (benzal chloride), [21] (acid chlorides).

4.2.1.1 Drivers for Performing Chloride Hydrolysis in Micro Reactors

The cleavage of two chloride groups on one C atom can be a very fast process. The hydrolysis of benzal chloride, for instance, is such a reaction between two immiscible media leading to huge heat release [46]. By uncontrolled mixing, the temperature can rise significantly accompanied by an increase in viscosity due to side reactions. For both reasons, the reaction can lead to a bursting of the whole processed sample. Therefore, the reaction is usually carried out by dropwise addition of one reactant and rigrous stirring. Accordingly, the driver for micro channel synthesis is to search for isothermal processing at high degrees of conversion and fast mixing.

Similar aggressive reaction conditions characterize the hydrolysis of acid chlorides, in particular when using short-chain alkyl-substituted acid chlorides such as propionic acid chloride. This fast reaction serves well as a model reaction for micro channel processing, especially for IR monitoring owing to the strong changes in the carbonyl peak absorption by reaction [21].

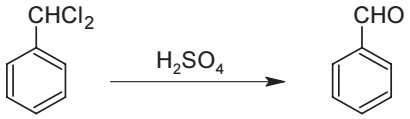
4.2.1.2 Beneficial Micro Reactor Properties for Chloride Hydrolysis

In the case of the above-mentioned dichloride hydrolysis, good mixing, i.e. emulsification, good heat transfer and restriction of residence time (to reduce side reactions) is demanded [46].

Concerning acid chloride hydrolysis, the advantage of micro chemical processing is that the micro reactor itself can be used as a flow-through cell for analysis, very unlike most large-scale conventional reactors [21]. For the case indicated, IR analysis is suitable and can be performed with silicon as encasing material, which is transparent for a wide range of the IR spectrum. In other cases, when reactions lead to color changes such as for the Wittig reaction [13], visible or UV detection may be required. Here, glass or quartz is the best micro-reactor construction material.

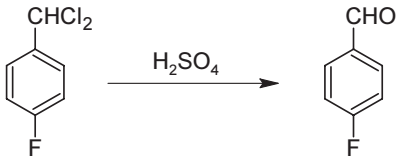
4.2.1.3 Chloride Hydrolysis Investigated in Micro Reactors

Organic synthesis 2 [OS 1]: Hydrolysis of benzal chloride



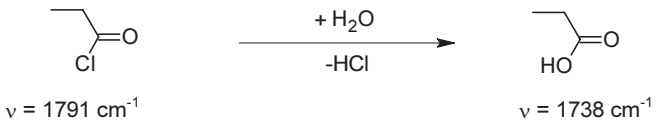
By reaction of sulfuric acid and benzal chloride benzaldehyde is generated. Both reactants are rather viscous and immiscible leading to the above mentioned reaction problems [46]. Due to temperature increase and too long reaction times, side reactions such as the oxidation to benzoic acid occur.

Organic synthesis 2 [OS 2]: Hydrolysis of 4-fluorobenzal chloride



This reaction is basically similar to [OS 1], but is expected to differ in reactivity owing to the I- and M-effects of the fluoro group.

Organic synthesis 3 [OS 3]: Hydrolysis of propionic acid chloride



This hydrolysis is accompanied by strong changes in IR absorption, particularly concerning a considerable shift of the carbonyl group peak (from 1791 to 1738 cm^{-1}) [21].

4.2.1.3 Experimental Protocols

[P 1] Through an interdigital micro mixer–tubular reactor set-up, sulfuric acid and benzal chloride (or 4-fluoro benzal chloride) are fed by piston pumps [46]. Sulfuric acid has to be used in excess; a ratio of acid to aromatic compound of 5 : 1 was applied. This also was chosen for reasons of emulsification, for the formation of small, relatively uniform droplets of the aromatic compound in the acid, the viscosity being not too high. Favorably high total flow rates, e.g. above 200 ml h^{-1}, had to be used to yield such patterns. At much lower flow rates, large segregated zones of the aromatic compound result, yielding worse reaction performance (Figure 4.37).

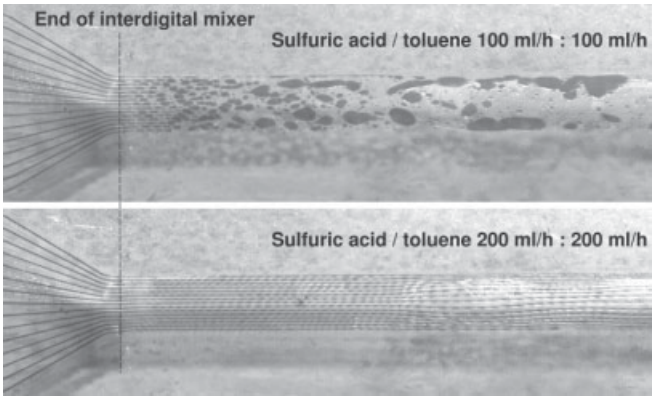


Figure 4.37 Images of contacting sulfuric acid with dyed (iodine) toluene in a rectangular-shaped interdigital micro mixer at two different flow rates. The system sulfuric acid/toluene (iodine) was taken as model for the reacting media sulfuric acid/benzal chloride [46].

4.2.1.4 Typical Results

Conversion/selectivity/yield

[OS 1] [R 20] [P 1] Yields range up to 69% (60 °C; 8 s). Nearly complete conversion is achieved for this parameter set [46].

Benchmarking to batch processing

[OS 1] [R 20] [P 1] The best yield obtained is 69% (60 °C; 8 s); batch synthesis is reported to result in a 65% yield [46].

Reaction temperature

[OS 1] [R 20] [P 1] The yield increases (Figure 4.38) from less than 10% at room temperature to 69% at 60 °C for a given residence time (8 s) [46].

Residence time

[OS 1] [R 20] [P 1] On increasing the residence time from 1 s to nearly 100 s the yield passed through a maximum, while conversion increased and reached a plateau. This was explained by the larger contribution of side reactions at longer residence times. Conversion, as to be expected, increased with residence time so that selectivity decreased. At about 10 s, nearly 100% conversion is achieved [46].

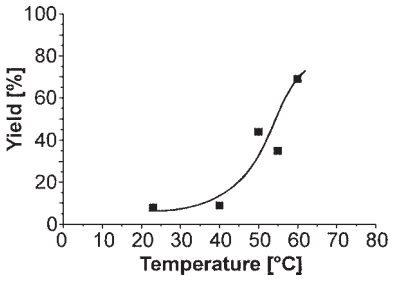


Figure 4.38 Increase in benzaldehyde yield with increase in reaction temperature by performing benzal chloride hydrolysis in a slit-shaped interdigital micro mixer [46].

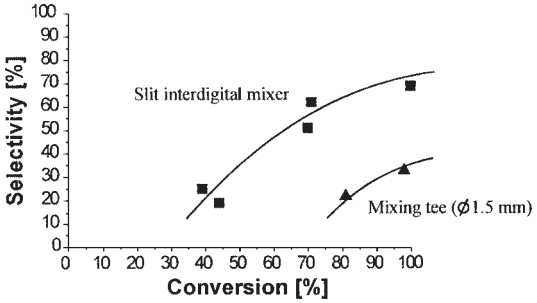


Figure 4.39 Comparison of benzal chloride hydrolysis performed in a slit-shaped micro mixer and in a mixing tee [46].

Internal diameter/benchmarking to mixing tee

[OS 1] [R 20] [P 1] A comparison of the selectivity/conversion behavior of an interdigital micro mixer–tube reactor with that of a mixing tee of about 1.5 mm inner diameter (and thus of larger internal dimensions) was made (Figure 4.39). For all data gathered, the performance of the micro mixer was much better, e.g. about 30% more selectivity at a given conversion [46].

Synthesis of a substituted derivative

[OS 2] [R 20] [P 1] The feasibility of the micro channel hydrolysis of 4-fluorobenzal chloride was shown [46]. A maximum yield of about 50% at 100% conversion was reached (20–70 °C). Higher yields at low conversions were found compared with benzal chloride hydrolysis.

In-line IR monitoring

[OS 3] [no protocol] The propionic acid chloride hydrolysis by water was characterized by in-line IR monitoring, using the micro reactor itself as a flow-through analysis cell that was placed in a commercial holder in a commercial IR spectrometer [21]. By following the decrease of the 1791 cm^{-1} peak (acid chloride-substituted carbonyl), and the corresponding increase of the 1738 cm^{-1}-peak (acid-substituted carbonyl) the course of the reaction can be monitored [21]. Different flow rates were investigated (0.002, 0.01 and 0.2 ml min^{-1}) showing the dependence of yield on residence time. Details on how to achieve a maximum signal-to-noise ratio by choosing proper silicon construction materials are given also [21].

4.2.2
Cyanodehalogenation – Preparation of Nitriles

Proceedings: [3].

4.2.2.1 Drivers for Performing Preparation of Nitriles in Micro Reactors

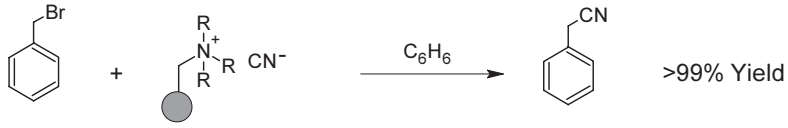
The carrying out of this reaction served to demonstrate organic synthesis on a newly developed porous-polymer-rod micro reactor [3].

4.2.2.2 Beneficial Micro Reactor Properties for Preparation of Nitriles

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

4.2.2.3 Preparation of Nitriles Investigated in Micro Reactors

Organic synthesis 4 [OS 4]: Nitrile synthesis from α-bromotoluene



α-Bromotoluene reacts with cyanide groups to give α-cyanotoluene [3].

4.2.2.4 Experimental Protocols

[P 2] α-Bromotoluene was nucleophilically substituted to give α-cyanotoluene in benzene at 70 °C (12 h) by cyanide coupled to a porous polymer resin [3]. The polystyrene polymer was cross-linked via linking divinylbenzene moieties in the main chain. Originally, the polymer contained benzylchloride groups, which were converted to quaternary ammonium groups. By means of ion exchange, functional anionic groups such as the reductive cyanide moiety can be introduced. Typical ion exchange capabilities of the micro reactor were about 0.1–1.0 mmol, depending on the polymer load.

4.2.2.5 Typical Results

Conversion/selectivity/yield

[OS 4] [R 3] [P 2] > 99% yield was obtained after 12 h of processing [3].

4.2.3 Thiocyanatodehydrogenation – Thiocyanation

Proceedings: [3].

4.2.3.1 Drivers for Performing Thiocyanation in Micro Reactors

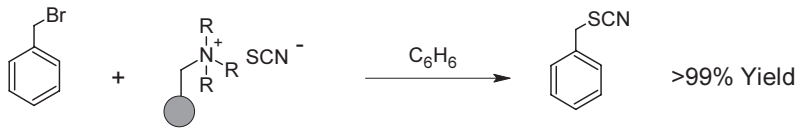
See Section 4.2.2.1.

4.2.3.2 Beneficial Micro Reactor Properties for Thiocyanation

See Section 4.2.2.1.

4.2.3.3 Thiocyanation Investigated in Micro Reactors

Organic synthesis 5 [OS 5]: Rhodanide substitution of α-bromotoluene



α-Bromotoluene reacts with rhodanide groups to give α-thiocyanidetoluene [3].

4.2.3.4 Experimental Protocols

[P 3] This protocol was performed identically with [P 2], with the exception of the reactants and conditions. α-Bromotoluene was nucleophilically substituted in benzene to give α-thiocyanotoluene at 70 °C (12 h) using rhodanide coupled to a porous polymer resin [3].

4.2.3.5 Typical Results

Conversion/selectivity/yield

[OS 5] [R 3] [P 3] > 99% yield was obtained after 12 h of processing [3].

4.2.4 Azidodehalogenation – Formation of Azides

Proceedings: [3].

4.2.4.1 Drivers for Performing Azide Substitutions in Micro Reactors

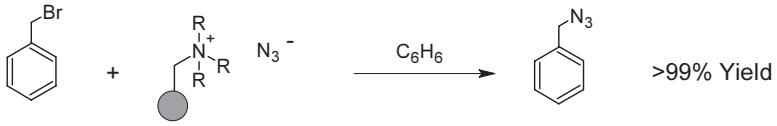
See Section 4.2.2.1.

4.2.4.2 Beneficial Micro Reactor Properties for Azide Substitutions

See Section 4.2.2.1.

4.2.4.3 Azide Substitutions Investigated in Micro Reactors

Organis synthesis 6 [OS 6]: Azide substitution of α-bromotoluene



α-Bromotoluene reacts with azide groups to give α-azidotoluene [3].

4.2.4.4 Experimental Protocols

[P 4] This protocol was performed identically with [P 2], with the exception of the reactants and conditions. α-Bromotoluene was nucleophilically substituted in benzene to give α-azidotoluene at 70 °C (12 h) by azide coupled to a porous polymer resin [3].

4.2.4.5 Typical Results

Conversion/selectivity/yield

[OS 6] [R 3] [P 4] > 99% yield was obtained after 12 h of processing [3].

4.2.5 Aminodehalogenation – Menschutkin Reaction (Formation of Quaternary Amines)

Proceedings: [78]; sections in review: [79, 80].

4.2.5.1 Drivers for Performing the Menschutkin Reaction in Micro Reactors

Most of the known organic reaction yield sooner or later precipitates or involves directly the addition of solid reagents [78]. Hence fouling phenomena are rather

the rule than the exception when dealing with organic synthesis. By choosing another solvent, enhancing temperature, decreasing concentration, using an antifouling coating in micro channels or even changing the processing route, there are ways to cope with fouling. However, this often leads to compromises. Accordingly, one wants to have novel micro flow concepts that are virtually insensitive to fouling.

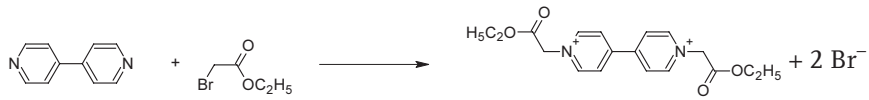
The Menschutkin reaction was carried out as a test reaction to show the feasibility of such novel micro flow concepts that allow to process fouling-sensitive reactions (see also Section 4.2.6; here another test reaction is decribed for the same purpose) [78]. The reaction of alkyl bromide with ternary bases such as pyridine or triethylamine gives quaternary salts insoluble in most solvents. Often, fairly rapid precipitation of this salt occurs, hence ideally serving as a test reaction for fouling sensitivity of micro-channel devices. The reaction of 4,4′-bipyridyl and ethyl bromoacetate [78] belongs to the category of fast-precipitating Menschutkin reactions, as the halide function is activated by the carbonyl function.

4.2.5.2 Beneficial Micro Reactor Properties for the Menschutkin Reaction

The reduction of fouling sensitivity refers to new microfluidic concepts, based on delaying mixing or on free-flow guiding [81]. With regard to these criteria, the Menschutkin reaction is just one prominent example among a vast number of others, also chosen for reasons of having a very high reaction rate.

4.2.5.3 Menschutkin Reaction Investigated in Micro Reactors

Organic synthesis 7 [OS 7]: Formation of quaternary salts from 4,4′-bipyridyl and ethyl bromoacetate



This formation of a quaternary salt is performed in dichloromethane as solvent [78]. The halide function is a good leaving group owing to the presence of the neighboring carbonyl function, ensuring a fast reaction. Owing to the double-ionic character and the rigid core, hardly without any flexible chains, of the product, fast precipitation occurs when the reaction has proceeded to a certain conversion (see also Section 4.2.6; here another test reaction is decribed for monitoring fouling sensitivity).

4.2.5.4 Experimental Protocols

[P 5] Layers of 4,4′-bipyridyl (0.3 mol l^{-1} in dichloromethane), ethyl bromoacetate (0.3 mol l^{-1} in dichloromethane) and a separation layer of dichloromethane were fitted into each other by means of a concentric separation mixer (three-fluid nozzle with three tubes having diameters of 1.5, 3 and 4 mm, slotted into each other) [78]. Thereby, two circular liquid layers of a thickness of 200 µm and a center stream of 1.5 mm diameter were generated. The reaction temperature was 22 °C. The reaction solution was inserted as droplets or a continuous stream either directly or via

the tubular reactor in the beaker. The precipitate solution yielded was passed through a frit and the remaining solid was washed with dichloromethane and dried at elevated temperature and weighed.

Experiments with the following individual flow rates of the three liquids were performed [78]: 5 : 25 : 5; 5 : 100 : 5; 5 : 200 : 5; 5 : 250 : 5; 25 : 250 : 25; 50 : 150 : 50; 300 : 600 : 300; 300 : 1000 : 300 as bipyridyl in dichloromethane : dichloromethane : ethyl bromoacetate in dichloromethane in ml h^{-1}.

4.2.5.5 Typical Results

Conversion/selectivity/yield

[OS 7] [R 22] [P 5] Reactions were performed with wide variations of flow rates, ranging from 5 : 25 : 5 to 300 : 1000 : 300 (each value in ml h^{-1}) [78]. The corresponding yields were all about 75%. These yields are of the same order as for laboratory-batch operation [82].

Plug-free operation

[OS 7] [R 22] [P 5] For a set of flow rate variations, ranging from 5 : 25 : 5 to 300 : 1000 : 300 (each value in ml h^{-1}), stable operation for at least 2 h, sometimes ranging up to 8 h, could be achieved for the three streams of a separation-layer micro mixer [78].

Analysis and prevention of fouling in tubes attached to micro mixers

[OS 9] [R 23] [P 7] See discussion in Section 4.2.6; here another test reaction is decribed for monitoring fouling sensitivity) [78].

4.2.6 Aminodehalogenation – Acylation of Amines

Peer-reviewed publications: [23, 83]; proceedings: [78]; sections in reviews: [79, 80].

4.2.6.1 Drivers for Performing Acylations of Amines in Micro Reactors

In one example, the acylation of various types of amines (aliphatic/aromatic; branched/non-branched; varying alkyl chain length; straight chain/cyclic) was used to demonstrate the feasibility of a serial screening concept for liquid single-phase reactions [83]. In another investigation, this served to show novel micro flow concepts that allow one to process fouling-sensitive reactions [78]. Acylations with amines often use auxiliary bases that react with the hydrochloric acid released to give insoluble quaternary salts. In some cases, e.g. when using triethylamine, this is a rather fast precipitation, hence ideally serving as a test reaction for the fouling sensitivity of micro-channel devices.

For another investigation, amide formation was used as a model reaction to demonstrate the performance of parallel processing in micro-channel devices [23]. The target of such processing is combinatorial synthesis, the provision of multiple substances within one run.

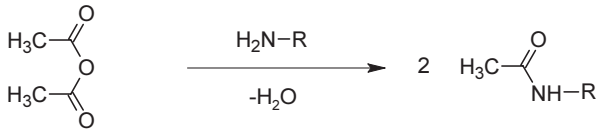
4.2.6.2 Beneficial Micro Reactor Properties for Acylations of Amines

The first aim given above is methodologically oriented on the capability of performing serial screening with a small amount of back-mixing and consumption of low volumes. This is valid not only for amine acylation, but also for any other reaction. The second argument, reduction of fouling sensitivity, refers to new microfluidic concepts, based on delaying mixing or on free-flow guiding [81]. With regard to these criteria, the acylation reaction is just one prominent example among a vast number of others, also chosen for reasons of having a very high reaction rate.

Referring to highly parallel synthesis, the smallness of the micro-channel dimensions enables one to combine several micro unit operations on one chip [23]. By using multi-layered chip architecture complicated fluidic circuits with $n \times m$ combinations of fluid streams can be made. By this means, truly combinatorial parallel processing can be achieved.

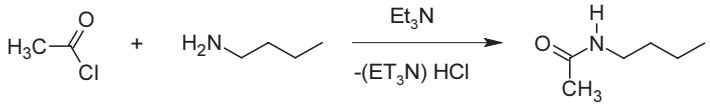
4.2.6.3 Acylations of Amines Investigated in Micro Reactors

Organic synthesis 8 [OS 8]: Acetic anhydride acylation of diverse amines



This acylation reaction is performed in the presence of triethylamine using DMF or dioxane as solvent [83].

Organic synthesis 9 [OS 9]: Acetyl chloride acylation of n-butyl amine

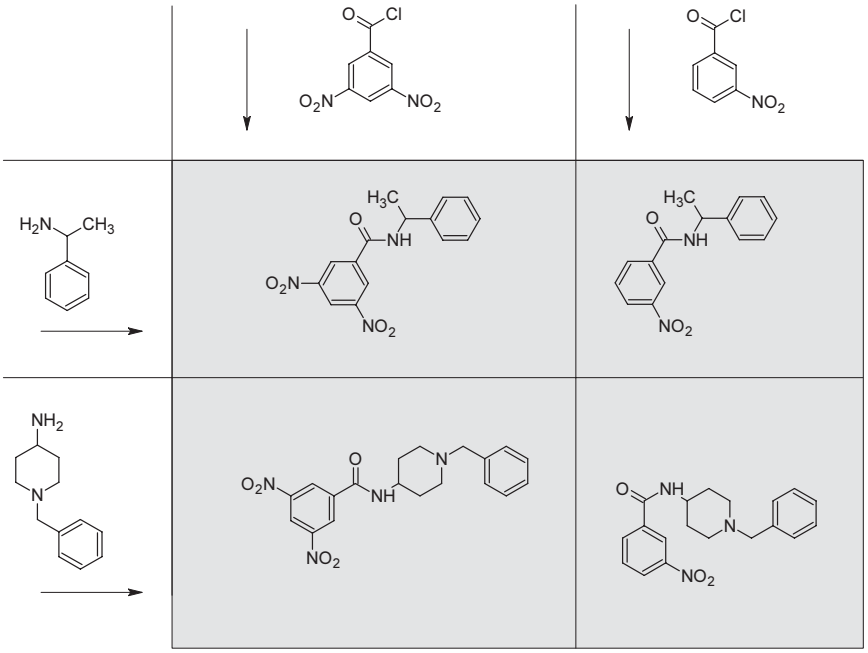


This acylation reaction is performed in the presence of triethylamine using THF as solvent [78].

Organic synthesis 10 [OS 10]: 2 × 2 library from nitro- and dinitrobenzoyl chlorides and two amines

3-Nitrobenzoyl chloride and 3,5-dinitrobenzoyl chloride were each reacted with DL-1-phenylethylamine and 4-amino-1-benzylpiperidine using a phase-transfer reaction [23]. The amines were in the aqueous phase and the acid chlorides in the organic phase. By this means, a 2 × 2 library was created in one experimental run.

The reactions proceed via a phase-transfer mechanism [23]. The amine diffuses from the aqueous phase into the organic phase and reacts with the acid chloride. The amide formed remains in the organic phase, while the salt generated from the released HCl and the auxiliary base is transferred to the aqueous phase.



4.2.6.4 **Experimental Protocols**

[P 6] No protocol was given in [83].

[P 7] Layers of acetyl chloride (0.79 mol l^{-1}) in tetrahydrofuran (THF), *n*-butylamine (0.80 mol l^{-1}) and triethylamine (0.80 mol l^{-1}) in THF, and a separation layer of THF were fit into each other by means of the concentric separation mixer (three-fluid nozzle with three tubes having inner diameters of 1.5, 2.5 and 3.4 mm slotted into each other) [78]. Thereby, two circular liquid layers of a thickness of 200 µm and a center stream of 1.5 mm diameter were generated. The reaction temperature was 22 °C. The reaction solution was inserted as droplets or as continuous stream either directly or via the tubular reactor in a beaker containing water. By rigorous stirring, hydrolysis of the acid chloride and hence termination of the reaction were achieved. The phases were separated and the water phase was extracted with THF. The combined THF phases were dried over anhydrous Na_2SO_4. After filtration, the THF solvent was evaporated at 25 mbar. The remaining amide product was characterized by FTIR spectroscopy.

In a second experiment, higher concentrations were applied: acetyl chloride (0.198 mol l^{-1}), *n*-butylamine (0.200 mol l^{-1}) and triethylamine (0.200 mol l^{-1}) [78].

Experiments with the following individual flow rates of the three liquids were performed [78]: 5 : 25 : 5; 5 : 100 : 5; 5 : 200 : 5; 5 : 250 : 5; 25 : 250 : 25; 50 : 150 : 50; 300 : 600 : 300; 300 : 1000 : 300 as acetyl chloride in THF : THF : *n*-butylamine + triethylamine in THF in ml h^{-1}.

[P 8] A jet of acetyl chloride (0.197 mol l^{-1}) in THF at a flow rate of 1000 ml h^{-1} and a jet consisting of *n*-butylamine (0.200 mol l^{-1}) and triethylamine (0.200 mol l^{-1})

in THF at a flow rate of 1000 ml h^{-1} were generated by using an impinging-jet mixer (two 350 µm openings, separated by 3 mm, and inclined to each other by 45°) [78]. Both jets merged in a Y-type flow configuration. The rest of this experimental protocol is identical with [P 7].

[P 9] DL-1-Phenylethylamine and 4-amino-1-benzylpiperidine were dissolved in 0.1 M NaOH aqueous solution [23]. 3-Nitrobenzoyl chloride and 3,5-dinitrobenzoyl chloride were used as ethyl acetate solutions. The concentration of all reactants was set to 0.01 M. Syringe pumps served for liquid feed. The flow rate was 50 µl min^{-1} and room-temperature processing was applied. No further temperature control was exerted as the reaction is only mildly exothermic. After having passed the micro reactor, the phases were settled in test-tubes and the organic phase was withdrawn for analysis.

4.2.6.5 Typical Results

Conversion/selectivity/yield

[OS 9] [R 22] [P 7] Reactions were performed with wide variations of flow rates, ranging from 5 : 25 : 5 to 300 : 1000 : 300 (each value in ml h^{-1}) [78]. The corresponding yields were between 87 and 100%. The lower yields were obtained at high total flow rates.

[OS 8] [R 25] [P 6] The acylation of acetic anhydride with various amines was investigated; all yields ranged from 75 to 100% with the exception of one value of 46% [83]. The lowest yield was obtained for 1-naphthylamine and the highest for 1-hexylamine. Throughputs were from 3.8 to 68.3 g l^{-1}.

[OS 10] [R 10] [P 9] Yields of 82–93% were obtained for a set of two amines and two acid chlorides by means of a phase-transfer reaction (Figure 4.40) [23].

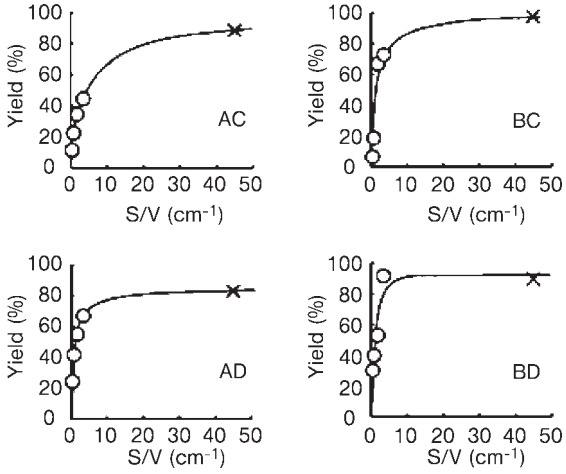


Figure 4.40 Dependence of yield on specific interfacial area between aqueous or organic phase. The four combinations AC–BD refer to the respective reactions between DL-1-phenyl-ethylamine (A), 4-amino-1-benzylpiperidine (B), 3-nitrobenzoyl chloride (C), and 3,5-dinitrobenzoyl chloride (D) [23].

Plugging-free operation

[OS 9] [R 22] [P 7] For a set of flow rate variations, ranging from 5 : 25 : 5 to 300 : 1000 : 300 (each value in ml h^{-1}), a stable operation of at least 1 h could be achieved for the three streams of a separation-layer micro mixer [78]. Particularly advantageous was the setting of the flow rates to 5 : 250 : 5. Here, the reaction could be operated for 3 h.

Analysis and prevention of fouling in tubes attached to micro mixers

[OS 9] [R 23] [P 7] Two set-ups comprising an impinging-jet micro mixer were tested, both being mixer–tubular reactor configurations [78]. These set-ups differ in the type of tube used. A first set-up was equipped with a spirally wound steel tube and the second comprised a straight glass tube. Both set-ups used a home-made housing in which the impinging-jet mixer was inserted. The housing chamber is tapered like a funnel in order to collect the liquid mixture and to introduce it directly into the tubular reactor attached, without any wake.

The first set-up comprised a 3.30 m long, spirally wound tube of 4 mm inner diameter, mounted vertical [78]. When performing the amide reaction (0.200 mol l^{-1}, total flow rate 1000 ml h^{-1}), this set-up was plugged after only a 42 s operation time. The second set-up using a 0.75 m straight glass tube of 0.3 mm inner diameter could be used for a much longer period of about 20 min. Regarding this value, it should be pointed out that, owing to the large amount of chemicals and solvents consumed, all operations described here were deliberately stopped instead of waiting for a stop caused by plugging.

The flow in the glass tube was relatively undisturbed [78]. Partly, bubble formation due to HCl gas evolution and passing of Et_3NHCl lumps was observed. These phases were moving with the liquid mixture and were always rinsed out of the tube, and hence were not obstacles causing a breakdown of the flow.

In a further run, the reactant concentration was doubled; 0.395 mol l^{-1} acetyl chloride in THF and 0.400 mol l^{-1} *n*-butylamine and 0.400 mol l^{-1} Et_3N in THF were processed in the second set-up with the straight tube at a total flow rate of 2000 ml h^{-1} [78]. Although extensive precipitation of Et_3NHCl was observed, these lumps are still carried out of the tube. For a 38 min operation, no plugging was observed.

The importance of the linear arrangement of mixer/funnel/tubular reactor is shown when processing in a set-up with a curved flow element (0.3 m long bent Teflon tube of 0.3 mm inner diameter) in between the funnel and tubular reactor [78]. If a straight tube of equal dimensions as given above is used, plugging occurs after 30 s. Hence even short curved flow passages are detrimental for micro-channel-based amidation studies.

Interfacial area

[OS 10] [R 10] [P 9] The specific interfacial area was varied for a phase-transfer reaction for four amide formations from two amines and two acid chlorides [23]. This was done by filling the solutions in normal test-tubes of varying diameter (1–5 × cm^{-1}) and using a micro reactor which had the largest specific interface (45 × cm^{-1}). The yields of all four reactions are highly and similarly dependent on

the specific interface, as to be expected for a phase-transfer reaction (Figure 4.40). The micro reactor yields approach 80–95%.

2 × 2 parallel synthesis – a first step towards combinatorial chemistry

[OS 10] [R 10] [P 9] The feasibility of 2 × 2 parallel synthesis using two amines and two acid chlorides for a phase-transfer reaction was demonstrated [23]. This paves the way for $n \times m$ parallel reaction combinations as a new micro flow approach for combinatorial chemistry.

The flow distribution was far from ideal [23]. Collected volumes at the individual outlets ranged from 2.15 to 3.65 ml, thus, differing by more than 50% at maximum. This was seen to be due to differences in pressure drops resulting from imperfections in microfabrication.

Despite the differences in the volumes collected, and hence in the concentrations for the various channel processing, the yields are (surprisingly) comparable to those from single micro reactors which do not suffer from flow deviations. The yields of the 2 × 2 processing (82–93%) were essentially the same as when the same products were obtained by single-micro-reactor processing (yields ranging from 83 to 98%) [23]. This good reactor performance, in lieu of the flow imperfections, can only be explained by having carried out the reaction at lower flow deviations as reported above. Indeed, the authors report strongly changing flow for the single channels when they disconnect one outlet port and reassemble it.

[OS 10] [R 10] [no protocol] In another study, the above-mentioned features were also investigated. Two amines, 0.01 M DL-1-phenylethylamine and 4-amino-1-benzylpiperidine as solutions in 0.1 M NaOH, were reacted with two acids, 0.01 M 3,5-dinitrobenzoyl chloride and 3-nitrobenzoyl chloride in ethyl acetate [24]. By using a 2 × 2 micro channel glass chip reactor, four separate flow passages were realized, each connected to two of the four feed streams (one amine and one acid chloride). Thereby, the formation of the four possible amides was demonstrated and hence the feasibility of micro-channel processing for parallel liquid screening in one chip. Especially, it was confirmed by thin layer chromatographic (TLC) analysis that from each channel mainly pure solutions were obtained, i.e. there was no detectable cross-over of reactant streams. The latter indicated proper distribution of reactant streams.

4.2.7
Aminodehalogenation – Acylating Cleavage with Acetyl Chloride

Proceedings: [75]; literature on micro reactor and microfabrication used: [76, 77].

4.2.7.1 Drivers for Performing Acylating Cleavage in Micro Reactors

The motivation for investigating the acylating cleavage stems from using it as a test reaction for showing the feasibility a newly developed miniaturized system (*[R 36]*) for performing ultra-high throughput screening [75]. Modern apparatus can test more than 100 000 compounds per day. The titer plate formate, consequently, has increased from 96 wells to 1536 wells. Conversely, the sample amount has decreased from several mg to < 1 mg. Solid-phase organic chemistry (SPOS) can reach this goal with only a few tens of milligrams of polymer resin. However, the purchase of

such apparatus is not state of the art, but needs self-developed, specialized solutions such as the micro reaction system [R 36].

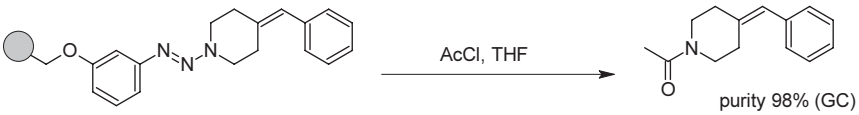
4.2.7.2 Beneficial Micro Reactor Properties for Acylating Cleavage

SPOS has the benefit of employing an excess of reactant, which can be washed off afterwards, and of driving reactions in this way to completion [75]. Difficult purification steps are avoided. SPOS is facile as it needs only a few repetitive unit operations.

However, current solutions suffer from speed of the slowest step (e.g. filling with robots) or lack of automation [75].

4.2.7.3 Acylating Cleavage Investigated in Micro Reactors

Organic synthesis 11 [OS 11]: Synthesis of piperazine



4.2.7.4 Experimental Protocols

[P 10] The reaction was performed on 100 mg of Merrifield resin [75]. Absolute tetrahydrofuran was used as solvent and 4 h of agitation was employed. No other details are given in the reference. Generally, about 2 min were needed to perform a complete washing cycle.

4.2.7.5 Typical Results

[OS 11] [R 36] [P 10] The feasibility of performing the acylating cleavage of T2-triazene resin (100 mg) in absolute tetrahydrofuran to give piperazine was demonstrated [75]; 4 h of processing was required.

4.2.8 Alkoxydehydroxylation – Enzymatic Esterification of Acids with Alcohols

Proceedings: [84].

4.2.8.1 Drivers for Performing Enymatic Esterifications in Micro Reactors

By the enzymatic esterification of diglycerol with lauric acid, the corresponding monolaurate ester is obtained [84]. This is an important industrial reaction for the cosmetic, pharmaceutical and feed industries, since this ester is used as biodegradable non-ionic surfactant. In recent years, the synthesis of this and other polyglycerols with fatty acids has attracted growing interest in industry, leading also to a demand for enantiomerically and isomerically pure products.

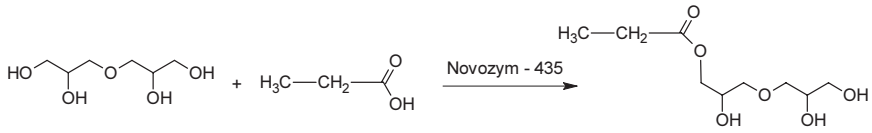
4.2.8.2 Beneficial Micro Reactor Properties for Enymatic Esterifications

For the reasons mentioned above, the development of miniature test processes becomes increasingly important for such biotransformation reactions [84]. Micro reactors can handle small volumes and process them in a well-defined manner and have been shown to have high test throughput frequencies. Hence waste reduc-

tion, quality and robustness of information and speed of analysis qualify micro reactors as testing tools also for enzymatic esterifications.

4.2.8.3 Enymatic Esterifications Investigated in Micro Reactors

Organic synthesis 12 [OS 12]: Esterification of diglycerol with lauric acid with Novozym-435™



4.2.8.4 Experimental Protocols

[P 11] Reactions were performed in a completely stirred tank reactor of 10 ml volume [84]. The stirrer was set to 700 rpm. The reactor was immersed in a water bath. Owing to the small size of the reactor, special precautions had to be taken for stirring and for temperature control of the bath [84].

The catalysts was added after the reactants were fed in the tank reactor and pressure and temperature were set to the target values [84]. The study was performed using an immobilized lipase, Novozym-435™, as biocatalyst. The temperature was set to 65–75 °C and the pressure was reduced (60 mmHg). A catalyst concentration of 1–5% with an acid : alcohol ratio of 1 : 3, 1 : 1 or 3 : 1 was used.

4.2.8.5 Typical Results

Feasibility – comparison with kinetic model

[OS 12] [reactor given in [84]] [P 11] In [84], the scale-down from a 250 ml batch reactor to a 10 ml batch reactor is described. The validity of applying a pseudo-second-order kinetic model for the scaled-down processing was confirmed (Figure 4.41).

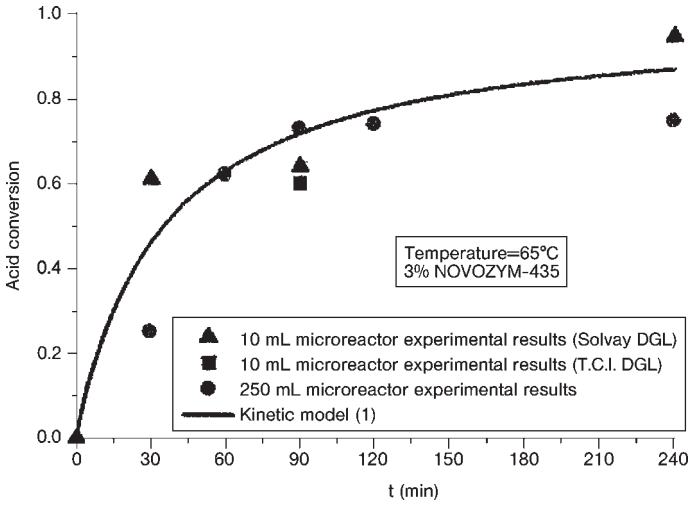


Figure 4.41 Comparison between experimental results and data from kinetic model [84].

Sample consumption

It was confirmed that much less of the reactants needs to be consumed for testing, which will be important if expensive compounds are used such as enantiomerically and isomerically pure products [84]. Hence the feasibility of mini-scale biotransformation processing was demonstrated using a model reaction and now allows this testing procedure to be extended to other more important reactions.

4.2.9 Amidodeamidation (trans-Amidation) – Desymmetrization of Thioureas

Proceedings: [85]; Reviews: [42]; sections in reviews: [42].

4.2.9.1 Drivers for Performing Desymmetrization of Thioureas in Micro Reactors

The investigations were carried out in the framework of an industrial study on the general applicability of micro reactors to organic synthesis for pharmaceutical applications, in the long run aiming at performing combinatorial chemistry by micro flow processing [85] (see a more detailed description in [42]). The scouting studies focused on determining suitable reaction parameters and monitoring yields as a function of time.

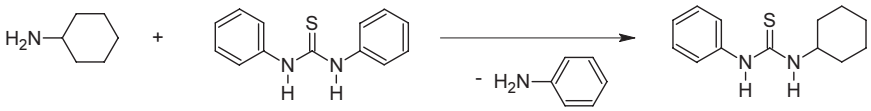
4.2.9.2 Beneficial Micro Reactor Properties for Desymmetrization of Thioureas

The studies mentioned above referred to the general advantages of micro flow processing in terms of enhanced heat and mass transfer [85] (see a more detailed description in [42]).

4.2.9.3 Desymmetrization of Thioureas Investigated in Micro Reactors

Organic synthesis 13 [OS 13]: Thiourea from phenyl isothiocyanate and cyclohexylamine

Organic synthesis 14 [OS 14]: Thiourea from diphenylthiourea and cyclohexylamine



4.2.9.4 Typical Results

Conversion/selectivity/yield

[OS 13] [R 17] [no protocol] Using a micro mixer/commercial tube reactor, the synthesis of a thiourea from phenyl isothiocyanate and cyclohexylamine at 0 °C was carried out [85] (see a more detailed description in [42]). A single mixing device connected to a stainless-steel tube of about 10 m length and 0.25 mm diameter was used. The feasibility of performing a nearly spontaneous reaction could be shown.

[OS 14] [R 17] [no protocol] Further studies related to the desymmetrization of thioureas showed that for the diphenylthiourea/cyclohexylamine system reasonable reaction rates and conversions were achieved [42, 85]. It is notable that the temperatures of up to 91°C applied slightly exceed the boiling point of the solvent acetonitrile.

4.2.10
Aminodehydroxylation – Acylation of Amines by Acids (Peptide Synthesis)

Peer-reviewed journals: [5, 86, 87]; proceedings: [88]; sections in reviews: [14, 89, 90].

4.2.10.1 Drivers for Performing Peptide Syntheses in Micro Reactors

Dipeptides and longer peptides are typically synthesized by solid-phase chemistry at polymer beads, a route discovered by and named after Merrifield [5, 88]. Disadvantages of this approach are that the polymer support is expensive and additional steps for linkage to and cleavage from the polymer are required. Hence solution chemistries are an alternative to the Merrifield approach.

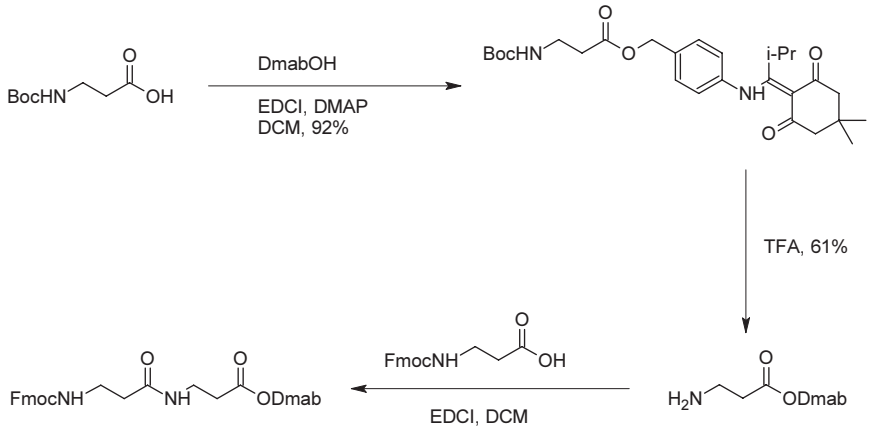
Peptide synthesis from β-amino acids is particularly attractive for first feasibility micro-reactor tests as there are no chiral centers which may complicate analysis of the products [5, 88]. β-Peptides are also attractive owing to their structural and biological properties, especially concerning the stability versus degradation by peptidases as compared with their α-analogues (see original citations in [5]).

4.2.10.2 Beneficial Micro Reactor Properties for Peptide Syntheses

Micro reactors are continuous-flow devices consuming small reaction volumes and allowing defined setting of reaction parameters and fast changes. Hence they are ideal tools for process screening and optimization studies to develop solution-based chemistries.

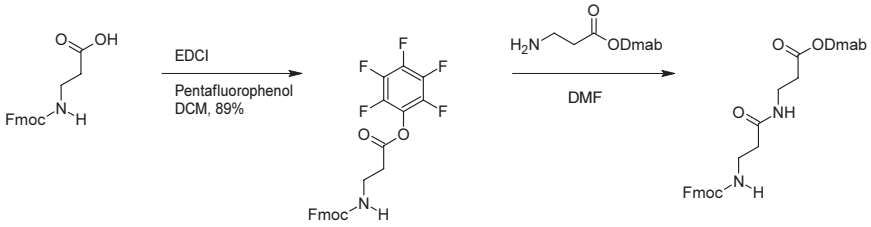
4.2.10.3 Peptide Syntheses Investigated in Micro Reactors

Organic synthesis [OS 15]: β-Dipeptide synthesis by carbodiimide coupling using Dmab *O*-protection



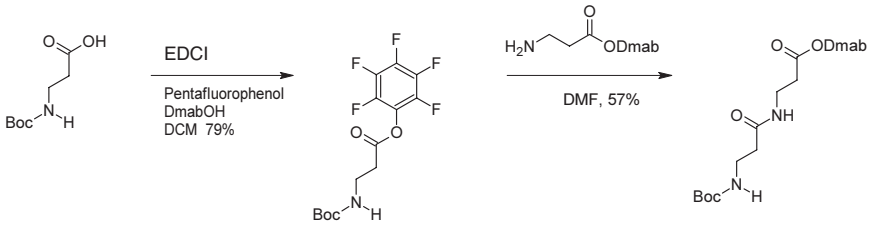
Boc-β-alanine was *O*-protected (carboxylic moiety) by DMAP coupling (4-dimethylaminopyridine) yielding Dmab-β-alanine, whereas the Fmoc group was used for *N*-protection of β-alanine [88]. Thereby, orthogonal protecting groups were established. By carbodiimide coupling, Dmab-β-alanine and Fmoc-β-alanine reacted and the synthesis of the corresponding β-dipeptide was realized.

Organic synthesis 16 [OS 16]: β-Dipeptide synthesis using pentafluorophenyl *O*-activation



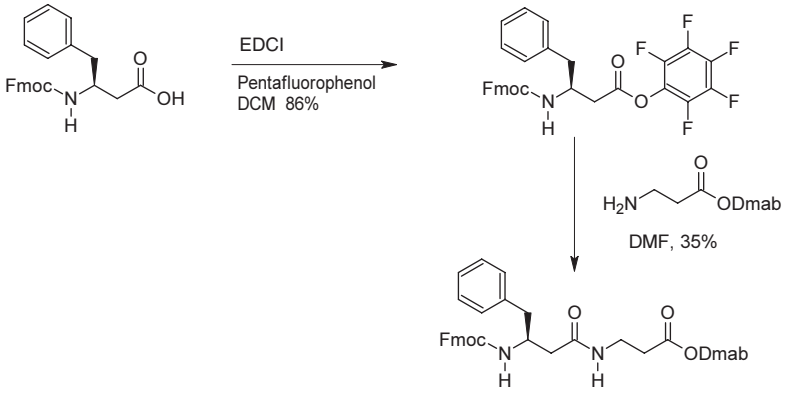
Fmoc-β-alanine was pre-activated by introducing the pentafluorophenyl function as an ester group [88]. Dmab-β-alanine and the pentafluorophenyl ester of Fmoc-β-alanine reacted and the synthesis of the corresponding β-dipeptide was realized.

Organic synthesis 17 [OS 17]: β-Dipeptide synthesis using pentafluorophenyl *O*-activation



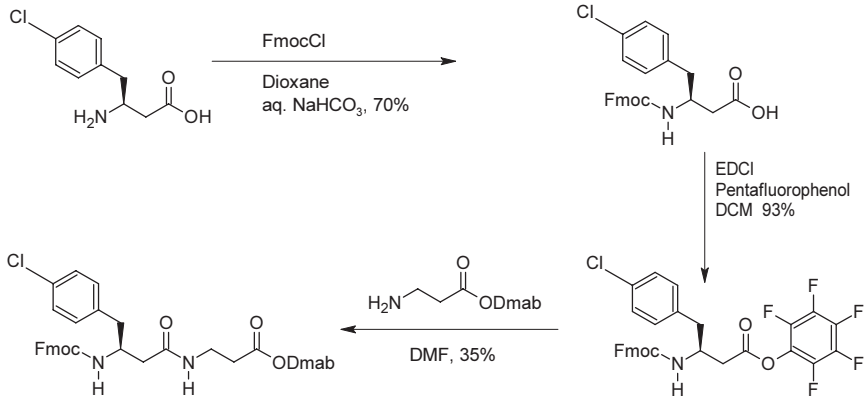
Boc-β-alanine was pre-activated by introducing the pentafluorophenyl function as an ester group [88]. Dmab-β-alanine and the pentafluorophenyl ester of Boc-β-alanine reacted and the synthesis of the corresponding β-dipeptide was realized.

Organic synthesis 18 [OS 18]: Dipeptide from Fmoc-L-β-homophenylalanine



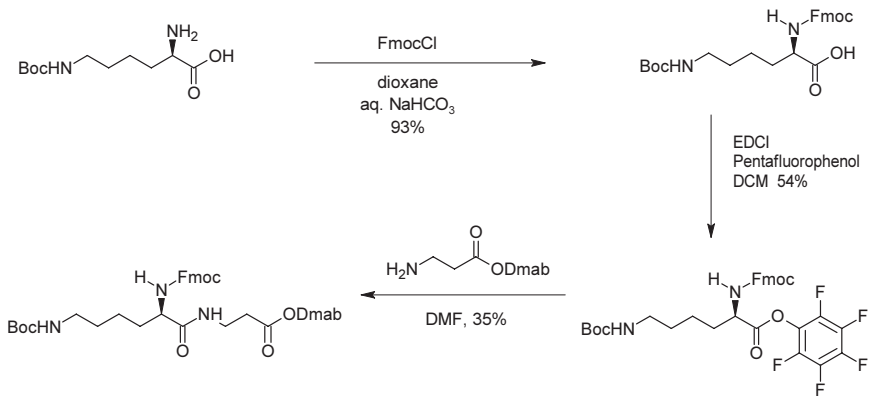
Dmab-β-alanine and Fmoc-L-β-homophenylalanine were reacted to give the dipeptide [5].

Organic synthesis 19 [OS 19]: Dipeptide from Fmoc-L-β-homo-*p*-chlorophenylalanine



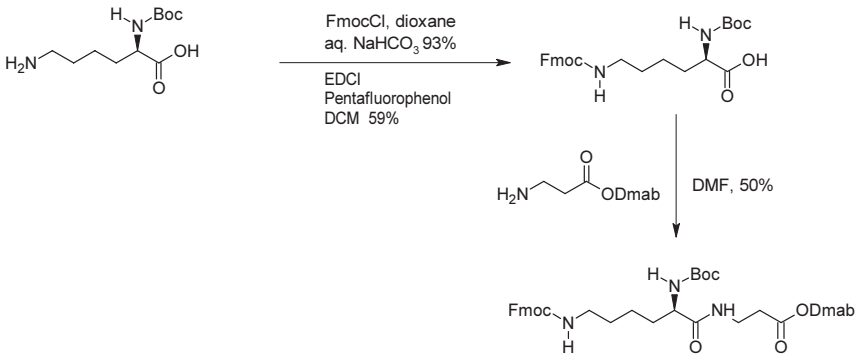
Dmab-β-alanine and Fmoc-L-β-homo-*p*-chlorophenylalanine were reacted to give the dipeptide [5].

Organic synthesis 20 [OS 20]: Dipeptide from *N*-ε-Boc-L-lysine



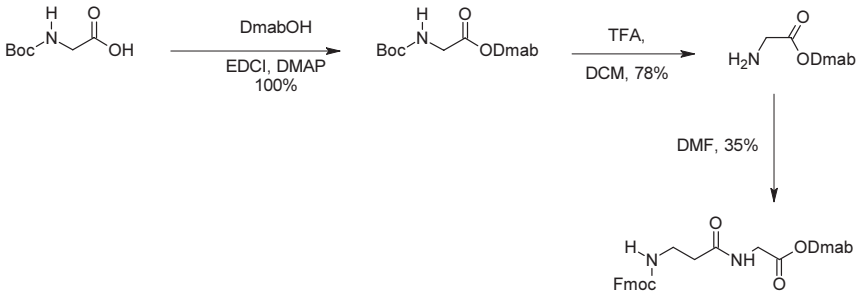
N-ε-Boc-L-lysine is a more complex peptide owing to the additional amino function [5]. Dmab-β-alanine and *N*-ε-Boc-L-lysine were reacted to give the dipeptide.

Organic synthesis 21 [OS 21]: Dipeptide from *N*-α-Boc-L-lysine



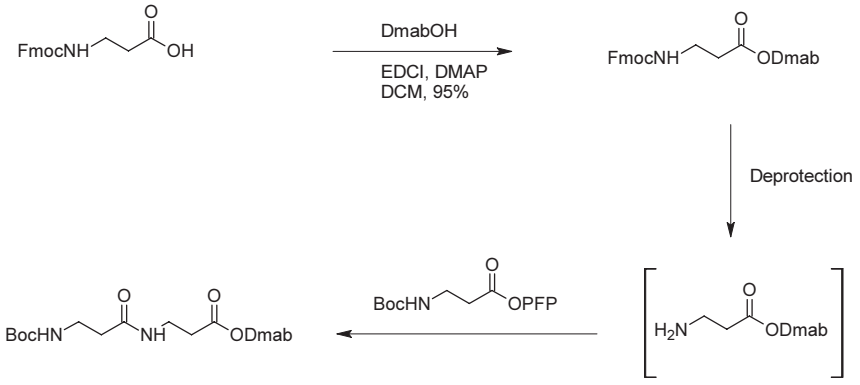
This is a similar reaction to *[OS 20]* [5].

Organic synthesis 22 [OS 22]: Dipeptide from Dmab-Boc-glycine



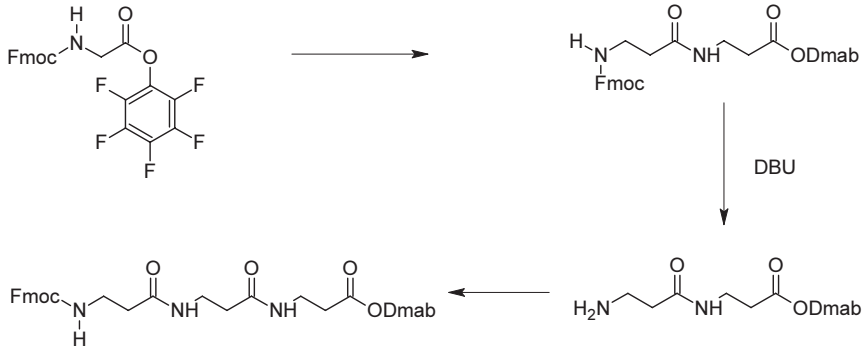
Dmab-Boc-glycine and the pentafluorophenyl ester of Boc-β-alanine were reacted to give the dipeptide [5].

Organic synthesis 23 [OS 23]: Diverse deprotection and peptide bond-forming reactions



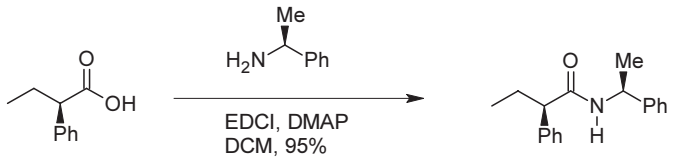
In order to extend the results obtained by undergoing *[OS 15]*, *[OS 16]* and *[OS 17]* reactions, routes for the preparation of longer chain peptides in micro reactors were searched for [88]. Therefore, deprotection and peptide bond forming reactions were needed.

Organic synthesis 24 [OS 24]: Tripeptide synthesis



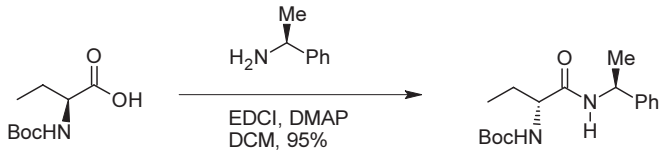
Fmoc-β-alanine and two equivalents of Fmoc-β-alanine were reacted to give the corresponding tripeptide [5].

Organic synthesis 25 [OS 25]: α-Dipeptide synthesis from (R)-2-phenylbutyric acid



(*R*)-2-Phenylbutyric acid and (*S*)-α-methylbenzylamine react to the corresponding dipeptide via an EDCI coupling [86]. In a control experiment, (*R*)-2-phenylbutyric acid and (*R*)-α-methylbenzylamine were also reacted.

Organic synthesis 26 [OS 26]: α-Dipeptide synthesis from (S)-α-methylbenzylamine



Boc-D-alanine and (*S*)-α-methylbenzylamine react to give the corresponding dipeptide via an EDCI [3-ethyl-1-(3-dimethylaminopropyl)-carbodiimid] coupling [86]. In a control experiment, Boc-L-alanine and (*S*)-α-methylbenzylamine also reacted.

4.2.10.4 **Experimental Protocols**

[P 12] The micro channels were primed with anhydrous *N,N*-dimethylformamide (DMF) to remove air and moisture before carrying out the reaction [88]. A 50 µl volume of a solution of Fmoc-*β*-alanine (0.1 M) in anhydrous DMF was placed in one reservoir of a micro chip, driven by electroosmotic flow. A 50 µl volume of a solution of EDCI (0.1 M) in anhydrous DMF and 50 µl of a solution of Dmab-*β*-alanine (0.1 M) in anhydrous DMF were inserted in the other two reservoirs. Anhydrous DMF was placed in the fourth reservoir, for collection of the product. Room temperature was applied for reaction for a 20 min period. The voltage was set in the range 500–700 V.

[P 13] The micro channels were primed with anhydrous DMF to remove air and moisture before carrying out the reaction [5, 88]. A 50 µl volume of a solution of the pentafluorophenyl ester of Fmoc-*β*-alanine (0.1 M) in anhydrous DMF was placed in one reservoir of a micro chip, driven by electroosmotic flow (Figure 4.42). A 50 µl volume of a solution of Dmab-*β*-alanine (0.1 M) in anhydrous DMF was inserted in another reservoir. Anhydrous DMF was placed in the fourth reservoir, for collection of the product. Room temperature was applied for reaction for a 20 min period. The voltage was set in the range 600–700 V.

[P 14] For the reaction of the pentafluorophenyl ester of Fmoc-*β*-alanine with Dmab-*β*-alanine, a similar protocol to that for *[P 13]* was used [5, 88].

[P 15] Diverse protocols for routes for deprotection and peptide bond-forming reactions in micro reactors have been reported [5, 88]. These are needed for preparation of longer chain peptides.

[P 16] First reservoir 50 µl of a solution of the pentafluorophenyl ester of Fmoc-*β*-alanine (0.1 M; 1000 V) in anhydrous DMF; second reservoir, 50 µl of a solution of Dmab-*β*-alanine (0.1 M; 1000 V) in anhydrous DMF; third reservoir, 50 µl of a solution of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (0.1 M; 400 V) in anhydrous DMF; fourth reservoir, 50 µl of a solution of the pentafluorophenyl ester of Fmoc-*β*-alanine (0.1 M; 700 V) in anhydrous DMF; fifth reservoir, 40 µl of anhydrous DMF [86]. Room-temperature processing.

[P 17] First reservoir, 30 µl of a solution of the pentafluorophenyl ester of (*R*)-2-phenylbutyric acid (0.1 M; 600 V) in anhydrous DMF; second reservoir, 30 µl of a solution of (*S*)-*α*-methylbenzylamine (0.1 M; 1000 V) in anhydrous DMF; third reservoir, 30 µl of anhydrous DMF [86]. Room-temperature processing; 20 min reaction time.

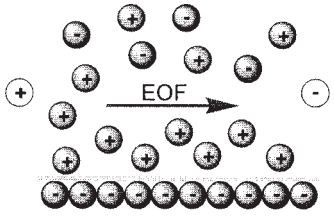


Figure 4.42 Principle of electroosmotic flow: movement of charged molecules under the action of an external electrical field [5].

[P 18] First reservoir, 30 µl of a solution of the pentafluorophenyl ester of Boc-D-alanine (0.1 M; 1000 V) in anhydrous DMF; second reservoir, 30 µl of a solution of (*S*)-α-methylbenzylamine (0.1 M; 1000 V) in anhydrous DMF; third reservoir, 30 µl of anhydrous DMF [86]. Room-temperature processing.

4.2.10.5 Typical Results

Conversion/selectivity/yield

[OS 15] [R 5] [P 12] Using stoichiometric ratios of reactants and adjusting the flow rate by setting the voltage (700 V) yielded only 10% conversion [88]. Increasing the residence time by decreasing the voltage to 500 V did not improve conversion. Using more coupling reagent EDCI (2.0 mol l^{-1} instead of 1.0 mol l^{-1}), however, increased the conversion to 20%. With stopped-flow techniques, periodically 'pushing' and so mixing the flow, an increase to 50% was reached (2.5 s injection; 10 s stop). A further increase in the concentration of the coupling reagent necessitated a change from EDCI to dicyclohexylcarbodiimide (DCC) for reasons of limited solubility in DMF of the first agent. Applying a 5.0 mol l^{-1} DCC solution resulted in a 93% yield of the dipeptide.

Benchmarking to Batch Processing

[OS 15] [R 5] [P 12] Batch synthesis of Dmab-β-alanine and Fmoc-β-alanine using EDCI to the corresponding β-dipeptide gave a yield of 50% [5]. The electroosmotic-driven micro-reactor processing resulted in 50% at best; using another coupling reagent (DCC), a 93% yield was obtained in the micro reactor [88] (see Conversion/selectivity/yield, above).

[OS 16] [R 5] [P 13] Using continuous flow in an electroosmotic-driven micro reactor gave a quantitative yield of the dipeptide in only 20 min (600 V for Dmab-β-alanine; 700 V for the Fmoc ester) [5, 88]. Batch synthesis under the same conditions gave only a 40–50% yield [5] (46% in [5]), needing 24 h.

[OS 17] [R 5] [P 14] Using continuous flow in an electroosmotic-driven micro reactor gave a quantitative yield of the dipeptide in only 20 min (700 V for both Dmab-β-alanine and the Boc ester) [88]. Batch synthesis under the same conditions gave only a 40–50% yield [5] (57% in [5]), needing 24 h.

Variation in amino acid composition

[OS 18] [R 5] [P 13] (adapted) Subsequent to making dipeptides from protected β-alanines, the dipeptide from Dmab-β-alanine and Fmoc-L-β-homophenylalanine was prepared [5]. Using continuous flow in an electroosmotic-driven micro reactor gave a quantitative yield of the dipeptide in only 20 min (600 V for Dmab-β-alanine; 900 V for the Fmoc ester) [88]. Batch synthesis under the same conditions gave only a 35% yield, needing 24 h [5].

[OS 18] [R 5] [P 13] (adapted) The same was done using Fmoc-L-β-homo-*p*-chlorophenylalanine [5]. Batch, 36%; micro reactor, quantitative in 20 min.

[OS 20] [R 5] [P 13] (adapted) Using more complex peptides such as *N*-ε-Boc-L-lysine is also feasible by micro-channel processing [5]. Batch, 9%; micro reactor, quantitative in 20 min.

[OS 21] [R 5] [P 13] (adapted) *N*-α-Boc-L-lysine has been used [5]. Batch, 50%; micro reactor, quantitative in 20 min.

[OS 22] [R 5] [P 13] (adapted) The Dmab ester of Boc-glycine was also used [5]. Batch, 35%; micro reactor, quantitative in 20 min.

Reaction rate – comparison of batch with micro reactor

[OS 18] [R 5] [P 13] (adapted) Using 0.05 M solutions of Dmab-β-alanine and Fmoc-L-β-homophenylalanine, a comparison between batch and micro-reactor processing was made [5]. Whereas the micro reactor gave a 100% yield in 20 min, only about 5% was reached by batch. Even after 400 h, only 70% conversion was achieved.

First steps to extended-peptide chain formation

[OS 23] [R 5] [P 15] Deprotection and peptide bond-forming reactions in a micro reactor and their yields have been described [5, 88]. Establishing protocols for these reactions paves the way to the preparation of longer chain peptides in micro reactors.

Formation of tripeptides

[OS 24] [R 5] [P 16] Dmab-β-alanine and Fmoc-β-alanine were reacted to give a dipeptide [5]. After cleavage of the Fmoc function, Fmoc-β-alanine was added to such a dipeptide resulting in tripeptide formation with 30% yield [5].

Racemization of α-dipeptides

[OS 25] [R 4] [P 17] For dipeptide formation from the pentafluorophenyl ester of (*R*)-2-phenylbutyric acid and (*S*)-α-methylbenzylamine an extent of racemization of 4.2% was found [86]. At higher concentration (0.5 instead of 0.1 M), a higher degree of racemization was found (7.8%). This experiment also served to demonstrate monitoring of the racemization of a simple carboxylic acid used in peptide synthesis.

[OS 26] [R 4] [P 18] For dipeptide formation from the pentafluorophenyl ester of Boc-D-alanine and (*S*)-α-methylbenzylamine an extent of racemization of 5.6% was found [86]. This experiment also served to demonstrate monitoring of the racemization of an α-amino acid used in peptide synthesis.

4.2.11 Hydroxydearyloxy Substitution + O-Aryl, O-Alkyl Substitution – Hydrolysis and Transglycosylation

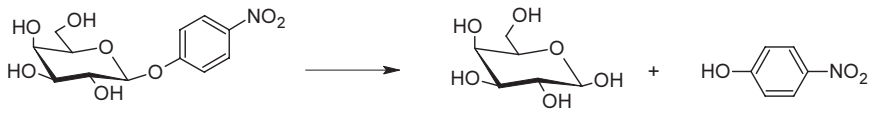
Peer-reviewed journals: [26, 27].

4.2.11.1 Drivers for Performing Hydrolysis and Transglycosylation in Micro Reactors

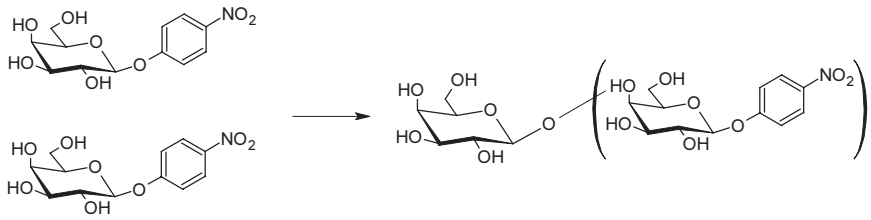
The synthesis of glycoconjugates opens the route to one of the most important class of biomolecules which play an active role in relevant biological reactions [26]. One way to do so is to use enzymes, which, however, suffer from instability and slow reaction rates.

4.2.11.2 **Beneficial Micro Reactor Properties for Hydrolysis and Transglycosylation**
Given the feasibility of micro-channel devices for enzyme-based oligosaccharide synthesis, enhancement of mass transfer therein could speed up this reaction. Also, it may be hoped that enzyme degradation may be reduced, for reasons that are not so straightforward.

4.2.11.3 **Hydrolysis and Transglycosylation Investigated in Micro Reactors**
Organic synthesis 27 [OS 27]: Hydrolysis of p-nitrophenyl-β-D-galactopyranoside



Organic synthesis 28 [OS 28]: Transgalactosylation of p-nitrophenyl-2-acetamide-2-deoxy-β-D-glucopyranoside



4.2.11.4 **Experimental Protocols**
[P 19] Two micro syringes were filled with 0.32 mM *p*-nitrophenyl-β-D-galactopyranoside in phosphate buffer (pH 8) and β-galactosidase (20 U) in 10 ml of the same buffer [26]. Both solutions were pumped into the micro channel at the same flow rate (a few μl min^{-1}). The reaction was carried out for 0–30 min at 37 °C using a hot-plate. The residence time was set by adjusting the flow rate. After passing the micro channel, the reaction mixture was dropped into hot water to inactivate the enzyme.

The micro channel may be pre-treated before processing in the following way: first, the channel is charged with β-galactosidase in phosphate buffer; then, only buffer solution is passed; finally, only *p*-nitrophenyl-β-D-galactopyranoside (without enzyme) is filled [26]. The respective flow rates orient on the protocol given above.

[P 20] Via two micro syringes, a mixture of 0.32 M *p*-nitrophenyl-β-D-galactopyranoside and β-galactosidase and 3.2 mM *p*-nitrophenyl-2-acetamide-2-deoxy-β-D-glucopyranoside in 50% phosphate buffer (pH 8)–acetonitrile and β-galactosidase (20 U) in 10 ml of the same solvent system were fed into the micro channel [26]. Identical flow rates were used and the reaction was carried out for 0–30 min at 37 °C.

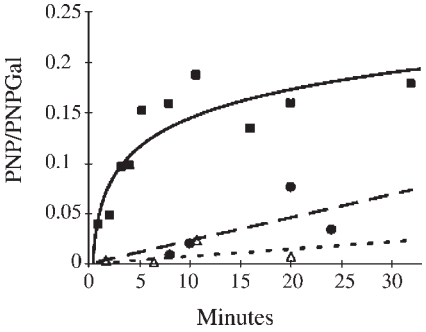


Figure 4.43 Benchmarking of untreated and pre-treated Y-piece micro reactors to a commercial micro test-tube for the hydrolysis of *p*-nitrophenyl-*β*-D-galactopyranoside. Y-piece micro reactor (■); commercial micro test-tube (●); pre-treated Y-piece micro-reactor (△) [26].

4.2.11.5 **Typical Results**

Conversion/selectivity/yield – benchmarking to batch processing

[OS 27] [R 12] [P 19] When monitoring the molar ratio of *β*-galactosidase and *p*-nitrophenyl-*β*-D-galactopyranoside (a measure for analyzing the product yield of D-galactose) as a function of time, hydrolysis in a micro-channel chip is about five times faster than in a commercial micro test-tube [26]. The ratios found were in the range 0.01–0.17. The test-tube was not stirred to avoid inactivation of the enzyme. As a possible explanation, faster diffusion in the micro channel compared with the bulk fluid is suggested. To underline this, experiments with a pre-treated micro channel were undertaken, leading to strongly reduced activity (Figure 4.43).

[OS 28] [R 12] [P 20] The rate of transgalactosylation, the reverse hydrolysis reaction (see above), was also increased by micro-channel processing [26]. The ratio of galactosylated *p*-nitrophenyl-2-acetamide-2-deoxy-*β*-D-glucopyranoside and *p*-nitrophenyl-2-acetamide-2-deoxy-*β*-D-glucopyranoside was taken as measure for yield determination as a function of time (Figure 4.44). The ratios were found to be in the range 0.005–0.05.

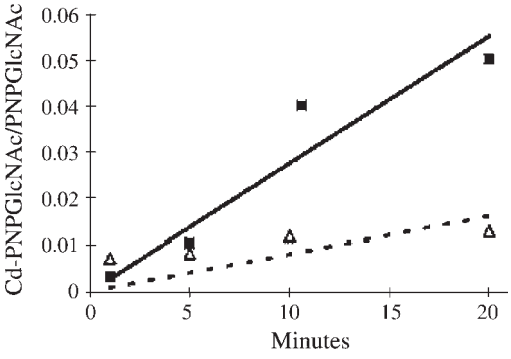


Figure 4.44 Benchmarking of the Y-piece micro reactor to a commercial micro test-tube for the transglycosylation of *β*-D-galactopyranoside. Y-piece micro reactor (■); commercial micro-test tube (△) [26].

4.2.12
Alkoxydehydroxylation – Esterification of Acids

Peer-reviewed publications: [91].

4.2.12.1 Drivers for Performing Esterifications in Micro Reactors

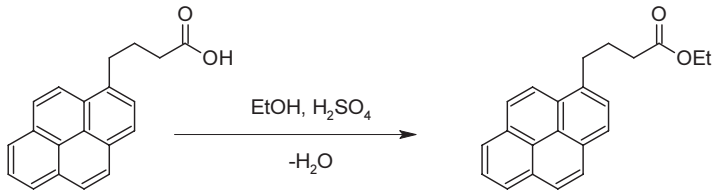
First investigations revealed a comparison of batch-scale performance with micro-channel processing [91]. Further investigations of the role of surface effects catalyzing the esterification concerned the deliberate enhancement in the number of silanol groups on the glass surface of such micro-channel reactors.

4.2.12.2 Beneficial Micro Reactor Properties for Esterifications

Concerning the impact of surface-induced reactions, the large specific surface area of the micro channels provides a correspondingly large number of reaction sites that are available without transport resistance [91]. By this means, a former bulk reaction may be changed to a heterogeneous reaction or combined heterogeneous–heterogeneous reaction. This may have a significant impact on the choice of reactants and auxiliary additives and also on reaction speed and process parameters such as temperature and concentration.

4.2.12.3 Esterifications Investigated in Micro Reactors

Organic synthesis 19 [OS 29]: Esterification of 4-(1-pyrenyl)butyric acid



4-(1-Pyrenyl)butyric acid reacts with ethanol in the presence of sulfuric acid [91].

4.2.12.4 Experimental Protocols

[P 21] Solutions of 10^{-4} M 4-(1-pyrenyl)butyric acid in ethanol and 10^{-4} M sulfuric acid in ethanol were contacted in a micro-mixing tee/micro channel flow configuration at room temperature and at 50 °C [91]. Pressure-driven feed was used. The glass surface of the micro channels was either tuned hydrophobic (by exposure to octadecyltrichlorosilane) or hydrophilic (by wetting with a sulfuric acid/hydrogen peroxide mixture).

4.2.12.5 Typical Results

Conversion/selectivity/yield – benchmarking to batch processing

[OS 29] [similar to R 12, details in [91]] [P 21] A 15–20% yield for a 4-(1-pyrenyl)butyric acid ester was obtained by micro-channel processing after 40 min of reaction at room temperature [91]. In turn, no reaction occurred at room temperature or at

50 °C by carrying out a batch experiment. At 50 °C, micro-channel processing resulted in a maximum yield of 83% (40 min; 0.1 μl min^{-1}).

Residence time

[OS 29] [similar to R 12, details in [91]] [P 21] On varying the residence time by changing the flow rate from 0.1–1 μl min^{-1} for micro-channel processing at 50 °C, the yields decrease from 83 to 17%. No figures of residence times are given in [91].

Absence of acid catalyst/role of silanol surface

[OS 29] [similar to R 12, details in [91]] [P 21] Without the presence of sulfuric acid no reaction to a 4-(1-pyrenyl)butyric acid ester was found in the micro reactor [91]. On activating the surface with a sulfuric acid/hydrogen peroxide mixture, however, a yield of 9% was achieved after 40 min at 50 °C. On making the surface hydrophobic by exposure to octadecyltrichlorosilane, no product formation was found. Using silica gel in a laboratory-scale batch experiment resulted in detectable conversion, however, being substantially lower than in the case of the micro reactor. The yield was no higher than 15% (40 min; 0.1 μl min^{-1}), whereas the best micro reactor result was 83% (40 min; 0.1 μl min^{-1}).

4.2.13
Allyldehydro-Substitution – C–C Bond Formation with Acyliminium Cations

Peer-reviewed journals: [66]; proceedings: [67, 92]; sections in reviews: [90].

4.2.13.1 Drivers for Performing Electrochemical C–C Bond Formation with Cations

Carbocations are highly reactive species that can be used for C–C bond formation. One driver for using continuous micro chemical processing is to employ also unstable cations, which are not amenable to batch synthesis because they decompose before they can actually be used [66, 67].

As C–C bond formation is an important step in organic synthesis, particularly for pharmaceutical applications, it is useful to look for operation modes of chemical micro processing that allow one to carry out combinatorial chemistry investigations. As such, the serial introduction of multiple reactant streams by flow switching was identified [66, 67]. The wide availability of precursors for acyliminium cations has led to the expression 'cation pool' [66, 67].

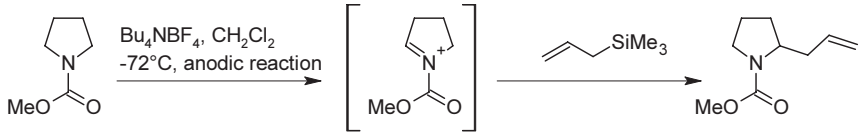
4.2.13.2 Beneficial Micro Reactor Properties for Electrochemical C–C Bond Formation with Cations

Micro reactors show, under certain conditions, low axial flow dispersion; reactions with unstable intermediates can be carried out in a fast, stepwise manner on millisecond time-scales. Today's micro mixers mix on a millisecond scale and below [40]. Hence in micro reactors reactions can be carried out in the manner of a quench-flow analysis, used for determination of fast kinetics [93].

Concerning combinatorial operation, micro reactors can be operated in both a highly parallel a and fast serial manner. The latter approach has been realized for the 'cation flow' method for C–C bond formation [66, 67].

4.2.13.3 Electrochemical C–C Bond Formation with Cations Investigated in Micro Reactors

Organic synthesis 30 [OS 30]: Electrooxidative C–C bond formation of carbamates



A substrate containing an amine carboxylate moiety is converted in an electrolyte solution in the presence of a strong acid to a cationic intermediate, an *N*-acyliminium cation, by electrooxidative reaction. This species is immediately reacted with an allylsilane [66, 67]. By nucleophilic reaction, C–C bond formation is achieved.

4.2.13.4 Experimental Protocols

[P 22] A 0.05 M solution of methyl pyrrolidinecarboxylate with 0.3 M Bu_4NBF_4 electrolyte in dichloromethane was fed by syringe pumping (2.1 ml h^{-1}) into the anodic chamber (carbon felt) of the electrochemical micro flow reactor at a temperature of –72 °C [66, 67]. Into the cationic chamber equipped with a platinum wire as electrode, a solution of the electrolyte and trifluoromethanesulfonic acid as a proton source was fed. The cationic intermediate was generated by low-temperature electrolysis (14 mA) and then immediately transferred to another reaction vessel where the final product was obtained by nucleophilic attack. Between the first and second reaction steps monitoring by a continuous-flow IR analyzer (ATR method) was undertaken, revealing the concentration of the carbocation (Figure 4.45).

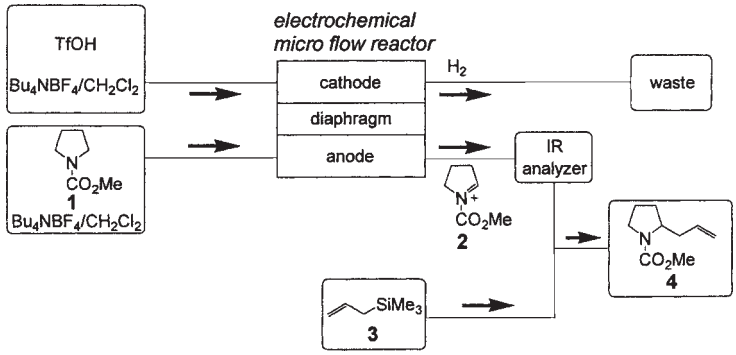


Figure 4.45 Schematic of the 'cation flow' system [66].

4.2.13.5 Typical Results

Conversion/yield/selectivity

[OS 30] [R 30] [P 22] The synthesis of nine C–C bonded products was made from four carbamates and five silyl enol ethers [66, 67]. Conversions ranged from 49 to 69%; the corresponding selectivities ranged from 67 to 100%. Similar performance was achieved when serially processing the same reactions (see Serial combinatorial synthesis).

Cation pool – a variety of carbamates synthesized

[OS 30] [R 30] [P 22] The feasibility of generating a cation pool, i.e. of performing multiple reactions with various reactants, by means of electrooxidative micro flow processing was demonstrated [66, 67]. The micro reaction system was consequently termed 'cation flow'. By this means, various C–C bonded products were made from carbamates, having pyrrolidine, piperidine, diethylamine and trihydroisoquinoline moieties. These carbamates were combined with various silyl enol ethers, yielding nine products.

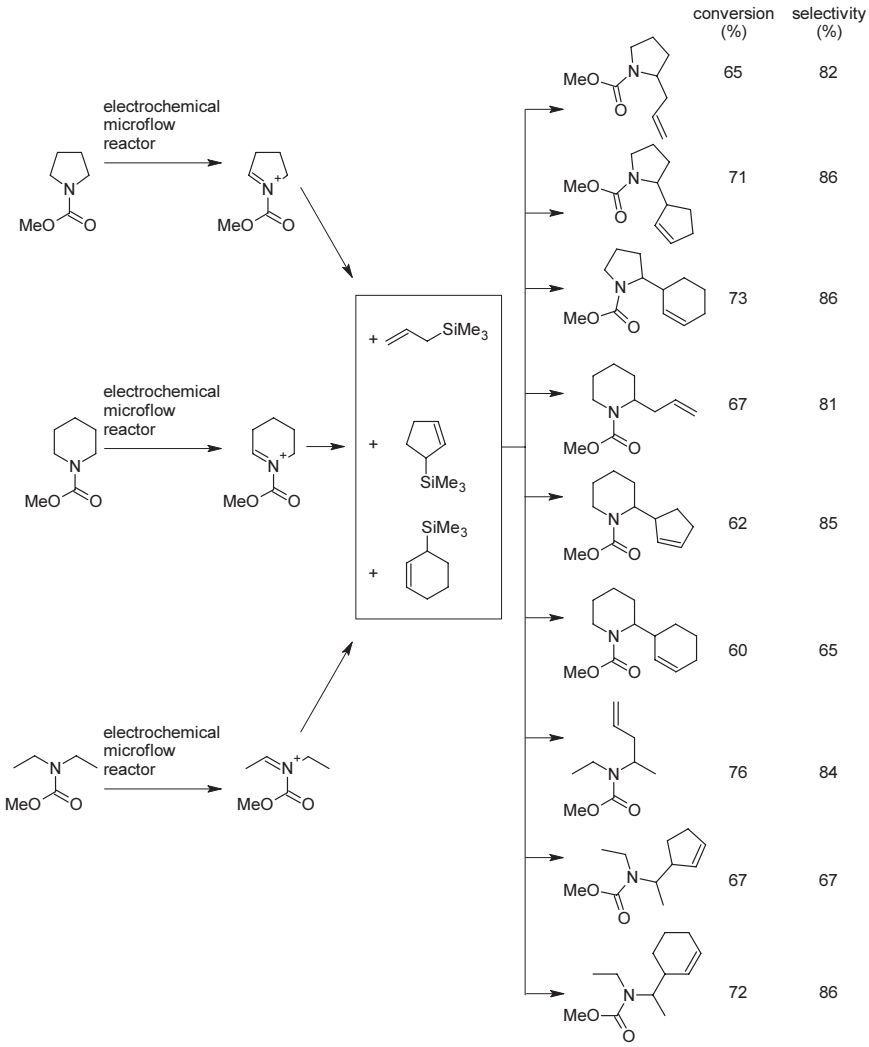


Figure 4.46 Schematic of serial combinatorial synthesis for creating a cation pool from diverse carbamates and silyl enol ethers [66].

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