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Microflow Technology in Polymer Synthesis

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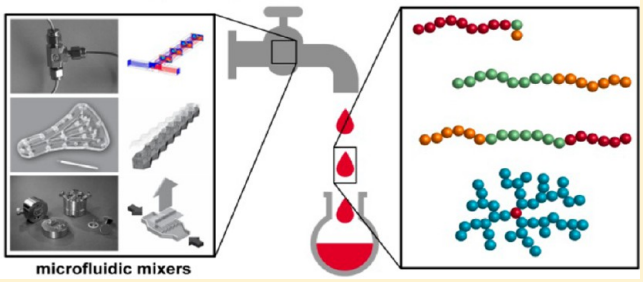
ABSTRACT: Microflow technology, i.e., the use of microfluidic devices for continuous flow synthesis, represents a highly useful and increasingly popular method in organic chemistry. Recently, also an increasing number of polymer synthesis protocols attain benefit from this technique. In particular, the control of highly exothermic, fast polymerization reactions can be improved due to the excellent heat and mass transfer within the small dimensions of the microreactors. Continuous flow setups with different micromixer geometries and flow patterns are currently used for the preparation of a variety of macromolecular architectures by ionic and (controlled) radical polymerization techniques. This Perspectives reviews recent developments in synthetic strategies and reactor design for the homogeneous synthesis of polymers in microflow systems and emphasizes future challenges and promise for applications. Polymer synthesis by radical, anionic, cationic, and coordinative polymerization is considered as well as different polymer topologies generated (linear, branched, and dendritic architectures).



1. INTRODUCTION

The round-bottom flask is the classical reaction vessel for synthetic chemists to carry out chemical reactions in the laboratory from the milligram to the kilogram scale. A major drawback in this case is the difficult control over highly exothermic reactions due to poor heat dissipation and the occurrence of "hot spots". In addition, due to the given volume, reactions cannot be stopped right after the desired transformation. These key issues can be overcome by utilizing continuous flow systems providing efficient heat dissipation properties. Thus, microreaction technology represents a laboratory enrichment for synthetic chemists in both academia and industry.[1] In particular, in the past two decades the fascinating field of continuous flow synthesis has received increasing attention and represents a rapidly growing research area in organic as well as polymer chemistry.[2−5] In addition, the topic has been included in the curricula at several universities.[6,7]

"*Microreactor*" can be considered as an umbrella term for all small microfluidic devices utilized in continuous flow chemistry. Microreactors, also referred to as "*microstructured reactors*" or "*flow reactors*", encompass various reaction platforms with different mixing geometries.[8−10] The small dimensioned devices offer unique properties, which are unattainable by utilizing conventional reaction vessels. In particular, they enable extremely rapid mixing due to short diffusion pathways. This results in improved mass transport and presents ideal conditions for reactions with very fast kinetics.[10,11] Furthermore, such reactors possess a very large, specific surface area (surface-area-to-volume ratio) with 10 000−50 000 m^2 m^{-3} compared to conventional reactors with 100−1000 m^2 m^{-3}, permitting superior heat exchange properties, which renders extremely fast cooling and heating possible.[12−14] Because of the efficient thermal management and the remarkable mixing efficiency, the formation of side products and hot spots can be suppressed, and the control over highly exothermic reactions can be improved. Additionally, slow reactions can be intensified by increasing temperature and pressure in the microreactors. Moreover, the small dimensions of the continuous flow reactors can contribute to the safety of the operator, who has to handle only small quantities of potentially exothermic, toxic, or explosive reaction mixtures that for safety reasons cannot be employed in conventional reactors.[15,16] In comparison to conventional processes, microflow reaction devices permit facile control and adjustment of reaction parameters like temperature, residence time, and reactant stoichiometry during the ongoing synthesis.

Based on these features, a rapidly increasing variety of applications in different areas of chemistry has been established to date. Continuous flow procedures can lead to higher selectivity, improved yield, and increased purity of the respective products.[17−19] Moreover, the use of specially engineered or commercially available microreactors[20] under drastic conditions such as pressurizing or heating the reactor offers access to an enlarged "processing window". For example, single- and multiphase reactions with low-boiling solvent or lowered amount of catalyst can be carried out.[21−24] For

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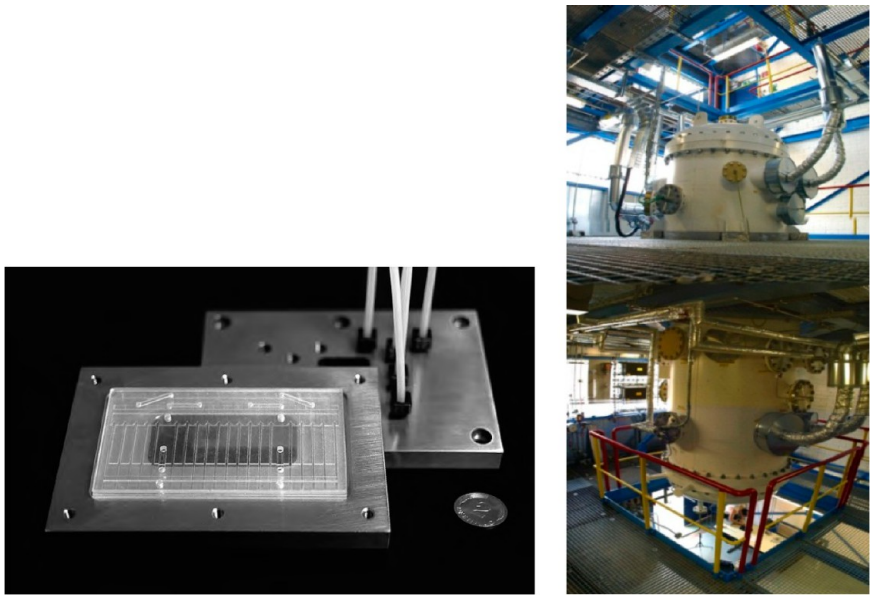


Figure 1. "Microreactors" in different dimensions from a credit-card (left) (mikroglas chemtech GmbH, Germany)[80] to a two-storey house (Evonik, former Degussa, Germany)[80] (right) with microdimensional structures inside.

specialty products even an implementation in industry with larger production scales is possible.[25,26] The size of microstructured reactors can be varied from credit-card to shoe-box size.[27] In addition, a stable microfluidic system enables production for extended periods of time, thereby generating large quantities of materials ("scale-out" principle). The limitation caused by small product scales can also be overcome by connecting several reactors/subunits with identical conditions in parallel ("numbering up").[28−33] The availability of flexible continuous flow systems decreases the dependency on the market demand, and the required amount of product/intermediate can be synthesized, while simultaneously minimizing the storage costs at any time. This represents an advantage of continuous flow chemistry for industrial processes.[34−36]

In organic chemistry microflow technology has received increasing interest, resulting in industrial applications.[37−53] Bogdan et al. realized the preparation of ibuprofen, a high-volume anti-inflammatory drug, using an efficient three-step continuous flow synthesis. Purification as well as the isolation of intermediates was not necessary, which is a significant improvement compared to the conventional synthesis.[54] In an impressive work, Lévesque and Seeberger prepared the antimalaria drug artemisinin from artemisinic acid in a continuous reactor. This led to a tremendous reduction of cost compared to established batch syntheses and offers great potential to decrease the high number of deaths caused by malaria around the world by providing low-cost medication.[55]

In polymer science the use of microreaction technology represents an emerging field at present. Especially highly exothermic and rapid polymerizations,[56] like the living carbanionic polymerization of vinyl monomers, can benefit from the continuous flow process. In this context it has to be emphasized that the pioneering reports on anionic polymerization in continuous flow were published long ago by Szwarc and co-workers[57−59] as well as Schulz and co-workers[60,61] already in the 1960s. Both research groups investigated the reaction kinetics of the anionic styrene polymerization in detail, benefitting from a fast and turbulent mixing process within macroscopic glass tubes. In a seminal work, this approach was extended by Müller and co-workers, who carried out detailed kinetic analyses of the anionic polymerization of methyl methacrylate in a four-way jet mixing device, using stopped-flow type experiments. Through their innovative designed reactor, Müller and co-workers achieved effective mixing in less than 1 ms. The high flow rates (≤6 mL/s) combined with the small internal volumes (diameter of the capillary tubes ≤1 mm) in their experiments led to a characteristic Reynolds number exceeding 3000, guaranteeing turbulent mixing.[62−65] In the reports of Schulz et al. and Müller et al. impressive molecular weight control was achieved by simply varying the flow rate ratios or the length of the flow tube. It has to be emphasized that recently developed continuous flow protocols[66,67] are based on these fundamental works of Szwarc, Schulz, Müller, and co-workers devoted to the polymerization kinetics. However, increasing interest for the actual preparation of polymeric materials based on microreaction technology started only in the late 1990s, most probably due to the challenging reaction conditions and the oftentimes high viscosity of polymer solutions and melts.[66−68]

An additional, fast developing field of research in this context, which will not be highlighted in this Perspective, is the preparation of polymer particles with tailored shapes, size, and composition by applying microflow reactors.[69−74] In this case multiphase polymerization (synthesis of polymer beads and interfacial polymerization) is employed. Impressive progress in this field was accomplished by Kumacheva and co-workers. The development of new strategies for producing complex and patterned microparticles (mono- to multiphase) in different shapes and morphologies has recently been described and reviewed as well as the encapsulation and study of cells in microdroplets.[75−79]

Here, we summarize current perspectives of the microreaction technology with different types of mixing geometries in the field of homogeneous polymer synthesis, where reagents and products are dissolved throughout the polymerization. Recent advances for all types of polymerization techniques as well as in the synthesis of complex polymer architectures are highlighted. Major achievements, recent developments, and

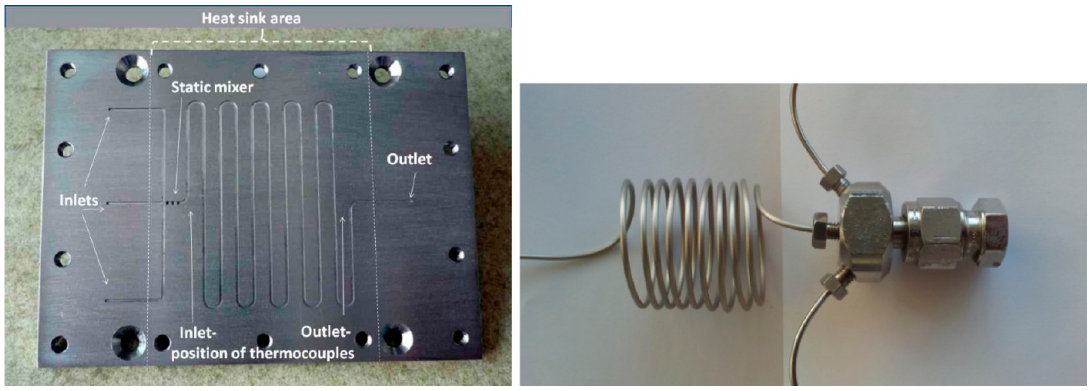


Figure 2. Microreactors with different dimensions: (left) a 2-dimensional microreactor with an integrated static mixer;[83] (right) a 3-dimensional micromixer-tube reactor.

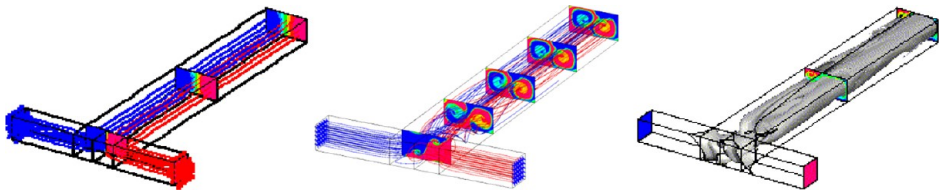


Figure 3. Flow pattern in a T-shaped mixer after 2 mm depending on the *Re*: (left) straight laminar and vortex flow; (middle) engulfment and periodic pulsation; (right) chaotic flow with bursts (by courtesy of Norbert Kockmann).[85]

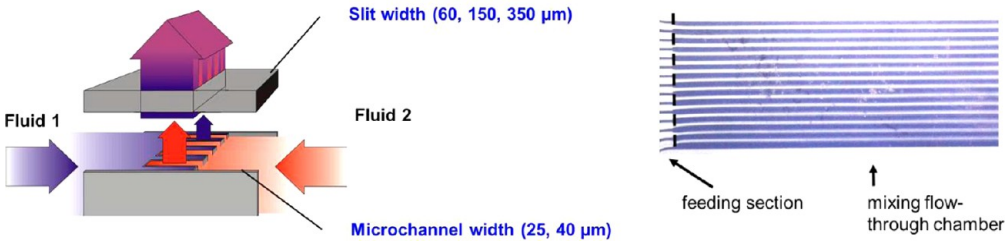


Figure 4. Multilamination mixing principle (left) and visualization of laminar flow pattern with colorized and noncolorized water streams (source IMM, Institut für Mikrotechnik Mainz GmbH).

future challenges of microreaction technology in polymer science will be discussed.

2. MICROFLUIDIC TECHNOLOGY

"Microstructured reactors" provide a large variety of reaction platforms with different mixing geometries.[8−10] The term "microstructured reactor" comprises continuous flow systems with 3-dimensional elements in micrometer dimensions. There are two possibilities to influence a chemical reaction: (i) improvement of mass transport by accelerating the mixing procedure, particularly when a transformation is significantly faster than the mixing time. Furthermore, the backmixing of product with educts is often undesired. (ii) Improvement of heat transfer by rapid cooling or heating of the reactor. Suitable reactors or reactor systems have to be provided to carry out a reaction at the kinetic limit. The corresponding systems should generate microstructured fluids but do not necessarily have to be microstructured itself. Thus, the continuous flow chemistry is not limited to small dimensions. "Microreactors" can range from credit-card to two-storey house setups (Figure 1).

In the rapidly growing area of microflow technology uncommon reaction conditions can easily be applied. For instance, high pressure and temperature with fast heating or cooling cycles can be implemented in a continuous flow setup, which can improvee yield and selectivity.[81,82] Complete and fast mixing of the reactants is important to obtain higher yield or selectivity compared to conventional systems. In the current literature, different general mixing principles are discussed, which also apply to polymer synthesis. In general, the flow rates in microstructured reactors are small (Reynolds number (Re) ≤ 1000, oftentimes below 100), and lamellar flow can be assumed. In this case the mixing process is dominated by diffusion between preshaped fluid layers, and the mixing time is only dependent on the fluid film thickness and the diffusion coefficient. Since the diffusion coefficient represents a temperature-dependent and material-specific parameter, an increased mixing efficiency can only be achieved, if very thin fluid layers are realized.

Although contrary opinions exist, the channel-based lab-on-chip systems (2-dimensional reactor systems) represent no significant difference compared to 3-dimensional elongated tube and capillary reactors. In particular, both reactor types show similar flow profiles as well as an increased mass and heat transfer due to similar surface-to-volume ratios. As can be seen in Figure 2, two-dimensional lab-on-chip microreactors possess integrated mixers (left), whereas the common setup combines an external mixer with corresponding flow tubes (right).

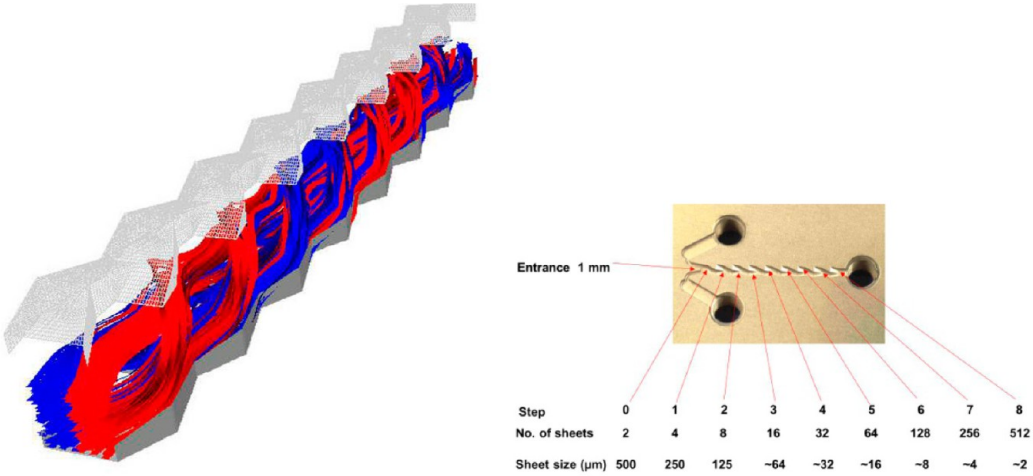


Figure 5. Split-and-recombine micromixer. The flow pattern (left) shows the secondary flow instead of multilamination and the steps in combination with number of stacked lamellae are depicted in the right image (source IMM, Institut für Mikrotechnik Mainz GmbH).

A classic example for a simple lamination mixer often used in polymer synthesis is a commercially available T-piece. Although this type of mixer is easily accessible, it exhibits some disadvantages compared to the more sophisticated lamination mixers. Applying reaction conditions with $Re < 10$ increases the mixing time due to a bilamination of the two reactants. Inefficient mixing is caused by the long pathways of the molecules by diffusion through the complete cross section of the reaction tube. With $Re > 200$ uncontrolled turbulence with pulsation occurs, which impedes the mixing process. Higher Re (>1000) requires fluidic jet streams, and a controlled mixing process is not possible. Only at Reynolds numbers ∼200 a secondary flow pattern creates additional fluid lamellae to intensify the mixing behavior (Figure 3).[84]

In contrast to T-pieces, commercially available multilamination mixers present clearly improved mixing patterns. Micrometer thin fluid layers (lamellea) get split up prior to the mixing process. The mixing occurs by diffusion between the fluid lamellae, which leads to rapid mixing within milliseconds due to the ultrathin layers (microchannel width 25 and 40 μm) (Figure 4). Such multilamination mixers are also available for high-pressure applications.[86]

Another type of mixing is represented by split-and-recombine mixers (Figure 5), which are especially beneficial for chemical reactions with low-viscosity materials and are thus less suitable for higher molecular weight polymers. Within such micromixers the fluid lamellae are split and subsequently recombined. The repetition of this process in each step (n) of the mixers creates 2^n stacked fluid lamellae. Hence, a mixer with eight steps and a hydraulic cross section of 1 mm theoretically creates 512 lamellea, each with a thickness of 2 μm. In addition, the process of this serial multilamination shows further dominant fluid dynamic effects, e.g., formation of secondary stream patterns, which improves the mixing efficiency significantly.

In summary, all mixing types show high potential for polymerization in continuous flow, depending on the degrees of polymerization desired. In the following section the currently established procedures, recent studies, and future challenges in polymer science utilizing different kinds of mixing geometries are discussed.

Microfluidic devices permit precise online monitoring of different stages of a reaction. In 2009, Penlidis et al. published an extensive review article, dealing with real-time online and in-line sensor technologies for polymerization reactors. On the one hand, the authors describe the sensor development to follow relevant physical parameters (pressure, flow, and temperature). On the other hand, they give a valuable overview of the different monitoring techniques for in-situ determinable polymer properties, such as molecular weight, chemical composition, particle size, and cross-linking density.[87] Using this large number of characterization opportunities, a detailed understanding of reaction kinetics and optimization possibilities is achieved. In a very recent work in this important area, Kumacheva and co-workers published a seminal kinetic study of the polymerization of *N*-isopropylacrylamide using in-situ attenuated total reflection Fourier transform infrared spectroscopy (ATR-FTIR) under different reaction conditions, benefiting from the rapid on-chip characterization method.[88]

3. HOMOPOLYMERIZATION BY IONIC AND RADICAL TECHNIQUES

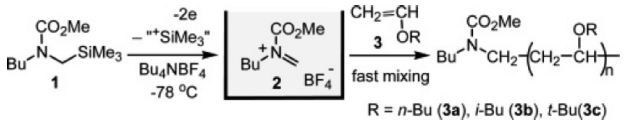
A central issue in current polymer science is the synthesis of complex polymer architectures with controlled molecular weight and narrow molecular weight distribution (MWD). In a continuous setup, precise control can be achieved by efficient mixing using microreaction technology. First reports on the continuous preparation of homopolymers were published already in the 1960s by Szwarc as well as Schulz and co-workers.[57,61] In these early works, the authors conducted kinetic studies of the anionic styrene polymerization in continuous flow tube reactors. Suprisingly, the area remained almost dormant in academic research, until the late 1990s, which are marked by the implementation of different polymerization techniques in microreactors. This renaissance comprises the successful execution of anionic, cationic, free radical, and controlled radical homopolymerization of different monomers in continuous flow, which will be outlined in this section.

In the following paragraphs, the achievements in ionic polymerization in the flow will be discussed. For this type of polymerization, the reaction kinetics is strongly influenced by the solvent and counterion. In particular, a more polar solvent leads to accelerated reaction kinetics, and control of the highly exothermic reaction becomes demanding.[89,90] Another essential requirement for the preparation of well-defined polymers with

"living" polymerization techniques is rapid initiation, which requires fast and efficient mixing of initiator and monomers. Furthermore, the living character and the sensitivity of the carbanionic chain ends demand strictly anhydrous and sealed reaction conditions. Both anionic and cationic polymerizations can proceed extremely rapidly, which is important für transfer to microfluidic systems. Microreaction technology provides suitable reaction compartments with high mixing efficiency to control extreme reaction conditions. In addition, the sealed reaction environment in a microfluidic device that enables living polymerization without tedious purification steps is a key feature.

The first carbocationic polymerization was transferred to a microfluidic device by Nagaki et al. in 2004. The polymerization of different butyl vinyl ethers within a multilamination micromixer was described, and the *N*-acyliminium "cation pool"[91,92] served as an efficient initiator. The polymerization was controlled by adjusting the flow rate ratio and was completed within 0.5 s at −78 °C, resulting in an impressive decrease of polydispersities ($M_w/M_n \geq 1.14$) compared to the batch reactor ($M_w/M_n \geq 2.2$) (Scheme 1). Furthermore, the living character was confirmed by end-capping the polymer with allyltrimethylsilane.[93,94]

Scheme 1. Preparation of Cation Pool as Initiating Species for the Continuous Carbocationic Polymerization of Different Butyl Vinyl Ethers[93]



The challenging reaction conditions (−78 °C) can be avoided by utilizing trifluoromethanesulfonic acid (TfOH) as an initiator. In this case a controlled polymerization can be realized at temperatures of 25 °C.[95] The same microfluidic setup was used to increase the indane unit content during the polymerization of 1,4-diisopropylbenzene.[96] Paulus et al. studied the microwave-assisted cationic ring-opening polymerization of 2-ethyl-2-oxazoline in a tube reactor. Here, under microwave irradiation complete conversion but broader MWDs ($M_w/M_n \geq 1.3$ vs $M_w/M_n = 1.14$ in batch reactions) were achieved because the flow profile was nonuniform, which results in inefficient mixing.[97]

Anionic polymerization also represents a highly suitable polymerization technique for microfluidic processes, especially due to the well-contained reaction zone. Reaction time and experimental effort can be reduced significantly compared to established techniques and reactors.[98] Since polymerization rates in polar solvents like THF can be very high with k_p in the range of 1500−5000 L mol^{-1} s^{-1},[59] the formation of polymer chains with moderate molecular weights can be complete within less than 1s. The preparation of poly(methacrylate)s in the late 1990s by Müller and co-workers demonstrates the high potential for anionic polymerization in continuous flow. On the basis of efficient mixing, the authors obtained well-defined materials with narrow molecular weight distributions (M_w/M_n = 1.04−1.08).[63] Although this report could have been an initiation for further works, the next report in this field was not published until 2005 by Honda et al.[99] The authors developed the continuous flow polymerization of different amino acid anhydrides and compared the results to the corresponding batch reactions. A significant decrease of the PDI value was obtained when utilizing a silicon-based microreactor fabricated by a dry etching procedure. For instance, the preparation of poly(glutamine) revealed a PDI of 1.17, whereas the batch approach leads to higher values (M_w/M_n = 1.56). This underlines the excellent control over the polymerization with microfluidic devices. Employing a decreased flow rate leads to higher residence times and a gradual increase of molecular weight (cf. Figure 6). Furthermore, amino acid copolymers

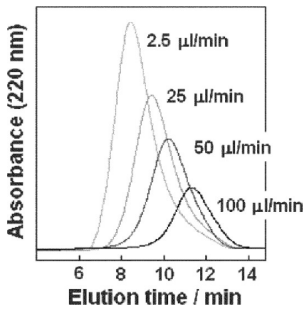


Figure 6. Molecular weight distributions of poly(lysine)s prepared with different flow rates. Reduction of the flow rate results in prolonged residence times in the microreactor, and thus higher molecular weights are obtained.[99]

consisting of lysine/alanine or lysine/leucine comonomers were synthesized. With respect to biomedical applications, these remarkable results offer a facile and novel access to poly(amino acid)s.[99,100]

In our group, the anionic polymerization of poly(styrene) (PS) was transferred to a microstructured reactor. The reactor consisted of capillary flow tubes and a slit interdigital micromixer with inner volume of 15 μL (IMM, Germany) as a mixing unit. The monomer and initiator (*sec*-butyllithium) solutions were combined in the micromixer to initiate the anionic polymerization at room temperature in a polar solvent. Using a short outlet tube, PS samples in a broad range of molecular weights (M_n = 2000−70 000 g mol^{-1}) with moderate to narrow molecular weight distributions (M_w/M_n = 1.09−1.20) were obtained. Compared to batch reactions, the reaction time could be reduced from hours to several seconds, giving facile access to large amounts of well-defined polymers in a short period of time. Furthermore, the adjustment of flow rate ratios afforded different molecular weights in a single experiment without interrupting the continuous flow process. It has to be mentioned that for these reactions the complete microreactor interior has to be made of stainless steel because the living carbanions react with most common materials, e.g., rubber or PTFE sealings.[101]

This work was extended to the preparation of specifically terminated polymers by investigating the end-capping process of living PS with different reagents in a microfluidic setup. For this purpose a second mixer (T-junction) was added to achieve direct termination of PS in a continuous process (Figure 7). In particular, living PS was end-capped with a variety of tailored glycidyl ethers (e.g., ethoxy ethyl glycidyl ether (EEGE), isopropylidene glyceryl glycidyl ether (IGG), phenyl-1,3-dioxane glycidyl ether (PDGE), and *N,N*-dibenzylaminoglycidol (DBAG)) to introduce additional hydroxyl or amine functions at the chain termini.[102,103] The end-functionalized polymers were recovered within several seconds, and quantitative end-capping was confirmed in all cases by matrix-

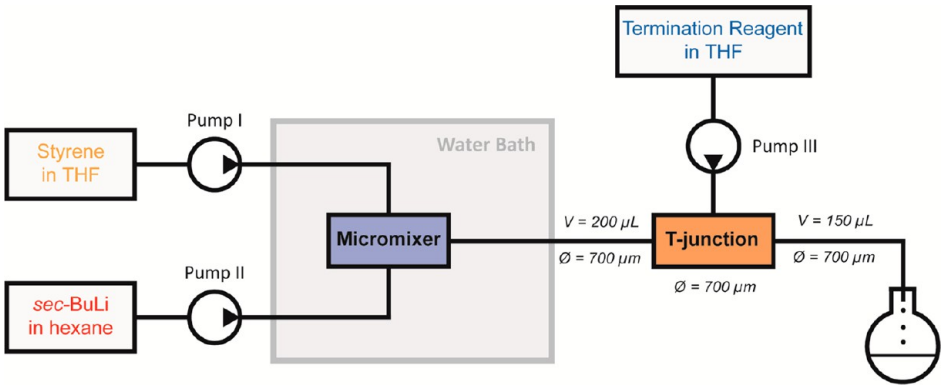


Figure 7. Schematic reactor setup for the quantitative end-functionalization of living poly(styrene) in continuous flow utilizing a HP-IMM micromixer.[102]

assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-ToF MS). An exemplary spectrum of DBAG-functionalized PS is depicted in Figure 8. This

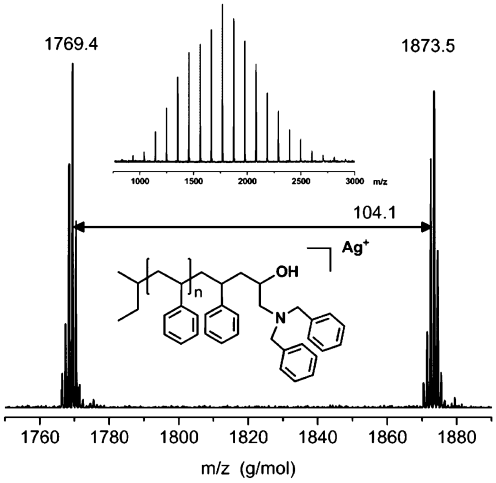


Figure 8. Quantitative end-functionalization of polystyrene in continuous flow was confirmed by MALDI-ToF MS. The single distribution mode can be assigned to the desired terminated macromolecules (here: PS-(DBAG)).[103]

continuous end-functionalization provides a valuable method for rapid and cost-efficient polymer screening with respect to novel end-functionalized polymers that can be utilized for the rapid generation of complex macromolecular architectures.

Recently, in analogy to the continuous homopolymerization of PS, other research groups extended this concept utilizing different mixing geometries or styrene derivatives.[104,105] Beers and co-workers investigated the anionic styrene and isoprene polymerization in nonpolar solvent (cyclohexane) and low-cost aluminum−Kapton microfluidic devices with different 2D flow designs (straight, periodically pinched, obtuse zigzag, and acute zigzag; cf. Figure 9). Polymerizations were carried out at elevated temperatures (60 °C) and high concentrations (up to 42 vol %), and the zigzag channels led to lower PDI values due to passive mixing in the appropriate reactor designs (elastic turbulence and laminar recirculation).[105]

Similar to the seminal works of Müller and co-workers,[63] Yoshida et al. studied the homopolymerization of different methacrylates in a syringe-based micromixer equipped with a T-piece (0.5−1 mm inner diameter (i.d.)). 1,1-Diphenylhex-

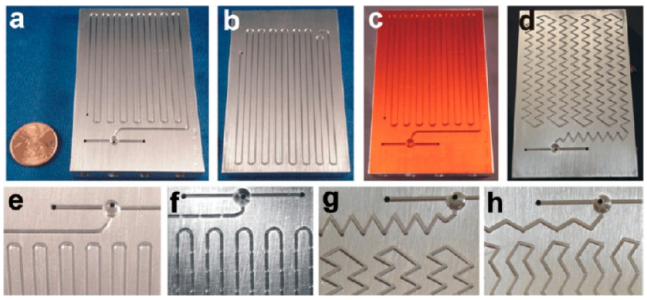


Figure 9. Different 2D designs cut into aluminum plates on both sides. The reactor was sealed by a Kapton film: (a, b, e) straight, (c) straight sealed with polyimide film, (d) zigzag, (f) periodic pinches, (g) acute zigzag, and (h) obtuse zigzag patterns.[105]

yllithium was used as an initiator, and in a controlled manner narrowly distributed polymers were obtained at higher temperatures than in conventional anionic methacrylate polymerization, ranging from −28 °C to room temperature.[106]

Free radical polymerizations can also be carried out in microfluidic devices. An important benefit of the transfer to continuous flow is the suppression of the Trommsdorff effect by the superior heat and mass transfer.[107] Because of the increased immobility of the growing polymer chain with increasing viscosity, the number of recombination steps decreases and the concentration of reactive chain ends increases, which leads to an uncontrolled autoacceleration of the polymerization rate that results in the loss of reaction control and the preparation of ill-defined products. Detailed studies of five different monomers in a free radical polymerization were accomplished by Yoshida et al.[108] The polymerizations were carried out using a T-piece with inner dimensions of 250−1000 μm in a controlled manner. The authors obtained a significant improvement of the MWD for the polymerization of benzyl methacrylate, methyl methacrylate (MMA), and butyl methacrylate compared to the corresponding batch reactions. In case of poly(butyl acrylate) the polydispersity could be decreased from ∼10 in a conventional reactor to 3.16 in the continuous flow process (Figure 10). This effect was less pronounced for the free radical polymerization of vinyl benzoate and styrene due to the decreased polymerization rate, leading to a reduced benefit from the efficient heat dissipation.

In addition, the successful implementation of the radical MMA polymerization to a larger scale was accomplished by Iwasaki et al. With a "numbering-up" approach eight microtube

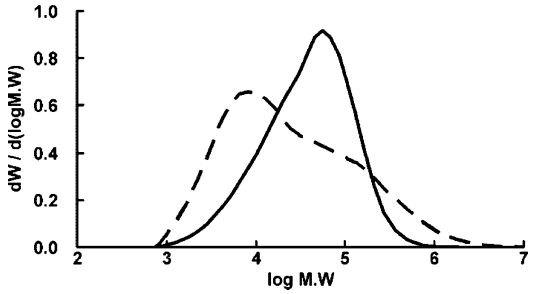


Figure 10. MWDs of poly(butyl acrylate) synthesized in a conventional batch reactor (dashed line) and T-piece (solid line).[108]

reactors were run in parallel for 6 days, and continuous operation with precise control of temperature, molecular weight, and MWD was achieved, indicating the inherent advantage of microflow systems (Figure 11). For instance, 4 kg of polymer within one week at a total flow rate of 60−110 mL/h was obtained.[109] Microchemical approaches are believed to have significant potential for specialty applications in industry. Moreover, industrial application of microflow polymerizations with continuously operating pumps has been described in several patents.[110−112]

Since the 1990s, a variety of novel techniques for the controlled synthesis of polymers by radical polymerization have been developed. These methods are generally designated "living" or "controlled radical polymerization (CRP)",[113] and they have extended the field of standard polymer syntheses procedures in an impressive way. Well-defined polymers with large monomer variation can be obtained in a facile manner. CRP can be subdivided in three major techniques viz. atomic transfer radical polymerization (ATRP),[114,115] nitroxide-mediated polymerization (NMP),[116,117] and reversible addition−fragmentation chain transfer polymerization (RAFT).[118] Although CRP techniques generally show slow reaction kinetics, one may benefit from microreaction technology. The challenge to transfer the major CRP techniques to flow systems has been taken up by several research groups in recent years.

First reports on the transfer of controlled radical polymerization into continuous flow reaction systems were published by Zhu and co-workers. A continuous column reactor packed with supported CuBr−HMTETA catalyst was utilized for the continuous supported ATRP (C-SATRP)[119] of MMA. The column exhibited good catalyst retention and a long-term catalytic reactivity, representing a promising development for commercial ATRP applications, since removal of copper subsequent to polymer synthesis is not necessary.[120] Recently, MMA was also polymerized homogenously in a tubular flow reactor with excellent control over the molecular properties (conversion ≈90%, M_n/M_n = 1.06).[121] Beers and co-workers employed an individually fabricated microstructured reactor (Figure 12) for the continuous ATRP of 2-hydroxypropyl

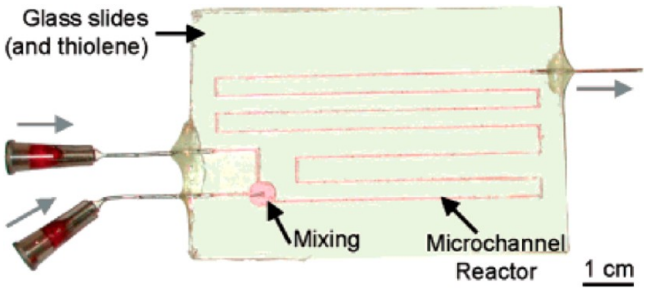


Figure 12. Microstructured reactor for the ARTP of HPMA, constructed by contact photolithography of a thiolene prepolymer with improved solvent resistance compared to PDMS (poly(dimethylsiloxane) devices. The reactor with one single reaction channel (dimensions 500 μm × 600 μm) is equipped with two inlet channels and one outlet channel. A miniaturized stir bar is included in the mixing chamber and is driven by a magnetic stir plate. To start the polymerization, the solutions of monomer/catalyst and initiator in a water/methanol mixture were added via syringe pumps into the two different inlet channels.[123]

methacrylate (HPMA). The system was compared to the batch process,[122] and monomer conversion was comparable to bulk reaction kinetics. The molecular variables (M_n = 1600−12 000 g mol^{-1}, M_w/M_n = 1.19−1.32) were controlled by variation of flow rates, polymerization time, or concentration of the reagents, allowing for a rapid screening of polymeric materials with different properties.

In a more tubular dimension, a rather long continuous reactor (150 m length, i.d. 2.2 mm) was employed to produce homopolymers of butyl acrylate and styrene by ATRP. Narrow molecular weight distributions and a slightly higher conversion were obtained compared to analogous batch experiments.[124] Further developments, i.e., avoiding purification of reagents, wider inner diameter (4.75 mm), and nonhazardous/inexpensive reducing agent, were applied to obtain industrially relevant conditions for the polymerization of butyl acrylate. Clogging problems were avoided by reducing the amount of

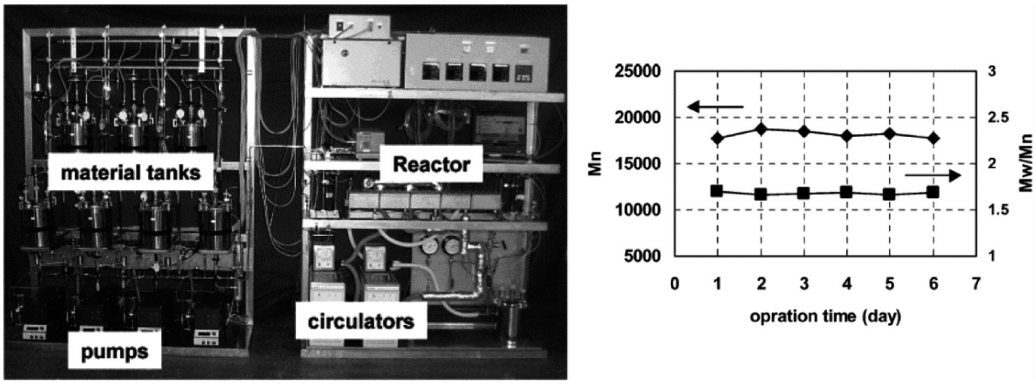


Figure 11. Image of the pilot plant with eight microtubes in parallel and a total inner volume of 18.4 mL (left) were run for 6 days with precise control of molecular weight and MWD (right).[109]

catalyst to parts per million (ppm) levels using "activator regenerated by electron transfer" (ARGET) ATRP.[125] An increased amount of reducing agent led to a faster and more robust ARGET ATRP, demonstrating the potential for industrial adoption.[126] Very recently, Junkers and co-workers synthesized a variety of functionalized RAFT-derived poly(*n*-butyl acrylate)s via continuous flow. The fundamental concept was the aminolysis followed by thiol−ene reaction of various termination reagents. Quantitative conversion was realized within 20 min and proven by soft ionization mass spectrometry.[127]

Reconsidering microdimensional devices, also other CRP techniques, e.g., NMP, were applied to continuous flow processes. Rosenfeld et al. investigated the high-temperature polymerization of two monomers (styrene and *n*-butyl acrylate) suitable for NMP[128] to increase the control of the reaction. In comparison to lab-scale batch reactors the exothermic polymerization of *n*-butyl acrylate can benefit from the superior heat release and provide a narrower MWD, whereas styrene shows no difference to the batch processes.[129] This system was utilized to develop an intriguing characterization method for continuous polymer synthesis, namely "continuous online rapid size-exclusion chromatography monitoring of polymerizations" (CORSEMP). This novel GPC characterization method allows the automatic sampling, dilution, injection, and analysis every 12 min of the crude (co)polymer samples, which are recovered from the reactor outlet. The monitoring in "near real time" of the molecular weight and MWD possesses promising potential for further implementation on both academic and industrial level (Figure 13).

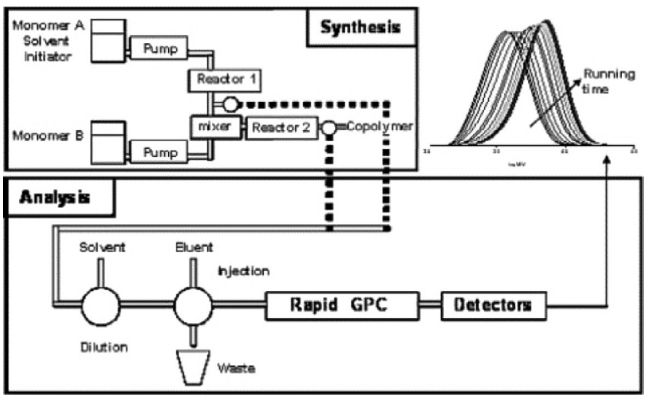


Figure 13. Schematic setup of the CORSEMP representing the continuous polymerization part (top, left) and the analysis section (bottom). The system monitors the molecular weight and the MWD "near real time" (top, right).

Compared to NMP and ATRP, RAFT polymerization permits the utilization of a larger variety of monomers, applying different chain transfer agents without using transition metal catalysts.[130] Recently, two research groups at the same time published on the initially homogeneous RAFT polymerization in continuous flow. Seeberger and co-workers used a syringe-based microreactor for the homogeneous RAFT polymerization of poly(*N*-isopropylacrylamide) (PNIPAM) in continuous flow.[133] PNIPAM represents an interesting poly(acrylamide) due to potential applications in the field of biomedicine[131] and stimuli-responsive materials.[132] The microfluidic process led to faster polymerization due to the excellent heat transfer, while maintaining the control over the polymer parameters (M_w/M_n = 1.15). Similar results were found for microwave-assisted RAFT polymerization, but the continuous process offers a pronounced scalable and cost-efficient procedure.[133] Hornung et al.[134] successfully conducted solution-phase RAFT polymerization under continuous and segmented flow conditions in a tubular flow reactor (i.d. 1000 μm). The comprehensive investigation considered polymerization under a large variety of conditions. Besides four different monomers (NIPAM, *n*-butyl acrylate (*n*BA), vinyl acetate (VAc), *N,N*-dimethylacrylamide (DMA)), various initiators, solvents, and RAFT agents were employed. High conversion (80−100%) and low polydispersities (1.15−1.20) could be obtained in both flow modes, showing potential for the synthesis of block copolymers in continuous fashion, an issue that will be highlighted in the following section.

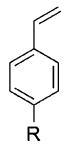
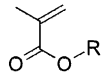
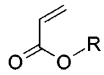
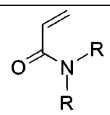
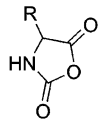
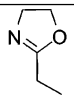
Controlled radical polymerization generally exhibits significantly slower polymerization kinetics compared to ionic or free radical polymerizations. Therefore, CRPs do not directly benefit from the microflow technology with its superior heat and mass transfer. Furthermore, additional requirements have to be fulfilled; e.g., the reaction mixture has to be homogeneous at all conversions and temperature ranges applied in the microfluidic reactors. Even a small amount of precipitated material is problematic and can lead to problems for the long-term stability of the microfluidic device.[124] Thus, the implementation of CRPs in continuous flow is more focused on the development of a simple and economical method for the generation of polymeric material "libraries", i.e., the rapid synthesis of a wide range of polymers that are well-defined in terms of molecular weights and architectures. Thus, from a scientific and industrial point of view it is advantageous to create a method for facile screening of the correlation between polymer architecture, composition, and reaction parameters.[123] Scale down can easily be obtained without wasting material during the screening process, and therefore the novel developed SEC method, viz. "CORSEMP", presents an ideal and convenient tool for the rapid characterization of such polymer libraries.

In summary, to date a variety of monomers has been polymerized homogeneously in various microfluidic devices with different polymerization techniques, such as anionic, cationic, free radical, and controlled radical polymerization (cf. summary in Table 1) in recent years. Although the basic feasibility of the synthesis of these homopolymers has been established in microfluidic setups, future challenges are the implementation of additional monomers for the preparation of block copolymers and other, nonconventional architectures using continuous flow strategies. An impressive technical implementation of microflow technology was presented by the ultrafast anionic (co)polymerization of methacrylate monomers leading to mainly syndiotactic polymers.[110] In this case a tangential jet mixer was used in a pilot plant at flow rates of up to 100 kg/h. The process profits from the high rate (k_p > 10^4 L mol^{-1} s^{-1}) in the case of the alkoxy alkoxide-mediated polymerization of methacrylates.

4. LINEAR BLOCK COPOLYMERS

The implementation of homopolymerizations in microfluidic systems represents an important foundation for the preparation of complex polymer architectures in microfluidic devices. The synthesis of linear block copolymers represents a key target, and in particular living polymerization techniques provide an ideal platform for the synthesis of multiblock copolymers, since

Table 1. Monomers Transferred into Microstructured Reactors with Corresponding References

Structure	R[a)]	Name	PM[b)]
	H[101, 102, 104, 105, 108, 124, 129]	styrene	A, F, CRP
	OMe_3[101]	4-*tert*-butoxystyrene	A
	$SiHMe_2$[104]	*p*-dimethylsilyl styrene	A
	OMe[104]	*p*-methoxystyrene	A
	OTBDMS[c)104]	TBDMS sytrene	A
	SMe[104]	*p*-metylthio styrene	A
	-C≡C-Bu[104]	*p*-(1-hexynyl)styrene	A
	Me[63, 106, 108, 109, 110, 120]	methyl methacrylate	A, F, CRP
	n-Bu[106, 126]	*n*-butyl methacrylate	A, CRP
	t-Bu[106]	*tert*-butyl methacrylate	A
	benzyl[108]	benzyl methacrylate	F
	2-hydroxypropyl[123, 135]	2-hydroxypropyl methacrylate	CRP
	*n*-Bu[63, 108, 124, 129, 134]	*n*-butyl acrylate	A, F, CRP
	NMe_2[134]	*N*,*N*-Dimethyl acrylamide	CRP
	NH-iPr[133, 134]	*N*-isopropyl acrylamide	CRP
	Et[95, 136]	ethyl vinyl ether	C
	n-Bu[93, 96, 136]	butyl vinyl ether	C
	t-Bu[93]	*tert*-butyl ether	C
	i-Bu[93, 95, 136]	isobutyl ether	C
	benzoate[108]	vinyl benzoate	F
	acetoxy[134]	vinyl acetate	CRP
	L-Boc-lys[99, 100]	*N*-*Boc*-L-lysine-NCA[d)]	A
	L-ala[99, 100]	L-alanine-NCA	A
	L-leu[99, 100]	L-leucine-NCA	A
	γ-Bzl-L-glu[100]	γ-benzyl-L-glutamate-NCA	A
	[105]	isoprene	A
	[97]	2-ethyl-2-oxazoline	C

[a]Corresponding residual and/or reference. [b]Polymerization technique utilized: carbanionic = A, carbocationic = C, free radical polymerization = F, controlled radical polymerization = CRP. [c]TBDMS = *tert*-butyl(dimethyl)siloxyl. [d]NCA = *N*-carboxy anhydride and Boc = *tert*-butyloxycarbonyl.

they can be prepared in a one-pot reaction by sequential addition of the desired monomers. By connecting several mixers in a microfluidic device, sequential addition of monomers can be achieved, enabling the preparation of block copolymers with different block length ratio and degree of polymerization within short time. As an alternative access, diblock copolymers can be obtained by semicontinuous polymerizations. Here, a conventionally synthesized macro-initiator can be introduced in the microfluidic devices to initiate the second polymerization, or the macroinitiator can be synthesized in continuous flow and utilized in a batch reactor for a subsequent block polymerization. In several reports the (semi)continuous flow synthesis of block copolymers has been described.

The first reports on carbocationic block copolymerization in flow chemistry was published by Sawamoto and co-workers.[136] The polymerization of different vinyl ether monomers (isobutyl vinyl ether (IBVE), *n*-butyl vinyl ether (NBVE), and ethyl vinyl ether (EVE)) in continuous flow (flow rates 1−4 mL min^{-1}) was investigated. Diblock and triblock copolymers were synthesized by connecting a second and third mixer in sequence for the introduction of monomer 2 and 3, respectively. A schematic setup of the microstructured reactor is depicted in Figure 14 (top). Because of the highly reactive carbocationic intermediates, the polymerization was carried out at −78 °C, and short polymerization times of 15−20 s per block were employed. Quantitative yields were obtained. The progress of the block formation was monitored by SEC

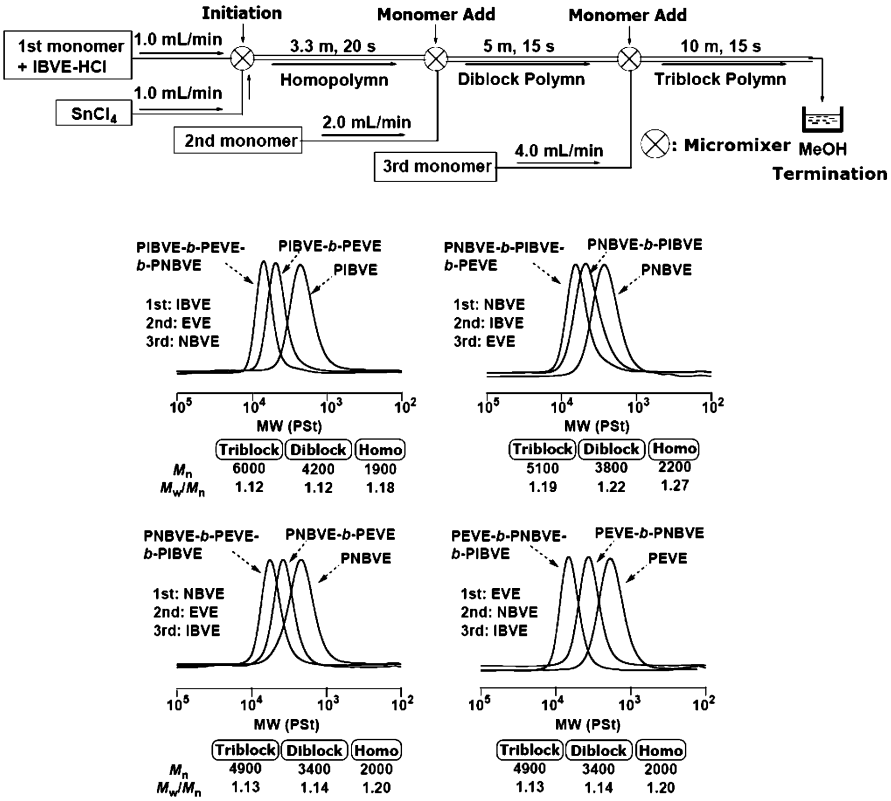


Figure 14. Carbocationic continuous block copolymerization of isobutyl vinyl ether (IBVE), *n*-butyl vinyl ether (NBVE), and ethyl vinyl ether (EVE) in different addition orders carried out in a microstructured reactor with three T-shaped micromixers (top). Control over molecular weight and MWD was monitored by SEC (bottom).[136]

(Figure 14, bottom). Sequential increase of molecular weights with each monomer addition and narrow MWDs ($M_w/M_n \approx 1.2$) indicate proper control of the macromolecular properties.

Iwasaki et al. carried out diblock copolymer synthesis with different order of monomer addition (monomers: IBVE, NBVE, and EVE). Moreover, the authors were able to increase the reaction temperature to −25 °C by using trifluoromethanesulfonic acid (TfOH) as an initiator.[95]

Controlled and rapid synthesis of block copolymers by anionic polymerization techniques in continuous flow was initially reported by Müller et al. in the late 1990s.[63] It is impressive to note that within less than 0.6 s a block copolymer of MMA and *n*-BuA (27 000 g mol^{-1}, M_w/M_n = 1.35) was obtained in a microfluidic setup with two mixers in sequence. Based on these works, poly(butadiene)-*b*-poly(methyl methacrylate) block copolymers were prepared in a pilot plant at Elf Atochem by ultrafast anionic polymerization.[110]

In our group a series of block copolymers were prepared in a very short time at room temperature using a microstrucutured reactor with two slit interdigital micromixers.[101] Adjustment of the block length ratios was achieved by variation of the flow rate ratio of the monomers (styrene and 4-*tert*-butoxystyrene (*t*-BuOS)) and initiator. Well-defined block copolymers were synthesized at room temperature with THF as solvent, and molecular weights in the range of 2000−25 000 g mol^{-1} and narrow MWDs (M_w/M_n = 1.1−1.2) were obtained (Table 2). Although the MWDs are not as narrow as those obtained by break-seal- and high vacuum-techniques[137] ($M_w/M_n \leq 1.1$), the materials are suitable for most relevant purposes of block copolymers, e.g., for the study of phase segregation and ordering. Nagaki et al.[104] prepared block copolymers in a similar setup using syringe pumps and two T-shaped mixing elements in series. The polymerization was carried out at 0−24 °C, and two different styrene derivatives (TBDMS-styrene and *p*-dimethylsilylstyrene) were copolymerized with styrene to synthesize low-molecular-weight block copolymers ($M_n \leq 3100$ g mol^{-1}).

Table 2. Results of the Anionic Block Copolymerization of Styrene Derivatives with Microstructured Reactors[a]

sample	S:*t*-BuOS[b]	M_n[c]	M_n[d]	M_n[e]	M_w/M_n[f]
PS-1	0:35	3600	3700	4200	1.21
PS-2	5:5	1400	1300	1500	1.18
PS-3	10:5	1900	1900	2100	1.22
PS-4	22:12	4400	4800	4700	1.17
PS-5	80:30	13600	13100	13600	1.15
PS-6	200:25	25300	24700	25600	1.14

[a]By variation of flow rate ratio different block ratios were obtained.[101] [b]Block ratio styrene (S)/4-*t*-butoxystyrene (*t*-BuOS) adjusted by flow rates. [c]Theoretical value of the number-average MWD in g mol^{-1}. [d]Number-average of the MWD in g mol^{-1} determined by SEC in tetrahydrofuran. [e]Number-average of the MWD in g mol^{-1} determined by multiangle light scattering (MALLS) in tetrahydrofuran (THF). [f]Polydispersity index determined with MALLS detector in THF.

An alternative route to these block copolymers is the reaction of two different living polymer chains with dichlorosilane.[104] Yoshida and co-workers expanded their work by preparing diblock copolymers of different methacrylates. MMA, *n*-butyl methacrylate (BuMA), and *tert*-butyl methacrylate (*t*-BuMA) were used as monomers to synthesize well-defined diblock copolymer without using any additives.[106]

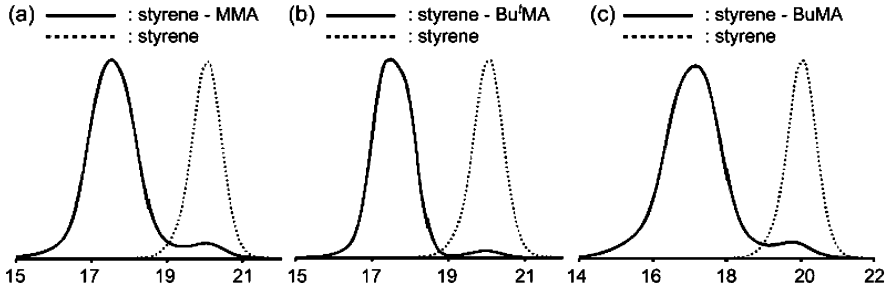


Figure 15. Molecular weight distributions of the block copolymerization of styrene and alkyl methacrylates in continuous flow. In all cases, the solid line represents the block copolymer and the dashed line the corresponding PS precursor. (a) Styrene−MMA, (b) styrene−*t*-BuMA, (c) styrene−BuMA.[138]

After the successful implementation of the anionic polymerization of methacrylates[106,110] and styrenes[101,104,105] in microfluidic devices, block copolymers consisting of both monomer types were produced in an integrated flow microreactor system equipped with up to four T-shaped microfluidic elements.[138] In the first mixer styrene was initiated with *sec*-BuLi. Because of the pronounced reactivity of the living chain end, the polymer was end-capped with 1,1-diphenylethylene (DPE) in the second T-piece with a high functionalization efficiency (80%). The resulting organolithium species could be used as a macroinitiator for methacrylate polymerizations, which were carried out in the third T-piece and a subsequent flow tube. Block formation was observed by SEC analysis, and diblock copolymers with a DPE unit at the junction point and precisely adjustable molecular weights were obtained (M_n = 3900−17 000 g mol^{-1}, M_n/M_w = 1.1−1.5, Figure 15).

As a first monomer styrene or *p*-dimethylsilylstyrene and as second monomer MMA, BuMA, or *t*-BuMA were used to obtain a large variety of different diblock copolymers. To provide the ideal reaction conditions for the different monomers, each part of the system was cooled to the optimized reaction temperature of the corresponding monomer in the range of −28 to 24 °C. Moreover, the microfluidic system was expanded with an additional mixer to prepare PS−(P(*t*-BuMA)−poly(alkyl methacrylate) triblock copolymers. The schematic overview of this multiple step continuous flow polymerization is shown in Figure 16. As a third monomer either MMA or BuMA was utilized, and the stepwise increase of the molecular weight was observable in SEC. In summary, the continuous polymerization of triblock copolymers was accomplished under easily accessible conditions similar to the carbocationic approaches for diblock copolymers and triblock copolymers mentioned above.[138] These results rely on the living nature of the anionic polymerization in continuous flow and enable facile access to structurally well-defined block copolymers.

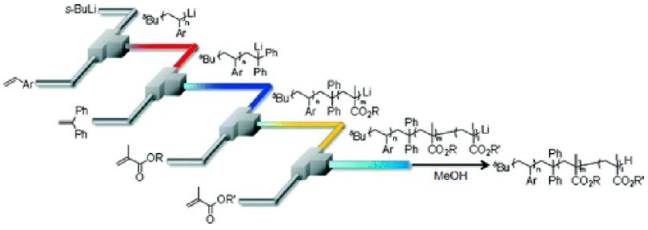


Figure 16. Schematic illustration of a flow microreactor system for the preparation of triblock copolymers: living PS is end-capped with DPE prior to the initiation of two alkyl methacrylate polymerizations in continuous flow.[138]

Very recently, a semicontinuous approach to amphiphilic block copolymers with an addressable amine functionality at the block junction was accomplished.[103] The first step was the continuous polymerization of styrene in a microstructured reactor with subsequent quantitative end-capping by *N,N*-dibenzylaminoglycidol (DBAG). Reaction of the living chain end with the highly strained epoxide ring yields a terminal hydroxyl group. In a second reaction step, the hydroxyl functionalities were utilized to initiate the oxyanionic ring-opening polymerization of ethylene oxide (EO), generating PS−PEO block copolymers with a protected amine group at the block interface. The amine functionality was released by hydrogenolysis, and addressability was proven by dye-labeling.

Another semicontinuous approach was described by Wu et al.[135] In a three-input CRP chip, the controlled radical polymerization (ATRP) of HPMA was started with a PEO macroinitiator (PEO-Br, M_n = 2900 g mol^{-1}). When applying constant concentration of all reagents, lower flow rates (240 μL h^{-1}) resulted in higher conversion (≤68%) due to the increased reaction time (188 min). Thus, the block length of P(HPMA) can be adjusted via the flow rate. Variation of the flow rate ratio of monomer and initiator represents an additional method to control the degree of polymerization. Maintaining a constant total flow rate (450 μL h^{-1}, reaction time 100 min) a decreasing initiator concentration leads not only to higher molecular weights but also to lower conversion. Quantitative initiation was confirmed by SEC analysis by the disappearance of the macroinitiator signals. Both methods afforded well-defined polymers (M_n = 5000−13 000 g mol^{-1}) with narrow molecular weight distributions (M_w/M_n = 1.18−1.30) and permit facile variation of the composition of block copolymers. The already introduced C-SATRP (vide supra) was also utilized by Zhu and co-workers for controlled radical block copolymerizations.[119] Two continuous column reactors packed with supported CuBr-HMTETA catalyst were connected in series and applied for the block copolymerization of MMA and BuMA at 80 °C. Because of a fraction of residual MMA from the first reactor, some MMA units were also incorporated in the BuMA block. However, the second block could be adjusted by the flow rate ratio of BuMA, and block copolymers with controlled molecular weight were obtained, confirming the living manner of the C-SATRP.

Capitalizing on this methodology, Du Prez, Barner-Kowollik, and co-workers developed a kinetic model for the continuous ATRP synthesis of block-like copolymers, enabling the calculation of the sequence distribution as a function of chain length in continuous flow reactors (Figure 17).[139]

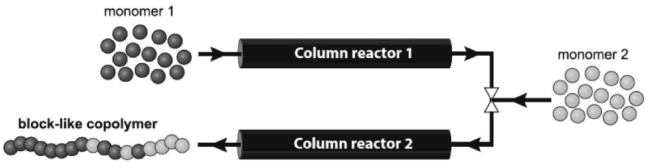


Figure 17. Synthesis of block-like copolymers by utilizing continuous supported atomic transfer radical polymerization (C-SATRP).[139]

Haddleton and co-workers utilized ATRP to synthesize block copolymers with tubular flow reactors. For the first block MMA and for the second block BuMA, benzyl methacrylate (BzMA), or BuA were used. The P(MMA)-*block*-P(BzMA) polymer showed the highest conversion (≥90%). The report describes a suitable continuous system for a facile approach to continuous ATRP processes.[121]

The nitroxide-mediated block copolymerization of butyl acrylate (BuA) and styrene was also carried out in continuous flow, and the influence of different lamellar mixing geometries on molecular weight and MWD was investigated. Two stainless steel microtube reactors at a constant pressure of 20 bar were used for the polymerization (Figure 18).

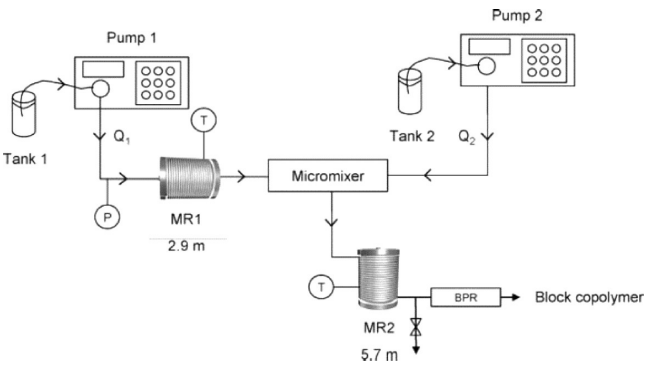


Figure 18. Schematic overview of the microreaction set up of Serra and co-workers for the nitroxide-mediated block copolymerization of BuA and styrene. The setup consists of two microtube reactors (MR1 and MR2), a micromixer, a pressure sensor P, two temperature probes T, and a back-pressure regulator (BPR).[140]

Three different geometries of multilamination micromixers with different "form factors" ($F = 1/N(W_C + W_L)$, N is the number of channels per inlet, W_C the channel width, and W_L the slit width) are used to combine the P(BuA) solution[141] with a styrene solution. Efficient mixing leads to a higher contact area between the P(BuA) and styrene phases and affords increased conversion and control of styrene polymerization in comparison to batch reactors (no significant increase of M_n, $M_w/M_n = 1.75$[141]). Efficient block formation was confirmed by comparing UV and RI signals in SEC characterization. Furthermore, by changing the flow rate ratio of styrene and P(BuA) from 9.3 to 26.5 μL min^{-1}, an increased molecular weight of the second block was achieved. The results can be helpful to optimize existing micromixers or to design other geometries for more efficient mixing.[140]

In summary, a variety of block copolymers have been successfully synthesized using microreaction technology to date. Cationic, anionic, and controlled radical polymerization techniques provide access to segmented polymer structures.

5. NONLINEAR POLYMER ARCHITECTURES

Nonlinear architectures like hyperbranched, star, or comb polymers as well as dendrimers bring about intriguing macromolecular and materials properties.[142,143] Particularly, dendrimers represent an unusual class of materials due to their monodisperse structure, precise molecular weight, and defined number of end groups. In seminal works of Vögtle, Tomalia, Hawker, Fréchet, and co-workers, the general synthesis strategy based on the divergent and convergent approach was introduced.[144−147] Dendrimers show potential for application in a variety of fields, most prominently for drug delivery, catalysis, as sensors, and for light harvesting.[148−150] However, the large scale synthesis of dendrimers is limited due to the time-consuming multistep synthesis and purification, which reduce the industrial potential of the materials. Thus, a fast and rapid synthesis using microreaction technology is favorable. In addition, the comparably low intrinsic viscosity[151,152] and increased solubility[153,154] of highly branched polymers are advantageous for transfer to dimensions in microscale.

In contrast to the preparation of linear polymers, the application of continuous flow conditions in the field of complex macromolecular architectures is still in its early stage. For example, Liu et al. prepared the first polyamide dendrons and dendrimers (second generation) by convergent approach in continuous flow, using an interdigital micromixer (Figure 19). Several advantages are obvious from the implementation of the micromixing process. On the one hand, the reaction time could be decreased from a few hours to minutes, which translates to reduced production cost of polyamide dendrimers for larger scale applications. In addition, the reaction could be carried out at convenient conditions (i.e., room temperature). Moreover, the continuously synthesized dendrimers were directly deposited on functionalized surfaces, which may be important to restrict protein adsorption or for antimicrobial coatings.

Despite lower structural perfection, hyperbranched polymers prepared in a single polymerization step show some similar properties as the perfectly branched dendrimers.[156] In particular, the synthesis of hyperbranched polyglycerol (PG) by slow glycidol monomer addition (SMA) represents a controlled access to the highly biocompatible[157] PG with randomly branched structure and other related copolymers.[158−161] Recently, our group established the ring-opening mulitbranching polymerization (ROMBP) of glycidol as a continuous flow process. The exothermic ring-opening multibranching reaction can benefit from the efficient heat and mass transfer (Figure 20).[162] Compared to classical batch methods, the experimental time and effort could be significantly reduced. Additionally, the reactive monomer glycidol can be handled in a safe reaction protocol in the microfluidic device. Residence times of 10−20 min were applied, and low molecular weights were targeted to keep the overall viscosity of the system low. Quantitative incorporation of the initiator molecule was confirmed by MALDI-ToF MS. Although the molecular weights achievable are limited to 2000 g mol^{-1} at present, this concept represents a rapid access to hyperbranched polyglycerols that can be extended to other hyperbranched materials as well.

The polycondensation of trialkoxysilane as a multifunctional monomer was also conducted in a microreactor setup (caterpillar split-recombine micromixer), and the polymer properties were investigated by changing the residence time.

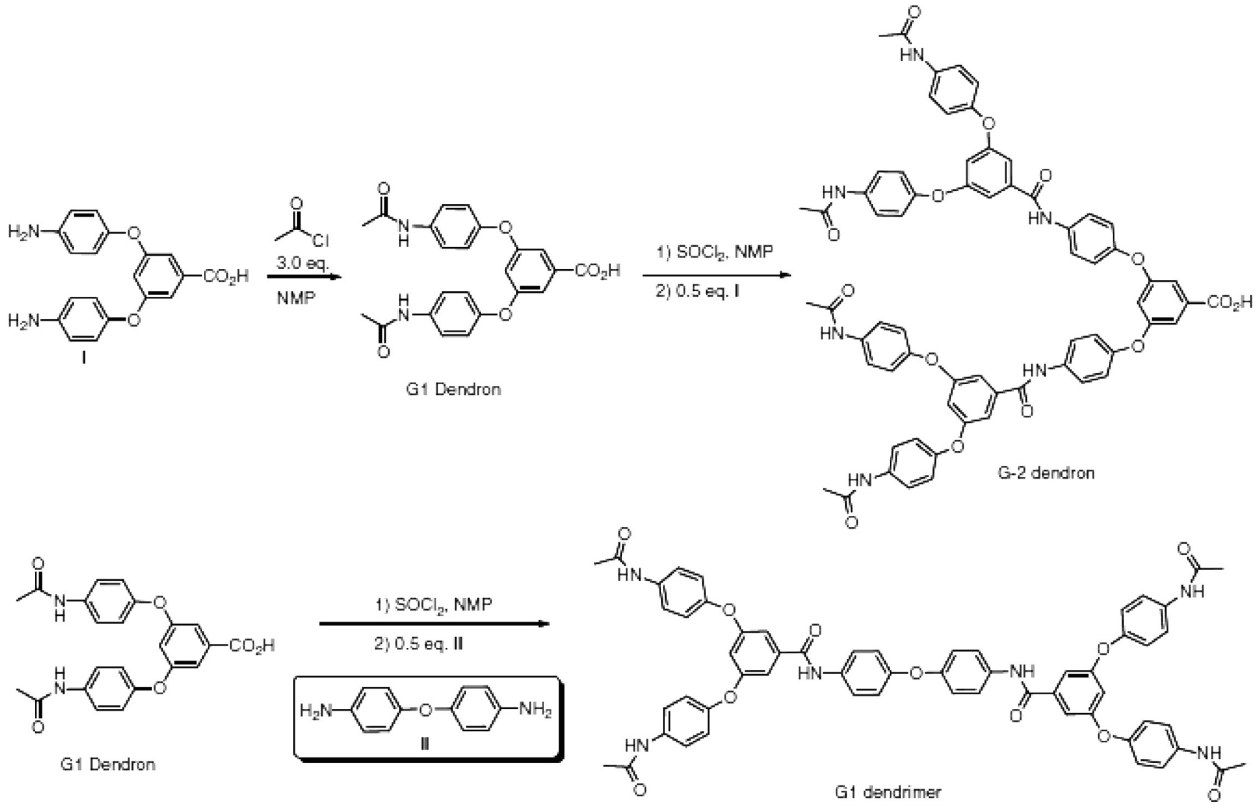


Figure 19. Synthesis of dendritic polyamide in a convergent multistep microreactor approach using a individually designed setup with an interdigital micromixer (IMM, Germany).[155]

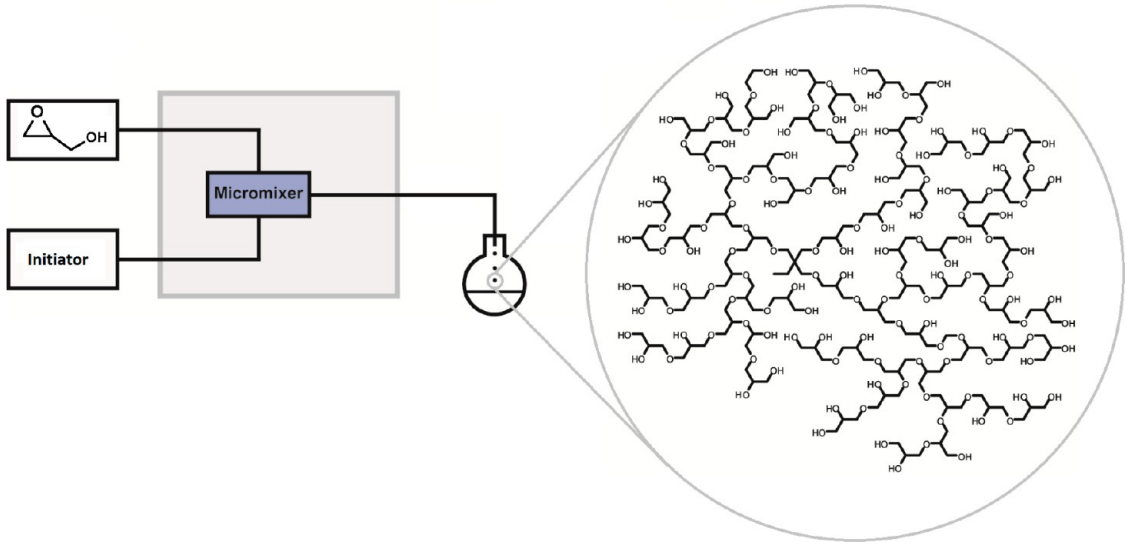


Figure 20. Synthesis of hyperbranched polyglycerol carried out in a microstructured reactor.[66]

The continuous flow synthesis of branched poly(silsesquioxane)s effected an increased yield and decreased polydispersity compared to the analogous batch process (M_n = 1900−11 000 g mol^{-1}, $M_w/M_n \leq 2$).[163]

The ATRP synthesis of branched macromolecular architectures in a tubular microreactor (i.d. 900 μm) was carried out by Bally et al.[164] The authors used the well-known self-condensing vinyl copolymerization (SCVCP) developed by Fréchet et al.[165] and adapted to ATRP by Matyjaszewski et al.[166] The branching efficiency can be optimized with the operating conditions,[167] which is important if a functionalization of the final product is desired. Branched poly(methacrylate)s were synthesized by SCVCP via ATRP in a tubular reactor with 2-(2-bromoisobutyryloxy)ethyl methacrylate (BIEM) as inimer. The feeding ratio of BIEM was varied between 0 and 5% to generate linear and different branched polymers in a controlled manner (M_w/M_n = 1.42−2.15). The authors conclude that altered initiation kinetics and the reduced diffusion pathways in the confinement of the microreactor lead to improved branching efficiency, denser polymeric architecture, and increased functionality compared to batch reactors.[168]

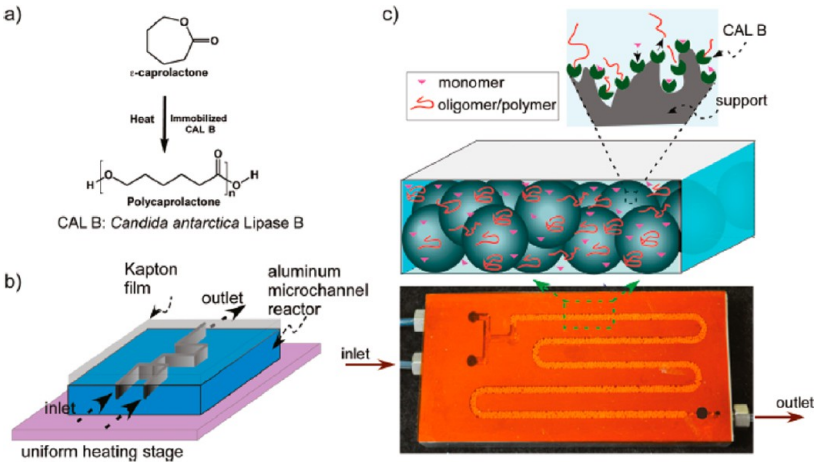


Figure 21. Enzyme-catalyzed polymerization of ε-caprolactone in continuous flow: (a) reaction scheme; (b) schematic overview of the micoreactor setup; (c) image of a reactor used in the study. The zoom-in explains the construction and the mechanism of the reaction in the microchannels.[170]

Seeberger and co-workers have demonstrated in an elegant recent work a photofunctionalization of poly(lysine) with dendrons in continuous flow. In particular, three or nine mannose- or galactose-bearing dendrons were selectively connected to a poly(L-lysine) backbone by a [2 + 2] photocycloaddition in water. The glycol-conjugated polymer was used as a platform to study carbohydrate−pathogen interactions, which show potential application as a sensitive and selective biosensor for mannose-binding *E.coli*.[169]

In summary, first reports on the preparation of nonlinear architectures in microreaction processes have been published. Dendrimers, hyperbranched, and dendronized polymers could be synthesized in continuous flow, mostly with superior molecular characteristics compared to the corresponding batch reactions. The facile scale-up and reduction of production cost in combination with promising applications like biosensor or drug delivery systems show the high potential of continuous flow synthesis in terms of such macromolecular architectures.

6. CATALYZED POLYMERIZATION

As indicated above, in the past decade several polymerizations techniques have been transferred to continuous flow systems for the preparation of a variety of polymer architectures. However, recently a novel synthesis strategy for catalyzed reactions has been developed. In this special case, the reaction tube is not only the sealed compartment, through which the reaction solution is passed, but it represents the necessary catalyst for the polymerization. Beers and co-workers developed the first solid supported enzyme-catalyzed polymerization in continuous flow (Figure 21).[170]

As a model reaction they studied the ring-opening polymerization of ε-caprolactone by using immobilized *Candida Antarctica* Lipase B (CALB) in the form of Novozyme 435 (N435) beads (diameter 400 ± 50 μm) as a biocatalyst, which is commercially available. The polymerization was carried out in the temperature range from 55 to 100 °C and compared to the corresponding reaction in a batch system. The apparent rate of reaction is at least 1 order of magnitude higher due to the special reaction conditions in the microreactor. As a consequence of the small diameter (2 mm width, 1 mm depth) of the reaction tube, the reactants are forced to be in contact with the enzyme. Because of the high surface-to-volume ratio, many active sites of the enzyme are available during the course of the reaction. The results are promising, especially with regard to future applications, like screening reactions for different catalyst systems.

In another report Beers and co-workers investigated a microchannel-confined surface-initiated polymerization technique (μSIP) to synthesize gradient polymer brush layers of poly(2-hydroxyethyl methacrylate) (PHEMA) by ATRP (Figure 22).[171] To this end the authors prepared an initiator-functionalized monolayer on the surface of a silicon microchannel. As expected, there is a linear correlation of the thickness of the polymer brushes and the distance from the inlet to the outlet (representing the length of the initiator functionalized silicon microchannel) and consequently with the reaction time.

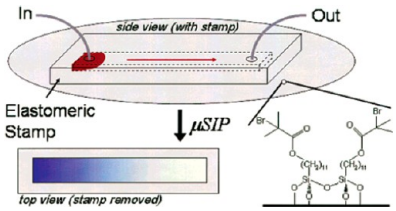


Figure 22. Syntheses of gradient polymer brush by μSIP.[171]

In a further interesting study Beers and co-workers were able to synthesize random copolymer brushes of *n*-butyl methacrylate (BMA) and 2-(*N*,*N*-dimethylamino)ethyl methacrylate (DMAEMA) with a gradient structure in a modified continuous flow setup.[172]

To date, it has not been possible to perform a living radical polymerization of vinyl chloride (VC) with an inner-sphere radical process, e.g., ATRP. The corresponding intermediate of VC (i.e., I−CH_2−CH(Cl)−X, with I = initiator and X = halide of the initiator) is sufficiently reactive toward the Cu(I) species to start the polymerization.[173] In 2001, Percec and co-workers developed a novel strategy for the polymerization of VC in an almost controlled fashion by using I−CH_2−Ph−CH_2−I/Cu(0)/2,2′-bipyridyl as initiator system at a temperature of 130 °C. The observed monomer conversion was in most cases lower than 40% due to the formation of inactive species via chain transfer to monomer. The authors obtained a linear correlation of M_n to monomer conversion and simultaneous decrease of the polydispersity ($M_w/M_n \approx 1.5$).[174] The Cu^0-

initiated polymerization presents a breakthrough in terms of VC polymerization. With this work Percec et al. established the outer-sphere single-electron-transfer living radical polymerization (SET-LRP).[175,176] A variety of monomers were investigated, and high molecular weights with narrow MWDs as well as negligible bimolecular termination at room temperature were achieved. Compared to inner-sphere radical processes, the SET-LRP shows fast reaction kinetics due to decreased activation energy.[177] The high reaction rates inspired Hutchinson and co-workers to transfer this new LRP method to a microfluidic system for the polymerization of methyl acrylate (MA) in dimethyl sulfoxide (DMSO).[178] Inexpensive and commercially available copper tubes were used as initiator, offering large surface area and hence efficient catalysis (Figure 23). Additionally, the authors demonstrated the pronounced living character of the continuous flow LRP method by further chain extension experiments.

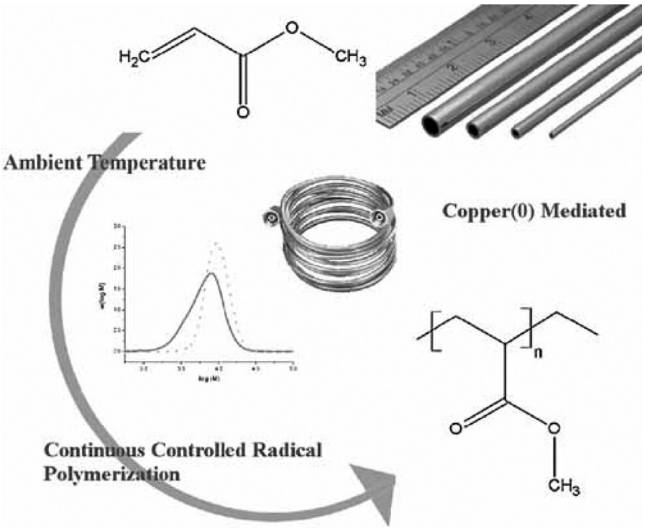


Figure 23. Polymerization of methyl acrylate in DMSO at room temperature by SET-LRP in continuous flow.[178]

Further studies in a continuous tank reactor underline the high potential of this reaction, especially in terms of possible industrial scale processes.[179]

Very recently, Hutchinson and co-workers improved the synthesis of poly(methyl acrylate) (PMA) in continuous flow.[180] Inspired by ARGET ATRP,[181] they studied the influence of ascorbic acid in SET-LRP in both batch and continuous flow systems. In conventional reactors ascorbic acid was added to the catalyst, which leads to an enormous boost of the reaction, which is, however, accompanied by a loss of control ($M_w/M_n \approx 3.3 \pm 0.2$). To avoid this undesired effect, the reaction was initiated with the copper wire, and in a second step the wire was removed and ascorbic acid was added. The mixture of existing copper species and ascorbic acid in the reaction was sufficient to establish control of the reaction. The conversion was up to 95%, and polydispersities of 1.20 were obtained.

Based on this knowledge, the ascorbic acid stimulated SET-LRP was investigated in detail by transferring the corresponding polymerization to a special designed reactor (Figure 24). After initiation of the reaction in a copper tube (i.d. 1.6 mm), ascorbic acid was added using a T-piece and the polymerization

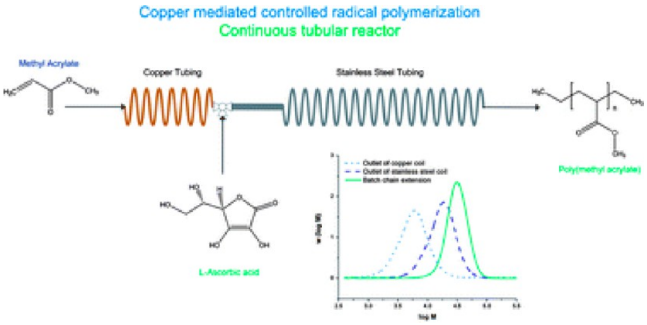


Figure 24. Copper-mediated SET-LRP of methyl acrylate in the presence of ascorbic acid using a continuous flow microreactor.[180]

proceeded in a stainless steel tube. This procedure afforded polymers with decreased copper content of less than 10^2 ppm.

Iron represents a more attractive metal for ATRP due to its lower price and lower toxicity in comparison to copper. In 2010, Wang and Matyjaszewski demonstrated the ATRP of methyl methacrylate (MMA) in an elegant work, using $FeBr_2$ as a catalyst in the absence of additional ligands.[182] Various polar solvents not only dissolve the catalyst; additionally, the solvents might operate as ligands for the catalyst and adjust the catalytic activity. This approach has recently been transferred to the SET-LRP in continuous flow by Chen et al. The polymerization of acrylonitrile (AN) using iron tubes (Fe^0) as a catalyst and 2-bromopropionitrile (BPN) as an initiator without addition of any ligands was investigated.[183] The linear correlation between the molecular weights of the resulting polymers with conversion suggests that the polar solvents like *N*-methyl-2-pyrrolidone (NMP) and *N,N*-dimethylformamide (DMF) could act as ligands in this system. In batch reactors the authors verified the living nature of the continuously synthesized PAN by subsequent block copolymerization with MMA.

7. CONCLUSION AND OUTLOOK

Although microfluidic polymerization strategies based on flow tubes have been known since the 1960s and have been employed to study the kinetics of anionic polymerization reactions, only since the 1990s microflow technology is increasingly used as a valuable reaction platform for polymer synthesis. The reported works on ionic as well as (controlled) radical polymerizations benefit from the small dimensions with excellent heat and mass transfer in such systems. Avoiding hot spots and inhomogenous stirring, microflow techniques enable to work at the kinetic limit of polymerizations. Consequently, the advantageous conditions in microreactors often lead to higher conversion and short polymerization times. Individually designed microreactors provide a hermetically sealed system, which is ideal for ionic polymerizations, given the related high sensitivity toward protic impurities. Besides the continuous synthesis of linear polymers, particular progress has also been made for the rapid preparation of nonlinear architectures. For example, pathways to dendrimers, (hyper)branched, and dendronized polymer with reduced experimental effort have been established in recent years.

Generally, continuous flow polymerization enables rapid screening and optimization of reaction parameters and the generation of (co)polymer libraries. A convincing example for the industrial application potential of micromixing strategies was presented already in the 1990s, showing that a continuous

polymerization process for preparation of homopolymers or copolymers by free-impinging-jet micromixing of monomer(s) and an initiator system can be used for the preparation of polymethacrylate homo- and block copolymers on a technical scale.[110]

Beyond the mere transfer of known polymerization reactions and their acceleration in microfluidic devices, this technique offers other intriguing features and challenges that have by no means been fully exploited to date. On the one hand, the direct integration of online characterization techniques in the microfluidic setup represents an important step.[88] On the other hand, microreactors may eventually permit to polymerize metastable monomer structures, such as e.g. vinyl alcohol, directly, if thermodynamically favored tautomerism and rearrangement reactions can be circumvented due to rapid polymerization. In addition, the possibility to heat and cool extremely rapidly offers potential for exceptional kinetic control of polymerizations.

Recently, tubular reactors have been used directly to catalyze polymerization in continuous flow. This shows first approaches to go beyond the borders of batch systems. The online implementation of postpolymerization reactions appears to be another promising prospect to reduce reaction time and purification steps compared to the conventional procedures. Although microflow processes are prone to clogging of the microchannels, current studies show the high potential of microflow processes for both academic and industrial applications in polymer science. The current challenges and the promising potential of polymer synthesis in microfluidic systems will undoubtedly inspire polymer scientists for more research in this fascinating area.

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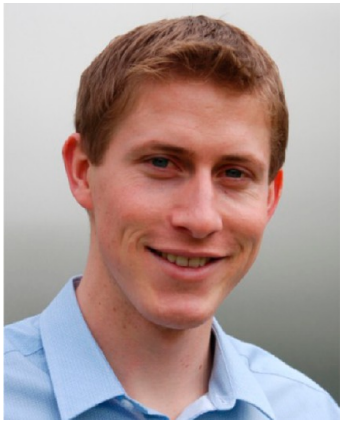
Author Contributions

The manuscript was written with contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

Biographies



Christoph Tonhauser received his diploma degree in chemistry from the Johannes Gutenberg Universität Mainz in 2009. After a temporary stay at the Polymer Science and Engineering Department, University of Massachusetts in Amherst in the group of E. Bryan Coughlin, he worked on his Ph.D. thesis in the group of Holger Frey. His research focused on the preparation of functional polymers in microstructured reactors. He held a scholarship from the Max-Planck Graduate Center (MPGC) and a fellowship of the MAINZ graduate school of excellence.

Adrian Natalello studied chemistry at the Johannes Gutenberg University Mainz and gained his diploma degree in 2011. During his temporary stay in 2009 in the group of Dr. Lian R. Hutchings, Department of Chemistry, University of Durham, his research was focused on monomer sequence control in living anionic polymerization. Currently he is working on his Ph.D. thesis in the group of Holger Frey. His work includes a variety of topics. Besides the polymerization in microstructured reactors he focuses on novel block copolymers and functional polymers. He holds a scholarship of the graduate school of excellence MAINZ.

Holger Löwe obtained his Ph.D., after some years of work in industry, in 1984 from the former Technical University Merseburg. Later he moved to the Technical University in Ilmenau/Germany. In 1991 he started his work at the IMM (Institut fuer Mikrotechnik Mainz, GmbH) and later in 1999 as a Director of R&D of this institute. He established the Chemistry/Microreaction Technology Department and a Biomicrofluidic group at IMM. Since 2005 he is Professor for Micro Process Technology at Mainz University. In 2007 he was appointed as visiting professor at the Dalian University of Technology, since 2008 as guest professor at the East China University, Shanghai, and since 2011 as professor at Zhejiang University, Hangzhou (all China). His current research activities comprise chemical synthesis, and engineering and processing in combination with aspects of microfluidics. Presently, the application of magnetic ionic liquids for C−C coupling reaction and the combination of micronanoparticles for catalytic purposes are topics of major research interest in his group.

Holger Frey studied Chemistry at the University of Freiburg. Following a stay at Carnegie-Mellon University in Pittsburgh (Kris Matyjaszewski), he obtained the Ph.D. for research on polysilane copolymers at the University of Twente (NL) in the group of Martin Moeller (1993). After his Habilitation at the University of Freiburg (1998) on polycarbosilanes, he moved to the Johannes Gutenberg University (JGU) at Mainz in 2001. Since 2003 he holds a Full Professorship in Organic and Macromolecular Chemistry at JGU. His research interests are directed at novel linear and branched functional polymer structures with unusual topology and biomedically relevant materials in general. He has published 240 peer-reviewed original contributions and reviews and is a coinventor of 13 patents.

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