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Viewpoint

Polymerizations in Continuous Flow: Recent Advances in the Synthesis of Diverse Polymeric Materials

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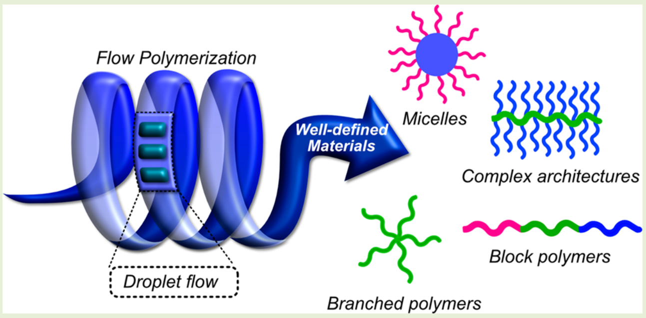
ABSTRACT: The number of reports using continuous flow technology in tubular reactors to perform precision polymerizations has grown enormously in recent years. Flow polymerizations allow highly efficient preparation of polymers exhibiting well-defined molecular characteristics, and has been applied to a slew of monomers and various polymerization mechanisms, including anionic, cationic, radical, and ring-opening. Polymerization conducted in continuous flow offers several distinct advantages, including improved efficiency, reproducibility, and enhanced safety for exothermic polymerizations using highly toxic components, high pressures, and high temperatures. The further development of this technology is thus of relevance for many industrial polymerization processes. While much progress has been demonstrated in recent years, opportunities remain for increasing the compositional and architectural complexity of polymeric materials synthesized in a continuous fashion. Extending the reactor processing principles that have heretofore been focused on optimizing homopolymerization to include multisegment block copolymers, particularly from monomers that propagate via incompatible mechanisms, represents a major challenge and coveted target for continuous flow polymerization. Likewise, the spatial and temporal control of reactivity afforded by flow chemistry has and will continue to enable the production of complex polymeric architectures. This Viewpoint offers a brief background of continuous flow polymerization focused primarily on tubular (micro)reactors and includes selected examples that are relevant to these specific developments.



Performing chemical reactions under conditions where the product is generated in a continuous manner holds many advantages. The continuous production of chemical components via reactions performed in a tubular reactor, for example, presents inherent safety improvements during highly exothermic processes. Heat dissipation is more easily realized in a tubular reactor, with high surface-to-volume ratios, than in batch reactors holding in some cases more than a ton of reactants. Additional benefits include straightforward scalability, and as such continuous flow technology is increasingly applied in the manufacturing of commercial chemicals and polymers.

The utilization of continuous synthetic processes is standard practice in several commodity chemical and polymer manufacturing arenas, but is typically limited to relatively simple processes such as the manufacturing of homopolymers and copolymers containing polyethylene terephthalate (PET) or polystyrene (PS). This is in contrast to the elegant continuous flow processes that produce complex molecules by telescoping multistep organic synthesis. The complementary development of both flow technology and synthetic methodology has enabled coupling reaction sequences that employ several orthogonal mechanistic transformations.[1,2] The pharmaceutical industry has enthusiastically adopted continuous chemistry for both scale-up and library synthesis of diverse molecular scaffolds.[3,4]

Harnessing the potential of multistep continuous flow chemistry in polymer science requires developing systems capable of implementing the sophisticated synthetic protocols required to make complex polymer compositions, architectures, and functional nanomaterials. While batch polymer synthesis (i.e., reactions performed in flasks) and successive isolation, functionalization, and polymerization sequences provides access to increasingly complex materials, the high synthetic cost can hinder translation. Increasing the complexity of polymer materials using continuous flow technology may provide commercially realistic pathways to bespoke constructs that have heretofore been considered niche materials. Furthermore, rationally designed flow polymerizations may

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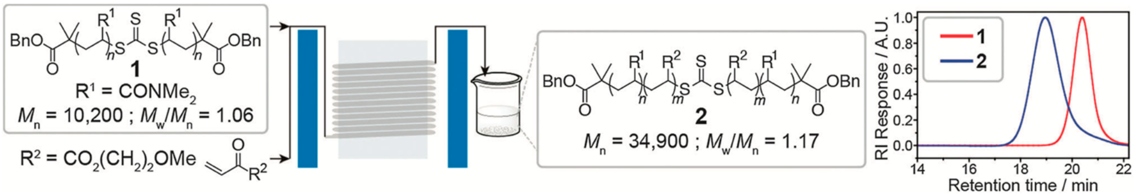


Figure 1. Macro-chain transfer agent trithiocarbonate used to prepare ABA triblock copolymers in a tubular reactor upon exposure to UV radiation. SEC traces of the starting material **1** and resulting block copolymer **2** after extension are shown. Adapted and reproduced with permission from ref 34. Copyright 2015 Royal Society of Chemistry.

enable the production of new materials with properties that are prohibitively difficult to obtain by other means.

While many reports have emerged describing the concept of flow polymerizations, there remains ample opportunity for further progress. Several recent reviews have captured the historical development of flow polymerizations and, as such, are beyond the scope of this Viewpoint.[5−13] Additionally, major advances have been reported in commercially important arenas (e.g., olefin polymerizations) related to continuous processes, but these remain outside the scope, and recent reviews offer a comprehensive coverage of the topic.[14] While much progress has been made in the development of flow technology generally in the last 50 years, the previous decade has seen a resurgence in interest owing largely to the emergence of advanced reactor engineering and (photo)-controlled polymerization techniques. We primarily focus on continuous polymerizations in tubular (micro)reactors, wherein the reaction contents are continually traversing through the reactor. The innovative aspects of recent developments are largely attributed to the application of emerging controlled polymerization within a tubular reactor. Contemporary catalytic systems can often benefit from (micro)tube reactors, providing access to materials with well-controlled molecular characteristics. Here we briefly review the current state of the art in development of the technology applied to polymerizations, and provide some perspective into where we think the field is headed. We suggest several areas where we think flow polymerization technology will evolve in the coming decades and provide an overview of proposed strategies to achieve these aspirational goals.

Block polymers via continuous flow: Block polymers are segmented macromolecules composed of at least two sequences of different repeating units that are covalently connected.[15] Polymers having immiscible blocks tend to self-organize into a variety of well-defined nanostructures.[16,17] These nanostructured materials have found use as precursors in an astounding range of potential applications, from drug transport vehicles to selective membranes for separations.[18−20] Increasingly complex nanostructures with expanded phase spaces can be readily accessed by incorporating three, four, or more different types of repeating units.[21−25]

Just as with a multistep organic synthesis, the multistep preparation of block polymers typically proceeds via individual reactions for each specific block, which is collectively energy and resource intensive owing to iterative workup and purification.[26] This is particularly true for block polymers in which mechanistically incompatible monomers are incorporated. This is often accompanied by the need for additional functionalization steps to convert end-groups into appropriate initiators for subsequent transformations.[27−29]

Block polymers from macroinitiators: Synthesizing a block polymer from a macroinitiator in flow is essentially an extension of a single-step polymerization, but additionally requires tuning reaction conditions to accommodate a starting solution with a high viscosity and different dielectric properties. Nevertheless, several notable examples described herein provide an important proof-of-concept for chain extension to meet the requirements of translating this concept to an inline, multistep polymerization of different monomers in a sequential manner.

Several controlled radical polymerization strategies have been demonstrated under continuous flow conditions, whether in microreactor-type setups or larger tubular reactors. For example, reversible addition−fragmentation transfer (RAFT) polymerizations using various thiocarbonate chain transfer agents (CTAs) have been shown to be effective for generating homopolymers with narrow molar mass distributions and targeted molar mass.[30,31] Building on this premise, block copolymers of various acrylates were produced by the sequential isolation and chain extension using a single microreactor. In this manner, up to five different blocks were incorporated, with each extension performed using macro-CTAs. While perfect end-group fidelity was not observed, each subsequent polymerization resulted in a clear increase in molar mass, suggesting the formation of pentablock terpolymers.[32]

Junkers and co-workers demonstrated the same strategy of sequential polymerizations employing an alternative mechanism of photoinduced radical polymerization mediated by a copper catalyst.[33] The sequential isolation and macroinitiator strategy for block formation was utilized, where fairly high end-group fidelity and living character were identified based on SEC.

Johnson and Chen reported the use of a photoactivated CTA in the RAFT polymerization of several functional monomers including dimethyl acrylamide and ethylene glycol methacrylate in a tubular reactor.[34] They further demonstrated the efficacy of using a symmetric macro-chain transfer agent to prepare ABA-type triblock copolymers through a two-step polymerization (Figure 1). Photoiniferter RAFT polymerization is an alternative mechanism, in which chain transfer agents are used that do not require an exogenous radical source to initiate polymerization.[35,36] Photoiniferter RAFT polymerization of *n*-BuMA and methyl acrylate (MA) was described shortly thereafter in a microreactor, with very high end-group fidelity observed.[37] This allowed for the successful synthesis of block polymers from these two monomers via the macroinitiator (i.e., macroCTA) strategy.

Guo and co-workers describe the synthesis of graft block copolymers generated via reversible deactivation radical polymerization (RDRP) mechanism employing a copper catalyst.[38] The block polymers were synthesized starting from a macroinitiator consisting of poly(vinylidene fluoride-*co*-chlorotrifluoro ethylene) [P(VDF-*co*-CTFE)], which was prepared separately in a batch process. Thus, flow polymer-

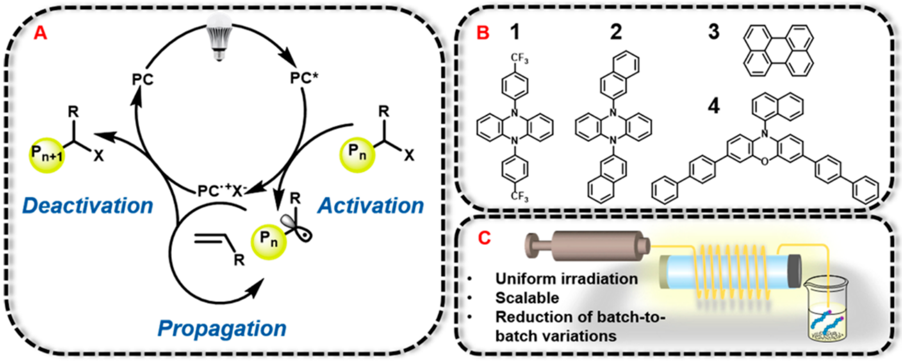
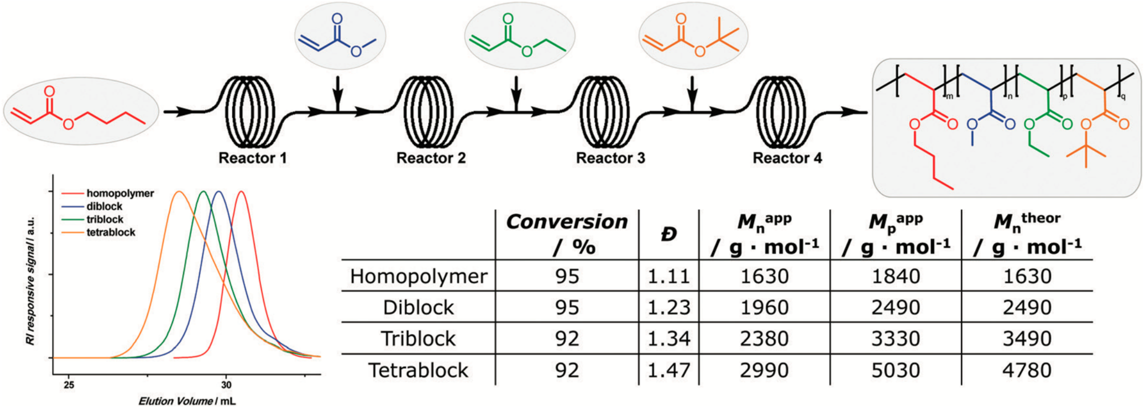


Figure 2. (A) O-ATRP conducted by a photoredox process using (B) various photoredox catalysts conducted using a (C) continuous flow polymerization in a tubular reactor. Adapted and reproduced with permission from ref 46. Copyright 2017 American Chemical Society.



	Conversion / %	Đ	M_n^{app} / g · mol^{-1}	M_p^{app} / g · mol^{-1}	M_n^{theor} / g · mol^{-1}
Homopolymer	95	1.11	1630	1840	1630
Diblock	95	1.23	1960	2490	2490
Triblock	92	1.34	2380	3330	3490
Tetrablock	92	1.47	2990	5030	4780

Figure 3. Cascade flow microreactor for the synthesis of tetrablock quarterpolymers in a single stream. Adapted and reproduced with permission from ref 52. Copyright 2017 Royal Society of Chemistry.

ization was used to polymerize MMA initiated from the chloro groups situated along the P(VDF-*co*-CTFE) backbone. Junkers and co-workers also described a copper-catalyzed, light mediated controlled polymerization of MMA in a tubular reactor demonstrating low dispersities and well-controlled molar masses.[39] They subsequently employed the isolated PMMA-Br homopolymer as a macroinitiator to initiate polymerization of methyl acrylate (MA) to form PMMA-*b*-PMA copolymers. RAFT polymerization was also recently employed to make block polymers from commercially relevant styrene and isoprene monomers to make thermoplastic elastomers.[40] This was done in a rapid photoiniferter RAFT polymerization by isolating a polyisoprene macroinitiator and subsequently chain extending with styrene.

The emergence of several highly effective organic photoredox catalysts for ATRP has opened many new opportunities in photocatalyzed polymerizations, including the increased efficiency of performing these polymerizations in tubular reactors.[41−45] Photoredox organic ATRP (O-ATRP) conducted in a continuous flow tubular reactor emerged very recently after the first mechanistic reports (Figure 2).[46] Block polymers were formed by first preparing a PMMA macroinitiator and, after isolation, performing chain extensions via polymerization of BnMA or EtMA.

Similarly, Junkers and co-workers described the coupling reaction between two preformed polymers utilizing a copper-catalyzed click reaction. Interestingly, they employed a two stage reactor, where chain end-functionalization was performed in flow before combining the two components for the final coupling reaction.[47]

Block polymers from sequential monomer polymerization: One of the first reports of controlled radical polymerization employing a microfluidic device for continuous production was demonstrated with ATRP by Beers and co-workers.[48] This was pioneering for translating a controlled radical polymerization process conventionally conducted in flasks (i.e., batch reactors) to continuous production in a flow microreactor. Soon after, the concept was extended to the synthesis of block copolymers.[49] Haddleton and co-workers showed the ATRP of MMA in flow could be regulated to reach 90% monomer conversion after 4 h at 90 °C in flow. High conversions are an essential attribute of polymerizations to form block copolymers in one pot, ensuring sharp block junctions and minimizing gradient block transitions. While unambiguous evidence for defined block architectures was missing in this report, the experiment paved the way for the further development of multistage, sequential monomer polymerization. More recently, the concept of O-ATRP using a photoredox catalyst has been shown to be effective for preparing block copolymers in a tubular reactor in series, whereby a fluorinated methacrylate and MA were sequentially polymerized.[50]

The group of Zhenping Cheng and Lifen Zhang have recently described the extension of RAFT polymerization to aqueous and sequential two-stage reactions using a tubular reactor that yield water-soluble block polymers from 3-sulfopropyl methacrylate potassium salt and poly(ethylene glycol) methyl ether methacrylate.[51] This was an important extension of the RAFT polymerization concept, demonstrating that the intermediate functional homopolymer from the first polymerization step needn't be isolated before conducting the chain extension. The Junkers' group also reported the so-called cascade RAFT polymerization to prepare multiblock copolymers in a single stream continuous microreactor system.[52] They sourced from a wide variety of acrylates and acrylamides, ultimately showing that flow polymerization was effective at incorporating up to four separate monomers to produce tetrablock quarterpolymers (Figure 3). Junkers and co-workers went on to report the well-controlled preparation of block polymers through sequential monomer addition in an photoiniferter RAFT polymerization strategy.[53]

An innovative adaptation of this series of microreactors was demonstrated by employing a looped reactor setup.[54] In this manner, a single injection port was used for each subsequent monomer addition, greatly simplifying the setup required for accessing complex molecular architectures. This allowed for the time-efficient and structurally robust production of multiblock copolymers utilizing a thiocarbonate transfer agent for RAFT polymerization. A looped flow reactor has also been applied for the living anionic polymerization of styrene and butadiene, forming multiblock copolymers, albeit with a mixture of segment numbers for a given sample.[55]

In related work, Cyrille Boyer and co-workers have developed a robust RAFT polymerization system that is mediated by photoirradiation, and further largely tolerant to the presence of otherwise detrimental components such as oxygen (i.e., air).[56,57] In the photoelectron transfer (PET-RAFT) process, they have shown several variants of organic, oxygen tolerant systems that are activated with a variety of different wavelength radiation, demonstrating remarkable versatility.[58,59] Furthermore, the light-mediated nature of the PET-RAFT system is ideal for tubular reactors and microreactors owing to the very short path length inside the tubes during irradiation and leading, consequently, to highly uniform reaction conditions.[60] This contrasts sharply with photomediated batch reactions, where light intensity decreases sharply as path length increases.[10] Boyer described tubular reactors employing PET-RAFT polymerization to prepare poly(*N*,*N*-diethylacrylamide) (PDEAm) by exposure to LEDs (Figure 4a).[61] They went on to demonstrate the formation of block polymers by adding a second monomer, *N*,*N*-dimethylacrylamide (DMAm). Because they did not reach quantitative conversion after the first block and did not isolate the product, they describe the polymers as block-like gradient copolymers. Nevertheless, this is a powerful demonstration of an oxygen tolerant system that forms segmented copolymers, albeit containing very similar monomers (Figure 4b). Most recently, they have extended the concept of oxygen tolerant PET RAFT in a series of tubular multistage reactors to elegantly demonstrate the straightforward synthesis of di- and triblock polymers.[62]

In an additional extension of this concept, Boyer and co-workers showed that the dispersity (Đ) could be finely tuned in homopolymers and block copolymers in a dual tubular reactor by introducing monomers in series.[63] They demonstrated this elegantly via photoiniferter RAFT polymerization of DMAm, *N*-acryloyl morpholine (Nam), and benzyl acrylate (BzA), accessing a variety of block compositions having various targeted MMDs. This is a well-known strategy to tailor the physical properties of block polymers.[64]

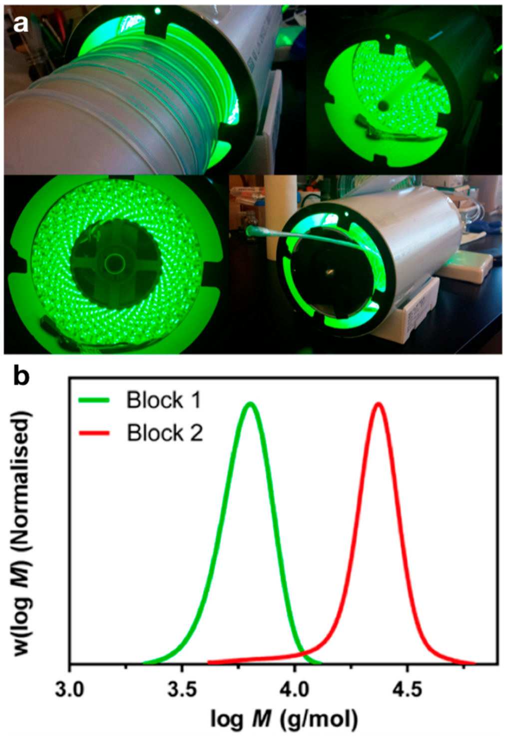


Figure 4. (a) Reactor setup showing LED illumination surrounding a tubular reactor wrapped around a column. (b) SEC chromatograms of the first and second blocks after sequential monomer introduction. Adapted and reproduced with permission from ref 61. Copyright 2016 American Chemical Society.

Anionic polymerization has also been demonstrated in a continuous flow tubular reactor, during which very fast polymerizations can be realized to generate polymers with low dispersities and well-defined molar mass.[65] This concept was also extended to sequentially polymerize styrene and 4-*t*-butylstyrene to form block copolymers.[66] This was among the earliest examples of sequential block copolymerization in a continuous flow tubular setup. Exquisitely detailed experiments showing diblock and triblock polymers via anionic polymerization were later described by Yoshida and co-workers.[67−69] These experiments represent a powerful development in this technology by combining monomers with very different reactivities. Furthermore, they showed that the livingness of the anionic chain ends could be extended and the reactivity attenuated by capping with a diphenylethylene group. This functionalization reaction was carried out within the continuous flow reactor, as one step in the multistage sequence. They also showed high end-group fidelity consistent with the corresponding chain extension as measured with size-exclusion chromatography (SEC).[68]

A similar approach was described several years later by the Noh group, in which the preparation of PS-*b*-PMMA block copolymers was demonstrated using anionic polymerization.[70] Yoshida and co-workers also went on to demonstrate multistage anionic polymerization of various fluoro-containing (meth)acrylate derivatives to form high surface energy block copolymers.[71] These results showed similar end-group fidelity and chain extension efficiencies as their previous work. Utilizing a similar reactor setup, the group of Yoshida has also employed cationic polymerization to afford block copolymers from polymerization of various vinyl ethers.[72]

They demonstrated equally impressive block integrity during the sequential polymerization of *tert*-butyl vinyl ether and *n*-butyl vinyl ether.

Ring-opening transesterification polymerization (ROTEP) of cyclic lactones has also been reported on several occasions, including for block polymers produced by sequential polymerization in a tubular reactor. Kai Guo and co-workers have reported the successful preparation of block polymers based on poly(δ-valerolactone) (PVL) and poly(ε-caprolactone) (PCL) using an organocatalyst for the ring-opening polymerization.[73] Enzymatic catalysis was later employed to prepare similar copolymers in continuous flow conditions.[74,75] The same group has also reported the synthesis of other block polymers produced from lactone monomers, including D,L-lactide (LA) and cyclic carbonates in a microreactor.[76] The evidence for chain extension and corresponding block polymer formation was primarily supported by SEC measurements. While photoinduced polymerizations have been recently described for the ROTEP of LA, the demonstration of this technology in continuous flow has not yet been reported to our knowledge.[77,78]

Very recently, the groups of Boyer, Junkers, and Zetturlund have collaborated to show that synthesis of block polymers can be combined with polymerization induced self-organization into micellar assemblies.[79,80] This represents a major step toward the fabrication of complex nanostructures in a continuous stream combined with the synthetic protocols employed to prepare the macromolecular building blocks.

Block polymer self-organization outlook: Block polymers described in the literature are often prepared with a specific nanotechnology in mind. The various technologies in which block polymers are envisioned exploit the inherent nanoscopic dimensions associated with the organized mesophases that are typically adopted. However, conventional wisdom is that the segregation strength (χN) between the constituent segments must be above a critical value for adopting these structures. The strategy for accessing well-defined morphologies typically lies in choosing components that are intrinsically immiscible, having either incompatible functional groups or surface energies. The immiscibility that arises from the contrast in atomic/molecular structure often necessitates very different conditions for synthesis. Therein lies the challenge in applying a single stream, "one-pot" system, like flow polymerization, in series to prepare block polymers with highly immiscible segments.

Without exception, the block polymers described in the examples provided in this Viewpoint have employed a single mechanism. Often, methacrylates or acrylates were the monomers of choice. Many (meth)acrylate repeating units have low intersegmental interaction parameters (χ), with the obvious exception of fluoro-derivatives. Thus, purely (meth)-acrylate block polymers rarely undergo microphase separation. An additional challenge lies in transitioning between different mechanisms within a single continuous flow reactor series in order to polymerize monomers that are mechanistically incompatible. As an additional complication, transitioning between mechanisms often necessitates postpolymerization functionalization steps after the first block is prepared. For example, the preparation of end-functional polymers via functionalization strategies receives abundant attention in the literature.[29,81−83]

Nevertheless, the technology of flow chemistry has been developed to an advanced stage for the synthesis of complex organic molecules requiring multiple synthetic steps.[1,84] As such, the barrier to applying complex conditions in what is essentially a multistep synthesis to generate block polymers with various segments can be overcome. This holds the potential to facilitate the transition of complex polymer architectures and nanotechnologies from an academic curiosity to a commercial manufacturing reality.

The influence of fluid dynamics on polymer attributes: The flow profile of fluid flowing through a tube has a significant impact on the resulting polymer structure, molar mass, composition, and molar mass distribution (MMD).[85] Recent studies have illuminated quantitative relationships that relate polymer residence time distribution (RTD) to polymer structure (Figure 5A).[86,87] RTD is defined as the distribution of time it takes for simultaneously injected fluid to fully traverse and exit a flow reactor. Fundamental studies have enabled the rational design of complex reactor geometries that provide more control over polymer characteristics. In particular, the majority of continuous flow polymerizations are conducted in the laminar flow regime, which is characterized by fluid moving through a tube with a Reynolds number less than 2000. A consequence of laminar flow is the development of a parabolic velocity profile that develops due to frictional forces between the interface of the moving fluid phase and the stationary tubing. This velocity profile leads to RTDs within the reactor where fluid toward the center of the tubing has a shorter residence time compared to fluid close to the outer edges of the tubing. Leibfarth and co-workers recently quantitated the detrimental influence of this RTD on the ability to control the molar mass, composition, and MMD during controlled polymerizations.[86] Thorough experimental data derived from various reactor geometries demonstrated that the magnitude of the RTD is highly dependent on tube diameter, residence time, and viscosity. Significantly, the RTD of a polymerization reaction was found to have a more pronounced parabolic velocity profile compared to analogous small molecule reactions due to the decreased radial diffusion caused by the higher viscosity typical of polymer solutions. In a similar study, Boyer and co-workers found that the effect of laminar flow was exacerbated for photopolymerizations because polymer near the tubing−liquid interface simultaneously experienced longer retention times, and more intense light exposure compared to liquid flowing in the center of the tubing, ultimately leading to higher viscosities and RTD amplification.[87] Schork and co-workers studied the RTD of a RAFT polymerization in miniemulsion droplets within a continuous flow tubular reactor.[88] Slippage of the dispersed droplets along the walls of the fluoropolymer tubing caused a flow profile that deviated from the expected laminar regime. This effect, in combination with the diffusive effects of each individual emulsion droplet being able to move freely throughout the aqueous continuous phase, contributes to the observed broadening of the RTD. As the aforementioned studies indicate, RTD has been identified as a crucial parameter to optimize in order to produce well-defined polymers in flow.

A variety of approaches have been pursued to minimize the influence of RTD on polymer structure (Figure 5B).[89−91] Guironnet and co-workers exploited a Taylor dispersion effect that resulted in plug-like flow of even viscous polymerizations.[92] While this worked well to precisely control the addition of discrete building blocks for bottle-brush copolymer synthesis, the approach relies on small diameter tubing and

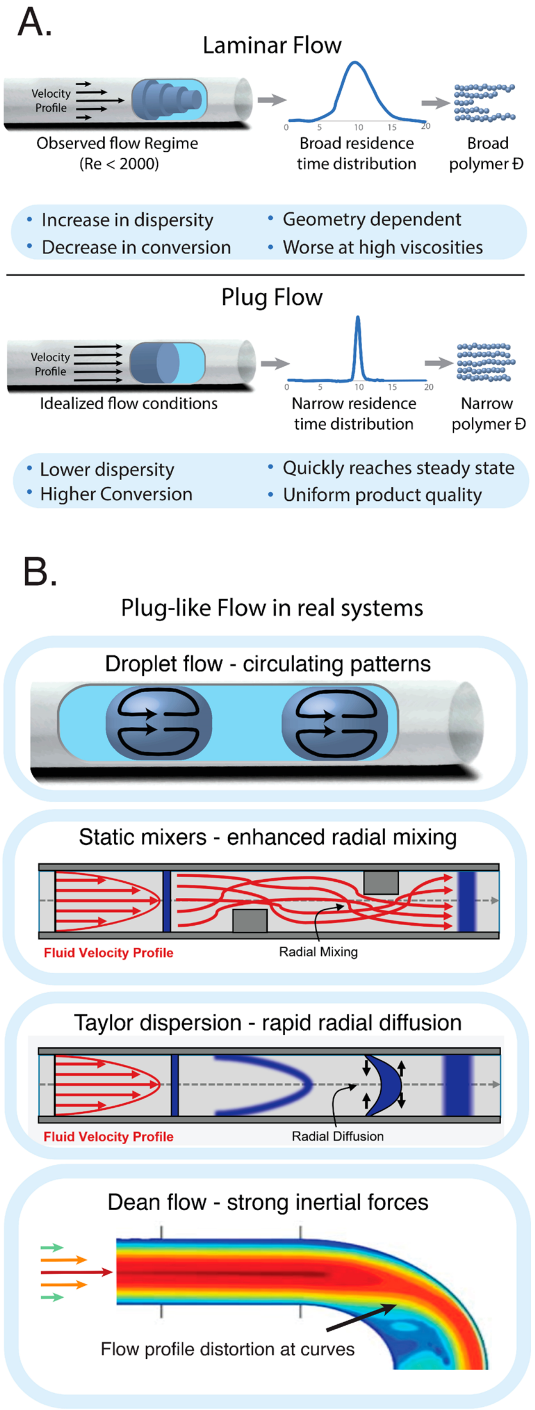


Figure 5. (A) Comparison between idealized and experimentally observed fluid flow during continuous flow polymerization; (B) Strategies pursued to achieve plug-like fluid flow in continuous flow reactors. Adapted and reproduced with permission from refs 86, 89, and 90. Copyright 2019 American Chemical Society (refs 86 and 89); Copyright 2018 Taylor and Francis (ref 90).

long reaction times. An alternative approach is the use of droplet flow, where slugs of a reaction mixture are compartmentalized by an immiscible mobile phase.[86−88,93−95] Each droplet has a small RTD, while recirculation within each droplet enhances mixing. Droplet flow has the added benefit of translating seamlessly between tubing of different inner diameter.[86] Choosing a suitable immiscible phase is crucial for droplet flow. Using an inert gas simplifies purification and can be a sustainable solution, but such a compressible fluid will change volume over different pressure and temperature regimes, thus, complicating the synthesis. An immiscible oil phase is less compressible, but the oil complicates purification, and thus, care must be taken to ensure no reagents partition into the oil phase.

Static mixers are a well precedented approach to enhance radial mixing and decrease RTD, although they typically lead to an increase in the pressure drop across the reactor.[96] The mixing efficacy with a static mixer depends strongly on the fluid flow rate, solution viscosity, and liquid miscibility. Consequently, using a static mixer in the research and development stage of a project, wherein reaction parameters may change rapidly, is not always practical. An additional limitation is the availability of small-scale static mixers for laboratory use. A recent innovation by Jensen and co-workers, however, outlined an elegant solution. The simple thermoforming of commercially available fluoropolymer tubing into a screw-like geometry using an aluminum mold was shown to improve radial mixing and substantially reduce the RTD (Figure 6).[97] An alternative to static mixers is to create Dean vortices that result from the centripetal forces of fluid flowing in tubes with a tight curvature, coil flow inversion, and oscillatory fluid motion.[98−100] Such secondary flow fields, however, are challenging to create for viscous solutions, with few examples related to polymer synthesis.

Engineering innovations enable opportunities to analyze and control polymer structure: The fundamental understanding of how to control polymerization processes in continuous flow has recently translated to advanced reactor setups that provide precise reaction parameters. This understanding has enabled the systematic variation of parameters such as reaction time, temperature, and reagent stoichiometry in situ, without stopping the flow system. This reveals opportunities to use flow as an analytical tool for understanding polymerization kinetics. As an example, Leibfarth and co-workers developed a method for determining comonomer reactivity ratios through iteratively changing monomer stoichiometry while simultaneously controlling reaction time to ensure low monomer conversion. This approach allowed the authors to rapidly generate libraries of copolymer samples and subsequently extract reactivity ratios (Figure 7). The work ultimately allowed the determination of previously unreported comonomer reactivity ratios in under 4 h.[101] In a similar fashion, a droplet flow reactor was used by Lu and Wang to quantify the kinetics of ROTEP. Using a standard 6-port 2-position injection valve, a sample loop was filled with the reaction solution before being injected through the reactor by gas delivered from an upstream mass flow controller.[93] Material waste was minimized by avoiding the need for the system to achieve a steady state between samples. Junkers and co-workers showed that microreactor technology could be used in conjunction with theoretical kinetic models to acquire insight into polymerization mechanisms. Using Predici, two different possible kinetic models were developed. Utilizing a microreactor with both rapid mixing and precise timing of initiation and quenching, high quality kinetic data was generated that distinguished which pathway the polymerization was proceeding.[102] Lastly, Baxendale and co-workers screened the influence of reaction temperature and time on the free radical polymerization of poly(acrylic acid) to rapidly screen a large reaction space. Using the data generated in flow, a kinetic model was constructed that successfully allowed the authors to

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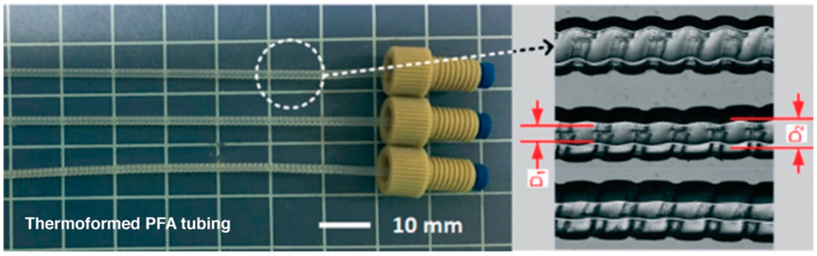

Figure 6. Static mixing devices made from the thermoforming of commercial fluoropolymer tubing. Adapted and reproduced with permission from ref 97. Copyright 2018 Royal Society of Chemistry.

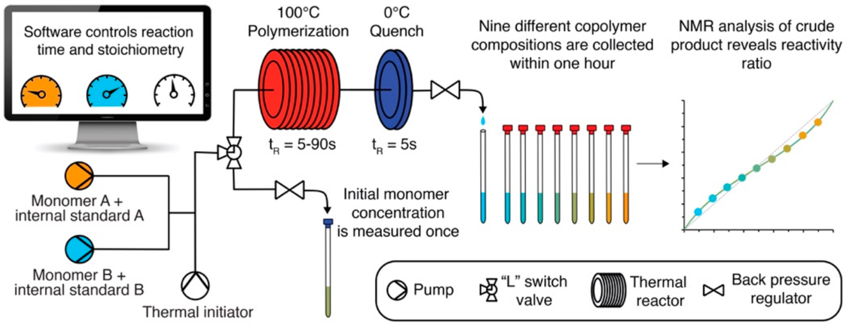

Figure 7. Flow system designed for the rapid quantification of comonomer reactivity ratios. Adapted and reproduced with permission from ref 101. Copyright 2018 Royal Society of Chemistry.

target the molar mass of poly(acrylic acid) made through an uncontrolled chain growth process.[103]

Flow systems that provide precise and reproducible control of reaction parameters also enable complementary approaches to control polymer structure compared to traditional batch synthesis. As an example, Walsh and Guironnet demonstrated how the temporal separation of two sequential, mechanistically distinct polymerizations (ROTEP and ring-opening metathesis polymerization) provided an approach toward shape-controlled bottle-brush copolymers.[89,104] Saubern and co-workers showed how slow addition of reagents in flow could be achieved using tube-in-tube reactors. The time-dependent diffusion of a comonomer out of an etched stainless-steel inner tube results in the slow addition of that comonomer into a tubular reactor at all points along the reactor. This concept facilitated the production of gradient copolymers that deviated from the reactivity ratios of the individual comonomer pairs due to the slow addition of one component from the inner tube.[105] The concept proved general to a wide variety of comonomer pairs, but the study was restricted to the evaluation of polymers made by a RAFT mechanism. While viscosity has long been a limitation to producing high molecular weight polymers in flow, Yundong and co-workers demonstrated the use of droplet flow with a fluorous immiscible phase. The fluorous oil preferentially coated and lubricated the fluoropolymer tubing walls, facilitating synthesis of polyacrylamides that exceeded a molar mass of 1 million g/mol. Inline purification methods have also provided unique opportunities to telescope multistep procedures. Baxendale and co-workers developed a membrane ultrafiltration method to continuously purify poly(acrylic acid) from a crude reaction mixture.[106] Bally et al. demonstrated another example of an inline purification utilizing nanoprecipitation to simultaneously recover a synthesized polymer and remove residual monomer and catalyst. The introduction of a nonsolvent post-polymerization resulted in a colloidal suspension of nanoparticles with a narrow particle size distribution.[107] Further innovations in the inline purification of polymeric materials will be necessary to allow the integration of a polymer synthesis with property testing.

Building from the pioneering work by Beers and co-workers, advances in reactor design have spurred the construction of flow systems for the high-throughput synthesis of diverse polymeric materials.[108] Leibfarth et al. constructed a flow system that greatly expedited the synthesis of sequence-defined polymers by semiautomated iterative exponential growth (IEG). The Flow-IEG system conducted three reactions and an in-line extraction in a single system and its increased throughput enabled a systematic study of the influence of sequence and connectivity on the thermal properties of well-defined oligomers.[109,110] In an approach that took advantage of chain-growth processes, Chen and co-workers demonstrated an automated system that used droplet flow to simultaneously avoid problems with residence time distribution and viscosity for photoinduced electron transfer RAFT polymerization. This method resulted in the synthesis of a library of 11 statistical copolymers in 11 min (Figure 8A).[95] In a truly high-throughput approach, Park and co-workers took advantage of a urea anion catalyzed ring-opening polymerization of lactones and cyclic carbonates. Controlled polymerizations were complete in residence times as low as 6 ms. Furthermore, an in situ catalyst switching strategy enabled the synthesis of well-defined block copolymers from comonomers with drastically different reactivities. Interfacing this powerful chemistry with automation facilitated the generation of a two-dimensional library of 100 diblock copolymers in a total reaction time of under 9 min (Figure 8B).[111]

Complex reactor geometries outlook: A deeper understanding of how fluid dynamic phenomenon influence the polymer structure and composition in continuous flow polymerizations has enabled the realization of powerful synthetic technology. For a high-throughput polymer synthesis,

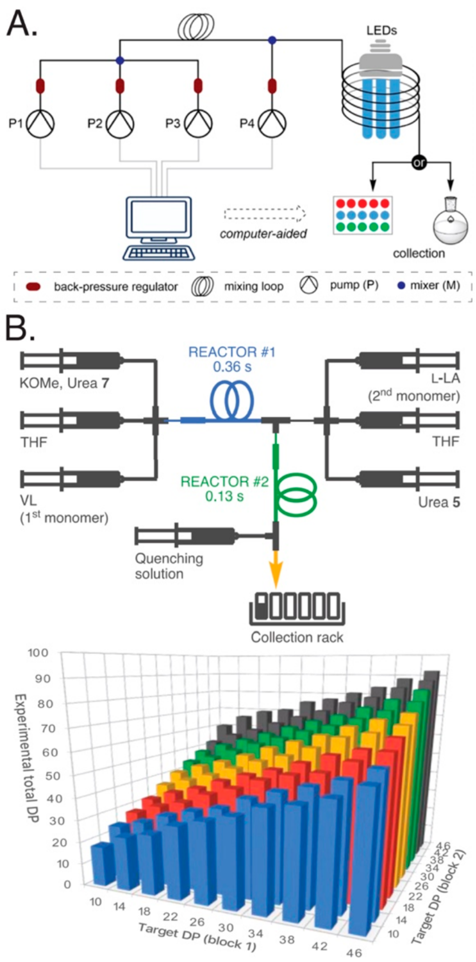

Figure 8. (A) Droplet flow system for the synthesis of copolymer libraries, where pump 4 delivers an immiscible fluid for droplet formation; (B) High-throughput block copolymer synthesis achieved using a catalyst switching strategy. Adapted and reproduced with permission from refs 95 and 111. Copyright 2019 American Chemical Society.

the ability to modulate continuous variables in situ provides an operationally simple method to rapidly synthesize a large diversity of polymer samples. While similar throughput could be, in principle, achieved through the use of robotic tools in batch, the small footprint and easily programmable nature of continuous flow systems provide a broadly accessible and user-friendly approach to generating libraries of copolymers. The ultimate value of a high-throughput synthesis, however, will only be realized if relevant analytical techniques can be performed on a commensurate time scale to synthesis. While some progress has been made in this area, further innovations are needed.[107,112,113] The integration of such analytical technology would enable seamless integration of the artificial intelligence algorithms to guide the synthetic hardware, thus, creating a closed-loop system that optimizes polymer structure toward a desired function.[114] The integration of artificial intelligence and continuous flow polymerization has the potential to create complex copolymer solutions for multivariate challenges, especially those where interdependent variables make discrete structure−property relationships difficult to discern.

In conclusion, only a tiny fraction of the range of intricately designed, multicomponent and multisegmented, architecturally diverse copolymers have been synthesized in a continuous flow setup. In some cases, the advantages of employing flow chemistry for polymerizations cannot justify the effort required to build customized synthetic setups. However, as the field progresses further, the equipment and experimental setups required to make both simple and complex polymers alike will become more readily available. Continuous flow technology may become a standard fixture in the polymer chemist's toolbox, whereby even nonexperts in chemical synthesis can make custom materials in a user-friendly and continuous process. Ultimately, a continuous-flow polymer synthesis represents an emerging and enabling synthetic tool to unlock polymeric materials with precisely controlled architectures and desirable properties for a wide variety of commercial applications. Further investigation, including a detailed analysis of fluid dynamics, for example, will expedite this process and expand our access to new and diverse polymer constructs.

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Notes

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■ REFERENCES

(1) Bedard, A. C.; Adamo, A.; Aroh, K. C.; Russell, M. G.; Bedermann, A. A.; Torosian, J.; Yue, B.; Jensen, K. F.; Jamison, T. F. Reconfigurable system for automated optimization of diverse chemical reactions. *Science* **2018**, *361*, 1220−1225.

(2) Britton, J.; Raston, C. L. Multi-step continuous-flow synthesis. *Chem. Soc. Rev.* **2017**, *46*, 1250−1271.

(3) Adamo, A.; Beingessner, R. L.; Behnam, M.; Chen, J.; Jamison, T. F.; Jensen, K. F.; Monbaliu, J. C. M.; Myerson, A. S.; Revalor, E. M.; Snead, D. R.; Stelzer, T.; Weeranoppanant, N.; Wong, S. Y.; Zhang, P. On-demand continuous-flow production of pharmaceuticals in a compact, reconfigurable system. *Science* **2016**, *352*, 61−67.

(4) Porta, R.; Benaglia, M.; Puglisi, A. Flow Chemistry: Recent Developments in the Synthesis of Pharmaceutical Products. *Org. Process Res. Dev.* **2016**, *20*, 2−25.

(5) Hu, X.; Zhu, N.; Fang, Z.; Guo, K. Continuous flow ring-opening polymerizations. *React. Chem. Eng.* **2017**, *2*, 20−26.

(6) Junkers, T. Precise Macromolecular Engineering via Continuous-Flow Synthesis Techniques. *J. Flow Chem.* **2017**, *7*, 106−110.

(7) Junkers, T. Precision Polymer Design in Microstructured Flow Reactors: Improved Control and First Upscale at Once. *Macromol. Chem. Phys.* **2017**, *218*, 1600421.

(8) Plutschack, M. B.; Pieber, B.; Gilmore, K.; Seeberger, P. H. The Hitchhiker's Guide to Flow Chemistry(II). *Chem. Rev.* **2017**, *117*, 11796−11893.

(9) Su, Y. H.; Song, Y.; Xiang, L. Continuous-Flow Microreactors for Polymer Synthesis: Engineering Principles and Applications. *Top. Curr. Chem.* **2018**, *376*, 376.

(10) Buss, B. L.; Miyake, G. M. Photoinduced Controlled Radical Polymerizations Performed in Flow: Methods, Products, and Opportunities. *Chem. Mater.* **2018**, *30*, 3931−3942.

(11) Chan, N.; Cunningham, M. F.; Hutchinson, R. A. Copper-mediated controlled radical polymerization in continuous flow processes: Synergy between polymer reaction engineering and innovative chemistry. *J. Polym. Sci., Part A: Polym. Chem.* **2013**, *51*, 3081−3096.

(12) Hu, X.; Zhu, N.; Fang, Z.; Li, Z. J.; Guo, K. Continuous flow copper-mediated reversible deactivation radical polymerizations. *Eur. Polym. J.* **2016**, *80*, 177−185.

(13) Tonhauser, C.; Natalello, A.; Löwe, H.; Frey, H. Microflow Technology in Polymer Synthesis. *Macromolecules* **2012**, *45*, 9551−9570.

(14) Stürzel, M.; Mihan, S.; Mülhaupt, R. From Multisite Polymerization Catalysis to Sustainable Materials and All-Polyolefin Composites. *Chem. Rev.* **2016**, *116*, 1398−1433.

(15) Feng, H. B.; Lu, X. Y.; Wang, W. Y.; Kang, N. G.; Mays, J. W. Block Copolymers: Synthesis, Self-Assembly, and Applications. *Polymers* **2017**, *9*, 494.

(16) Matsen, M. W.; Bates, F. S. Block copolymer microstructures in the intermediate-segregation regime. *J. Chem. Phys.* **1997**, *106*, 2436−2448.

(17) Cochran, E. W.; Garcia-Cervera, C. J.; Fredrickson, G. H. Stability of the gyroid phase in diblock copolymers at strong segregation. *Macromolecules* **2006**, *39*, 2449−2451.

(18) Jackson, E. A.; Hillmyer, M. A. Nanoporous Membranes Derived from Block Copolymers: From Drug Delivery to Water Filtration. *ACS Nano* **2010**, *4*, 3548−3553.

(19) Grimm, O.; Wendler, F.; Schacher, F. H. Micellization of Photo-Responsive Block Copolymers. *Polymers* **2017**, *9*, 396.

(20) Rosler, A.; Vandermeulen, G. W. M.; Klok, H. A. Advanced drug delivery devices via self-assembly of amphiphilic block copolymers. *Adv. Drug Delivery Rev.* **2012**, *64*, 270−279.

(21) Liu, M. J.; Li, W. H.; Qiu, F.; Shi, A. C. Stability of the Frank-Kasper sigma-phase in BABC linear tetrablock terpolymers. *Soft Matter* **2016**, *12*, 6412−6421.

(22) Chanpuriya, S.; Kim, K.; Zhang, J. W.; Lee, S.; Arora, A.; Dorfman, K. D.; Delaney, K. T.; Fredrickson, G. H.; Bates, F. S. Cornucopia of Nanoscale Ordered Phases in Sphere-Forming Tetrablock Terpolymers. *ACS Nano* **2016**, *10*, 4961−4972.

(23) Zhang, G. J.; Qiu, F.; Zhang, H. D.; Yang, Y. L.; Shi, A. C. SCFT Study of Tiling Patterns in ABC Star Terpolymers. *Macromolecules* **2010**, *43*, 2981−2989.

(24) Matsushita, Y.; Hayashida, K.; Takano, A. Jewelry Box of Morphologies with Mesoscopic Length Scales - ABC Star-shaped Terpolymers. *Macromol. Rapid Commun.* **2010**, *31*, 1579−1587.

(25) Hayashida, K.; Dotera, T.; Takano, A.; Matsushita, Y. Polymeric quasicrystal: Mesoscopic quasicrystalline tiling in ABC star polymers. *Phys. Rev. Lett.* **2007**, *98*, na.

(26) Webb, D.; Jamison, T. F. Continuous flow multi-step organic synthesis. *Chem. Sci.* **2010**, *1*, 675−680.

(27) Kubo, T.; Easterling, C. P.; Olson, R. A.; Sumerlin, B. S. Synthesis of multifunctional homopolymers via sequential post-polymerization reactions. *Polym. Chem.* **2018**, *9*, 4605−4610.

(28) Blasco, E.; Sims, M. B.; Goldmann, A. S.; Sumerlin, B. S.; Barner-Kowollik, C. 50th Anniversary Perspective: Polymer Functionalization. *Macromolecules* **2017**, *50*, 5215−5252.

(29) Gauthier, M. A.; Gibson, M. I.; Klok, H. A. Synthesis of Functional Polymers by Post-Polymerization Modification. *Angew. Chem., Int. Ed.* **2009**, *48*, 48−58.

(30) Diehl, C.; Laurino, P.; Azzouz, N.; Seeberger, P. H. Accelerated Continuous Flow RAFT Polymerization. *Macromolecules* **2010**, *43*, 10311−10314.

(31) Hornung, C. H.; Guerrero-Sanchez, C.; Brasholz, M.; Saubern, S.; Chiefari, J.; Moad, G.; Rizzardo, E.; Thang, S. H. Controlled RAFT Polymerization in a Continuous Flow Microreactor. *Org. Process Res. Dev.* **2011**, *15*, 593−601.

(32) Vandenbergh, J.; Ogawa, T. d. m.; Junkers, T. Precision synthesis of acrylate multiblock copolymers from consecutive microreactor RAFT polymerizations. *J. Polym. Sci., Part A: Polym. Chem.* **2013**, *51*, 2366−2374.

(33) Wenn, B.; Conradi, M.; Carreiras, A. D.; Haddleton, D. M.; Junkers, T. Photo-induced copper-mediated polymerization of methyl acrylate in continuous flow reactors. *Polym. Chem.* **2014**, *5*, 3053−3060.

(34) Chen, M.; Johnson, J. A. Improving photo-controlled living radical polymerization from trithiocarbonates through the use of continuous-flow techniques. *Chem. Commun.* **2015**, *51*, 6742−6745.

(35) Arrington, K. J.; Matson, J. B. Assembly of a visible light photoreactor: an inexpensive tool for bottlebrush polymer synthesis via photoiniferter polymerization. *Polym. Chem.* **2017**, *8*, 7452−7456.

(36) McKenzie, T. G.; Fu, Q.; Wong, E. H. H.; Dunstan, D. E.; Qiao, G. G. Visible Light Mediated Controlled Radical Polymerization in the Absence of Exogenous Radical Sources or Catalysts. *Macromolecules* **2015**, *48*, 3864−3872.

(37) Wenn, B.; Junkers, T. Continuous Microflow PhotoRAFT Polymerization. *Macromolecules* **2016**, *49*, 6888−6895.

(38) Zhu, N.; Hu, X.; Zhang, Y. J.; Zhang, K.; Li, Z. J.; Guo, K. Continuous flow SET-LRP in the presence of P(VDF-co-CTFE) as macroinitiator in a copper tubular reactor. *Polym. Chem.* **2016**, *7*, 474−480.

(39) Chuang, Y. M.; Wenn, B.; Gielen, S.; Ethirajan, A.; Junkers, T. Ligand switch in photoinduced copper-mediated polymerization: synthesis of methacrylate-acrylate block copolymers. *Polym. Chem.* **2015**, *6*, 6488−6497.

(40) Lauterbach, F.; Rubens, M.; Abetz, V.; Junkers, T. Ultrafast PhotoRAFT Block Copolymerization of Isoprene and Styrene Facilitated through Continuous-Flow Operation. *Angew. Chem., Int. Ed.* **2018**, *57*, 14260−14264.

(41) McCarthy, B. G.; Pearson, R. M.; Lim, C. H.; Sartor, S. M.; Damrauer, N. H.; Miyake, G. M. Structure-Property Relationships for Tailoring Phenoxazines as Reducing Photoredox Catalysts. *J. Am. Chem. Soc.* **2018**, *140*, 5088−5101.

(42) Pearson, R. M.; Lim, C. H.; McCarthy, B. G.; Musgrave, C. B.; Miyake, G. M. Organocatalyzed Atom Transfer Radical Polymerization Using N-Aryl Phenoxazines as Photoredox Catalysts. *J. Am. Chem. Soc.* **2016**, *138*, 11399−11407.

(43) Theriot, J. C.; Lim, C. H.; Yang, H.; Ryan, M. D.; Musgrave, C. B.; Miyake, G. M. Organocatalyzed atom transfer radical polymerization driven by visible light. *Science* **2016**, *352*, 1082−1086.

(44) Theriot, J. C.; McCarthy, B. G.; Lim, C. H.; Miyake, G. M. Organocatalyzed Atom Transfer Radical Polymerization: Perspectives on Catalyst Design and Performance. *Macromol. Rapid Commun.* **2017**, *38*, na.

(45) Chen, M.; Zhong, M. J.; Johnson, J. A. Light-Controlled Radical Polymerization: Mechanisms, Methods, and Applications. *Chem. Rev.* **2016**, *116*, 10167−10211.

(46) Ramsey, B. L.; Pearson, R. M.; Beck, L. R.; Miyake, G. M. Photoinduced Organocatalyzed Atom Transfer Radical Polymerization Using Continuous Flow. *Macromolecules* **2017**, *50*, 2668−2674.

(47) Vandenbergh, J.; Tura, T.; Baeten, E.; Junkers, T. Polymer End Group Modifications and Polymer Conjugations via " Click" Chemistry Employing Microreactor Technology. *J. Polym. Sci., Part A: Polym. Chem.* **2014**, *52*, 1263−1274.

(48) Wu, T.; Mei, Y.; Cabral, J. T.; Xu, C.; Beers, K. L. A new synthetic method for controlled polymerization using a microfluidic system. *J. Am. Chem. Soc.* **2004**, *126*, 9880−9881.

(49) Noda, T.; Grice, A. J.; Levere, M. E.; Haddleton, D. M. Continuous process for ATRP: Synthesis of homo and block copolymers. *Eur. Polym. J.* **2007**, *43*, 2321−2330.

(50) Gong, H.; Zhao, Y.; Shen, X.; Lin, J.; Chen, M. Organocatalyzed Photocontrolled Radical Polymerization of Semifluorinated (Meth)acrylates Driven by Visible Light. *Angew. Chem., Int. Ed.* **2018**, *57*, 333−337.

(51) Li, Z.; Chen, W.; Zhang, L.; Cheng, Z.; Zhu, X. Fast RAFT aqueous polymerization in a continuous tubular reactor: consecutive synthesis of a double hydrophilic block copolymer. *Polym. Chem.* **2015**, *6*, 5030−5035.

(52) Baeten, E.; Haven, J. J.; Junkers, T. RAFT multiblock reactor telescoping: from monomers to tetrablock copolymers in a continuous multistage reactor cascade. *Polym. Chem.* **2017**, *8*, 3815−3824.

(53) Rubens, M.; Latsrisaeng, P.; Junkers, T. Visible light-induced iniferter polymerization of methacrylates enhanced by continuous flow. *Polym. Chem.* **2017**, *8*, 6496−6505.

(54) Kuroki, A.; Martinez-Botella, I.; Hornung, C. H.; Martin, L.; Williams, E. G. L.; Locock, K. E. S.; Hartlieb, M.; Perrier, S. Looped flow RAFT polymerization for multiblock copolymer synthesis. *Polym. Chem.* **2017**, *8*, 3249−3254.

(55) Mastan, E.; He, J. Continuous Production of Multiblock Copolymers in a Loop Reactor: When Living Polymerization Meets Flow Chemistry. *Macromolecules* **2017**, *50*, 9173−9187.

(56) Xu, J.; Jung, K.; Boyer, C. Oxygen Tolerance Study of Photoinduced Electron Transfer-Reversible Addition-Fragmentation Chain Transfer (PET-RAFT) Polymerization Mediated by Ru(bpy)(3)Cl-2. *Macromolecules* **2014**, *47*, 4217−4229.

(57) Xu, J. T.; Shanmugam, S.; Duong, H. T.; Boyer, C. Organophotocatalysts for photoinduced electron transfer-reversible addition-fragmentation chain transfer (PET-RAFT) polymerization. *Polym. Chem.* **2015**, *6*, 5615−5624.

(58) Shanmugam, S.; Xu, J. T.; Boyer, C. Aqueous RAFT Photopolymerization with Oxygen Tolerance. *Macromolecules* **2016**, *49*, 9345−9357.

(59) Shanmugam, S.; Xu, J. T.; Boyer, C. Photocontrolled Living Polymerization Systems with Reversible Deactivations through Electron and Energy Transfer. *Macromol. Rapid Commun.* **2017**, *38*, 1700143.

(60) Gardiner, J.; Hornung, C. H.; Tsanaktsidis, J.; Guthrie, D. Continuous flow photo-initiated RAFT polymerisation using a tubular photochemical reactor. *Eur. Polym. J.* **2016**, *80*, 200−207.

(61) Corrigan, N.; Rosli, D.; Jones, J. W. J.; Xu, J. T.; Boyer, C. Oxygen Tolerance in Living Radical Polymerization: Investigation of Mechanism and Implementation in Continuous Flow Polymerization. *Macromolecules* **2016**, *49*, 6779−6789.

(62) Zaquen, N.; Kadir, A.; Iasa, A.; Corrigan, N.; Junkers, T.; Zetterlund, P. B.; Boyer, C. Rapid Oxygen Tolerant Aqueous RAFT Photopolymerization in Continuous Flow Reactors. *Macromolecules* **2019**, *52*, 1609−1619.

(63) Corrigan, N.; Manahan, R.; Lew, Z. T.; Yeow, J.; Xu, J.; Boyer, C. Copolymers with Controlled Molecular Weight Distributions and Compositional Gradients through Flow Polymerization. *Macromolecules* **2018**, *51*, 4553−4563.

(64) Lynd, N. A.; Meuler, A. J.; Hillmyer, M. A. Polydispersity and block copolymer self-assembly. *Prog. Polym. Sci.* **2008**, *33*, 875−893.

(65) Janata, M.; Lochmann, L.; Vlcek, P.; Dybal, J.; Muller, A. H. E. Mechanisms and Kinetics of the Anionic-Polymerization of Acrylates 0.2. Polymerization of Tert-Butyl Acrylate in a Flow Tube Reactor and Effect of Lithium-Chloride and Lithium Tert-Butoxide. *Makromol. Chem.* **1992**, *193*, 101−112.

(66) Wurm, F.; Wilms, D.; Klos, J.; Loewe, H.; Frey, H. Carbanions on tap - Living anionic polymerization in a microstructured reactor. *Macromol. Chem. Phys.* **2008**, *209*, 1106−1114.

(67) Nagaki, A.; Miyazaki, A.; Tomida, Y.; Yoshida, J.-i. Anionic polymerization of alkyl methacrylates using flow microreactor systems. *Chem. Eng. J.* **2011**, *167*, 548−555.

(68) Nagaki, A.; Miyazaki, A.; Yoshida, J.-i. Synthesis of Polystyrenes-Poly(alkyl methacrylates) Block Copolymers via Anionic Polymerization Using an Integrated Flow Microreactor System. *Macromolecules* **2010**, *43*, 8424−8429.

(69) Nagaki, A.; Takahashi, Y.; Akahori, K.; Yoshida, J.-i. Living Anionic Polymerization of tert-Butyl Acrylate in a Flow Microreactor System and Its Applications to the Synthesis of Block Copolymers. *Macromol. React. Eng.* **2012**, *6*, 467−472.

(70) Kim, J. S.; Kweon, J. O.; Lee, J. H.; Noh, S. T. Synthesis of High Molecular Weight Poly(styrene-b-methyl methacrylate) Using a Plug Flow Reactor System by Anionic Polymerization. *Macromol. Res.* **2015**, *23*, 100−110.

(71) Nagaki, A.; Akahori, K.; Takahashi, Y.; Yoshida, J. Flow Microreactor Synthesis of Fluorine-Containing Block Copolymers. *J. Flow Chem.* **2014**, *4*, 168−172.

(72) Nagaki, A.; Takumi, M.; Tani, Y.; Yoshida, J.-i. Polymerization of vinyl ethers initiated by dendritic cations using flow microreactors. *Tetrahedron* **2015**, *71*, 5973−5978.

(73) Zhu, N.; Feng, W. Y.; Hu, X.; Zhang, Z. L.; Fang, Z.; Zhang, K.; Li, Z. J.; Guo, K. Organocatalyzed continuous flow ring-opening polymerizations to homo- and block-polylactones. *Polymer* **2016**, *84*, 391−397.

(74) Zhu, N.; Huang, W. J.; Hu, X.; Liu, Y. H.; Fang, Z.; Guo, K. Enzymatic Continuous Flow Synthesis of Thiol-Terminated Poly(δ-valerolactone) and Block Copolymers. *Macromol. Rapid Commun.* **2018**, *39*, 1700807.

(75) Zhu, N.; Huang, W. J.; Hu, X.; Liu, Y. H.; Fang, Z.; Guo, K. Chemoselective polymerization platform for flow synthesis of functional polymers and nanoparticles. *Chem. Eng. J.* **2018**, *333*, 43−48.

(76) Huang, W. J.; Zhu, N.; Liu, Y. H.; Wang, J.; Zhong, J.; Sun, Q.; Sun, T.; Hu, X.; Fang, Z.; Guo, K. A novel microfluidic enzyme-organocatalysis combination strategy for ringopening copolymerizations of lactone, lactide and cyclic carbonate. *Chem. Eng. J.* **2019**, *356*, 592−597.

(77) Kuroishi, P. K.; Dove, A. P. Photoinduced ring-opening polymerisation of L-lactide via a photocaged superbase. *Chem. Commun.* **2018**, *54*, 6264−6267.

(78) Eisenreich, F.; Kathan, M.; Dallmann, A.; Ihrig, S. P.; Schwaar, T.; Schmidt, B. M.; Hecht, S. A photoswitchable catalyst system for remote-controlled (co)polymerization in situ. *Nature Catalysis* **2018**, *1*, 516−522.

(79) Zaquen, N.; Azizi, W.; Yeow, J.; Kuchel, R. P.; Junkers, T.; Zetterlund, P. B.; Boyer, C. Alcohol-based PISA in batch and flow: exploring the role of photoinitiators. *Polym. Chem.* **2019**, *10*, 2406−2414.

(80) Zaquen, N.; Zu, H. J.; Kadir, A.; Junkers, T.; Zetterlund, P. B.; Boyer, C. Scalable Aqueous Reversible Addition Fragmentation Chain Transfer Photopolymerization-Induced Self-Assembly of Acrylamides for Direct Synthesis of Polymer Nanoparticles for Potential Drug Delivery Applications. *ACS Applied Polymer Materials* **2019**, *1*, 1251−1256.

(81) Amin, S. B.; Marks, T. J. Versatile pathways for in situ polyolefin functionalization with heteroatoms: Catalytic chain transfer. *Angew. Chem., Int. Ed.* **2008**, *47*, 2006−2025.

(82) Tasdelen, M. A.; Kahveci, M. U.; Yagci, Y. Telechelic polymers by living and controlled/living polymerization methods. *Prog. Polym. Sci.* **2011**, *36*, 455−567.

(83) Anastasaki, A.; Willenbacher, J.; Fleischmann, C.; Gutekunst, W. R.; Hawker, C. J. End group modification of poly(acrylates) obtained via ATRP: a user guide. *Polym. Chem.* **2017**, *8*, 689−697.

(84) Sniady, A.; Bedore, M. W.; Jamison, T. F. One-Flow, Multistep Synthesis of Nucleosides by Bronsted Acid-Catalyzed Glycosylation. *Angew. Chem., Int. Ed.* **2011**, *50*, 2155−2158.

(85) Morsbach, J.; Muller, A. H. E.; Berger-Nicoletti, E.; Frey, H. Living Polymer Chains with Predictable Molecular Weight and Dispersity via Carbanionic Polymerization in Continuous Flow: Mixing Rate as a Key Parameter. *Macromolecules* **2016**, *49*, 5043−5050.

(86) Reis, M. H.; Varner, T. P.; Leibfarth, F. A. The Influence of Residence Time Distribution on Continuous-Flow Polymerization. *Macromolecules* **2019**, *52*, 3551−3557.

(87) Corrigan, N.; Zhernakov, L.; Hashim, M. H.; Xu, J. T.; Boyer, C. Flow mediated metal-free PET-RAFT polymerisation for upscaled and consistent polymer production. *React. Chem. Eng.* **2019**, *4*, 1216−1228.

(88) Russum, J. P.; Jones, C. W.; Schork, F. J. Impact of flow regime on polydispersity in tubular RAFT miniemulsion polymerization. *AIChE J.* **2006**, *52*, 1566−1576.

(89) Walsh, D. J.; Dutta, S.; Sing, C. E.; Guironnet, D. Engineering of Molecular Geometry in Bottlebrush Polymers. *Macromolecules* **2019**, *52*, 4847−4857.

(90) Hashemi, A.; Fischer, P. F.; Loth, F. Direct numerical simulation of transitional flow in a finite length curved pipe. *Journal of Turbulence* **2018**, *19*, 664−682.

(91) Valijam, S.; Veladi, H.; Baghban, H.; Zargari, S. High-efficiency passive micromixer using three-dimensional printed molds. *J. Micro/Nanolithogr., MEMS, MOEMS* **2018**, *17*, 1−6.

(92) Walsh, D. J.; Dutta, S.; Sing, C. E.; Guironnet, D. Engineering of Molecular Geometry in Bottlebrush Polymers. *Macromolecules* **2019**, *52*, 4847−4857.

(93) Lu, S.; Wang, K. Kinetic study of TBD catalyzed δ-valerolactone polymerization using a gas-driven droplet flow reactor. *React. Chem. Eng.* **2019**, *4*, 1189−1194.

(94) Song, J.; Zhang, S.; Wang, K.; Wang, Y. Synthesis of million molecular weight polyacrylamide with droplet flow microreactors. *J. Taiwan Inst. Chem. Eng.* **2019**, *98*, 78−84.

(95) Zhou, Y.; Gu, Y.; Jiang, K.; Chen, M. Droplet-Flow Photopolymerization Aided by Computer: Overcoming the Challenges of Viscosity and Facilitating the Generation of Copolymer Libraries. *Macromolecules* **2019**, *52*, 5611−5617.

(96) Lueth, F. G.; Pauer, W.; Moritz, H. U. Properties of smart-scaled PTFE-tubular reactors for continuous emulsion polymerization reactions. *Macromol. Symp.* **2013**, *333*, 69−79.

(97) Wang, K.; Zhang, H.; Shen, Y.; Adamo, A.; Jensen, K. F. Thermoformed fluoropolymer tubing for in-line mixing. *React. Chem. Eng.* **2018**, *3*, 707−713.

(98) Parida, D.; Serra, C. A.; Garg, D. K.; Hoarau, Y.; Bally, F.; Muller, R.; Bouquey, M. Coil flow inversion as a route to control polymerization in microreactors. *Macromolecules* **2014**, *47*, 3282−3287.

(99) Klutz, S.; Kurt, S. K.; Lobedann, M.; Kockmann, N. Narrow residence time distribution in tubular reactor concept for Reynolds number range of 10−100. *Chem. Eng. Res. Des.* **2015**, *95*, 22−33.

(100) McDonough, J. R.; Murta, S.; Law, R.; Harvey, A. P. Oscillatory fluid motion unlocks plug flow operation in helical tube reactors at lower Reynolds numbers ($Re \leq 10$). *Chem. Eng. J.* **2019**, *358*, 643−657.

(101) Reis, M. H.; Davidson, C. L. G.; Leibfarth, F. A. Continuous-flow chemistry for the determination of comonomer reactivity ratios. *Polym. Chem.* **2018**, *9*, 1728−1734.

(102) Zaquen, N.; Van Steenberge, P. H. M.; D'hooge, D. R.; Reyniers, M. F.; Marin, G. B.; Vandenbergh, J.; Lutsen, L.; Vanderzande, D. J. M.; Junkers, T. Improved Mechanistic Insights into Radical Sulfinyl Precursor MDMO-PPV Synthesis by Combining Microflow Technology and Computer Simulations. *Macromolecules* **2015**, *48*, 8294−8306.

(103) Brocken, L.; Price, P. D.; Whittaker, J.; Baxendale, I. R. Continuous flow synthesis of poly(acrylic acid): Via free radical polymerisation. *React. Chem. Eng.* **2017**, *2*, 662−668.

(104) Walsh, D. J.; Guironnet, D. Macromolecules with programmable shape, size, and chemistry. *Proc. Natl. Acad. Sci. U. S. A.* **2019**, *116*, 1538.

(105) Saubern, S.; Nguyen, X.; Nguyen, V.; Gardiner, J.; Tsanaktsidis, J.; Chiefari, J. Preparation of Forced Gradient Copolymers Using Tube-in-Tube Continuous Flow Reactors. *Macromol. React. Eng.* **2017**, *11*, 1600065.

(106) Brocken, L.; Price, P. D.; Whittaker, J.; Baxendale, I. R. Purification of poly(acrylic acid) using a membrane ultra-filtration unit in flow. *React. Chem. Eng.* **2017**, *2*, 656−661.

(107) Bally, F.; Serra, C. A.; Brochon, C.; Anton, N.; Vandamme, T.; Hadziioannou, G. A continuous-flow polymerization microprocess with online GPC and inline polymer recovery by micromixer-assisted nanoprecipitation. *Macromol. React. Eng.* **2011**, *5*, 542−547.

(108) Wu, T.; Mei, Y.; Xu, C.; Byrd, H. C. M.; Beers, K. L. Block copolymer PEO-b-PHPMA synthesis using controlled radical polymerization on a chip. *Macromol. Rapid Commun.* **2005**, *26*, 1037−1042.

(109) Leibfarth, F. A.; Johnson, J. A.; Jamison, T. F. Scalable synthesis of sequence-defined, unimolecular macromolecules by Flow-IEG. *Proc. Natl. Acad. Sci. U. S. A.* **2015**, *112*, 10617−10622.

(110) Wicker, A. C.; Leibfarth, F. A.; Jamison, T. F. Flow-IEG enables programmable thermodynamic properties in sequence-defined unimolecular macromolecules. *Polym. Chem.* **2017**, *8*, 5786−5794.

(111) Lin, B.; Hedrick, J. L.; Park, N. H.; Waymouth, R. M. Programmable High-Throughput Platform for the Rapid and Scalable Synthesis of Polyester and Polycarbonate Libraries. *J. Am. Chem. Soc.* **2019**, *141*, 8921−8927.

(112) Rubens, M.; Van Herck, J.; Junkers, T. Automated Polymer Synthesis Platform for Integrated Conversion Targeting Based on Inline Benchtop NMR. *ACS Macro Lett.* **2019**, *8*, 1437−1441.

(113) Haven, J. J.; Junkers, T. Online Monitoring of Polymerizations: Current Status. *Eur. J. Org. Chem.* **2017**, *2017*, 6474−6482.

(114) Audus, D. J.; de Pablo, J. J. Polymer Informatics: Opportunities and Challenges. *ACS Macro Lett.* **2017**, *6*, 1078−1082.