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# Continuous Flow Synthesis of Core Cross-Linked Star Polymers *via* Photo-Induced Copper Mediated Polymerization

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A convenient method to synthesize core cross-linked star polymers *via* a continuous flow photopolymerization process is developed. Photo-induced copper mediated radical polymerization was employed for arm and star synthesis. The arms of the core cross-linked star polymers are composed of poly(methyl acrylate) (with  $M_{n, arm}$  of 2600 or 4700 g·mol<sup>-1</sup>,  $\bar{D}_{arm} \approx 1.12$ ) and 1,4-butanediol diacrylate was used as core cross-linker. Flow polymerization enables rapid formation of star polymers (15–20 minutes,  $M_{w, star flow} = 170\,400$  g·mol<sup>-1</sup>, 33 arms). Further, a reactor cascade was build that combines arm synthesis and star synthesis without isolation of the intermediate product between both reactor stages. In this way star polymer is formed ( $M_{w, star} = 156\,500$  g·mol<sup>-1</sup>, 34 arms) in a one-pot fashion, yet under scalable conditions. Surface functionalized star polymers were obtained with similar molecular weights via alcohol-functional initiators. Finally, a flow reactor setup is demonstrated that allows for direct access to miktoarm star polymers. In there, two different arms are synthesized from photopolymerization in parallel and then simultaneously fed into a third reactor. The resulting miktoarm core cross-linked star polymers composed of poly(methyl acrylate) and poly(benzyl acrylate) arms ( $M_{w, star} = 189\,300$  g·mol<sup>-1</sup>, 33 arms). The reactor cascade enables rapid star polymer formation in a continuous process (within 40 minutes, when reactor conditions are stable) without intermediate purification, improved illumination and facile upscaling.

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## Introduction

Reactions performed in continuous flow provide unique opportunities for both small molecule<sup>1</sup> and macromolecular<sup>2</sup> synthesis. They are therefore a valuable addition to the chemist's toolbox of synthetic methodologies. In a continuous flow setup reagents are pumped through tubular reactors as opposed to the traditional "flask chemistry". Several advantages of flow chemistry are typically acknowledged, such as more stable reaction conditions, convenient scalability from milli- to kilogram scale, high reproducibility of processes and simplified handling of hazardous chemicals and intermediates.<sup>3,4</sup> These general advantages of flow also apply in the context of polymerizations. Reversible deactivation radical

polymerizations (RDRP) (e.g. reversible addition fragmentation chain transfer (RAFT)<sup>5</sup>, atom transfer radical polymerization (ATRP)<sup>6</sup>, single electron transfer living radical polymerization (SET-LRP)<sup>7</sup> and nitroxide mediated polymerization (NMP)<sup>8</sup> to name the most prominent allow the polymer chemist to synthesize high precision polymers in a facile manner. Yet, it has been shown that RDRP further benefits from the more stable reaction conditions achieved in flow reactors.<sup>9</sup> A comparison between both techniques for several RDRP reactions can be found in the following review.<sup>10</sup> An overall decrease in polydispersity is typically observed at otherwise same conversion when switched to a flow process, hence indicating higher precision. Also, acceleration of reactions is often observed. Especially in the case of photoflow polymerization a clear benefit arises concerning more efficient illumination of the reaction mixtures resulting in very rapid reactions compared to batch.<sup>9,11–18</sup> For example, recently the enhancing effect of continuous flow on the block copolymerization of styrene and isoprene with photoRAFT was demonstrated.<sup>19</sup> The reaction times of photoiniferter RAFT polymerization of isoprene were drastically reduced to less than 30 minutes in contrast to reaction times of 1–2 days in conventional synthesis. Aside from mere (block co)polymerization, continuous flow processing can provide polymers with compositional gradients as was recently demonstrated by Boyer and coworkers.<sup>20</sup> Reactor automation

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also opens avenues towards even more precise and on-demand synthesis of polymers with a specific desired molecular weight, as was recently demonstrated by combining flow reactors with online size exclusion chromatography (SEC).<sup>21</sup> The use of flow in this automated setup was key for its success as it adds another dimension by allowing to freely dial in any residence time by simply varying the flowrates of the reagent solution.

Although homogenous synthesis of (block co)polymers in a continuous flow system is by itself already interesting with respect to product purity, speed of synthesis and reproducibility, more advanced examples of the use of flow in a polymer context start to arise. Polymerization induced self-assembly (PISA) nanoparticles synthesis was recently translated to flow by synthesizing poly(ethylene glycol) poly(hydroxypropyl methacrylate) block copolymers using RAFT photoiniferter in aqueous conditions.<sup>22</sup> There, it was observed that morphologies could be formed with better definition, while providing upscaled nanoparticle synthesis at the same time. Wessling reported the synthesis of thermoresponsive microgels in a continuous flow system *via* precipitation polymerization. The system was shown to be highly reproducible and allowed for easily tunable sizes of the produced microgels.<sup>23</sup> Their setup allowed for convenient regulation of reagent concentrations as well as temperature which would ensure on demand delivery of the desired microgel structure.

Another type of complex polymer materials are star polymers. Star polymers are structures composed of a central core from which several polymer chains radiate outwards in a star-like fashion. Due to this configuration they have a core-shell composition, yet in a highly compact three-dimensional structure. In some ways star polymers can be regarded as core cross-linked micelles. Several interesting star polymer structures can be realized (e.g. miktoarm, block copolymer and end-functionalized star polymers). Such complex macromolecules possess significantly different physicochemical properties as opposed to their linear counterparts (e.g. rheological and thermal properties).<sup>24–28</sup> This makes them very interesting for industrial applications for example as viscosity modifiers and defoamers. From an academic perspective, star polymers have, however, already matured far beyond such applications, and are used for drug/gene delivery or more recently as antimicrobial agents.<sup>29,30</sup> In this context it is noteworthy to mention that using flow-assisted technologies for pharmaceutical manufacturing is encouraged by the FDA.<sup>31</sup> Producing star polymers via a continuous process is therefore an interesting and rational avenue to explore.

While star polymer synthesis doesn't necessarily require controlled (radical) polymerization techniques, the rise of RDRP methods made these polymers more accessible and their synthesis less tedious as opposed to anionic or cationic polymerization routes requiring stringent reaction conditions. Generally, star polymers are accessible via the so-called core-first, arm-first and the grafting onto approach.<sup>32</sup> The core-first technique starts from a multifunctional initiator from which the polymerization is started.<sup>33</sup> The advantage of this approach is that number of arms of the resulting star is precisely known.

In arm-first approaches linear polymers are fused into a star shape. This is possible via a macroinitiator (MI)<sup>34–36</sup>, macromonomer<sup>37,38</sup> and self-assembly cross-linking<sup>39</sup> approach. In these approaches the number of arms is less defined, but high control over the average length per arm is given. Additionally, this method is ideal for the synthesis of miktoarm star polymers (i.e. star polymers having two or more chemically different arms, also referred to as hetero-arm star polymers).<sup>40</sup> A final approach is grafting onto, which has similarities with the arm-first approach where arms are synthesized before star formation. However, a higher control over the number of arms and the core structure is obtained since the arms are connected to pre-synthesized cores via specific coupling reactions such as copper-catalyzed azide-alkyne cycloadditions.<sup>41</sup>

Our group demonstrated the synthesis of core-first star polymers in a continuous flow process *via* photoinitiated copper mediated polymerization (photoCMP).<sup>42</sup> In here 4- and 6-arm initiators were polymerized in a microflow reactor resulting in defined star polymers. As stated earlier, the combination of photoCMP (and photochemistry overall) with flow reactors results in an increase in reaction rate and enables more convenient upscaling compared with conventional photo-batch reactions. However, as outlined above, the core-first synthesis approach limits the overall number of arms per star molecule. Additionally, the exact average length of the arms as well as its dispersity remains sometimes unclear. Exploring another route for star polymer synthesis in a continuous flow process is therefore a logical continuation. Star polymers made *via* the arm-first approach have been studied extensively for batch chemistry, more specifically the core cross-linked star (CCS) polymers. By reacting a pre-synthesized linear polymer with a difunctional monomer (e.g. diacrylate or divinyl benzene) a densely cross-linked core structure is formed from which the linear polymers (i.e. arms) project outwards. Since its synthesis for the first time *via* anionic polymerization in 1968, the field has expanded immensely.<sup>43</sup> A wide variety of interesting examples can be found in literature spanning several RDRP techniques both in a one- and two-pot procedure.<sup>36,44–48</sup>

Here, we describe for the first time a facile approach to synthesize star polymers in a completely continuous flow process starting from the basic CCS polymer building blocks (i.e. initiator, monomer and cross-linker) *via* photoCMP. The flow approach does not only allow for synthesis of the stars itself, but encompasses all necessary steps of linear polymer formation in a multireactor approach. Both miktoarm (i.e. CCS composed of two or more arm types) as well as surface functionalized star polymers (by using functional initiators) were synthesized in this cascade process in a facile and rapid manner.

## Experimental

### Synthesis of poly(methyl acrylate in flow

Linear poly(methyl acrylates (pMA) was synthesized in a continuous flow setup *via* a previous reported procedure.<sup>49</sup> Initiator EBiB (1 eq.), Cu<sup>II</sup>Br<sub>2</sub> (0.02 eq.), and Me<sub>6</sub>TREN (0.12 eq.)

were dissolved in DMSO in a 10 mL amber volumetric flask. A separate amber volumetric flask was filled with 10 mL MA monomer (40 or 80 eq.) and both were purged with N<sub>2</sub> for approximately 15 minutes. The monomer concentration for both targeted degrees of polymerization was 5.52 M. The solutions were transferred into 10 mL gastight syringes (VWR) and placed in a Chemyx Fusion 100 syringe pump. The syringes were connected to a 2 mL flow reactor (PFA tubing, Advanced Polymer Tubing GmbH, 1/16" OD, 0.75 mm ID) wrapped around a 15 W UV-light tube (Vilbour Lourmat,  $\lambda_{\text{max}}$  = 365 nm). The lamp created a reaction temperature between 50 and 55°C. A static micromixer (Upchurch Scientific) was used to mix the two reactant streams. A residence time of 20 minutes was chosen. An <sup>1</sup>H-NMR sample was taken for conversion determination. The product was dissolved in chloroform and washed 3 times with distilled water. After removing the solvent by rotary evaporation, the product was dissolved in THF and passed over a short silica column to remove any residual copper. An SEC sample was taken after rotary evaporation.

### Core cross-linked star polymer synthesis in flow

A 10 mL solution of pMA ( $M_n$  = 2600 g·mol<sup>-1</sup>,  $\bar{D}$  = 1.13), Cu<sup>II</sup>Br<sub>2</sub> and Me<sub>6</sub>TREN in DMSO was prepared. A second 10 mL solution of cross-linker BDDA and DMF in DMSO was made in a separate amber volumetric flask. (pMA : Cu<sup>II</sup>Br<sub>2</sub> : Me<sub>6</sub>TREN : BDDA : DMF = 1 : 0.02 : 0.09 : 10 : 1; [pMA] = 0.0325 M). DMF was used as internal standard for determination of the cross-linker conversion via <sup>1</sup>H NMR. When different equivalents of crosslinker to pMA were used the cross-linker concentration was kept constant and the amount of pMA was varied accordingly. Both solutions were loaded in separate 10 mL gastight syringes after purging with N<sub>2</sub> for 15 minutes and were placed in a syringe pump. The syringes were connected to a similar 2 mL flow reactor as described earlier, pictures of the used reactor can be found in the supporting information. Residence times were screened by adjusting the flow rate. Samples for SEC(-MALS) and <sup>1</sup>H-NMR were taken at different residence times (5, 10, 15, and 20 min). All samples for SEC(-MALS) were immediately quenched by diluting in THF, passing over a short silica column to remove the copper catalyst and by adding HQ.

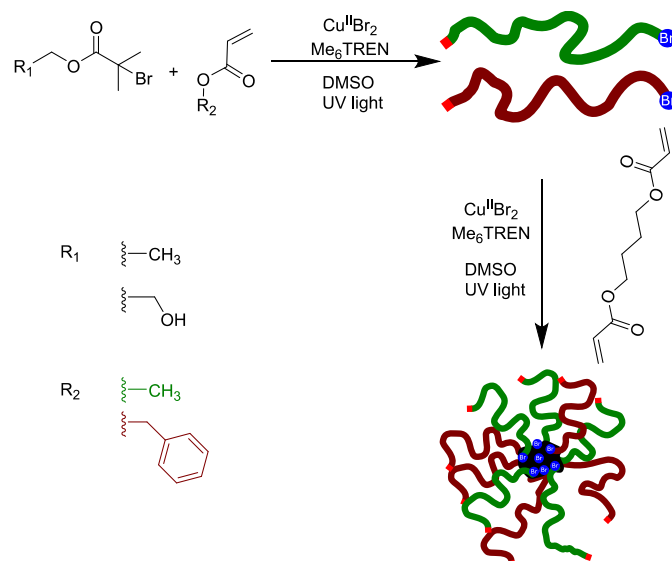
### Core cross-linked star polymer synthesis in a flow reactor cascade

One mixture of EBiB or HEBiB (alcohol functional initiator), Cu<sup>II</sup>Br<sub>2</sub> and Me<sub>6</sub>TREN dissolved in DMSO in a 10 mL amber volumetric flask and one mixture of MA in DMSO in a separate 10 mL amber volumetric flask (EBiB/HEBiB : Cu<sup>II</sup>Br<sub>2</sub> : Me<sub>6</sub>TREN : MA = 1 : 0.02 : 0.12 : 40 ; [EBiB/HEBiB] = 0.0650 M) was prepared for linear polymer synthesis. One mixture of BDDA and DMF dissolved in DMSO in a 10 mL amber volumetric flask and another mixture of Me<sub>6</sub>TREN in DMSO in a separate 10 mL amber volumetric flask were prepared (BDDA : Me<sub>6</sub>TREN : DMF = 10 : 0.09 : 1; [BDDA] = 0.650M) for the cross-linking step. After purging the solutions for 15 minutes with N<sub>2</sub> the solutions were loaded into four separate 10 mL gastight syringes. The syringes for the synthesis of linear polymer were placed in a syringe

pump and connected to a 1 mL flow reactor, similar to the ones described before. Pictures of the used reactor can be found in the supporting information. A static micromixer was used to mix the two reactant streams and a residence time of 20 minutes was targeted using a flowrate of 0.05 mL·min<sup>-1</sup>. After waiting two times the residence time, samples were collected for SEC and <sup>1</sup>H-NMR analysis. A sample for electrospray ionization mass spectrometry (ESI-MS) was also taken when HEBiB was used as initiator. Afterwards the syringes for the cross-linking step were connected to a static micromixer, connected to another static micromixer to combine the stream of synthesized linear polymer with the cross-linking mixture. This stream was then connected to a 2 mL flow reactor, similar to the ones described before. The flowrate of the cross-linking stream was 0.05 mL·min<sup>-1</sup> resulting in a total flowrate of 0.1 mL·min<sup>-1</sup> ensuring a residence time of 20 minutes in step 2. After waiting 2 times the residence time of step 1 and 2 times the residence time of step 2 (80 minutes), samples for SEC(-MALS) and <sup>1</sup>H-NMR were taken. All samples for SEC(-MALS) were immediately quenched by diluting in THF, passing over a short silica column to remove the copper catalyst and by adding HQ.

### Miktoarm core cross-linked star polymer synthesis in a flow reactor cascade

For the synthesis of miktoarm core cross-linked star polymers in a reactor cascade a similar tandem procedure was followed as described above. EBiB was used as initiator and the mixtures for the linear polymer were prepared in a similar manner targeting both the same molecular weight ( $M_n$  = 3200 g·mol<sup>-1</sup>) using MA and/or Benzyl acrylate (BnA) as monomers. For both arm types a similar  $M_n$  was targeted of 3200 g·mol<sup>-1</sup>. The syringes were connected to two separate 0.5 mL PFA flow reactors, similar to the ones described before. A residence time of 20 minutes was targeted using a flowrate of 0.025 mL·min<sup>-1</sup>. After waiting two times the residence time, samples were collected for SEC and <sup>1</sup>H-NMR analysis. The two different linear polymer streams are mixed with a static



**Fig. 1** Reaction scheme for the polymerization of (miktoarm) core cross-linked star (CCS) polymers in batch or flow.

micromixer which is then connected to a static micromixer that combines the polymer stream with the crosslinking stream. This stream was then connected to a 2 mL flow reactor. Pictures of the used reactor can be found in the supporting information. The flowrate of the cross-linking stream was  $0.05 \text{ mL} \cdot \text{min}^{-1}$  resulting in a total flowrate of  $0.1 \text{ mL} \cdot \text{min}^{-1}$  ensuring a residence time of 20 minutes. After waiting 2 times the residence time of step 1 and 2 times the residence time of step 2 (80 minutes), samples for SEC(-MALS) and  $^1\text{H}$ -NMR were taken. All samples for SEC(-MALS) were immediately quenched by diluting in THF, passing over a short silica column to remove the copper catalyst and by adding HQ.

## Results and discussion

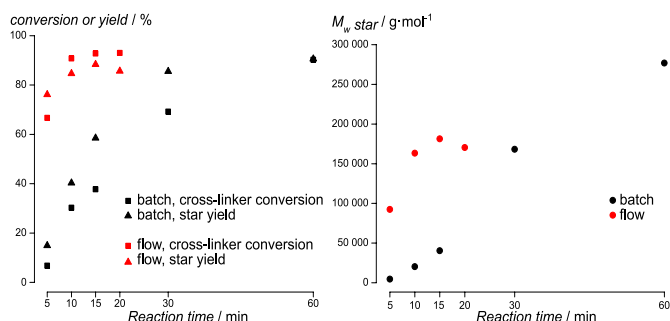
Many polymerization techniques have been used in the past to produce star polymers. Examples where light is employed to initiate polymerization are, however, rare.<sup>50–52</sup> Mc Kenzie *et al* employed photoiniferter polymerization in a batch setup to produce star polymers.<sup>36</sup> PhotoCMP as polymerization technique, as shown in Fig. 1, has so far not been used to synthesize CCS polymers. The combination of photoCMP with continuous flow processing is rather advantageous as discussed earlier (i.e. improved illumination efficiency and promise for convenient upscaling).

### Core cross-linked star polymer synthesis, comparing batch and continuous flow

To have a reference point for later flow investigations, we first synthesized CCS star polymers in a conventional batch setup. Premade linear pMA polymers ( $M_n = 2600 \text{ g} \cdot \text{mol}^{-1}$ ,  $\bar{D} = 1.13$ ) were mixed with the reagent solution ( $\text{Cu}^{\text{II}}\text{Br}_2/\text{Me}_6\text{TREN}$  and BDDA) and reacted for 60 minutes in a photo-batch reactor. Samples were taken at different timepoints to monitor the reaction and the results are shown in Fig. 2 (black dots). Afterwards, the reaction was performed in a flow setup by taking samples at increasing reaction times as well (red dots). As expected for a photo-process, CCS polymers are obtained in shorter times in flow compared to batch. However, when observing the molecular weight increase of the star polymer throughout the reaction, the flow-based procedure seems to stagnate earlier while the batch-based star polymers reach

higher molecular weights (up to  $276\,800 \text{ g} \cdot \text{mol}^{-1}$ ) and slightly higher star yields (91%). The number of arms that is achievable seems thus to be higher in batch. A potential explanation for this difference may be found in the mechanism of CCS polymer formation. Macroinitiator and crosslinker first form short block copolymers bearing pendant vinyl groups. These block copolymers can then continue to react with further crosslinker or with the pendant vinyl groups of other block copolymers. A lightly cross-linked core eventually starts to form in which more block copolymers (or even other CCS polymers if sterically accessible) can be linked. Intramolecular cross-linking becomes the main process when most block copolymers are fixed in the core of the star polymer resulting in a densely cross-linked core.<sup>53</sup> The observed halt in molecular weight increase of the star polymer in Fig. 2 could therefore be coupled to high star yields achieved in relatively short timespans (15–20 minutes), meaning that the majority of MIs has in fact already been immobilized in the core of a star polymer. Additionally, the high crosslinker conversion accompanying the high star yield also indicates that in the flow process at the same time points much less reactive double bonds are available in the highly cross-linked core compared with the batch process. Table 1 summarizes the results for CCS polymers formed in the current work. Indeed, the number of arms is decreased when going from batch ( $N_{\text{arm}} = 59$ ) to flow ( $N_{\text{arm}} = 33$ ) under otherwise identical conditions (see SI for SEC elugrams). It should be noted that for both batch and flow processes some remaining linear polymer is present, which wasn't taken into account for the number of arm calculation (see supporting information for calculation methods). Only few examples in literature exist where no residual linear polymer is retained, and the herein observed behaviour is rather typical.<sup>36,45</sup>

By modifying reaction conditions the number average amount of arms per star polymer can be tuned as shown in Table 1. When decreasing the amount of crosslinker per arm (MI:cross-linker from 1:10 to 1:5, entry 3) we observed a decrease in the number of arms (from 33 arms to 23). An increase in the number of arms was observed (from 33 arms to 39) when increasing the amount of cross-linker per MI (MI:cross-linker from 1:10 to 1:15, entry 4). It should be noted however that this condition exhibited an increased chance to block the flow reactor, hence the lower reported residence time of 15 minutes. Increasing the molecular weight of the arm (from  $M_n = 2600 \text{ g} \cdot \text{mol}^{-1}$  to  $M_n = 4700 \text{ g} \cdot \text{mol}^{-1}$ , entry 5) led to a similar molecular weight of the star ( $M_w = 182\,300 \text{ g} \cdot \text{mol}^{-1}$ ), however the number of arms was reduced (from 33 arms to 26). Diluting the total reaction mixture (from  $[\text{MI}] = 0.0325 \text{ M}$  to  $[\text{MI}] = 0.02 \text{ M}$ , entry 6) gave similar results as entry 3 in which the amount of crosslinker was reduced. Similar observations were also found in literature for varying these reaction conditions.<sup>45</sup> For all further experiments we used the conditions from entry 2 yielding stars in good yields (star yield = 86%) with a decent number of arms ( $\approx 33$ ) and no reactor blocking. As a first conclusion it can thus be stated that the flow procedure yields stars with a lower average number of arms. Nevertheless, the process provides fast and scalable synthesis of CCS polymers.



**Fig 2** Comparison of core cross-linked star (CCS) polymer formation in batch and flow. Left, cross-linker conversion and star yield through residence/reaction time in batch (black) and flow (red). Right,  $M_{w,\text{star}}$  evolution through residence/reaction time in batch (black) and flow (red). Reagent ratio of pMA :  $\text{Cu}^{\text{II}}\text{Br}_2$  :  $\text{Me}_6\text{TREN}$  : BDDA = 1 : 0.02 : 0.09 : 10 and  $[\text{pMA}] = 0.0325 \text{ M}$  was used in both processes.

**Table 1** Overview of the synthesized core cross-linked star (CCS) polymers

entry	[MI]:[CL]	$M_{n, MI}$ ( $\text{g}\cdot\text{mol}^{-1}$ )	$D_{MI}$	residence time (min)	Conv.-Cross-linker (%)	star yield <sup>b</sup> (%)	$M_{w, star}^c$ ( $\text{g}\cdot\text{mol}^{-1}$ )	$N_{arm}^d$
1	1:10 <sup>a</sup>	2600	1.13	60	90	91	276 800	59
2	1:10	2700	1.11	20	93	86	170 400	33
3	1:5	2600	1.13	20	94	85	86 130	23
4	1:15	2700	1.11	15	93	83	271 700	39
5	1:10	4700	1.11	20	91	89	182 300	26
6	1:10 <sup>e</sup>	2700	1.11	20	96	86	88 790	17
7	1:10 <sup>f</sup>	2300	1.23	20	88	85	156 500	34
8	1:10 <sup>f, g</sup>	2400	1.22	20	89	84	156 500	33
9	1:10 <sup>f, h</sup>	2300	1.25/1.27 (pMA/pMA)	20	91	89	162 800	36
10	1:10 <sup>f, i</sup>	3207 <sup>j</sup>	1.19/1.41 <sup>c</sup> (pMA/pBnA)	20	94	84	189 300	33

<sup>a</sup> Synthesized in batch. <sup>b</sup> Calculated by peak area integration of the RI profile. <sup>c</sup> Measured via SEC-MALS. <sup>d</sup> Calculated using literature known formulas, method can be found in the supporting information. <sup>e</sup> More diluted reaction mixture was employed. <sup>f</sup> Star polymers were synthesized in a reactor cascade. <sup>g</sup> Linear polymers were synthesized using an alcohol containing initiator (HEBiB). <sup>h</sup> "pseudomiktoarm" core cross-linked star polymers were synthesized with all arms composed of pMA. <sup>i</sup> Miktoarm core cross-linked star polymers were synthesized with arms composed of pMA and pBnA. <sup>j</sup> Calculated using literature known formula, method can be found in the supporting information.

### Core cross-linked star polymer synthesis in a reactor cascade

In the next step we integrated the star synthesis into a reactor cascade. In a first photoreactor, the linear precursor polymer is formed from initiator, catalyst/ligand and monomer via photoCMP. In a second stage the star is then formed by the method discussed above. The cascade is simple in design. The same light source is hereby used, and the two tubular reactors are wrapped around the light bulb at different location (see Fig S1 for photos of the reactor). Such cascade is the flow equivalent to a one-pot reaction in batch. A residence time of 20 minutes was targeted for both steps and the reaction mixture of the MI synthesis step was chosen to yield similar MI concentration entering the second reactor stage as in the experiments listed in Table 1. Besides adding the cross-linker in step two a low amount of Me<sub>6</sub>TREN (0.09 eq.) was added to ensure continued solubilization of Cu<sup>II</sup>Br<sub>2</sub> and to compensate for loss of ligand in the first polymerization stage. Fig. 3 presents the outcome of the cascade process. pMA MI was synthesized with a high monomer conversion (96%) in the first stage, in good agreement with literature. A shift and decrease of the MI

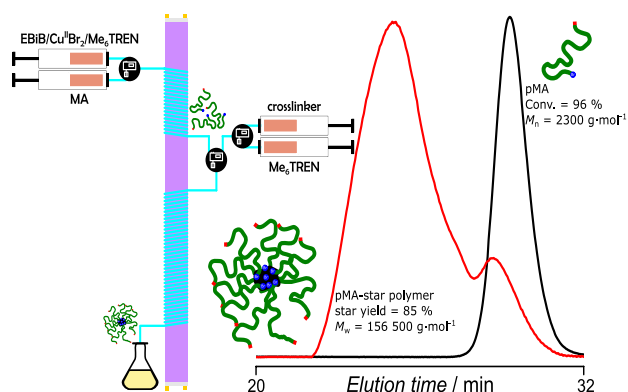
peak and the appearance of a higher molecular weight distribution indicated that the CCS polymer is formed in the consecutive step. The star polymers are formed in similar yield (85%) and possess a similar molecular weight ( $M_w = 156\,500\text{ g}\cdot\text{mol}^{-1}$ ) in the cascade compared with the uncoupled process (see Table 1, entry 2 and 7). Thus, the coupled process already enables to form star polymers in a rapid, facile and scalable manner.

Surface functionalities can be conveniently implemented as well by using an initiator with a specific functional group such as HEBiB (i.e. alcohol functionality). Alcohol surface functional CCS polymers are then formed by continuing the polymerization in a crosslinking step. These results are given in Table 1 (entry 8) and in the supporting information (Fig. S4 and S5).

### Core-crosslinked miktoarm star polymer synthesis in a reactor cascade

To further increase the complexity, we extended the reactor cascade to allow for miktoarm star polymer formation. This requires two parallel reactor stages in which different linear polymers are produced, before mixing and subsequent star formation. Such complex architectures are of interest for several applications ranging from nanostructured thin films to drug delivery.<sup>54,55</sup> Miktoarm star polymer synthesis typically requires several steps with intermediate purification and a combined flow process is thus highly attractive to access such materials in a single step directly from monomers.

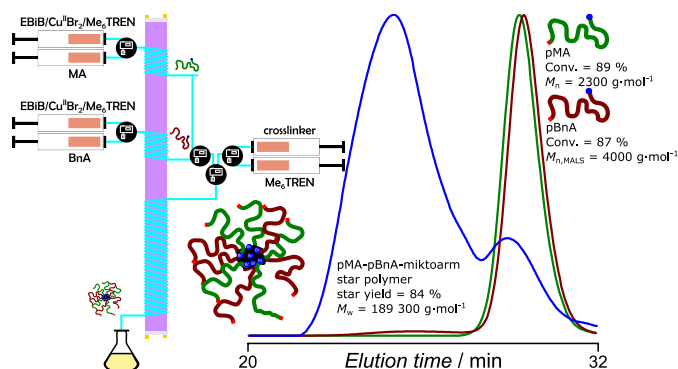
To realize such flow process, we first investigated "pseudo-miktoarm" CCS polymer formation. To this end, two identical parallel reactor stages were used in which the same monomer (MA) was polymerized. This was to prevent any potential detrimental effects such as viscosity differences that could lead to mixing issues when combining both streams. The results for these experiments are given in the supporting information (Fig. S6) and Table 1 (entry 9). Both arm mixtures showed similar monomer conversions (90%) and molecular weight distributions ( $M_n=2300\text{ g}\cdot\text{mol}^{-1}$ ). Successful star formation with similar star properties as in the previous example is observed after coupling both reactors to the cross-linking step. Based on



**Fig. 3** Core cross-linked star (CCS) polymer synthesis in a reactor cascade. Left, schematic visualisation of the reactor. Right, SEC elugram of the MI and resulting CCS polymer. Monomer conversion, star yield,  $M_{n, MI}$  and  $M_{w, CCS\text{ polymer}}$  are also given. A reaction ratio of EBiB:MA : Cu<sup>II</sup>Br<sub>2</sub> : Me<sub>6</sub>TREN : BDDA = 1 : 40 : 0.02 : 0.09 : 10 corresponding to a targeted [pMA] = 0.0325M in the second step of the coupled process.



these encouraging results, one of the prepolymer reactors was switched to benzyl acrylate (BnA) polymerization. BnA polymerizes readily under the same reaction conditions in photoCMP. A similar  $M_n$  of 3200 g·mol<sup>-1</sup> was targeted for both arms instead of a similar degree of polymerization (DP) as to minimize viscosity differences. Both arms were synthesized with similar monomer conversions (89–87%), however the molecular weight distributions differed slightly. The results are given in Fig. 4 and Table 1 (entry 10).



**Fig. 4** Miktoarm core cross-linked star (CCS) polymer synthesis in a reactor cascade. Left, schematic visualisation of the reactor. Right, SEC elugram of the MIs and resulting miktoarm CCS polymer. Monomer conversion, star yield,  $M_n$ ,  $M_w$  and  $M_w$ , CCS polymer are also given. A reaction ratio of EBIB : MA/BnA : Cu<sup>II</sup>Br<sub>2</sub> : Me<sub>6</sub>TREN : BDDA = 1 : 40/21 : 0.02 : 0.09 : 10 corresponding to a targeted [MI] = 0.0325M.

Star formation ( $M_w = 189\,300$  g·mol<sup>-1</sup>) was observed in the second step with expected star yields (84%) and cross-linker conversion (94%), underpinning successful miktoarm star polymer formation without need for intermediate purification. The molecular weight results in an average of 33 arms per miktoarm star polymer. Assuming equal reactivity of the pMA and pBzA block roughly equal amounts of arms for each polymer should be found in the star, yet a correct determination of these numbers is not trivial. Star polymers are synthesized rapidly since arm and star synthesis both take 20 minutes after reaction conditions are stabilized. Therefore, (miktoarm) stars are synthesized in 40 minutes. It should be noted that already with this fairly small scale lab-scale reactor cascade roughly 25 g of star polymer material is produced per day with constant product characteristics. A tenfold scale-up on laboratory scale is typically achieved without loss in synthesis efficiency, giving access to very substantial amounts of material. Purification of such stars to remove unreacted arms would remain, however, an issue to be solved. This is inherent to the arm-first method and cannot be completely eliminated, thus is also difficult for batch-wise synthesis of CCSs. Linear polymers can be removed from the product mixture in principle *via* fractional precipitation steps or preparative SEC.<sup>56</sup> However for upscaling purposes this is not an attractive solution. Using other polymerization techniques able to increase the star yield is therefore a more fruitful avenue to explore. Implementation of other RDRP methods to a flow-based procedure are currently underway in our laboratories.

## Conclusions

This work presents for the first time the synthesis of CCS polymers in a continuous flow process. Star polymers were synthesized *via* photoCMP within 20 minutes reaction times in yields of >80% and with an average of 30 arms per star ( $M_w = 170\,400$  g·mol<sup>-1</sup>). The arm number could be tuned from 17 to 39 by varying several reaction parameters (MI to cross-linker ratio, dilution and DP of the MI). In the next step CCS polymers were formed in a single continuous process by direct coupling of the arm and star synthesis reactors. The reactor cascade enabled rapid star polymer formation (within 40 minutes) without intermediate purification ( $M_w = 156\,500$  g·mol<sup>-1</sup>, 34 arms). By using an alcohol containing initiator the resulting star polymers possessed alcohol surface functionalities and had a similar molecular weight and number of arms compared with unfunctionalized stars. The MIs of these stars were investigated with ESI-MS proving the presence of the alcohol functionalities, prior CCS polymer synthesis. Furthermore, by coupling two parallel flow reactors that each yield distinctly different linear precursors to a third reactor – in which the cross-linker is added – the possibility to produce miktoarm CCS polymers in a facile and very direct manner ( $M_{w, star} = 189\,300$  g·mol<sup>-1</sup>, 33 arms) was demonstrated. This work provides therefore an interesting tool to continuously produce (miktoarm) CCS polymers without intermediate purification in a rapid and facile manner and with promise for convenient upscaling.

## Conflicts of interest

There are no conflicts to declare.

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