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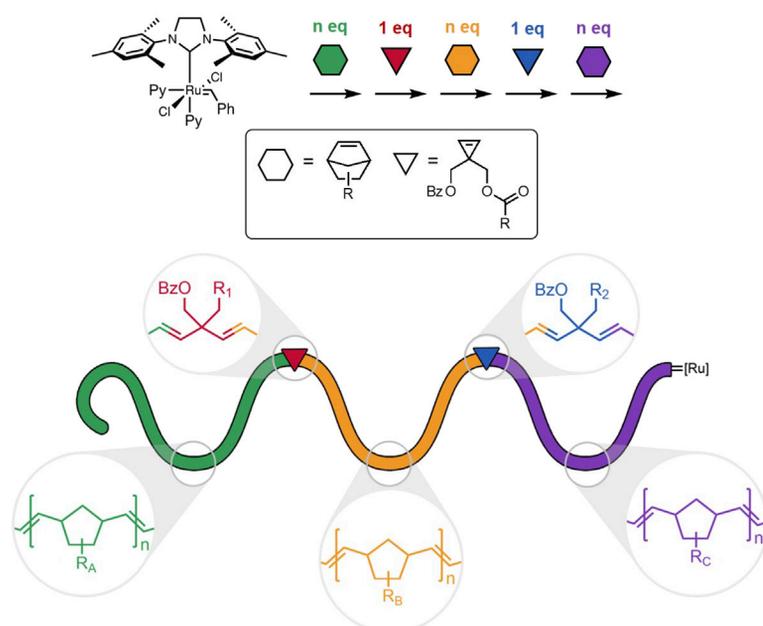
Precise Placement of Single Monomer Units in Living Ring-Opening Metathesis Polymerization

Single Addition of Cyclopropenes

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Precise Placement of Single Functional Units in a Living Polymer Chain

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HIGHLIGHTS

Single units of cyclopropenes are precisely inserted in living ROMP

Functionalities can be placed at any desired location(s) in homo or block co-polymers

Single addition of macromonomers or initiators leads to precisely branched polymers

The locations and sequence of discrete monomers along a polymer chain can affect polymer properties and behaviors but are challenging to control even in living polymerizations. Xia and co-workers report selective single additions of a type of cyclopropene to precisely place various functional moieties at desired locations in a narrow-disperse homopolymer or block copolymer chain, opening the door to precise synthesis of polymer structures and architectures and thus control of polymer properties and self-assembly.

9 INDUSTRY, INNOVATION AND INFRASTRUCTURE

12 RESPONSIBLE CONSUMPTION AND PRODUCTION

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Precise Placement of Single Monomer Units in Living Ring-Opening Metathesis Polymerization

Benjamin R. Elling,[1,2] Jessica K. Su,[1,2] John D. Feist,[1] and Yan Xia[1,3,*]

SUMMARY

Precise control of the location and sequence of monomers in a narrow-disperse polymer chain remains a significant challenge. Our strategy uses selective and quantitative single additions of cyclopropene (CPE) derivatives to precisely place functional moieties at desired locations along a polymer chain during the living ring-opening metathesis polymerization (ROMP) of norbornenes (NBEs). In order to completely reinitiate the chain end after single addition of a CPE, we lowered the reaction temperature and added a labile ligand. Under our optimized conditions, we demonstrated the exclusive placement of single moieties at pre-determined locations along a polynorbornene (PNBE) homo or block co-polymer while maintaining narrow MW distributions and controlled MWs. Some polymers were used to synthesize precisely controlled branched architectures. The ability to control the location and number of individual functional groups in a polymer chain opens exciting opportunities for the precise synthesis and manipulation of polymer structures, architectures, assemblies, and properties.

INTRODUCTION

Precise control of monomer addition sequence and placement of specific functionalities during a living polymerization remains a central challenge in polymer chemistry.[1-3] Recent examples have demonstrated that even relatively simple monomer sequences can affect polymer behaviors.[4-10] While significant advances have been made in the past decade to encode primary structures of polymers via solid-phase synthesis,[11,12] iterative synthesis,[13-16] or the use of biological templates,[17] these approaches are often limited in the length of polymers or oligomers that can be prepared and the synthetic scalability while requiring complex chromatographic purification. Periodic polymer sequences can be accessed via alternating polymerizations,[18-22] multicomponent reactions,[23-25] polymerization of short sequences,[26,27] and exponential growth methods.[28,29]

As hallmark strategies in polymer chemistry, living polymerizations allow the synthesis of narrow-disperse polymers and block co-polymers (BCPs) with excellent control over molecular weight (MW) and dispersity. However, it remains challenging to place single units of monomers at desired positions along a living polymer chain: simply adding one equivalent of a monomer results in a Poisson distribution of additions to the growing chains,[30] with some extended by more than one monomer unit and others by none. Termination also usually becomes problematic as the monomer is fully depleted. Several strategies have been reported to develop non-propagating monomers in order to synthesize sequence-regulated oligomers or polymers. Single unit monomer

The Bigger Picture

Sequence of monomer units and placement of functionalities along a polymer chain can significantly affect polymer properties and behaviors. Advances in living polymerizations have allowed us to synthesize polymers with well-controlled molecular weights and architectures, but precise single additions of monomers during a living polymerization remain a significant challenge. Here, we describe a method to achieve selective single addition of one type of monomers during the living polymerization of other types of monomers. Therefore, single units of functionalities or functional motifs, such as chromophores, side chains, dendrons, responsive motifs, and supramolecular motifs, can be placed at any desired locations along a narrow-disperse homopolymer or block copolymer chain. This unprecedented synthetic capability will allow precisely controlled synthesis of polymer architectures and fine-tuning of the polymer properties and behaviors, such as self-assembly, for numerous applications.

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insertion in a reversible addition-fragmentation chain transfer (RAFT) process has been investigated,[31,32] but only monomeric species or very short oligomers were synthesized. Sawamoto and co-workers have designed special methacrylate monomers either with a bulky substituent[14,15] or that favor intramolecular cyclization[13] to suppress homopropagation under an atom transfer radical polymerization (ATRP) mechanism. The repeated cleavage and regeneration steps at the reactive site allowed only the synthesis of oligomers and required column purification to remove byproducts in each step. Sampson and co-workers reported interesting carboxylated cyclobutenes whose electronics disfavor homoaddition via olefin metathesis. These cyclobutenes were used to synthesize alternating polymers and oligomers,[33–35] but the products exhibited relatively high dispersities. Targeting single monomer additions in a long polymer chain, Lutz and co-workers have extensively investigated the addition of single equivalents of maleimides in the controlled radical polymerizations of styrene to install narrow distributions of chosen functional groups at desired positions in a polystyrene chain.[36–40] While maleimides do not readily homopropagate, the addition of the functional maleimides was not strictly single, since remaining styrene could crossover onto the added maleimide and allow for the incorporation of additional maleimide units.[1,37,41] Recently, Xu and co-workers have prepared discrete oligomers via alternating single additions of maleimides and indene in a RAFT process.[42] Judicious selection of the donor and acceptor monomer pair was crucial to suppress multiple monomer additions and favor cross propagation[32] and column separation of oligomers was still required after each monomer addition. In general, highly selective and quantitative single addition of monomers in a long polymer chain during a living polymerization remains a significant challenge.

Living ring-opening metathesis polymerization (ROMP) has emerged as a powerful living polymerization method with high reactivity, excellent MW control, functional group tolerance, and ease of operation.[43,44] Norbornene (NBE) derivatives have been widely used as monomers for living ROMP with a distinct advantage that monomers can reach full conversion without termination, thus allowing the facile synthesis of BCPs via sequential addition of different monomers. In theory, single addition of a special non-propagating monomer during living ROMP may present exciting opportunities to precisely place such monomer units and thus their appended functionalities in a growing chain, provided that the single-addition cyclic olefin not only strictly prohibits homopropagation but also allows for fast reinitiation for other subsequent monomers. We have recently reported a class of unusual cyclopropenes (CPEs) that undergo exclusive single addition even in the presence of a large excess of these CPEs. We have used a range of such functionalized CPEs to form alternating copolymers[18] and quantitatively functionalize the ω-chain end of living polynorbornenes (PNBEs).[45]

Herein, we report our efforts to achieve the seemingly straightforward single additions of such CPEs at desired locations in a living polymer chain by overcoming a reinitiation challenge after CPE addition. Under optimized conditions, we were able to place discrete functionalities at multiple pre-determined positions along a narrow-disperse PNBE homopolymer or multiblock copolymer chain via additions of single equivalents of different CPEs (Figure 1). This strategy gives more accurate control of the location and number of various functional motifs or functionalities for post-polymerization modifications during a living polymerization than previous strategies, allowing for the synthesis of branched BCPs with a precisely controlled branching point or controlling of the distances between functional motifs, such as chromophores, as we demonstrated. This advance in polymer chemistry opens many exciting opportunities to manipulate functionalities along well-controlled polymer chains for understanding the effects of their placement and sequence on polymer

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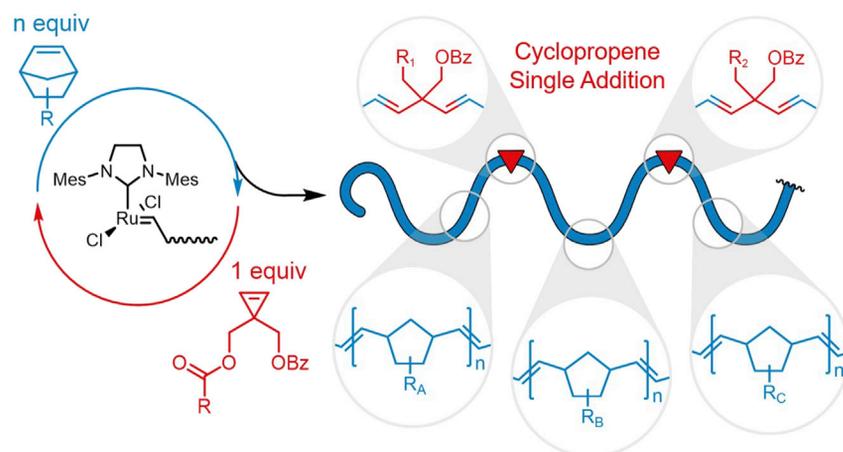
Figure 1. Precise Placement of Multiple Functionalities at Desired Locations in a Homopolymer or Block Copolymer Chain via Single Additions of Functionalized CPEs

behaviors, controlling polymer folding and assembly, as well as synthesizing polymers with more complex nonlinear architectures with precision.

RESULTS AND DISCUSSION

Reinitiation After CPE Single Addition

NBEs are predominantly used as monomers for living ROMP because of their high reactivity, absence of secondary metathesis, and simple and diverse functionalization, allowing for the synthesis of BCPs via sequential monomer additions.

To test the efficacy of reinitiating the ROMP of NBE from a CPE end-capped PNBE, we began by targeting the synthesis of a PNBE containing a single ring-opened CPE at 1/3 of the length of the chain, which is otherwise challenging to synthesize from a chain-centered initiator. Following the polymerization of 25 equiv of **NBE-iPr** using Grubbs catalyst [(H$_2$IMes)(py)$_2$(Cl)$_2$Ru = CHPh] (**G3**) in tetrahydrofuran (THF) at room temperature, we added 1 equiv of CPE **1** to **G3** (or 1.1 equiv for small-scale reactions to ensure that enough CPE was used). After 1 h, all chains were extended with a single ring-opened **1** as indicated by MALDI-TOF MS. To the ROMP solution was then added 50 equiv of **NBE-iPr**, whose ROMP from the Ru chain end occurred significantly faster than the minute amount of residual CPE, if any, in the solution. Upon full conversion of NBE, ROMP was quenched with vinyl ether. The resulting polymer, however, showed a bimodal distribution, with some remaining PNBE$_{25}$ (DP = 25) and a main narrow-disperse peak at shorter retention times which corresponded to a MW higher than expected for the targeted PNBE$_{25}$-1-PNBE$_{50}$ (Figure 2, purple trace). This observation suggested incomplete reinitiation of PNBE$_{25}$ after CPE end-capping, but the reinitiated fraction underwent fast enough reinitiation to enable controlled polymerization. By deconvoluting the gel permeation chromatography (GPC) peaks, we determined that only about half of the CPE-capped PNBE chains had reinitiated.

Our first concern with the incomplete reinitiation was that a fraction of the catalyst had become metathesis inactive or terminated during the course of CPE ring-opening. However, we deemed this unlikely as we had previously observed that the Ru complex with appended ring-opened CPE at the ω-chain end can quantitatively undergo cross metathesis with an excess of an internal olefin.[45] Further, if termination

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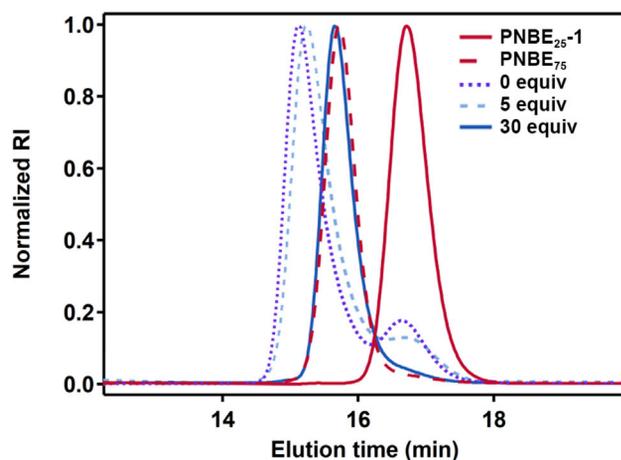
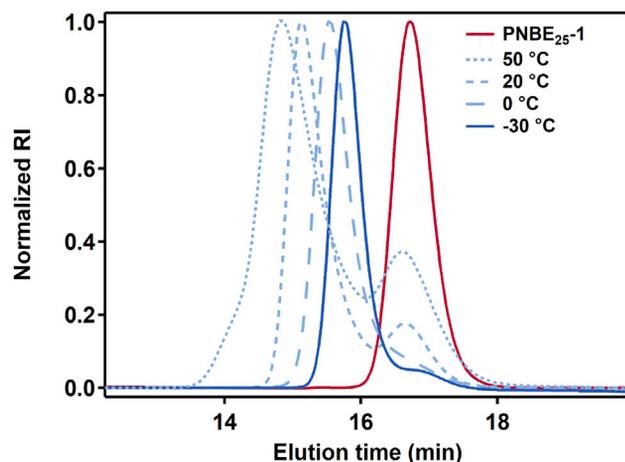**Figure 2. GPC Traces Showing Chain Extension after CPE Addition in the Presence of Varying Amounts of 3BP**

GPC traces of **PNBE-iPr** (DP = 25) with terminal ring-opened **1** (red) and final **PNBE-iPr$_{25}$-1-PNBE-iPr$_{50}$** initiated from the **PNBE-iPr** macroinitiator directly (purple) or following the addition of varying amounts of 3BP (blue dashed and solid) at room temperature. A control **PNBE-iPr** (DP = 75) synthesized by sequential addition of NBE without added CPE is included for reference (red dashed).

gradually occurred after CPE addition, the fraction of chains that are not reinitiated should increase over time. However, nearly identical GPC traces of the final polymers were observed from polymerizations reinitiated 1 or 4 h after CPE addition (Figure S1). Therefore, we believed that the incomplete reinitiation was not due to an irreversible termination reaction but rather a strong reversible coordination interaction involving the chain end Ru complex, which does not allow reinitiation.

Catalyst **G3** becomes metathesis active following ligand dissociation of pyridine to allow olefin coordination.[46] We hypothesized that when the catalyst is adjoined with a ring-opened CPE, the ester substituent on CPE may form an oxygen-chelate with Ru to result in a five-membered ring similar to that in a Grubbs-Hoveyda catalyst. The closest backbone olefin may also coordinate to the catalyst. These potential chelates of similar energies, together with the pyridine-bound resting state, may be under slow equilibrium and could have very different initiation rates where only the pyridine-bound Ru complex initiates fast.

We reasoned that a relatively labile ligand, such as 3-bromopyridine (3BP), added in excess may be able to compete with these potential intramolecular interactions and shift the equilibria toward the fast-initiating species. Thus, after ring-opening of **1** at the end of PNBE$_{25}$, either 5 or 30 equiv of 3BP were added to the solution before the second batch of **NBE-iPr** was added at room temperature. GPC analysis of the final polymers showed that adding 5 equiv of 3BP was insufficient to give complete reinitiation, but adding 30 equiv of 3BP resulted in nearly complete reinitiation to give a very narrow-disperse peak matching the expected MW (Figure 2, solid blue trace). Additionally, adding 3BP during or after the ring-opening of CPE each gave monomodal final polymers with the expected MW (Figure S2).

We hypothesized that temperature may also affect the equilibrium of different Ru species after reaction with CPE, and lower temperature may favor the species with intermolecular pyridine chelation, which initiates fast due to a smaller entropic cost. To
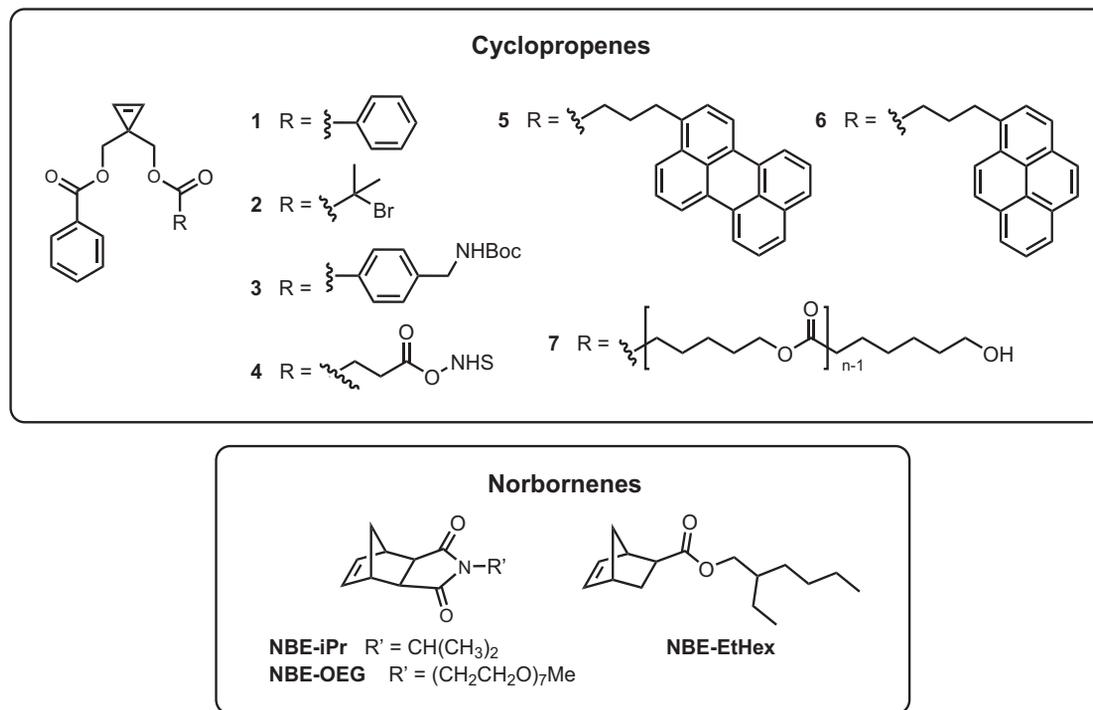
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Figure 3. GPC Traces showing Chain Extension after CPE Addition at Various Temperatures
GPC traces of **PNBE-iPr** with terminal ring-opened **1** (red) and final **PNBE-iPr** initiated off the **PNBE-iPr** macroinitiator, polymerized at 50°C, rt, 0°C, or −30°C (blue).

probe the effect of temperature on the extent of reinitiation, following CPE **1** addition to living PNBE$_{25}$, we adjusted the reaction temperature to either 50, 0, or −30°C or maintained it at room temperature for 15 min. Then, 50 equiv of **NBE-iPr** were added at each designated temperature. After an additional 30 min of being held at these temperatures, all of the reactions were brought to room temperature and quenched with vinyl ether. GPC analysis of the final polymers clearly showed that, upon decreasing the temperature, the fraction of unextended chains was significantly reduced and the peak for the extended chains moved to longer elution times, becoming closer to their theoretical MW (Figure 3), suggesting significantly improved reinitiation. Chain extension at 50°C gave the highest fraction of unextended chains and a broad dispersity of the high MW peak. These observations supported our hypothesis that lower temperatures favor the fast-initiating Ru species under equilibrium.

To gain more insight into this phenomenon, we performed ^{1}H NMR spectroscopy on the reaction of **G3** with 1 equiv of CPE. Within 40 min at room temperature, the starting sharp benzylidene signal at 19.2 ppm disappeared to become a broad alkylidene signal at lower chemical shifts between 18.9–19.1 ppm (Figure S3). Upon lowering the temperature to −23°C, the broad peak became two distinct peaks at 19.0 and 19.2 ppm, with relative integrations of 0.15 and 0.85, respectively. Interestingly, the peak at 19.2 ppm remained as the major signal when 10 equiv of pyridine were added, and the sample was warmed to room temperature. This observation indicated that at lower temperatures or in the presence of excess pyridine, the dominant catalyst resting state is the pyridine-bound Ru, which readily initiates to give polymers with a narrow, monomodal MW distribution.

With these considerations in mind, we found that complete reinitiation was best achieved in the presence of 15 equiv of 3BP at −30°C. Under these conditions, a single unit of ring-opened CPE was added to a living PNBE chain within 4 h, followed by the second batch of NBE to extend the chain. The final polymer had an exceptionally low dispersity index (Đ = 1.04) and a MW identical to the theoretical value (Figure S4). MALDI-TOF MS of both the intermediate and final polymers confirmed that all of the chains contained exactly one unit of CPE (Figure S5). Additionally, the entire mass envelope moved to the high MW range, agreeing with the observed complete reinitiation by GPC.

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Scheme 1. Structures of CPEs and NBEs Used in This Study

Single Addition of Functional CPEs

With our optimized method for single CPE addition within a living PNBE chain, we sought to synthesize polymers containing functional groups at desired locations along the chain. We synthesized a series of monofunctional CPEs containing an ATRP initiator (2), Boc-protected amine (3), and NHS ester (4) (Scheme 1). After polymerizing a PNBE$_{25}$ block, we added 1 equiv of each CPE, followed by 15 equiv of 3BP at $-30°$C and an additional 25 equiv of NBE to place the ring-opened CPE at the chain center. MALDI-TOF MS showed that each polymer contained only one unit of CPE (Figure S6). ^{1}H NMR spectra of the polymers clearly showed the signals corresponding to the expected phenyl and methylene end groups, and the incorporated CPE was at equal equiv to the end groups in all cases (Figures S7–S9). The GPC traces of the final polymers all showed narrow and monomodal peaks corresponding to their expected MW (Table 1, entries 1–3, Figure S10). The MS, NMR, and GPC results revealed well-controlled single addition for all of these functionalizable CPEs in the middle of a living ROMP polymer.

We also demonstrated that this method was equally effective for NBEs with different substitution patterns and solubility, using for example **NBE-EtHex** and **NBE-OEG** (Scheme 1, vide infra).

Since Förster resonance energy transfer (FRET) is highly distance dependent, we sought to use FRET to illustrate the effect of precise placement of chromophores in a polymer chain. Pyrene and perylene are a commonly used FRET pair; using perylene and pyrene functionalized CPEs **5** and **6**, respectively, we placed a pyrene motif at the ω-chain end of a PNBE (total DP = 100) and varied the placement of the perylene motif at three distinct locations: the α-chain end, chain center, or 5 repeat units from the ω-chain end (Figure 4). We synthesized this series of three polymers by simply adjusting the equiv of NBE fed into the ROMP solution before and after the single addition of **5** and then end-capping the polymers using **6**. ^{1}H NMR

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Table 1. Characteristics of PNBE$_{50}$ Polymers Containing a Single Equivalent of Ring-Opened CPE in the Center of the Chain

| Entry	NBE	CPE	$M_{n,\ theo}$[a] (kDa)	$M_{n,\ MALLS}$[b] (kDa)	$Đ_M$[b]
1	NBE-iPr	2	10.7	9.2	1.06
2	NBE-iPr	3	10.8	8.9	1.04
3	NBE-iPr	4	10.8	9.0	1.08
4	NBE-iPr	7	14.5	16.4	1.08
5	NBE-EtHex	2	13.0	13.9	1.15

[a]Theoretical MW.
[b]Determined by GPC-MALLS analysis in THF.

spectroscopy confirmed the single unit incorporation of **5** and **6** in PNBE (Figure S11). Fluorescence emission from the polymers was measured by exciting pyrene using 335 nm radiation in THF. FRET between pyrene and perylene in the polymers clearly reflected the distance difference between the chromophores (Table S1). As expected, when the FRET pair was separated by only 5 NBE units, the emission spectrum was dominated by perylene emission. On the other hand, when the perylene motif was moved further away from pyrene by 50 and then 100 NBE units, the FRET efficiency was progressively and significantly reduced.

Synthesis of Branched Polymers via Singly Incorporated Functionalities

The exceptional control and fidelity of CPE single addition allowed us to synthesize a range of polymers with different branched architectures (Figure 5). PNBE with singly incorporated **2** containing one α-bromoisobutyrate (Table 1, entry 5) was used as a macroinitiator for ATRP to synthesize a 3-arm star polymer (Figure 5A). ATRP of methyl methacrylate in anisole at 70°C gave a poly(methyl methacrylate) arm with DP = ~80 based on ^{1}H NMR spectroscopy. GPC analysis of the resulting polymer showed a narrow-disperse peak that was uniformly shifted to shorter elution times from the PNBE macroinitiator (Figure S12). The symmetric, narrow peak and the absence of a shoulder supported that only one unit of ATRP initiator was incorporated in the PNBE macroinitiator via CPE single addition.

Additionally, we transformed PNBE with a single NHS ester in the middle of the chain (Table 1, entry 3) into a 4-arm star polymer by reacting the polymer with 0.5 equiv of hexanediamine with respect to PNBE (Figure 5B). GPC analysis of the crude polymer product showed the clean and complete shift of the parent polymer peak to shorter elution times, corresponding with an approximate doubling in MW (Figure S13).
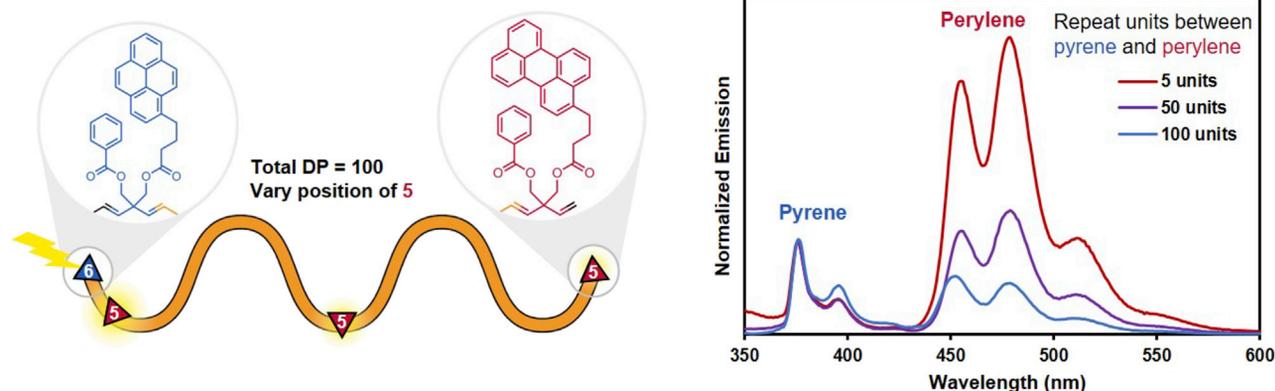
Figure 4. Emission Spectra of PNBEs Containing Pyrene and Perylene Motifs Separated by 5, 50, or 100 NBE Units
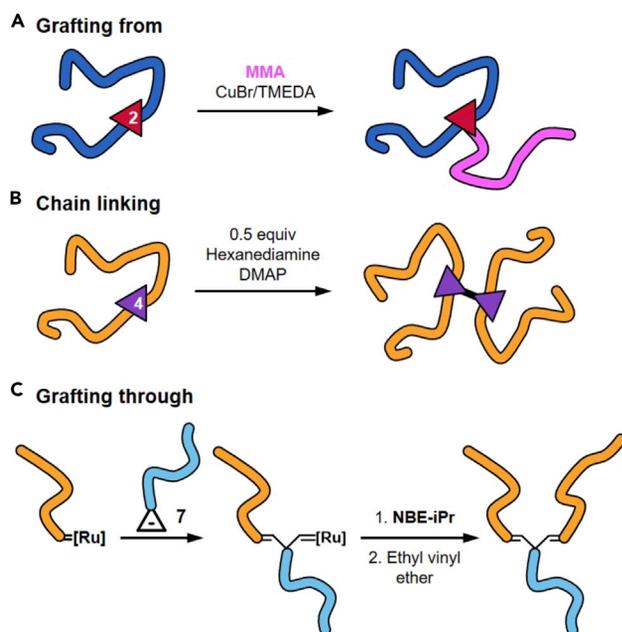
Figure 5. Star Polymers Synthesized from (A and B) PNBEs Containing a Single Functionality from Ring-Opened CPE or (C) Direct Single Addition of a CPE Macromonomer

Finally, encouraged by the high reactivity of CPE, we attempted the single addition of a CPE macromonomer (MM) (Figure 5C). We synthesized a CPE-appended poly-caprolactone MM (**7**) of 4.1 kDa. Because of the intrinsic precision limitations in measuring the exact molar mass of a MM, 1.1 equiv of the MM was used to ensure that a sufficient amount of CPE was added. MM addition was completed within 2 h as revealed by GPC analysis. Fifteen equiv of 3BP was then added at −30°C followed by 25 equiv of NBE to extend the chain. The slight excess of **7** was easily removed by precipitating the crude polymer into methanol to obtain the star polymer cleanly (Figures S14 and S15).

These examples demonstrate the power of selectively introducing single unit functionalities at arbitrary pre-determined locations in a polymer chain, allowing easy syntheses of more complex and precise polymer architectures and multiblock copolymers in the future.

Multiple CPE Single Additions in a Living Polymer

We next sought to illustrate the power and utility of multiple CPE single additions within a polymer. As our first demonstration, we synthesized a narrow-disperse PNBE$_{75}$ homopolymer containing an ATRP initiator and a Boc-protected amine at 1/3 and 2/3 of the length of the chain (Figure S16), respectively, by adding 1 equiv of **2** and **3** in between additions of 25 equiv of NBE in the presence of 15 equiv of 3BP at −30°C.

To synthesize even more complex and precisely controlled polymer structures, we aimed to place different functionalities at various desired locations in a multiblock copolymer chain via multiple single additions of CPEs in a one-pot reaction. During the living ROMP of a NBE triblock copolymer, 1 equiv each of CPEs **2**, **3**, and **4** were added sequentially to the ROMP solution after polymerizing a block of **PNBE-EtHex**, **PNBE-iPr**, and **PNBE-OEG**, respectively, to install a functionality at the block

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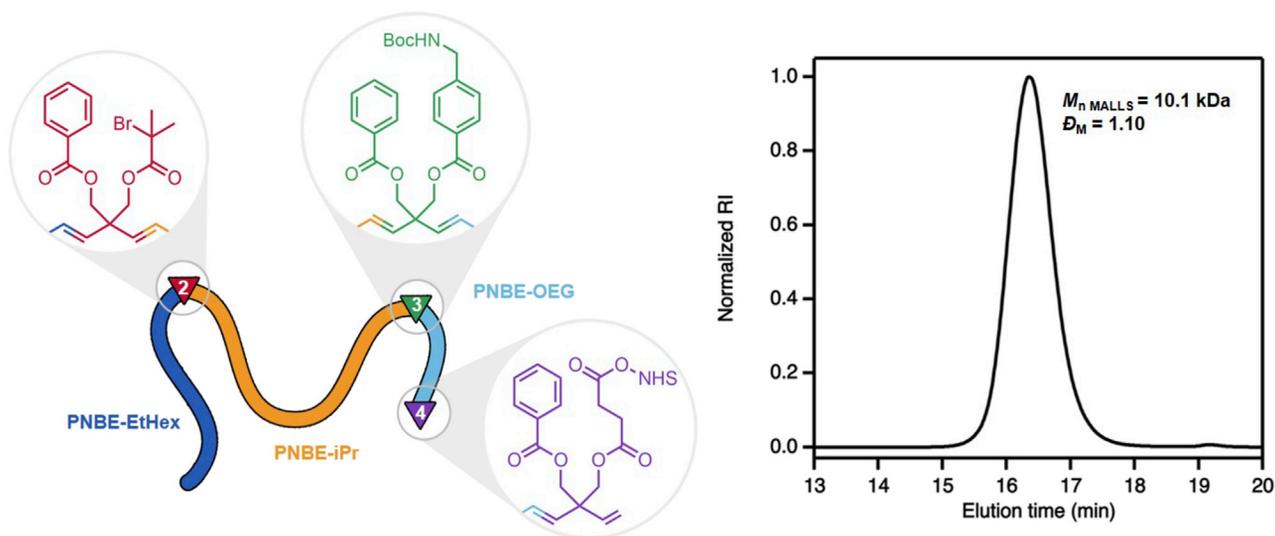
Figure 6. GPC Trace of a PNBE Triblock Copolymer PNBE-EtHex-2-PNBE-iPr-3-PNBE-OEG-4 Containing Ring-Opened CPE 2, 3, and 4 at Desired Locations along the Polymer Chain

junctions and ω-chain end (Figure 6). The GPC trace of the resulting polymer showed a monomodal and narrow peak with the expected MW (Figure 6), and ^{1}H NMR spectroscopy of the polymer showed the three incorporated CPEs with expected integrations of the signals in the aromatic region from both the added CPEs and the benzyl group from the initiator (Figure S17). We used **NBE-EtHex**, **NBE-iPr**, and **NBE-OEG** as monomers here to obtain a low T_g, high T_g, and water-soluble block, respectively, to exemplify the diverse properties that can be obtained from PNBEs. Considering the large number of various NBE derivatives reported for living ROMP, this strategy provides a versatile and broadly applicable means to place specific functional motifs at desired locations along these living polymer chains.

Conclusions

We have demonstrated a powerful method to precisely insert single units of functional CPEs and place various functional groups or motifs at desired positions along a narrow-disperse PNBE chain during living ROMP. While initial attempts showed significant fractions of unextended PNBE after single addition of CPE, this issue was circumvented by the addition of weakly coordinating 3BP and/or lowering the reaction temperature. The remarkable efficiency and fidelity of CPE single addition even allowed single addition of a CPE macromonomer. We further demonstrated the use of well-controlled homopolymers and BCPs containing precisely placed single functionalities to synthesize more complex branched polymer structures and illustrated the effect of controlled spacing between chromophores on a polymer using FRET. The repeated single additions in living ROMP represent unprecedented control of the positions of discrete monomers or functionalities in a polymer chain, opening exciting avenues for precise synthesis of polymer architectures, placement of functional moieties, and control of monomer sequence to explore their effects on polymer folding and BCP assembly in the future.

SUPPLEMENTAL INFORMATION

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AUTHOR CONTRIBUTIONS

B.R.E. and J.K.S. contributed equally. B.R.E., J.K.S., and Y.X. designed this project. B.R.E. and J.K.S. performed the majority of experiments. J.D.F. synthesized the polymers for the FRET study and performed the FRET study. B.R.E. and Y.X. wrote the manuscript with input from all authors.

DECLARATION OF INTERESTS

The authors declare no competing interests.

REFERENCES

1. Gody, G., Zetterlund, P.B., Perrier, S., and Harrisson, S. (2016). The limits of precision monomer placement in chain growth polymerization. Nat. Commun. 7, 10514.

2. Jean-François, L., Makoto, O., Mitsuo, S., and Tara, Y.M. (2014). Sequence-controlled polymers: synthesis, self-assembly, and properties (American Chemical Society).

3. Lutz, J.F., Ouchi, M., Liu, D.R., and Sawamoto, M. (2013). Sequence-controlled polymers. Science 341, 1238149.

4. Davidson, E.C., Rosales, A.M., Patterson, A.L., Russ, B., Yu, B., Zuckermann, R.N., and Segalman, R.A. (2018). Impact of helical chain shape in sequence-defined polymers on Polypeptoid block copolymer self-assembly. Macromolecules 51, 2089–2098.

5. Judzewitsch, P.R., Nguyen, T.K., Shanmugam, S., Wong, E.H.H., and Boyer, C. (2018). Towards sequence-controlled antimicrobial polymers: effect of polymer block order on antimicrobial activity. Angew. Chem. Int. Ed. Engl. 57, 4559–4564.

6. Kametani, Y., Sawamoto, M., and Ouchi, M. (2018). Control of the alternating sequence for N-Isopropylacrylamide (NIPAM) and methacrylic acid units in a copolymer by cyclopolymerization and transformation of the cyclopendant group. Angew. Chem. Int. Ed. Engl. 57, 10905–10909.

7. Li, G., and Sampson, N.S. (2018). Alternating ring-opening metathesis polymerization (AROMP) of hydrophobic and hydrophilic monomers provides oligomers with side-chain sequence control. Macromolecules 51, 3932–3940.

8. Li, J., Rothstein, S.N., Little, S.R., Edenborn, H.M., and Meyer, T.Y. (2012). The effect of monomer order on the hydrolysis of biodegradable poly(lactic-co-glycolic acid) repeating sequence copolymers. J. Am. Chem. Soc. 134, 16352–16359.

9. Li, J., Stayshich, R.M., and Meyer, T.Y. (2011). Exploiting sequence to control the hydrolysis behavior of biodegradable PLGA copolymers. J. Am. Chem. Soc. 133, 6910–6913.

10. Srichan, S., Kayunkid, N., Oswald, L., Lotz, B., and Lutz, J.-F. (2014). Synthesis and characterization of sequence-controlled semicrystalline comb copolymers: influence of primary structure on materials properties. Macromolecules 47, 1570–1577.

11. Al Ouahabi, A., Charles, L., and Lutz, J.F. (2015). Synthesis of non-natural sequence-encoded polymers using phosphoramidite chemistry. J. Am. Chem. Soc. 137, 5629–5635.

12. Espeel, P., Carrette, L.L.G., Bury, K., Capenberghs, S., Martins, J.C., Du Prez, F.E., and Madder, A. (2013). Multifunctionalized sequence-defined oligomers from a single building block. Angew. Chem. Int. Ed. Engl. 52, 13261–13264.

13. Hibi, Y., Ouchi, M., and Sawamoto, M. (2016). A strategy for sequence control in vinyl polymers via iterative controlled radical cyclization. Nat. Commun. 7, 11064.

14. Oh, D., Ouchi, M., Nakanishi, T., Ono, H., and Sawamoto, M. (2016). Iterative radical addition with a special monomer carrying bulky and convertible pendant: a new concept toward controlling the sequence for vinyl polymers. ACS Macro Lett. 5, 745–749.

15. Oh, D., Sawamoto, M., and Ouchi, M. (2019). Precise control of single unit monomer radical addition with a bulky tertiary methacrylate monomer toward sequence-defined oligo- or poly(methacrylate)s via the iterative process. Polym. Chem. 10, 1998–2003.

16. Porel, M., and Alabi, C.A. (2014). Sequence-defined polymers via orthogonal allyl acrylamide building blocks. J. Am. Chem. Soc. 136, 13162–13165.

17. Niu, J., Hili, R., and Liu, D.R. (2013). Enzyme-free translation of DNA into sequence-defined synthetic polymers structurally unrelated to nucleic acids. Nat. Chem. 5, 282–292.

18. Elling, B.R., and Xia, Y. (2015). Living alternating ring-opening metathesis polymerization based on single monomer additions. J. Am. Chem. Soc. 137, 9922–9926.

19. Kanazawa, A., and Aoshima, S. (2015). Exclusive one-way cycle sequence control in cationic terpolymerization of general-purpose monomers via concurrent vinyl-addition, ring-opening, and carbonyl-addition mechanisms. ACS Macro Lett. 4, 783–787.

20. Parker, K.A., and Sampson, N.S. (2016). Precision synthesis of alternating copolymers via ring-opening polymerization of 1-substituted cyclobutenes. Acc. Chem. Res. 49, 408–417.

21. Satoh, K., Matsuda, M., Nagai, K., and Kamigaito, M. (2010). AAB-sequence living radical chain copolymerization of naturally occurring limonene with maleimide: an end-to-end sequence-regulated copolymer. J. Am. Chem. Soc. 132, 10003–10005.

22. Soejima, T., Satoh, K., and Kamigaito, M. (2016). Main-chain and side-chain sequence-regulated vinyl copolymers by iterative atom transfer radical additions and 1:1 or 2:1 alternating radical copolymerization. J. Am. Chem. Soc. 138, 944–954.

23. Konrad, W., Bloesser, F.R., Wetzel, K.S., Boukis, A.C., Meier, M.A.R., and Barner-Kowollik, C. (2018). A combined photochemical and multicomponent reaction approach to precision oligomers. Chemistry 24, 3413–3419.

24. Solleder, S.C., and Meier, M.A.R. (2014). Sequence control in polymer chemistry

Chem

through the Passerini three-component reaction. Angew. Chem. Int. Ed. Engl. *53*, 711–714.

25. Wu, Y.-H., Zhang, J., Du, F.-S., and Li, Z.-C. (2017). Dual sequence control of uniform macromolecules through consecutive single addition by selective Passerini reaction. ACS Macro Lett. *6*, 1398–1403.

26. Gutekunst, W.R., and Hawker, C.J. (2015). A general approach to sequence-controlled polymers using macrocyclic ring opening metathesis polymerization. J. Am. Chem. Soc. *137*, 8038–8041.

27. Nowalk, J.A., Fang, C., Short, A.L., Weiss, R.M., Swisher, J.H., Liu, P., and Meyer, T.Y. (2019). Sequence-controlled polymers through entropy-driven ring-opening metathesis polymerization: theory, molecular weight control, and monomer design. J. Am. Chem. Soc. *141*, 5741–5752.

28. Barnes, J.C., Ehrlich, D.J.C., Gao, A.X., Leibfarth, F.A., Jiang, Y., Zhou, E., Jamison, T.F., and Johnson, J.A. (2015). Iterative exponential growth of stereo- and sequence-controlled polymers. Nat. Chem. *7*, 810–815.

29. Binauld, S., Damiron, D., Connal, L.A., Hawker, C.J., and Drockenmuller, E. (2011). Precise synthesis of molecularly defined oligomers and polymers by orthogonal iterative divergent/convergent approaches. Macromol. Rapid Commun. *32*, 147–168.

30. Flory, P.J. (1940). Molecular size distribution in ethylene oxide polymers. J. Am. Chem. Soc. *62*, 1561–1565.

31. Houshyar, S., Keddie, D.J., Moad, G., Mulder, R.J., Saubern, S., and Tsanaktsidis, J. (2012). The scope for synthesis of macro-RAFT agents by sequential insertion of single monomer units. Polym. Chem. *3*, 1879–1889.

32. Xu, J., Fu, C., Shanmugam, S., Hawker, C.J., Moad, G., and Boyer, C. (2017). Synthesis of discrete oligomers by sequential PET-RAFT single-unit monomer insertion. Angew. Chem. Int. Ed. Engl. *56*, 8376–8383.

33. Song, A., Lee, J.C., Parker, K.A., and Sampson, N.S. (2010). Scope of the ring-opening metathesis polymerization (ROMP) reaction of 1-substituted cyclobutenes. J. Am. Chem. Soc. *132*, 10513–10520.

34. Tan, L., Li, G., Parker, K.A., and Sampson, N.S. (2015). Ru-catalyzed isomerization provides access to alternating copolymers via ring-opening metathesis polymerization. Macromolecules *48*, 4793–4800.

35. Tan, L., Parker, K.A., and Sampson, N.S. (2014). A bicyclo[4.2.0]octene-derived monomer provides completely linear alternating copolymers via alternating ring-opening metathesis polymerization (AROMP). Macromolecules *47*, 6572–6579.

36. Baradel, N., Fort, S., Halila, S., Badi, N., and Lutz, J.F. (2013). Synthesis of single-chain sugar arrays. Angew. Chem. Int. Ed. Engl. *52*, 2335–2339.

37. Lutz, J.F. (2013). Writing on polymer chains. Acc. Chem. Res. *46*, 2696–2705.

38. Lutz, J.F., Schmidt, B.V.K.J., and Pfeifer, S. (2011). Tailored polymer microstructures prepared by atom transfer radical copolymerization of styrene and N-substituted maleimides. Macromol. Rapid Commun. *32*, 127–135.

39. Pfeifer, S., and Lutz, J.F. (2007). A facile procedure for controlling monomer sequence distribution in radical chain polymerizations. J. Am. Chem. Soc. *129*, 9542–9543.

40. Zamfir, M., and Lutz, J.-F. (2012). Ultra-precise insertion of functional monomers in chain-growth polymerizations. Nat. Commun. *3*, 1138.

41. Pfeifer, S., and Lutz, J.F. (2008). Development of a library of N-substituted maleimides for the local functionalization of linear polymer chains. Chemistry *14*, 10949–10957.

42. Huang, Z., Noble, B.B., Corrigan, N., Chu, Y., Satoh, K., Thomas, D.S., Hawker, C.J., Moad, G., Kamigaito, M., Coote, M.L., et al. (2018). Discrete and stereospecific oligomers prepared by sequential and alternating single unit monomer insertion. J. Am. Chem. Soc. *140*, 13392–13406.

43. Bielawski, C.W., and Grubbs, R.H. (2007). Living ring-opening metathesis polymerization. Prog. Polym. Sci. *32*, 1–29.

44. R.H. Grubbs, and E. Khosravi, Eds. (2015). Handbook of metathesis. In Polymer Synthesis, [Second Edition], 3, (Wiley-VCH Press).

45. Elling, B.R., and Xia, Y. (2018). Efficient and facile end group control of living ring-opening metathesis polymers via single addition of functional cyclopropenes. ACS Macro Lett. *7*, 656–661.

46. Walsh, D.J., Lau, S.H., Hyatt, M.G., and Guironnet, D. (2017). Kinetic study of living ring-opening metathesis polymerization with third-generation Grubbs catalysts. J. Am. Chem. Soc. *139*, 13644–13647.