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Catalytic living ring-opening metathesis polymerization

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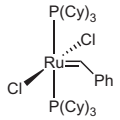
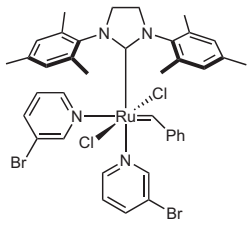
In living ring-opening metathesis polymerization (ROMP), a transition-metal–carbene complex polymerizes ring-strained olefins with very good control of the molecular weight of the resulting polymers. Because one molecule of the initiator is required for each polymer chain, however, this type of polymerization is expensive for widespread use. We have now designed a chain-transfer agent (CTA) capable of reducing the required amount of metal complex while still maintaining full control over the living polymerization process. This new method introduces a degenerative transfer process to ROMP. We demonstrate that substituted cyclohexene rings are good CTAs, and thereby preserve the 'living' character of the polymerization using catalytic quantities of the metal complex. The resulting polymers show characteristics of a living polymerization, namely narrow molecular-weight distribution, controlled molecular weights and block copolymer formation. This new technique provides access to well-defined polymers for industrial, biomedical and academic use at a fraction of the current costs and significantly reduced levels of residual ruthenium catalyst.

In olefin metathesis reactions, olefinic bonds are rearranged with the help of a transition-metal catalyst[1,2]. In the early days following the discovery of this reaction, ill-defined catalysts[3] were used to carry out this transformation. After Herisson and Chauvin[4] had proposed a reaction mechanism, the olefin metathesis reaction was better understood and soon gained much popularity. Typical catalysts used for olefin metathesis reactions include those based on ruthenium (developed mainly by the Grubbs group[5]), tungsten and molybdenum (developed mainly by the Schrock group[6]).

Owing to the low oxophilicity of ruthenium compared to those of molybdenum and tungsten, the ruthenium metathesis catalysts (commonly known as Grubbs' catalysts) are more tolerant towards many polar functional groups and residual impurities, as well as to water[7]. Therefore, these catalysts are the catalysts of choice in highly functional organic chemistry transformations as well as for the majority of metathesis polymerizations carried out today. Catalysts **G1** (first generation) and **G3** (third generation) are the most widely used ruthenium initiators for ring-opening metathesis polymerization (ROMP). In comparison to the **G1** initiator, the third-generation catalyst **G3** exhibits very fast initiation and propagation rates, and thereby gives polymers with very narrow dispersities and an excellent control over their molecular weights. Owing to its superior stability as well as the favourable polymerization kinetics, the third-generation Grubbs' catalyst **G3** was used for this work.



G1



G3

ROMP is a polymerization technique that uses the metathesis of cyclic olefins to synthesize linear polymers. Depending on the structure of the monomer, such polymerizations can be controlled perfectly to give polymers with a narrow molecular weight distribution and a controlled average molecular weight. Ring-strained monomers, like norbornene and its derivatives, are commonly used to accomplish so-called 'living' polymerizations, wherein irreversible chain-transfer events and termination reactions are absent. In a living ROMP polymerization, a ruthenium complex such as **G3** reacts with a cyclic olefin (monomer) to undergo a ring-opening metathesis reaction that finishes with the ruthenium complex located at the end of the growing polymer chain. It is therefore mechanistically determined that each ruthenium complex can form one polymer chain, that is, stoichiometric amounts of the ruthenium complex are required with respect to the number of polymer chains formed in a living ROMP.

However, metathesis polymers can also be obtained using only catalytic amounts of a ruthenium complex. Two examples are the acyclic diene metathesis method, which was extensively developed by Wagener's group[8–10] and follows a step-growth polymerization mechanism, or ROMP with an irreversible chain transfer in which a cyclic olefin monomer is polymerized in the presence of small quantities of an acyclic olefin. However, such polymerizations cannot be considered to be living, as molecular weight distributions are typically broad and block copolymers cannot be made[11].

One way of making a catalytic polymerization 'quasi-living' is to introduce a degenerative reversible chain-transfer step. This has been shown for radical polymerizations in the so-called RAFT (reversible addition–fragmentation chain-transfer) process[12] for ring-opening polymerizations in the 'immortal ring-opening polymerization' process[13] in coordinative chain-transfer polymerization[14,15] and, recently, in cationic RAFT polymerization[16]. In principle, any degenerative reversible chain-transfer polymerization requires only catalytic quantities of the propagating species as these are transferred quickly from one polymer chain to the next through a degenerative transfer and so simulate a quasi-simultaneous chain growth. (This process is not unlike the multitasking of a single microprocessor, which divides its attention to several tasks for short periods at a time and thereby gives the illusion of parallel processing.)

Here we present for the first time a catalytic living ROMP that uses a degenerative reversible chain-transfer polymerization

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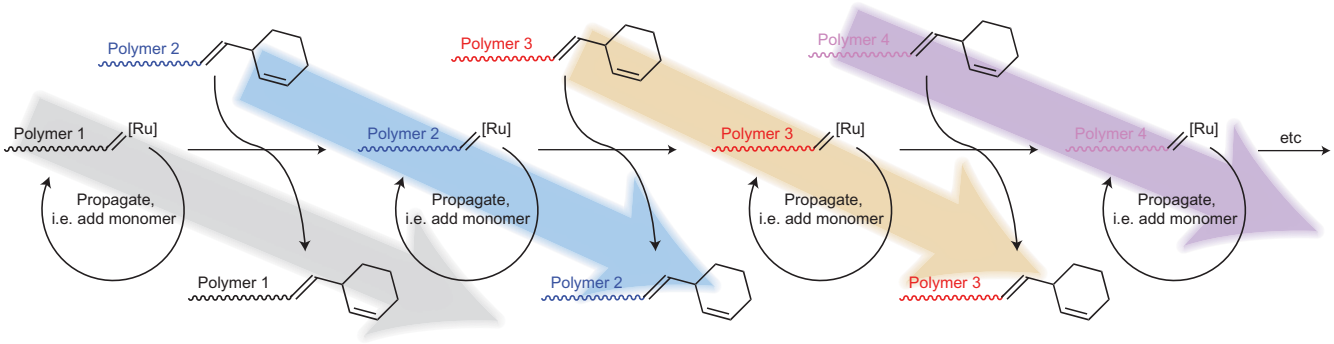

Figure 1 | Illustration of catalytic living ROMP. The kinetic chain of the metathesis-active ruthenium carbene complex can be followed from Polymer 1=[Ru] to Polymer 4=[Ru] (from left to right, following the straight arrows). Along this path, several polymer chains are temporarily activated to react with the monomer and then deactivated again (indicated by coloured arrows). Following the blue arrow as an example, Polymer 2 in its dormant form carrying a cyclohexenyl end group (top left of the arrow) is activated by Polymer 1 to form a propagating Polymer 2=[Ru] (middle of the arrow). After the propagation with a small number of monomers the active ruthenium end group is passed on to Polymer 3 and Polymer 2 adopts the dormant form again (bottom right of the arrow).

mechanism requiring only catalytic amounts of the ruthenium carbene complex **G3**. As represented in Fig. 1, initially a polymer chain (Polymer 1) carries the active ruthenium carbene end group. This allows Polymer 1 to propagate, that is, add a cyclic monomer to the chain end, and retain the active ruthenium carbene end group. The active ruthenium carbene end group of Polymer 1 can subsequently be exchanged (via a degenerative metathesis chain transfer) with a cyclohexenyl end group of another polymer (Polymer 2 in Fig. 1). This renders Polymer 1 temporarily inactive (dormant, non-propagating), whereas Polymer 2 can now add a cyclic monomer to its ruthenium carbene chain end, that is, propagate. After some time, determined by the concentration of monomer and the cyclohexenyl end groups as well as by the inherent reactivity difference between the monomer and cyclohexenyl end group (see below), the active ruthenium carbene end group is exchanged with the cyclohexenyl end group of Polymer 3 and so on. This mechanism allows a single ruthenium carbene species to activate one polymer chain end after another and thereby give the illusion that all the chains grow simultaneously. In other words, the kinetic chain length of the ruthenium carbene species manifests itself in chain extensions of many physical polymer chains.

The cyclohexenyl chain ends are initially introduced via chain-transfer agent 1 (**CTA1**) and, therefore, the number of CTAs defines the number of polymer chains being formed in the system. Once a degenerative metathesis chain transfer occurs, some of the dormant chains, after reacting with an active ruthenium carbene on the chain end of another polymer, become metathesis active and start to propagate with the newly added monomer. Figure 1 illustrates this concept.

The amount of residual ruthenium that remains in the final polymers is a major challenge for the use of ROMP in biomedical applications. The acceptable level of residual ruthenium for oral administration use is less than 5 ppm[17]. Numerous methods to reduce the level of ruthenium in metathesis products have been developed. Heterogeneous methods, such as supported metathesis catalysts, have been reviewed extensively[18–20]. However, supported catalysts have a few drawbacks, some of which are high catalyst loadings, low turnover numbers and tedious synthetic procedures. There have also been numerous attempts to reduce the ruthenium content in metathesis products by homogeneous work-up techniques—chromatography[21], chemical transformations[22], scavenging ruthenium residues using phosphines[23] (more than 10 equiv.) or 50 equiv. phosphine oxide with dimethylsulfoxide[24], oxidation using $Pb(OAc)_4$ (refs 25,26) or

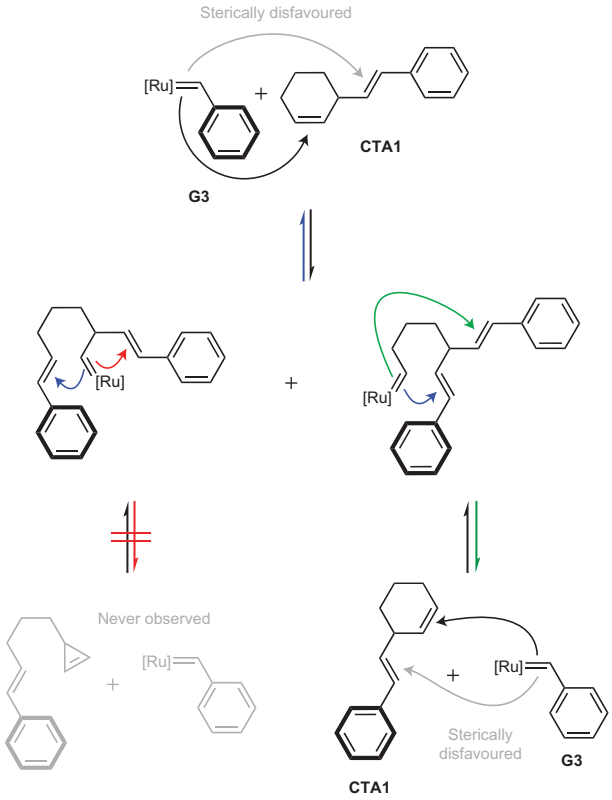

Figure 2 | Possible reactions of CTA1 with the G3 benzylidene complex. The ruthenium carbene complex **G3** reacts with **CTA1** in a substrate-selective and regioselective manner. The reactions indicated by grey arrows are sterically unfavourable. The left reaction pathway (red arrow) cannot proceed to a new ring-closing metathesis product as the ring strain of the hypothetical cyclopropene is too high. Only the degenerate pathway (right, green arrow) can be taken, in which a new cyclohexene ring can be formed by ring-closing metathesis that leads to the starting material **CTA1** and the **G3** benzylidene complex. The phenyl ring of the **G3** benzylidene complex (top left) is emphasized (bold) to be mechanistically distinguishable from the phenyl ring of **CTA1**.

H_2O_2 (ref. 27), vinyl ethers[28], purification based on monolithic materials[29] or using chelating compounds that assist with the extraction of the residue (mercaptonicotinic acid[30,31] and cystine[32]).

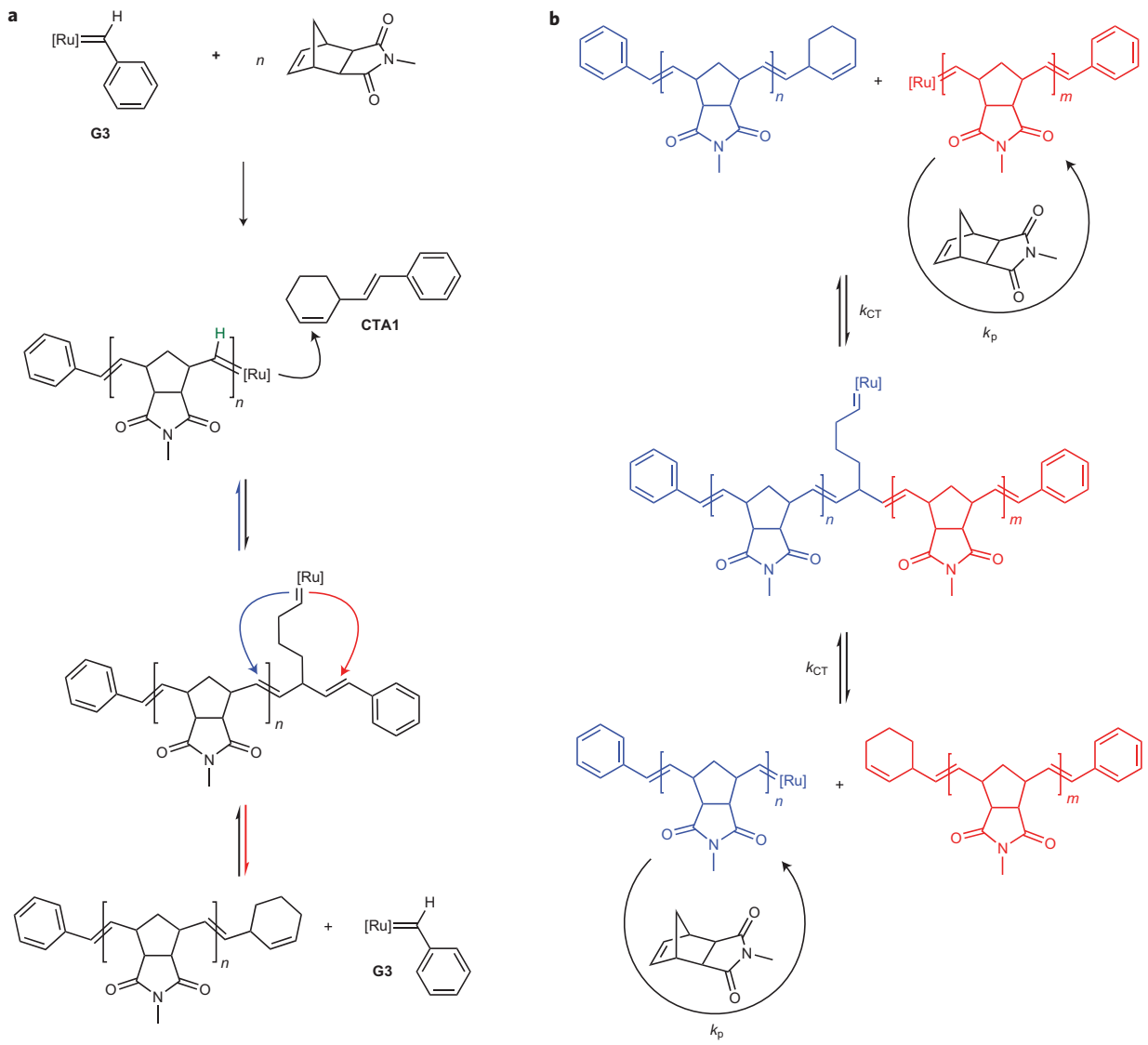

Figure 3 | The mechanism of the process of degenerative chain-transfer metathesis. a, The chain-end functionalization of a living ROMP polymer with **CTA1** regenerates the ruthenium benzylidene complex **G3** and installs a cyclohexenyl group at the polymer chain end. The reaction can be followed using the characteristic resonance of the ruthenium alkylidene proton, which appears at 18.5 ppm in the propagating polymer (green H) and at 19.1 ppm in the benzylidene complex **G3**. **b**, General mechanism of the process of degenerative chain-transfer metathesis. The monomer, methyl norborneneimide (**MNI**), is added slowly via a syringe pump to lower the rate of propagation relative to the rate of reversible chain transfer as $k_{CT} \ll k_p$. This allows chain-transfer reactions to occur frequently, a necessity for the quasi-simultaneous growth of all polymer chains.

Other approaches include the isocyanide-promoted degradation used by Diver and co-workers[33]. All these methods require a post-polymerization purification step along with an excess of added chemical agents, which makes ROMP commercially less attractive.

Metathesis polymerizations have been used to synthesize side-chain liquid-crystalline polymers using molybdenum[34] or ruthenium initiators[35,36]. Other very important materials accessible by ROMP are monolithic supports, reported by Buchmeiser and co-workers, which were used for the chromatography of biological samples, polymers and DNA fragments[37,38]. ROMP copolymers have also been used to synthesize stable emulsions of polymeric particles[39,40]. There are numerous other very interesting applications of functional ROMP polymers, some of which are high internal phase emulsions[41], bactericides and fungicides[42], separators in batteries[43], anion-exchange membranes[44] and so on. Metathesis polymers also have potential applications in the context of biological processes. Olefin metathesis for site-selective protein modification was reported by Davis and co-workers.[45] Kiessling and co-workers prepared polymers that contained bioactive groups and were used for the selective inhibition of proteins[46,47]. They also described novel strategies of protein binding using ROMP polymers[48,49]. Grubbs *et al.* described ROMP polymers that could be used in tumour therapy with the binding of integrins to proteins[50]. More recently, brush block copolymers of high molecular weight that self-assemble into nanostructures with photonic bandgaps were prepared by ROMP[51]. New catalyst developments have allowed the synthesis of *cis*-selective ROMP polymers using ruthenium[52], molybdenum and tungsten[53] catalysts.

The process described here has the inherent advantage of using very low amounts of ruthenium with no work up required, which makes this an attractive technique for ROMP polymers in biomedical applications. Inductively coupled plasma–optical emission spectroscopy data indicate ruthenium levels of less than 9 ppm without work up, which are reduced to 3 ppm after reprecipitation (see the Supplementary Information).

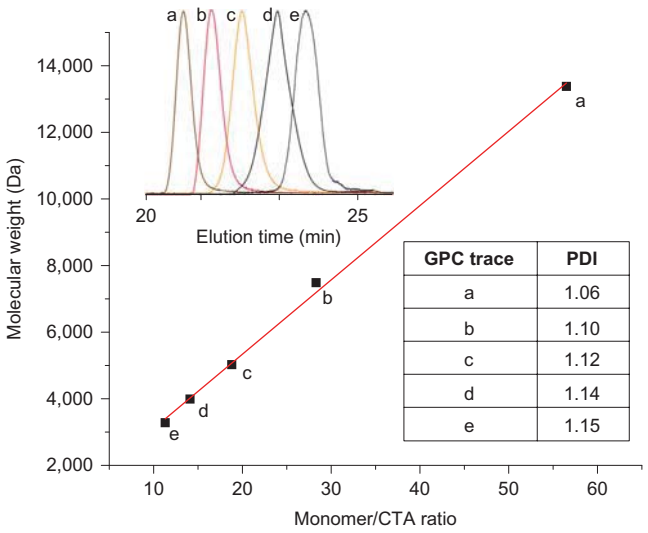

Figure 4 | Plot of the molecular weight obtained versus the monomer/CTA ratio. The linear dependence of the molecular weight of the polymers with the monomer/CTA ratio is a characteristic of living polymerization techniques. Left inset, GPC traces of the polymers a–e. Right inset, polydispersity indices (PDIs) of polymers a–e. Monomodal and narrow molecular weight distributions also point towards a superior control over the polymerization process as compared with 'non-living' polymerization methods.

Results and discussion

Our group has carried out extensive investigations into end functionalizations of ROMP polymers[54–57]. Based on our experience, we designed **CTA1**, which contains a cyclohexene ring. As this ring is virtually free of ring strain, **CTA1** cannot homopolymerize (Supplementary Fig. 3). Further, **CTA1** was designed such that in a tandem ring-opening–ring-closing metathesis sequence a cyclohexene ring would be opened and closed. We believed that this energetically degenerate process would possess a low activation energy and hence occur rapidly. Figure 2 shows the degenerative reaction of **G3** with **CTA1**. The olefin metathesis reaction of the ruthenium benzylidene complex with the styrenic olefin is not observed (Fig. 2, grey arrows). This double bond is sterically similarly substituted to the olefins present in the repeat units of polynorbornene backbones. These are known not to undergo rapid olefin-metathesis reactions, an important reason why norbornenes can be polymerized in a living fashion. Ring-opening olefin metathesis between the ruthenium benzylidene complex and the cyclohexene double bond most probably does not occur in a regioselective manner and gives rise to two new ruthenium alkylidene complexes (Fig. 2, middle). One pathway (Fig. 2, middle left, red arrow) cannot lead to a new ring-closing metathesis product because only a highly strained cyclopropene can be formed. The other pathway (Fig. 2, middle right, green arrow) leads to a new cyclohexene ring after ring-closing metathesis, and thereby reforms **CTA1** and the **G3** benzylidene complex. Hence, the apparent reaction displays substrate selectivity and regioselectivity.

To prove that **CTA1** does, indeed, react with a propagating polymer, **G3** was first reacted with a norbornene monomer, methyl norborneneimide (**MNI**) (17 equiv.), after which 20 equiv. **CTA1** were added. The ^{1}H NMR spectrum showed a complete shift of the resonances characteristic for the propagating ruthenium alkylidene (18.5 ppm) (Fig. 3a, green H and Supplementary Fig. 5) back to the original ruthenium **G3** benzylidene complex (19.1 ppm) (Fig. 3a, black H and Supplementary Fig. 5). This indicates that the polymer was fully end-functionalized with the **CTA1** moiety. Encouraged by this result, we then carried out a polymerization of **MNI** under living catalytic ROMP conditions. To ensure that the transfer of the catalytic propagating ruthenium complex **G3** from one chain end to the next occurred more rapidly than the consumption of monomer (the propagation reaction), we added the monomer slowly via a syringe pump. It was shown previously[58] that the rate of propagation of ring-strained monomers, such as norbornenes, is significantly faster than the olefin metathesis reaction with acyclic olefins, $k_{CT} \ll k_p$ (k_{CT}, rate constant of reversible chain transfer; k_p, rate constant of propagation) (see Fig. 3b). The monomer concentration was, therefore, kept low at all times using slow addition via a syringe pump. The process of the degenerative chain-transfer metathesis process is shown schematically in Fig. 3b.

When a strained monomer **MNI** was added very slowly (as a solution of 1 g per 10 ml in dichloromethane (DCM) at a rate of 0.5 ml per hour) to a reaction mixture that contained **G3** (10 μmol) and a tenfold excess of **CTA1**, the resulting solution showed complete consumption of the monomer and a polymer with a molecular weight much smaller than that calculated from the monomer/**G3** complex ratio. As predicted, the monomer/**CTA1** ratio determines the polymer molecular weight. Had the polymerization occurred via a classic living ROMP polymerization, the obtained molecular weights of the polymers would have always been 100 kDa (theoretically expected degree of polymerization = [monomer/G3] times the molecular weight of the monomer (= 565 × 177 = 100 kDa) (Supplementary Table 1)).

When a non-strained monomer (*cis*-cyclooctene) was used as the monomer for the degenerative metathesis chain-transfer polymerization, the secondary metathesis events (so-called 'back-biting') were still prevalent, and hence no control over the molecular weight could be achieved.

To prove the living character of the polymerization, different monomer/**CTA1** ratios were examined and the molecular weights of the obtained polymers plotted against the monomer/**CTA1** ratio. The amount of **G3** complex used in these experiments was kept at 10 μM and the monomer/**G3** ratio was kept at 565:1 (Supplementary Table 1). As shown in Fig. 4, a linear correlation between monomer/**CTA1** ratio versus molecular weight (determined by gel permeation chromatography (GPC)) was obtained. The molecular weight dispersity of the resulting polymers was very low, which provides a strong indication that the polymerization process is, indeed, quasi-living.

Matrix-assisted laser desorption time-of-flight mass spectrometry was used to determine the isotopically resolved molecular weights of the polymer chains. This proved unambiguously that the expected cyclohexenyl group that resulted from the reaction with **CTA1** was present at the chain end of all the polymers observed (Supplementary Figs 8 and 9).

When the purified mono-end functional polymers were redissolved, treated anew with a catalytic amount of **G3** complex and exposed to the slow addition of a second strained norbornene monomer, hexyl norborneneimide (**HNI**), block copolymers were formed, as observed by the shift of the molecular weight distribution (GPC) to higher values (see Supplementary Fig. 11). Therefore, our newly developed polymerization process fulfils all the criteria of a living RAFT polymerization, that is, the molecular weight is determined by the monomer/**CTA1** ratio, the molecular weight dispersity is low, block copolymers can be formed and the CTA fragment is covalently attached to the end of the polymer chain.

Choi and co-workers used the chain-transfer process in an ene–yne metathesis reaction to synthesize polymers that contain five-membered rings[59–61]. They took advantage of the sterics of the chain-transfer process and used cyclohexene as an inbuilt CTA. The observations reported by them also support our observation of the chain-transfer ability of the propagating ruthenium carbene to cyclohexene. In their case, no reversible chain transfer was observed because of the very different chain-transfer constants of

alkenes and alkynes towards ruthenium carbenes. The sterically demanding propagating carbene that results from an alkyne prevents the reversibility of the chain-transfer process.

Sampson and co-workers used cyclohexene in combination with strained substituted cyclobutenes to synthesize alternating ROMP polymers[62,63]. The substituted cyclobutenes do not propagate with ruthenium metathesis catalysts, and hence cyclohexene was used as a CTA to synthesize alternating polymers, incorporating the cyclohexene unit in the polymer backbone. This resulted in an efficient chain transfer of the propagating ruthenium carbene to cyclohexene that also supports the degenerative metathesis process in which the cyclohexene is carefully designed as a reversible CTA.

The polymers obtained by this new polymerization process are noticeably less coloured than those obtained by the classic living ROMP technique. This is a direct result of the greatly reduced residual amounts of ruthenium complex present in the final polymer. When 50 equiv. **CTA1** were used, the original ruthenium concentration was only 9 ppm. This amount of residual ruthenium was reduced to 3 ppm after two successive reprecipitations in methanol. Commercially, any post-polymerization purification step is a costly process and hence these low levels of residual ruthenium foster greater versatility and usability of ROMP in a commercial setting. In particular, biologically active polymers prepared by our living catalytic ROMP technique will benefit directly from the reduced toxicity because of the smaller amounts of ruthenium impurities. Catalytic living ROMP using Grubbs' third-generation ruthenium benzylidene complex provides a cheaper alternative to the classic living ROMP technique as it is both less wasteful in rare transition-metal complexes and provides equal control over the molecular weight and the molecular weight distribution.

Conclusion

In conclusion, we have demonstrated a new method of living ROMP that introduces degenerative chain transfer and requires substoichiometric amounts of ruthenium carbene complex. This new catalytic polymerization requires up to 50 times less of the ruthenium complex as compared to a typical living ROMP polymerization. Hence, this process of polymerization is potentially suited for industrial polymerization (by reducing the catalyst cost), biomedical applications (as the amount of toxic ruthenium complex required for the polymerization is much less) and coatings and aesthetics (because of the smaller catalyst loading as compared to the traditional ruthenium-catalysed living ROMP, the polymers do not retain any colour of the residual catalyst), as well as the synthesis of block copolymers using the same mechanism.

Mechanistically, we describe here a completely new polymerization method in polymer chemistry, very different from either living ROMP or RAFT, but that combines the advantages of both types of polymerizations. Our observations show that, with careful design, the stability of the six-membered cyclohexene ring can be exploited in a previously unobserved way. Catalytic living ROMP could pave the way for the industrial synthesis of ROMP polymers and still retain full control over the polymer structure and molecular weight.

Methods

In a typical procedure for living catalytic ROMP, the catalyst (**G3**, 1 equiv.), taken directly from the glove box in an argon atmosphere, was stirred continuously in degassed DCM in a Schlenk flask and the required amount of **CTA1** dissolved in degassed DCM was added. The monomer (**MNI**) was purged free of oxygen by three cycles of alternating vacuum and argon atmosphere, and dissolved in degassed DCM. This monomer solution was taken up in a gas-tight syringe and added to the **G3**/**CTA1** mixture at a rate of 0.5 ml h^{-1}. After complete addition, ethyl vinyl ether (100 equiv.) was added to quench any reactive metathesis species and the solution was poured into cold methanol to precipitate the polymer. The polymer was redissolved in DCM and reprecipitated once more, filtered and dried under high vacuum.

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Author contributions

A.A.N. and A.F.M.K. designed the experiments. A.A.N. performed the experiments. A.A.N. and A.F.M.K. wrote the main manuscript. Both authors reviewed the manuscript.

Additional information

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Competing financial interests

The authors declare no competing financial interests.