

Heterotelechelic polymers via ring opening metathesis and regioselective chain transfer

Peng Liu, Mohammad Yasir, Albert Ruggi and Andreas F.M. Kilbinger*

Abstract: Heterotelechelic polymers were synthesized via a kinetic telechelic ring opening metathesis polymerization method relying on the regioselective cross metathesis of the propagating Grubbs' first generation catalyst with cinnamyl alcohol derivatives. This procedure allowed the synthesis of hetero-bis-end-functional polymers in a one-pot setup. The molecular weight of the polymers could be controlled by varying the ratio between cinnamyl alcohol derivatives and monomer. The end functional groups can be changed using different aromatically substituted cinnamyl alcohol derivatives. Different monomers were investigated and the presence of the functional groups was shown by NMR spectroscopy and MALDI-ToF mass spectrometry. Labeling experiments with dyes were conducted to demonstrate the orthogonal addressability of both chain ends of the heterotelechelic polymers obtained.

Telechelic polymers, i.e. those carrying functional groups at either chain end, have been prepared using olefin metathesis since before well-defined ruthenium, molybdenum and tungsten (and many others) carbene complexes were reported mainly by Grubbs and Schrock. It was realized early on that adding acyclic olefins to a polymerization mixture of strained cyclic olefins would lower the molecular weight of the resulting polymer via chain transfer events. Furthermore, depending on the nature of the acyclic olefin, functional groups could be placed on the chain ends of the synthesized polymers.

Early examples for telechelic polymers by ring opening metathesis polymerization (ROMP) were reported by Hillmyer and Grubbs. There, cyclooctadiene was polymerized in the presence of suitably protected 1,4-*cis*-butene-diols using either well-defined tungsten or ruthenium carbene complexes.^[1] Alternatively, statistical copolymers between cyclooctadiene and dioxepines were prepared and the polymeric acetals hydrolyzed in a post-polymerization step.^[2] More recently, other functional groups such as epoxides and methacrylates,^[3] carboxylic acids and amines,^[4] trithiocarbonate RAFT initiators^[5] or nitroxide controlled radical polymerization initiators^[6] have been introduced via chain transfer agents (CTA). Carpentier and Guillaume most recently reported the syntheses of α,ω -bis(trialkoxysilyl) telechelic copolyolefins.^[7]

All of these synthetic methods rely on so-called back-biting

or secondary metathesis reactions (= chain transfer to the polymer) and can be carried out with catalytic amounts of transition metal carbene complexes. Due to the mechanistic necessity to undergo secondary metathesis reactions narrow molecular weight dispersities ($M_w/M_n < 2.0$) of the polymers cannot be achieved using this equilibrium driven synthetic strategy.

Polymers from norbornene and its derivatives do not readily undergo secondary metathesis reactions depending on the metal carbene initiator employed. However, using $WCl_6/SnMe_4$ ^[8] or Grubbs' 2nd generation ruthenium carbene complex^[9] telechelic poly(norbornene)s could be synthesized following the thermodynamically controlled procedure described above.

Polymers not undergoing secondary metathesis reactions can in principle be prepared in a living fashion, i.e. with narrow molecular weight distributions. For norbornenes, the so-called pulsed monomer addition has been successfully employed to prepare narrow molecular weight dispersity telechelic polymers.^[10] There, the transition metal carbene complex is first pre-functionalized with an excess of a symmetrical functional CTA before the first pulse of monomer is added. Functional initiation is followed by complete consumption of the monomer and subsequent chain transfer to the CTA thereby preparing a telechelic polymer and a new functional initiator. Upon addition of a second pulse of monomer a second polymer is prepared etc. While the carbene complex is recycled, and used for several monomer pulses, the method is not catalytic in metal complex as such.

Heterotelechelic polymers carry two different functional groups at either chain end. Such polymers are important macromolecular flexible spacers that allow the attachment of biologically active molecules,^{[11][12]} fluorescent and other labels or other functional compounds to one end of the polymer while the other is attached to macroscopic surfaces, nanoparticle surfaces, proteins etc. The attachment of proteins to surfaces is very important for applications in proteomics or biomaterials synthesis and long hetero-bis-endfunctional spacers, i.e. heterotelechelic polymers are an efficient way of connecting the two.

Heterotelechelic polymers have been prepared via many living polymerization techniques such as RAFT,^[13] ATRP,^[14] carbanionic polymerization^[15] and cationic polymerization.^[16] Few synthetic strategies have been reported that allow the synthesis of heterotelechelic polymers using ROMP. Non-catalytic methods involve the functional initiation of a polymerization followed by functional

[*] P. Liu, M. Yasir, Dr. A. Ruggi, Prof. Dr. A. F. M. Kilbinger
Department of Chemistry
University of Fribourg
Chemin du Musée 9, CH-1700 Fribourg, Switzerland
E-mail: andreas.kilbinger@unifr.ch

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termination with a different functional group or moiety.^[17] Catalytic polymerizations using mono-functionalized CTAs and sterically demanding cyclooctene derivatives produced mixtures of di and mono-end-functional polymers the latter representing heterotelechelic polymers.^[18] Hillmyer and coworkers used a particularly elegant approach employing a 3-substituted cyclooctene undergoing regioregular secondary metathesis reactions and a regioselective chain transfer to an acyclic functional olefin. This resulted in the synthesis of polymers with two different chain ends in a thermodynamically driven catalytic process. While mechanistically a heterotelechelic polymer was produced, one of the polymer end-groups was an alkyl chain that did not allow for post-polymerization functionalization.^[19] Katayama et al. reported true heterotelechelic ROMP polymers using functional vinyl ethers, vinyl thioethers and vinyl acetates that undergo regioselective chain transfer. Heterotelechelic poly(norbornene)s were obtained in a kinetically controlled catalytic process.^[20] Both former cases rely either on specially synthesized monomers^[19] or chain transfer agents,^[20] both typically prepared over several synthetic steps and are compatible with norbornene derivatives.

Here, we describe a straightforward synthesis of kinetically controlled heterotelechelic polymers using derivatives of commercially available cinnamyl alcohol as strictly regioselective chain transfer agents in ROMP. All cinnamyl alcohol derivatives reported here can be synthesized in few high yielding steps (see supporting information).

We obtained our first indication that cinnamyl alcohol undergoes regioselective cross-metathesis by using it as a terminating reagent for a **G1** (Figure 1) initiated poly(*exo*-N-methyl norbornene imide) (poly(**MNI**)). The polymerization reaction of **MNI** (**G1**: monomer = 1:30) was carried out in an NMR tube. Unreacted **G1**-benzylidene (20.02 ppm) as well as the propagating ruthenium carbene signal (19.43-19.47 ppm) could be observed as expected. After addition of 50eq. of cinnamyl alcohol the signal of the propagating carbene vanished within 5 min. and the intensity of the **G1**-benzylidene signal increased (polymer **1** see the supporting information). MALDI-ToF mass spectrometry showed that only alcohol terminated polymer chains were generated in the terminal cross metathesis reaction (supporting information).

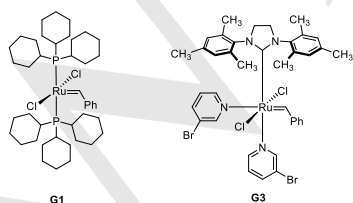
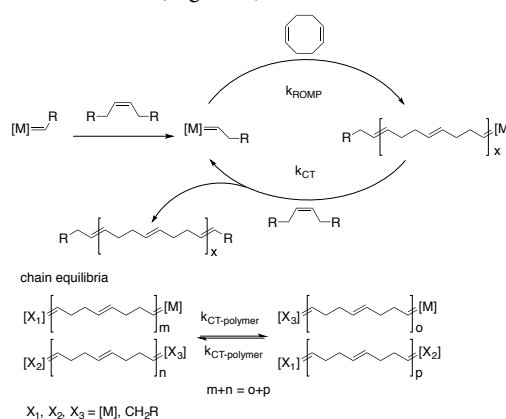


Figure 1. Two commercially available metathesis catalysts. Grubbs' first-generation (**G1**) and third-generation (**G3**) ruthenium benzylidene complexes.

When the same experiment was repeated with Grubbs' third generation initiator **G3** (Figure 1) no regioselective cross-metathesis step was observed (polymer **2**, supporting information). Two mass distributions, one with an alcohol and another with a phenyl end-group could be distinguished in the MALDI ToF mass spectrum (supporting information). A similar difference in selectivity was recently observed for the reaction of **G1** and **G3** with vinyl acetates.^[21] Furthermore, neither cinnamic aldehyde nor cinnamic acid showed any regioselectivity in the reaction with **G1** initiated poly(**MNI**).

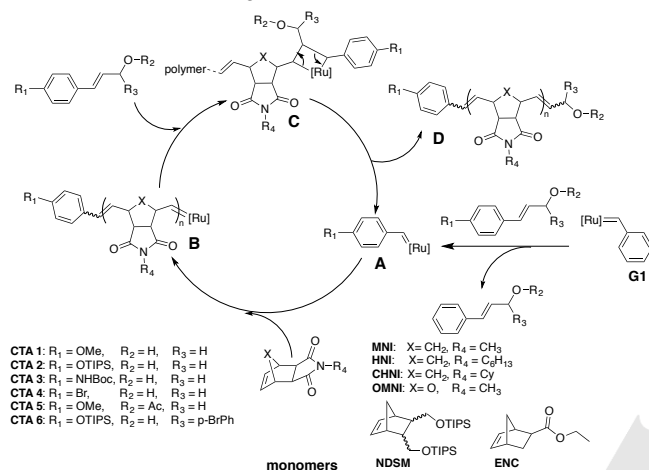
In order to be able to synthesize heterotelechelic polymers using a regioselective chain transfer step, polymers must be chosen for which the backbone olefins do not undergo secondary metathesis reactions such as poly(norbornene)s. During telechelic polymer syntheses under thermodynamic control the chain equilibria shown in scheme 1 (= chain transfer to the polymer) are essential for equilibration of the molecular weight distribution. If these chain equilibria occur in a non-regioselective manner (as is the case for the symmetrical cyclic olefin shown in scheme 1) heterotelechelic polymers cannot be obtained.

The relative rates of ring opening (k_{ROMP}) and chain transfer (k_{CT}) become important in the case where the chain equilibria are absent as is the case for a norbornene polymerization. Under such conditions heterotelechelic polymers can be obtained if a regioselective cross metathesis step to a CTA is involved. The molecular weights of the resulting heterotelechelic polymers will be determined by the relative rates k_{ROMP} and k_{CT} (scheme 1) and can be influenced by the monomer to CTA ratio. Even though the [monomer]:[CTA] ratio does not equate to the obtained molecular weights under kinetically controlled polymerization conditions, a good control over the molecular weight was achieved (Figure 2).



Scheme 1. Generalized synthesis scheme for the preparation of telechelic polymers via ring opening metathesis polymerization under thermodynamic control. [M]: transition metal carbene complex, R: functional group of a chain transfer agent, k_{ROMP} : rate constant of ring opening metathesis polymerization, k_{CT} , rate constant of chain transfer/cross metathesis.

We therefore synthesized chain transfer agents **CTA 1-6** (scheme 2) and investigated them towards their ability to produce heterotelechelic polymers in ROMP. **CTA 2** was chosen to optimize reaction conditions. As can be seen in table 1 varying the ratio of monomer (**MNI**) to **CTA 2** allowed the control over the resulting polymer molecular weight. For entries 1-8 (table 1) relatively low amounts of **CTA 2** with respect to **G1** were employed which made it necessary to pre-functionalize benzylidene catalyst **G1** with **CTA 2** (A in scheme 2) in order not to introduce the non-functional phenyl end-groups of the **G1** catalyst.



Scheme 2. Mechanism for the Synthesis of heterotelechelic ROMP polymers using cinnamyl alcohol derivatives. A: pre-functionalized **G1**-catalyst, B: propagating polymer, C: regioselective chain transfer, D: heterotelechelic polymer.

For entries 9-12 (table 1) the **CTA 2** to **G1** ratio (=200) was high enough not to introduce detectable amounts (by MALDI ToF mass spectrometry) of non-functional phenyl end-groups. In these cases, no pre-functionalization of **G1** was necessary. The pre-functionalization of the **G1** catalyst was optimized in NMR tube reactions varying the **CTA**:**G1** ratio, reaction time and temperature. Addition of an internal standard (1,3,5-trimethoxybenzene) allowed us to quantify and account for catalyst decomposition.

Two reaction conditions were found to give optimum results: **G1** was added to 35 eq. of the **CTA** in benzene-*d*₆ and the mixture heated from 40 to 55 °C (ca. 20 min.). In this case, the new carbene complex was formed in 69% yield (5% of residual **G1**-benzylidene). Alternatively, **G1** was added to 35 eq. of the **CTA** in dichloromethane-*d*₂ at r.t. for 4h. This gave the new carbene complex in 63% yield (3% of residual **G1**-benzylidene). All optimization results can be found in the supporting information.

All polymers obtained showed mono modal mass distributions by GPC (chloroform) and isotopically resolved MALDI ToF mass spectra matching the end groups

introduced by the respective **CTA** (supporting information). Broader molecular weight dispersities (around $\bar{D} = 2$, see table 1) are expected for a kinetically controlled catalytic synthesis of heterotelechelic. Lowering the reaction temperature to -20 °C (entries 11,12 table 1) slightly improved the molecular weight dispersity but also lowered the overall yield.

Different monomers such as *exo*-*N*-hexyl norbornene imide (**HNI**) (**polymer5**, $M_{n, GPC}(CHCl_3) = 4100 \text{ g mol}^{-1}$, $\bar{D} = 1.7$, $M_{peak}(MALDI-ToF) = 2495.51 \text{ g mol}^{-1}$), *exo*-*N*-cyclohexyl norbornene imide (**CHNI**) (**polymer6**, $M_{n, GPC}(CHCl_3) = 2700 \text{ g mol}^{-1}$, $\bar{D} = 1.9$, $M_{peak}(MALDI-ToF) = 2232.23 \text{ g mol}^{-1}$), *exo*-*N*-methyl oxanorbornene imide (**OMNI**) (**polymer7**, $M_{n, GPC}(CHCl_3) = 2400 \text{ g mol}^{-1}$, $\bar{D} = 1.7$, $M_{peak}(MALDI-ToF) = 1882.65 \text{ g mol}^{-1}$), *exo*-ethyl-5-norbornene carboxylate (**ENC**) (**polymer8**, $M_{n, GPC}(CHCl_3) = 6600 \text{ g mol}^{-1}$, $\bar{D} = 1.3$, $M_{peak}(MALDI-ToF) = 5254.38 \text{ g mol}^{-1}$) and 5-Norbornene-2,3-ditriisopropylsilylmethanol (*endo/exo* mixture, **NDSM**) (**polymer9**, $M_{n, GPC}(CHCl_3) = 4400 \text{ g mol}^{-1}$, $\bar{D} = 1.9$, $M_{peak}(MALDI-ToF) = 2604.10 \text{ g mol}^{-1}$) were polymerized using **CTA-1** and all showed isotopically resolved MALDI ToF MS spectra matching the two expected end-groups (supporting information).

Table 1 Polymerization Results and GPC Data for Different Molecular Weight Polymers^a

Entry	G1 : CTA 2 : MNI	$M_{n, max.}^b$	M_n^c	PDI ^c	Yield% ^d
1	1:35:10	1770	3300	1.2	70
2	1:35:25	4425	3500	1.8	83
3	1:35:35	6195	5300	1.9	84
4	1:70:70	12390	5300	2.1	77
5	1:100:100	17700	5600	2.4	82
6	1:35:175	30975	10300	3.1	94
7	1:35:350	61950	28500	2.2	98
8	1:35:700	123900	40700	2.7	97
9	1:200:200	35400	5000	1.9	99
10	1:200:1000	177000	13300	3.0	99
11	1:200:200	35400	8100	1.8	54
12	1:200:1000	177000	17300	1.9	77

^a All the reactions were carried out with **G1** (8.22 mg, 0.01mmol, 1.0 eq.), **CTA 2** and **MNI** in degassed DCM, entries 1-10 were carried out at room temperature and entries 11-12 were carried out at -20 °C (for more details see supporting information).^b $M_{n, max.} = [MNI]:[G1]$ represents the maximum theoretical molecular weight under non-catalytic conditions. ^c Measured by chloroform GPC. ^d The yields were calculated after precipitation.

Theoretical molecular weights of the polymers that would have been obtained under non-catalytic conditions are reported as $M_{n,max}$ in Table 1 ($M_{n,max}=[\text{monomer}]:[\text{catalyst}]$). Divergence of the observed molecular weights (M_n in Table 1) to lower values than given by $M_{n,max}$ indicates the catalytic behavior of the polymerization.

CTA 3-6 were investigated in polymerizations with **MNI**. All polymers gave mono-modal GPC traces and their MALDI ToF mass spectra matched exactly with the predicted heterotelechelic structures (**CTA 3: polymer 20**, **CTA 4: polymer 21**, **CTA 5: polymer 22** and **CTA 6: polymer 23**, see supporting information).

To demonstrate the orthogonal addressability of end groups in such heterotelechelic polymers, labelling experiments with dyes were conducted with **polymer 13** (table 1, entry 4). Rhodamine B was reacted with N,N' -dicyclohexylcarbodiimide (DCC), 4-(dimethylamino)pyridine (DMAP) and **polymer 13** in dichloromethane at room temperature to give **polymer 26** ($M_{n,GPC}(\text{CHCl}_3)=5800 \text{ mol}^{-1}$, $\bar{D} = 1.8$, $M_{peak}(\text{MALDI-ToF})=3387.62 \text{ g mol}^{-1}$) as a red solid. Next, the TIPS protecting group was removed (**polymer 27**, $M_{n,GPC}(\text{CHCl}_3)=5600 \text{ mol}^{-1}$, $\bar{D} = 1.8$, $M_{peak}(\text{MALDI-ToF})=2346.48 \text{ g mol}^{-1}$) and subsequently reacted with Coumarin 343 to give the bis-functionalized **polymer 29** ($M_{n,GPC}(\text{CHCl}_3)=5700 \text{ g mol}^{-1}$, $\bar{D} = 1.9$, $M_{peak}(\text{MALDI-ToF})=3321.12 \text{ g mol}^{-1}$, see also supporting information). Each reaction step was confirmed by $^1\text{H-NMR}$ and isotopically resolved MALDI ToF mass spectrometry (see supporting information). Förster resonance energy transfer (FRET) from the excited Coumarin to the Rhodamine dye proved the spatial proximity of the two hetero-functional polymer end-groups (supporting information).

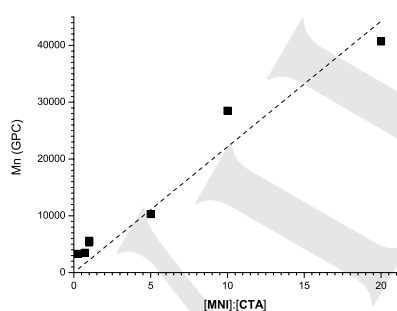


Figure 2. Polymer (entries 1-8, Table 1) molecular weight (GPC) vs. monomer (**MNI**) to **CTA** ratio. Dotted line: linear regression through the origin.

In conclusion, we have discovered that cinnamyl alcohol and its aromatic derivatives react regioselectively with Grubbs' first generation catalyst. This allowed us to prepare heterotelechelic polymers of norbornene derivatives via a

kinetically controlled procedure using only catalytic quantities of Grubbs' catalyst. The molecular weight dispersities of the heterotelechelic polymers are necessarily broader for such a kinetically controlled catalytic procedure. However, this heterotelechelic polymer synthesis process can easily be scaled up to multi gram quantities starting from easily accessible starting materials.

To prove the orthogonal reactivity of end groups, a heterotelechelic polymer carrying two different dyes at either chain end was synthesized. This new method presented here represents one of the most convenient methods for the synthesis of heterotelechelic ROMP polymers to date. The catalytic nature of the process reduces the levels of residual ruthenium which makes these heterotelechelic polymers attractive for potential applications in the biomedical area.

Acknowledgements

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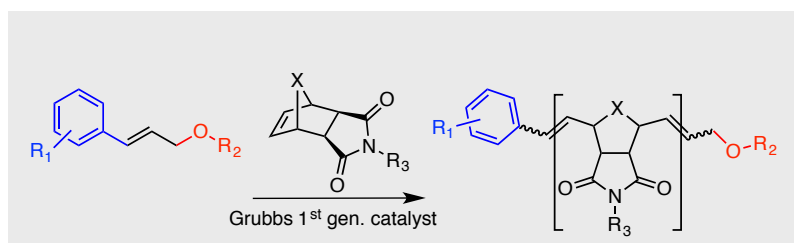
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