

Tandem Ring-Opening Ring Closing Metathesis for Functional Metathesis Catalysts

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Abstract: Use of a tandem Ring Opening Ring Closing Metathesis (RORCM) strategy for the synthesis of functional metathesis catalysts is reported. Ring opening of 7-substituted norbornenes and subsequent ring closing metathesis forming a thermodynamically stable 6-membered ring leads to a very efficient synthesis of new catalysts from commercially available Grubbs' catalysts. Hydroxy functionalized Grubbs' first and third generation catalysts have been synthesized. Mechanistic studies have been performed to elucidate the order of attack of the olefinic bonds. This strategy was also used to synthesize the ruthenium methylidene complex, which was previously accessible only by reaction of ethylene gas under pressure.

Olefin metathesis is a process in which a metal carbene is used to construct new carbon – carbon double bonds.¹ It has been widely used and extensively reviewed.² Historically, metathesis chemistry started with ill-defined catalysts,^{3,4} but the development of well-defined metathesis catalysts provided an impetus to extensive applications in synthetic organic and polymer chemistry. There are mainly two metals used in metathesis catalysts – molybdenum based catalysts developed by the Schrock group and ruthenium based catalysts developed by the Grubbs group.⁵ Although newer molybdenum based metathesis catalysts are much more tolerant towards water and oxygen,^{6,7} commercially available ruthenium based metathesis catalysts are the catalysts of choice for many polymer chemists.⁸

The first generation and the third generation of Grubbs' metathesis catalysts (Figure 1 **G1** and **G3**) are the most common catalysts used for polymer synthesis due to their favorable initiation/propagation rate ratio which makes them suitable for living polymerizations. However, their tolerance towards functional groups makes functional termination of polymerization reaction difficult. Ethyl vinyl ether is the most commonly used terminating agent transferring a methylene unit onto the polymer chain end. Substituted vinyl ethers^{9,10,11,12} acrylates,^{13,14} vinyl carbonates and lactones,¹⁵ protected amines,¹⁶ unsaturated acetals,¹⁷ metathesis with acyclic olefins¹⁸ and cyclic olefins¹⁹ have been used to terminate Ring Opening Metathesis Polymerization (ROMP) reactions. Such a functional termination can only ever give a mono-telechelic polymer, i.e. a polymer carrying a desired functional group on one chain end.

Homotelechelic polymers, i.e. polymers carrying the same functional group at both the chain ends, have been reported by the Grubbs' group²⁰ and our group.²¹ Heterotelechelic ROMP polymers were prepared using the sacrificial synthesis strategy.²² However, this strategy is limited to few functional groups and not atom economical.

Another route to the synthesis of heterotelechelic ROMP polymers is using prefunctionalized initiators.^{23,24,25,26} The initiators already carry a functional group and termination reactions would give a second, possibly different functional group. One way to synthesize new derivatives of the Grubbs-type ruthenium complexes is a simple metathesis step with excess of a substituted styrene derivative. However, in the case of first generation catalyst **G1**, the equilibrium constants for this reaction are typically not very high.²⁷ This strategy can work in case of Grubbs' third generation catalysts (**G3**). However, in both cases, an excess of the substituted styrene would have to be added which would need to be removed before carrying out polymerization reactions.

In order to synthesize a prefunctionalized Grubbs-type ruthenium carbene initiator for ring opening metathesis polymerization without the need of any purification step, we devised a scheme based on tandem ring opening-ring closing metathesis (RORCM) using a substrate carrying two double bonds of greatly differing reactivity (Scheme 1).²⁸

We hypothesized that the Grubbs benzylidene complex would ring open a strained norbornene double bond faster than undergoing cross-metathesis with the allylic ether (Scheme 1, $k_{\text{roPh}} \gg k_{\text{cm}}$). The newly formed ruthenium carbene would then ideally undergo intramolecular ring-closing metathesis faster than intermolecular reaction with another norbornene ($k_{\text{rc}} > k_{\text{p}}$, p = propagation). This would yield a hexahydrocyclopenta[*b*]pyran derivative (**HCP**) and a newly functionalized (R group) ruthenium carbene complex. If we further assume that the rate of ring opening metathesis of the new carbene complex with norbornene is slower than that of the ruthenium benzylidene complex ($k_{\text{roR}} < k_{\text{roPh}}$), the reaction should be irreversibly driven towards the

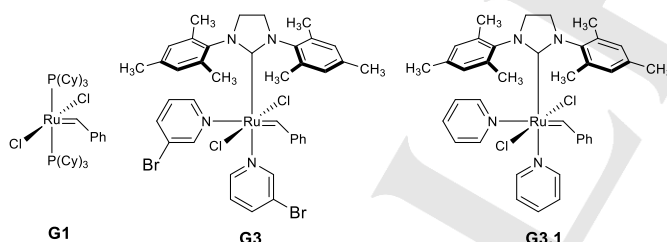


Figure 1. Two commercially available metathesis catalysts. 1st generation (**G1**) and 3rd generation (**G3**) Grubbs catalyst. The 3rd generation pyridine complex (**G3.1**) was prepared from **G3** by addition of excess pyridine.

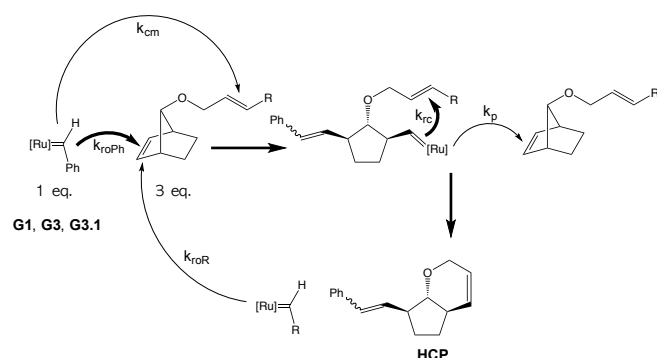
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formation of the new carbene complex. As the norbornene derivative was used in an excess (3 eq.), two equivalents would remain after all ruthenium benzylidene complex had reacted. These two equivalents would then react in a tandem ring opening–ring closing sequence with the newly formed carbene complex thereby re-generating the identical ruthenium carbene while consuming all excess of norbornene. In the end the reaction mixture should therefore only contain the newly formed ruthenium carbene complex and HCP derivatives which should exhibit low metathesis reactivity due to the lack of ring strain.

A subsequent polymerization reaction could simply be carried out by adding a strained monomer to the same reaction vessel without the need of intermediate purification.



Scheme 1. The generalized idea of using tandem ring opening – ring closing metathesis using two olefins of greatly differing reactivity to synthesize new metathesis catalysts. The sequence of metathesis reactions is defined by decreasing olefin reactivity. Bold arrows: desired reaction pathways / higher reaction rates expected. Normal arrows: side reactions / slower reaction rates.

Tandem ring opening – ring closing metathesis has been used many times and provides access to many complex organic structures.^{29,30,31} Most recently, the Choi group investigated ring opening – ring closing – cross metathesis reactions.^{32,33} However, there are no reports of new catalyst syntheses using such a methodology.

In order to test the RORCM hypothesis outlined in Scheme 1, compounds 1–7 were synthesized (see supporting information). When 7-*syn*-substituted norbornene (**1**) was added to a solution of **G1** no reaction could be observed by ¹H-NMR spectroscopy (see supporting info). A diminished reactivity of *syn*-substituted norbornene derivatives has already been reported.³⁴ Therefore, anti-substituted compound **2** was synthesized in order to circumvent the steric problems observed in **1**. The reaction of **2** with **G1** was followed by ¹H-NMR spectroscopy. The formation of the expected 4-methoxybenzylidene complex was observed, however, the reaction proceeded at a very slow rate with only 28 % formation of the new complex after 20 h of reaction time (see supporting information).

Acrylates have been used successfully in metathesis reactions,¹³ but they are relatively poor substrates owing to their electron deficient double bond. To increase the rate of the reaction, the electron deficient cinnamate group was replaced with allyl ether derivatives (**3–7**).

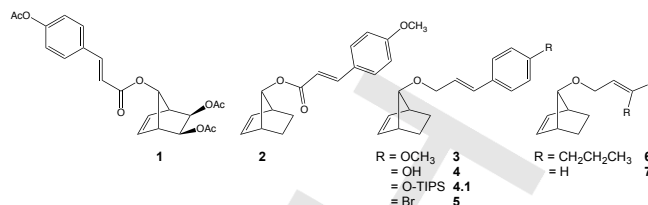


Figure 2. Ring-opening ring-closing metathesis (RORCM) substrates 1–7 investigated in this study.

When 3 equivalents of compound **3** were reacted with **G1**, the characteristic **G1** benzylidene signal (singlet, 20.02 ppm) in the ¹H-NMR spectrum diminished very quickly and a signal at 19.48 ppm which was attributed to the 4-methoxybenzylidene complex **G1-OMe**³⁵ appeared immediately. Within 15 minutes, 94% conversion was observed (Figure 3 a). The **G1** benzylidene signal almost completely disappeared within 35 min. and the new catalyst was quantitatively synthesized. It was furthermore evident from the ¹H-NMR spectrum that all norbornene double bonds had been consumed at this point.

This new complex crystallized on evaporation of the solvent (dichloromethane-*d*₂) with a slightly differently crystal structure than previously reported (see supporting information).³⁶

With the aim of a functional telechelic polymer in mind, we next prepared compound **4** which would yield a 4-hydroxybenzylidene ruthenium complex (see supporting information). Compound **4** reacted rapidly with **G1** and the benzylidene signal of **G1** was shifted to 19.39 ppm corresponding to the hydroxy substituted catalyst **G1-OH** within 20 minutes (Figure 3 b, 96 % yield by ¹H-NMR). There was no loss of intensity of the 4-hydroxybenzylidene signal with respect to residual protic solvent even after 6 hours which implies that the new catalyst is stable to phenolic OH groups. Unfortunately, all attempts to crystallize the new compound failed.

When 3 eq. of **4** were reacted with the more active **G3** catalyst, the ¹H-NMR signals of both, the **G3** benzylidene at 19.10 ppm and the new 4-hydroxybenzylidene catalyst at 18.40 ppm were observed as a 1:1 mixture.

Oligomers of the ring opening metathesis polymerization product were also detected by MALDI-ToF mass spectrometry. This implies that the more active **G3** catalyst prefers to polymerize the strained olefinic bonds rather than to form a stable six membered ring ($k_p > k_{rc}$, Scheme 1).

The propagating alkylidene undergoes a ring closing metathesis reaction to form the new carbene complex only when all the strained norbornene double bonds are consumed. As there were very few equivalents (3 eq.) of **4** added, not all of the initial amount of **G3** was consumed and remained therefore in the reaction mixture.

To slow down the rate of propagation of **G3**, 50 eq. of pyridine were added before the addition of **4**. The addition of pyridine slows down the propagation while also forming the new catalyst **G3.1** (Figure 1). On addition of 3 eq. of **4**, the ¹H-NMR benzylidene signal of **G3.1** (19.10 ppm) shifted quantitatively to the new carbene peak of **G3.1-OH** at 18.39 ppm within 10 min. (Figure 3 c).

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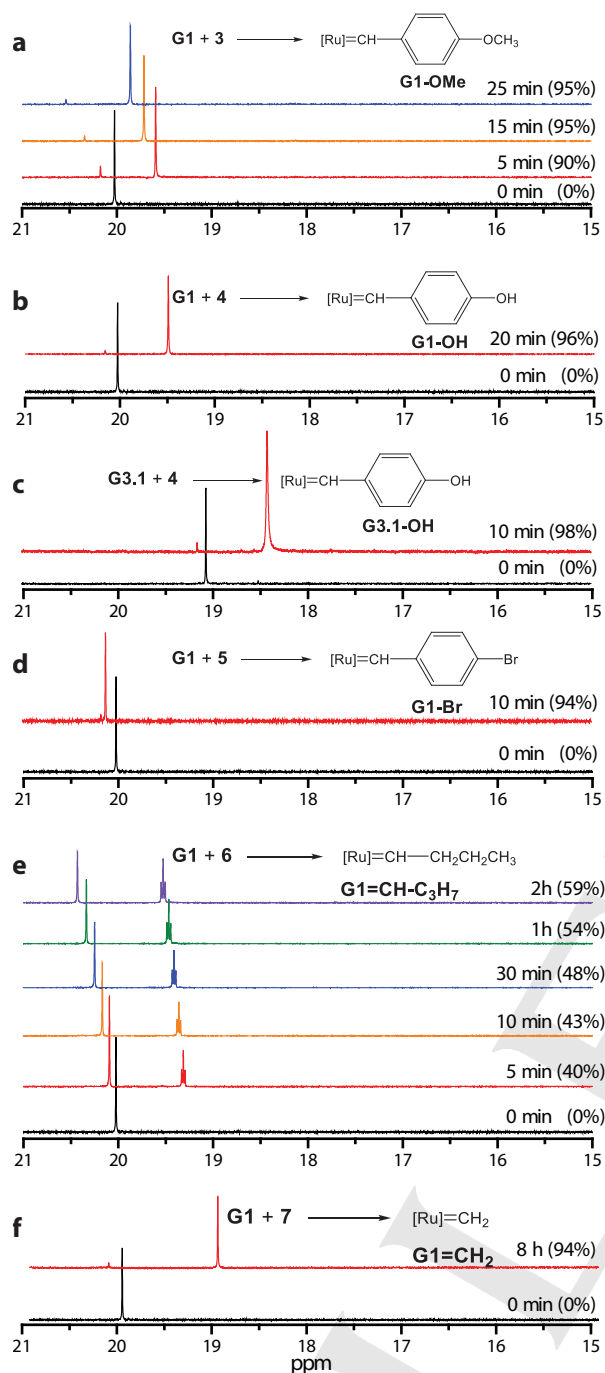


Figure 3. ^1H -NMR spectra (CD_2Cl_2 , 300 MHz) of the reactions of **3-7** with carbene complexes **G1** or **G3.1**. a) Reaction of **G1** with 3 eq. of **3** forming **G1-OMe** within 25 min. (95 % conversion). NMR traces are shifted progressively to the left by 0.2 ppm with increasing time for clarity. b) Reaction of **G1** with 3 eq. of **4** forming **G1-OH** within 20 min. (96 % conversion). Top NMR trace is shifted to the left by 0.2 ppm for clarity. c) Reaction of **G3.1** (formed by adding 50eq. of pyridine to **G3**) with 3 eq. of **4** forming **G3.1-OH** within 10 min. (98 % conversion). Top NMR trace is shifted to the left by 0.2 ppm for clarity. d) Reaction of **G1** with 3 eq. of **5** forming **G1-Br** within 10 min. (94 % conversion, the residual **G1** benzylidene signal is visible to the left of the newly formed **G1-Br** carbene). Top NMR trace is shifted to the left by 0.2 ppm for clarity. e) Reaction of **G1** with 3 eq. of **6** forming **G1=CH-C₃H₇** within 2 h (59 % conversion). NMR traces are shifted to the left by 0.1 ppm for clarity. f) Reaction of **G1** with 3 eq. of **7** forming **G1=CH₂** after 8 h (94 % conversion). Top NMR trace is shifted to the left by 0.2 ppm for clarity.

In order to elucidate the effect of the substituent in the para position, the 4-bromo substituted compound **5** was synthesized (Figure 2). As expected, the para substituent has little effect on the synthesis of the new 4-bromobenzylidene catalyst (**G1-Br**) and an almost quantitative conversion to a new carbene peak was observed in the ^1H -NMR spectrum (Figure 3 d, ^1H -NMR shift from 20.02 ppm to 19.98 ppm).³⁷ This indicates that the para substituent has no appreciable effect on the RORCM mechanism.

As was reported previously, the equilibrium constant for the reaction of **G1** with p-methoxystyrene ($K = 8.66$) is ca. 8 times greater than that for the reaction of **G1** with p-bromostyrene ($K = 1.10$).³⁷ However, the RORCM works equally well for **3** and **5** with identical amounts of substrate (3 equivalents), which indicates that the RORCM is indeed beneficial for syntheses of new ruthenium benzylidene catalysts even if the reaction with the corresponding styrene derivative has a small equilibrium constant. Grubbs et al. have also reported that the benzylidene ligand exchange with 4-chloro styrene is more than 20 times slower than that of 4-methoxy styrene.³⁸ The very fast syntheses of both the 4-bromo and the 4-methoxy substituted benzylidene complexes using RORCM demonstrates the advantage of using this strategy to synthesize new ruthenium benzylidene derivatives.

In order to investigate RORCM for the synthesis of alkylidene metathesis catalysts, compound **6** was synthesized (Figure 2). As most ruthenium alkylidenes are much more reactive compared to the **G1** benzylidene, we postulated that once a small amount of the alkylidene is formed, it would start consuming substrate **6** in a competition with **G1** benzylidene ($k_{\text{ROR}} \gg k_{\text{RORPh}}$, Scheme 1). This was indeed confirmed in a ^1H -NMR experiment with **G1** and 3 eq. of **6**. After 2 hours (Figure 3 e) 41% of the original Grubbs' catalyst was still remaining. The ^1H -NM signal of the new carbene complex (**G1=CH-C₃H₇**) can be clearly seen at 19.27 ppm.³⁷

A special case of a ruthenium alkylidene complex is the methyldene complex **G1=CH₂** which has previously been observed and isolated.^{35,39,40,41} However, its synthesis requires metathesis with ethylene gas at high pressures. In order to investigate whether RORCM could yield the methyldene complex, the 7-anti ally substituted norbornene **7** (Figure 2) was synthesized and reacted with **G1** (Figure 3 f). Upon addition of 3 eq. of **7** to **G1**, the ruthenium methyldene **G1=CH₂** was observed within 8 hours in 94 % yield at 18.95 ppm.³⁵

As a proof of principle, **G1** was reacted to give **G1-OH** as reported above and then monomer *exo-N*-methylnorbornene imide (**MNI**) was added. Upon quenching with ethyl vinyl ether, a monofunctional ROMP polymer was expected with the phenol at one end and a methylene group at the other. However, to our surprise, the polymer carried the cyclohexene (**HCP**) end group, which is the product of metathesis with the byproduct of RORCM (Scheme 3). As shown previously, the unsaturated six membered ring is not inert towards metathesis.⁴² Unfortunately, as the six membered ring reacts with the living polymer chain end, a simple terminal cross metathesis cannot be carried out. The same was true for initiation with **G3.1-OH**. **HCP** could also be used as a reversible chain transfer agent in a catalytic living ROMP.⁴² These results will be reported elsewhere.

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Following a similar protocol as reported previously by our group,²¹ a mixture of monomer **MNI** (17 eq.) and **MDHP** (20 eq.) (which is known to give an aldehyde end group)¹⁷ was added to **G1-OH**.

As shown in Scheme 3, the synthesis of **G1-OH** produces 3 equivalents of differently substituted **HCP** which are present during the subsequent polymerization reaction of **MNI** (see Scheme 3, 1st step). Due to the absence of ring strain in **HCP**, the highly strained **MNI** will polymerize exclusively until its concentration drops below a critical value. At this point the reaction with **HCP** becomes more favorable and the propagating chain terminates by reaction with **HCP** thereby reforming a **G1**-benzylidene derivative. Addition of **MDHP** to the polymerization reaction will lead to a reaction competition between **HCP** and **MDHP** for the propagating ruthenium alkylidene chain end. Here, all chains will be exclusively terminated by **MDHP** as it represents the more electron rich (vinyl ether) and hence more reactive double bond turning the ruthenium complex into a stable Fischer-carbene.

A heterotelechelic polymer with a TIPS and an aldehyde end group was also synthesized using this method. (see supporting info) This heterotelechelic polymer was further functionalized with 2,4-dinitrophenylhydrazine and a very high degree of functionalization was observed.

In conclusion, we have successfully developed a new one-pot strategy for the synthesis of functionalized first generation and third generation Grubbs' type metathesis initiators. The methoxy (**G1-OMe**), phenol (**G1-OH** and **G3.1-OH**), bromo (**G1-Br**), *n*-butyl (**G1-nBu**) and triisopropylsilyloxy (**G1-OTIPS**) catalysts were successfully synthesized in excellent yields. The ease of pre/post-functionalization of the phenolic OH group opens access to a multitude of functionalized metathesis catalysts. This atom economical approach requiring only 3 equivalents of the functionalized norbornene provides an easy and efficient access to heterotelechelic polymers and polymeric conjugates.

As a proof of principle, heterotelechelic polymers were prepared in a one pot strategy.

The tandem ring opening ring closing metathesis sequence, which has been used previously for synthesis of complex organic and polymeric compounds, was never investigated from the perspective of catalyst synthesis and modification. This route provides a new and efficient synthetic approach towards derivatives of the Grubbs-type ruthenium carbene complexes. Furthermore, the order of attack of the double bonds in the tandem RORCM was investigated, thereby providing a straightforward route to the ruthenium methylidene complex (**G1=CH₂**) avoiding the use of ethylene gas and high pressure.

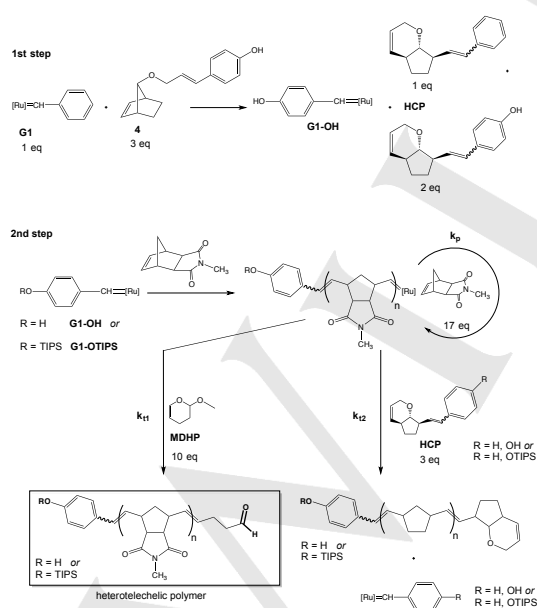
Experimental Section

Experimental details, procedures, NMR spectra, MALDI-ToF mass spectrometric characterization, GPC traces and x-ray single crystal structures provided in the supporting information.

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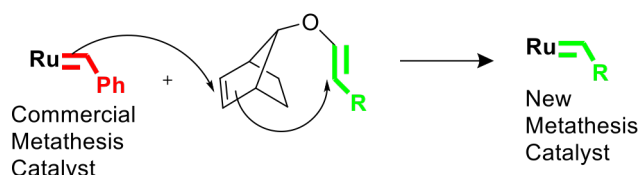
Keywords: olefin metathesis • Grubbs catalyst • ring opening metathesis polymerization (ROMP) • heterotelechelic polymer • ring opening ring - closing metathesis



Scheme 3. Synthesis of the heterotelechelic polymer by addition of a mixture of monomer and terminating agent to the reaction vessel containing **G1-OH**.

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The preferred reaction of the commercial ruthenium benzylidene complex with a highly strained norbornene followed by a fast intramolecular cyclization yields new ruthenium carbene complexes in excellent yields, ready for the functional initiation of polymers without the need of purification.

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