Functional Metathesis Catalyst Through Ring Closing Enyne Metathesis: One Pot Protocol for Living Hetero-telechelic Polymers

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ABSTRACT: Enyne ring closing metathesis has been used to synthesize functional group carrying metathesis catalysts from a commercial (Ru-benzylidene) Grubbs' catalysts. The new Grubbs-type ruthenium carbene was used to synthesize living hetero-telechelic ROMP polymers without any intermediate purification. Olefin metathesis with a mono substituted alkyne followed by ring closing metathesis with an allylic ether provided efficient access to new functional group carrying metathesis catalysts. Different functional benzylidene and alkylidene derivatives have been investigated in the synthesis of hetero-telechelic polymers in one pot.

Today, ruthenium and molybdenum-based metathesis catalysts [1], [2], [3] are extensively used to construct carbon-carbon double bonds. [4] The high functional group tolerance of the ruthenium based catalysts make them not only a popular choice in organic chemistry for ring-closing and cross-metathesis reactions but also in polymer chemistry for the polymerization of functional monomers. [5], [6] The first and third generation Grubbs' catalysts are the most common choice for polymer chemists due to their high initiation to propagation rate ratio (Figure 1, **G1** and **G3**), which allows their use in living polymerizations. [7]

In addition to main-chain functionality, polymers in which the chain ends can be addressed with high specificity are of great importance in a number of disciplines bordering chemistry, such as materials science, biochemistry or medicine. [8], [9], [10], [11]

Mono end-functional polymers can be made by functionally terminating living ring opening metathesis polymerizations. Many methods have been described to prepare polymers with alcohol, thiol, carboxylic acid, aldehyde or amine end groups in addition to the introduction of entire groups and moieties. [12], [13], [14], [15], [16], [17], [18], [19], [20]

Sacrificing the living character of the polymerization allows the synthesis of homo-telechelic polymers (Figure 1), typically from monomers such as cyclooctene or cyclooctadiene. [21], [22], [23], [24] Exploiting the propagation and cross-metathesis kinetics of the Grubbs' 3rd generation complex, homo-telechelics can also be prepared in a living manner. [25], [26]

Hetero-telechelic polymers (Figure 1) are, by nature, more difficult to synthesize. The sacrificial block copolymer method was used to prepare polymers carrying alcohol and either aldehyde or carboxylic acid end groups. [27] In one case, a regio-selective chain transfer agent was exploited to prepare hetero-telechelic polymers. [28] Functional polymer initiation followed by functional termination will allow the synthesis of hetero-telechelic polymers. Functional initiators can be prepared by cross-metathesis reactions using functional acyclic olefins. [29], [30], [31], [32], [33] However, the olefin is typically used in excess and the newly prepared initiator needs to be purified prior to polymerization.

Pre-functionalization agents (PFA) can be used in excess to pre-functionalize the ruthenium carbene complex without the need for purification as the excess is rendered metathesis inactive (or less active than the monomer that is introduced afterwards). Previously reported PFAs worked particularly well with **G1** but were limited to functional group bearing benzylidene complexes. [34]

Here, we report a new PFA which can be used with **G1** and **G3** yielding functional group carrying benzylidene and alkylidene complexes.
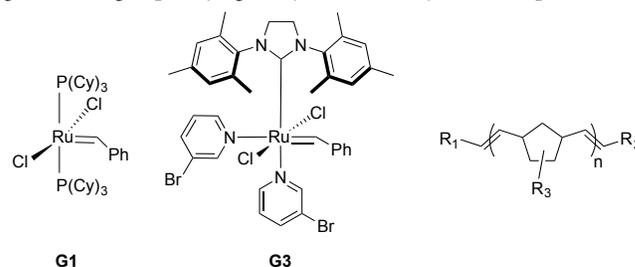

Figure 1. Left and center: first generation (**G1**) and third generation (**G3**) Grubbs' catalyst. Right: An end-functional polymer (here a polynorbornene derivative) is called homotelechelic (for $R_1=R_2$) or hetero-telechelic (for $R_1 \neq R_2$) assuming both groups R_1 and R_2 can undergo post-polymerization reactions.

The reactivity of alkynes towards olefin metathesis has been described. [35], [36], [37], [38] and enyne metathesis has been used in organic chemistry for many years.[39] Recently, the Choi group reported a tandem ring-opening ring-closing cross metathesis polymerization using an enyne sequence. [40], [41], [42] We hypothesized that the reactivity of a mono-substituted alkyne towards olefin metathesis would be higher than that of di or tri substituted allylic ethers. As a consequence, **G1** or **G3** would react faster with a terminal alkyne than an allylic olefin. The newly formed carbene (Scheme 1, A) would ideally undergo an intra-molecular ring closing reaction (Scheme 1, k_{RCM}) rather than an inter-molecular propagation reaction with another alkyne. This cyclization yields the new functionalized ruthenium carbene (Scheme 1, $Ru=CR_1R_2$) and a 2,5-dihydrofuran derivative (DHF, Scheme 1, B). As PFA **1**-**6** would be used in excess, the newly formed ruthenium carbene would undergo further enyne metathesis with excess **1**-**6** (Scheme 1, k_2), thereby producing a new DHF derivative (Scheme 1, C) and regenerating itself in the process. At the end of the cycle, the reaction mixture would only contain the two DHF derivatives (Scheme 1, B and C) and a functionalized ruthenium carbene. The DHF derivatives should ideally show lower metathesis reactivity due to a lack of ring strain and, therefore, a subsequent polymerization could be carried out by simply adding a strained monomer to the same reaction vessel without any purification or workup.

Scheme 1. Pre-functionalization of commercial **G1** and **G3** complexes using PFA **1**-**6**. For **G1** the reaction was carried out at rt. For **G3** the reaction was carried out at -10°C or at rt in the presence of 3-bromopyridine (30 equiv).
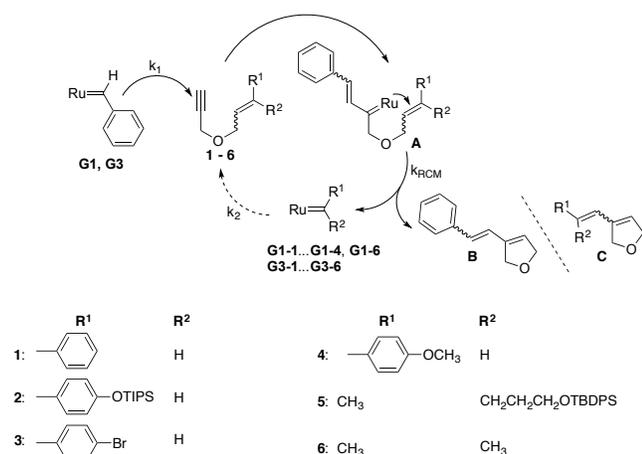
To verify our hypothesis, compounds **1-6** were synthesized (Scheme 1). As an initial test, **1** was subjected to 10 mol% of **G1** in dichloromethane-d_2 and the expected formation of 3-styryl-2,5-dihydrofuran (Scheme 1, B) could be observed immediately (see supporting information (SI) for characterization of E and Z isomers).

The pre-functionalization of **G1** using 3 equiv of either **2-4** was followed by ^{1}H-NMR spectroscopy in dichloromethane-d_2. The disappearance of the benzylidene carbene signal (20.03 ppm) and the formation of the respective new carbene signals in excellent yields could be observed (Figure 2 and SI Figure S1). As a proof of principle that the synthesis of hetero-telechelic polymers in one pot can be achieved following this route, *exo-N*-methyl norbornene imide (**MNI**, 17 equiv, 3h) was added to the pre-functionalized ruthenium carbene complexes **G1-2** and **G1-3** without any intermediate purification (Scheme 2). The **G1-2** initiated poly(**MNI**) was terminated with chain transfer agent (CTA) **10** (20 equiv, 1h, see Scheme 2), yielding a heterotelechelic polymer with a TIPS protected phenolic alcohol on one chain end and an aldehyde on the other (Mn_{GPC}= 5100 g mol^{-1}, Đ=1.2, **poly i**, see SI). The **G1-3** initiated poly(**MNI**) was terminated with CTA **9** resulting in a heterotelechelic polymer with an aryl bromide on one chain end and a BOC protected allylic amine on the other (Mn_{GPC}= 6300 g mol^{-1}, Đ=1.2, **poly h**, see SI).

The synthesis of ruthenium alkylidene initiators is of interest because of their faster rate of initiation compared to ruthenium benzylidenes. Reports for one pot syntheses of alkylidene initiators without the need for purification or workup are rare.[25],[26]

We therefore reacted 3 equiv of **6** with **G1** in dichloromethane-d_2. Unfortunately, only 36% of the benzylidene signal (20.03 ppm) disappeared over 3 h indicating that the ^{1}H-NMR silent ruthenium *iso*-propylidene complex could not have formed in high yield. We believe that the newly formed ruthenium *iso*-propylidene is faster at reacting with propargyl ether **6** (Scheme 1, k_2) than the **G1**-benzylidene (Scheme 1, k_1) resulting in incomplete conversion of the **G1**-benzylidene. To achieve higher conversions, the amount of **6** was increased (10 equiv). Unfortunately, only 64% conversion of **G1**-benzylidene into the *iso*-propylidene complex could be observed. (see SI) Similar observations had previously been made with a norbornene-based PFA and **G1**. [34]

Next, we investigated the pre-functionalization of **G3** (Figure 1) with PFA **1-6** (Scheme 1).
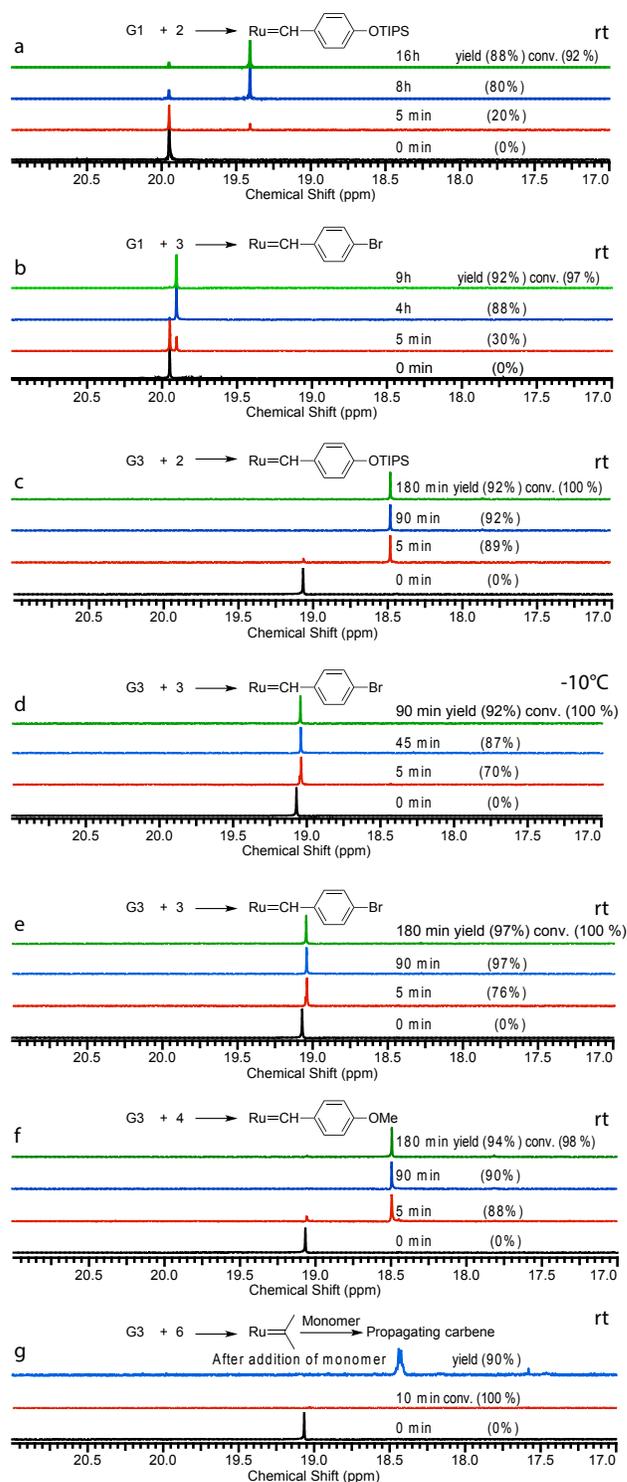

Figure 2. ^{1}H NMR spectra (CD$_2$Cl$_2$, 400 MHz) of reactions: a) **G1** with **2** forming **G1-OTIPS** (19.49 ppm), b) **G1** with **3** forming **G1-Br** (19.99 ppm), c) **G3** with **2** forming **G1-OTIPS** (18.55 ppm) at rt in presence of 30 equiv of 3-bromopyridine, d) **G3** with **3** forming **G3-Br** (19.05 ppm) at -10°C, e) **G3** with **3** forming **G3-Br** (19.05 ppm) at rt in presence of 30 equiv of 3-bromopyridine, f) **G3** with **4** forming **G3-OMe** (18.57 ppm) at rt in presence of 30 equiv of 3-bromopyridine and g) reaction of **G3** with **6** forming **G3**-isopropylidene followed by addition of **MNI** gives the propagating carbene (18.50 ppm) at rt in the presence of 30 equiv of 3-bromopyridine. (conv. = conversion)

Carrying out the reaction at rt in dichloromethane-d$_2$, we observed rapid catalyst decomposition by ^{1}H-NMR spectroscopy. Model experiments indicated that the **G3** benzylidene complex decomposes in the presence of 3-styryl-2,5-dihydrofuran as evidenced by new carbene species formed in the region of 18-19 ppm (Scheme 1 B and SI Figure S3). The mechanism of this decomposition is under investigation.

To avoid this decomposition, a RCEYM of **G3** with **3** was carried out at -10°C in dichloromethane-d$_2$ (Scheme 1). The reaction was followed by ^{1}H NMR spectroscopy. Within 45 min, the original **G3** benzylidene signal (19.06 ppm) shifted to a new carbene signal (19.05 ppm) with little loss of signal intensity (87%, Figure 2 d). The reaction of **2** and **4** with **G3** under identical conditions (Scheme 1) yielded new carbenes in high yields (90% for **2**, 96% for **4**, see SI).

The RCEYM of **G3** either with **5** or **6** was investigated by ^{1}H-NMR spectroscopy in dichloromethane-d$_2$ at -10°C (see SI Table 1). Unlike in the case of **G1** (see above), the **G3** benzylidene signal quantitatively shifted to an alkylidene carbene (complete disappearance of the benzylidene signal for **5** and **6**) using only 5 equiv of the corresponding PFAs **5** or **6** at -10°C. We assume that the rate of reaction between **G3** benzylidene and **5** or **6** (Scheme 1, k$_1$) is higher than the rate of ring closing metathesis (Scheme 1, k$_{RCM}$), leading to a fast consumption of the **G3** benzylidene complex. The newly formed carbenes **G3-5** or **G3-6** are, therefore, no longer in competition with the original **G3** benzylidene for the PFA substrates. The minimum excess of PFA was investigated for the reaction between **G3** and **4**. 1.5 equiv. of **4** (0.06 M) were sufficient to give 91% conversion into the new carbene species in the presence of 30 equiv. of pyridine (see SI).
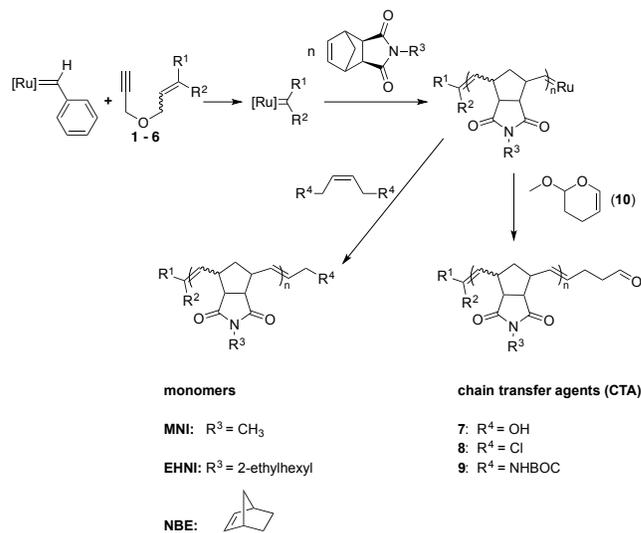
To lower its reactivity, we carried out the RCEYM of **G3** with **3** in the presence of 30 equiv of 3-bromopyridine in dichloromethane-d$_2$ at rt. ^{1}H-NMR spectroscopy revealed that the **G3** benzylidene signal shifted completely to the new benzylidene signal without appreciable loss of catalyst (19.05 ppm, 97%, Figure 2 e). The remaining substrates were subjected to **G3** at identical reaction conditions and generated the corresponding new carbene complexes in high yields (see Figure 2).

Heterotelechelic polymers were synthesized using both methods, i.e. low temperature pre-functionalization and 3-bromopyridine attenuation. **G3** was pre-functionalized with **4** at -10°C (120 min) followed by polymerization of **MNI** (30 equiv, 3 h) and functional termination with **7** (20 equiv, 1h) giving a methoxyphenyl initiated polymer with an allylic alcohol end group (Mn$_{GPC}$= 6100 g mol^{-1}, Đ=1.07, **poly a**, see SI). Similarly, heterotelechelic poly(**MNI**)s were prepared at -10°C via pre-functionalization with **3** and termination with **7** (Mn$_{GPC}$= 4500 g mol^{-1}, Đ=1.06, **poly b**, see SI), pre-functionalization with **2** and termination with **10** (Mn$_{GPC}$= 5200 g mol^{-1}, Đ=1.06, **poly c**, see SI) and pre-functionalization with **5** and termination with **10** (Mn$_{GPC}$= 7300 g mol^{-1}, Đ=1.06, **poly e**, see SI). Using norbornene as monomer at -10°C pre-functionalization with **3** and termination with **7** (Mn$_{GPC}$= 3900 g mol^{-1}, Đ=1.24, **poly g**, see SI) gave a poly(**NBE**) with an aryl bromide at one chain end and an allylic alcohol on the other.

Carrying out the polymerization of **MNI** at rt in the presence of 30 equiv of 3-bromopyridine, pre-functionalization with **6** (10 min), polymerization of **MNI** (60 equiv, 3h) and termination with **7** gave **poly d** (Mn$_{GPC}$= 11300 g mol^{-1}, Đ=1.06), pre-functionalization with **3** and termination with **8** gave **poly j** (Mn$_{GPC}$= 11300 g mol^{-1}, Đ=1.06) and pre-functionalization with **5** and termination with **9** gave **poly k** (Mn$_{GPC}$= 11300 g mol^{-1}, Đ=1.06). Using *exo-N*-(2-ethylhexyl)norbornene imide as monomer, pre-functionalization with **3** and termination with **7** gave heterotelechelic poly(**EHNI**) (**poly f**, Mn$_{GPC}$= 5300 g mol^{-1}, Đ=1.06, see also SI for all polymers).

GPC analysis showed narrow molecular weight distributions and MALDI-ToF mass spectrometry confirmed the presence of both functional end groups in all cases (see SI). A detailed ^{1}H-NMR end group analysis was carried out for **poly j** (see SI).

Scheme 2. One pot synthesis of hetero-telechelic polymers.

monomers

MNI: R^3 = CH$_3$

EHNI: R^3 = 2-ethylhexyl

NBE:

chain transfer agents (CTA)

7: R^4 = OH
8: R^4 = Cl
9: R^4 = NHBOC

To prove the presence of two different end functional groups, a polymer was prepared carrying a Coumarin 343 and Rhodamine B dye on opposite chain ends (see SI). Förster resonance energy transfer (FRET) from the excited Coumarin dye to the Rhodamine fluorophore proved the presence of both chromophores in close proximity (see SI).

In conclusion, we have successfully developed new PFAs for both **G1** and **G3**. Methoxy, bromo, triisopropylsiloxy and substituted alkylidene catalysts were synthesized in excellent yields. Hetero-telechelic polymers were prepared using these PFAs, **G1** and **G3** in one pot reactions without intermediate purification. End-functionalization was achieved using symmetrical olefin chain transfer agents to install allylic hydroxy, chloro or amine end groups or 2-methoxy-3,4-dihydro-2H-pyran to install aldehyde end groups. ^{1}H-NMR, FRET and GPC analyses show an excellent degree of end functionalization and good control over molecular weight confirming the living character of the polymerizations. This method provides an easy and efficient approach to functional Grubbs' metathesis catalysts using PFAs that can be prepared in few straightforward steps. The heterotelechelic polymers that are accessible via this route can serve as building blocks for preparing a wide range of new materials from functional bio-conjugates and well-defined co-polymer architectures to reactive surface coatings.

ASSOCIATED CONTENT

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Graphical abstract