

Understanding the effect of allylic methyls in olefin cross-metathesis

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Abstract

A series of NMR spectroscopy experiments have been conducted with both the model compound, 3-methyl-1-pentene and the corresponding ADMET monomer 3,6,9-trimethylundeca-1,10-diene (**11**) to better understand the effect of allylic methyls during olefin metathesis chemistry. Traditional ADMET catalysts such as Schrock's molybdenum (**1**), and Grubbs' ruthenium 1st and 2nd generation (**2** and **3**) were examined under cross-metathesis and ADMET conditions. Regardless of catalyst selection, 50% or less metathesis conversion was observed for all reactions, especially in the case of the more sterically encumbered diene. With Schrock's molybdenum catalyst **1**, the reaction leads to an accumulation of the non-productive metallacyclobutane, trapping the catalyst in an inactive form. With Grubbs' ruthenium catalysts **2** and **3**, the substrate coordinates to the metal center primarily to yield non-productive metathesis, which results in a build-up of the methylidene complex leading to catalyst decomposition. These results are directly correlated to the orientation of the substrate's bulk during the metallacyclobutane formation, the alkyl branch being adjacent to the metal center in the case of the molybdenum catalyst **1**, and opposite to it in the case of ruthenium catalyst **2** and **3**.

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1. Introduction

Olefin metathesis has been applied to a variety of organic synthetic challenges by allowing the simple formation of carbon–carbon double bonds in a single step where other routes would sometimes require several tedious steps [1]. The development of well-defined metathesis carbene catalysts, such as Schrock's molybdenum catalyst **1** [2], and the more recent Grubbs' ruthenium catalysts **2** [3] and **3** [4], has considerably widened the scope of olefin metathesis in both organic and polymer chemistry (Fig. 1) [5]. This success has inspired many catalyst modifications to introduce heterogeneous catalysts [6], water-soluble catalysts [7], recyclable catalysts [8], slower and faster initiators [9], so as to accommodate any particular set of conditions.

Despite the broad range of applications of these catalysts, challenges remain that must be addressed. On one

hand, Schrock's highly active carbene complexes are oxophilic which renders them sensitive to air and moisture, and thus inappropriate when used with certain functionalities such as aldehydes and alcohols [10]. On the other hand, ruthenium complexes, which possess a much higher functional group tolerance, are less active towards electron-poor or sterically demanding olefins [10,11]. Although the 2nd generation catalyst **3** displays activities comparable to early transition metal complexes [4,12], it also promotes double bond isomerization at elevated temperatures, competitively with metathesis, which can be problematic for the synthesis of precise polymer microstructures [13].

Part of our research effort has recently focused on building a family of α -olefin/ethylene copolymers to better understand the structure–properties relationship of widely commercialized polyethylene materials [14]. Using acyclic diene metathesis (ADMET), we have synthesized ethylene–propylene copolymers [EP($n + 1$)] with exact ethylene run length of $n = 4, 6, 8, 14, 18$ and 20 carbons, the methyl branch content being determined during the monomer

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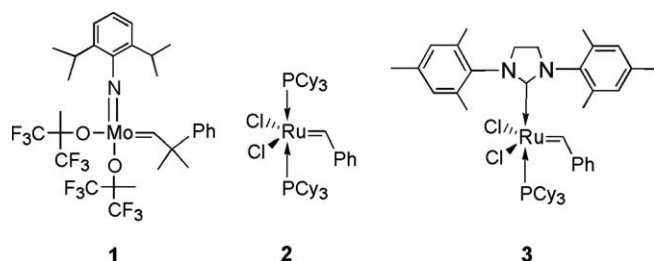


Fig. 1. Olefin metathesis catalysts.

design [15]. Although much progress has been made, we have been unable to polymerize the EP3 diene monomer (**11** in Fig. 2), since allylic methyl groups seem to pose problem.

Consequently, we decided to investigate the influence of allylic methyls in condensation metathesis chemistry using standard catalysts **1**, **2**, and **3**, in both cross-metathesis (CM) and ADMET conditions. Herein, we report an NMR spectroscopy study highlighting mechanistic features of both molybdenum and ruthenium metathesis catalysis in this reaction, and the importance of steric arrangement in the metallacyclobutane intermediate.

2. Results

ADMET monomer **11**, the target monomer possessing allylic groups, was synthesized starting with 3-methyl-4-pentenoic acid which was reduced and tosylated to yield diester **6** by addition to diethyl malonate (Fig. 2). Saponification and decarboxylation produced acid **8**, which then was reduced and tosylated. Substitution with LAH afforded monomer **11** in 29% overall yield.

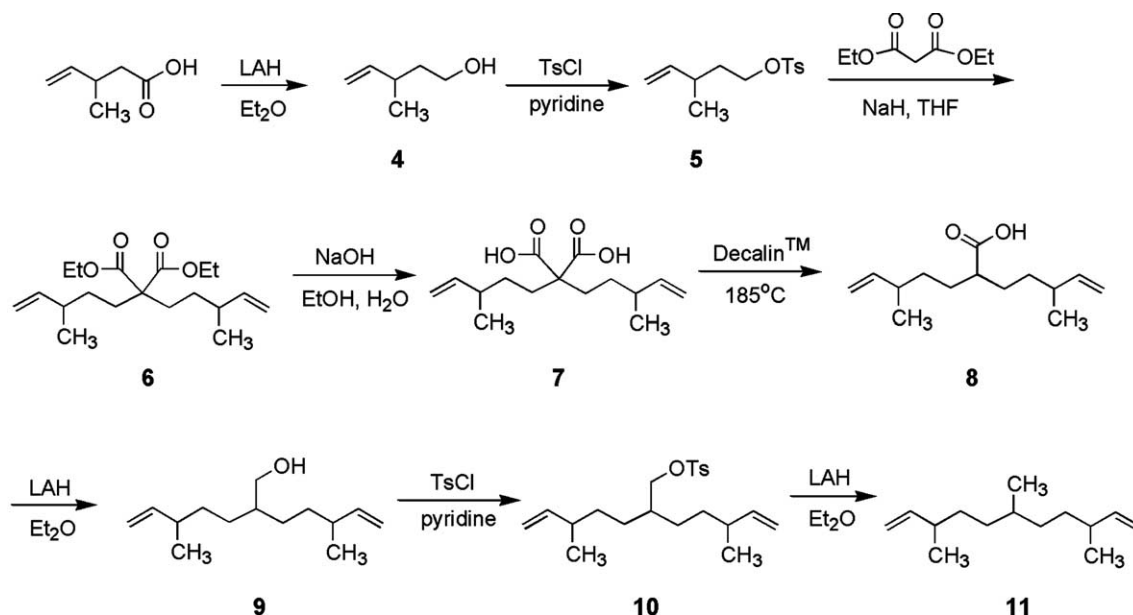
Efforts to polymerize **11**, 3,6,9-trimethylundeca-1,10-diene, to create unsaturated polyethylene containing

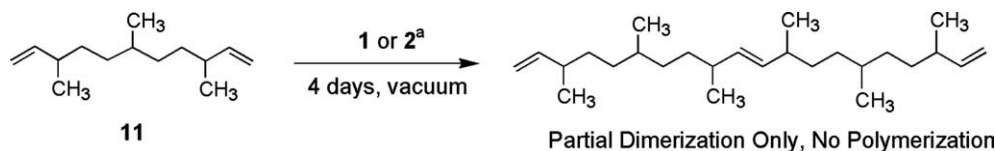
methyl branches on every third carbon led to little if any conversion (Fig. 3). Color changes during the reaction suggested catalyst decomposition very early in the reaction; olefin conversion was calculated at 4% for catalyst **1** and 8% for catalyst **2** at best. These results warranted a detailed NMR study with catalysts **1**, **2**, and **3**, probing for key intermediates during the catalytic cycle. To facilitate interpretation and broaden the scope of our study, the polymerization of **11** was examined more carefully along with the cross-metathesis reaction of 3-methyl-1-pentene, research which had been previously reported by Grubbs with catalyst **2** [16].

3. Schrock molybdenum catalyst

The experiments described below demonstrate that the dominant reaction pathway when using catalyst **1** leads to an accumulation of the non-productive metallacyclobutane intermediate, rather than full metathesis conversion. The experiments were set up using conditions that would allow monitoring dynamic catalytic behavior by NMR spectroscopy. For example, when examining the cross-reaction of 3-methyl-1-pentene (the “control” reaction for ADMET chemistry of monomer **11**), a typical experiment consisted of loading an NMR tube with a 0.2 M solution of olefin in C_6D_6 and 30 mol% of complex **1** [17].

After 30 min at room temperature, the proton NMR spectrum indicates the presence of the expected metathesis product 3,6-dimethyl-oct-4-ene (**A**), and products of the catalyst initiation (1,1-dimethyl-allyl)-benzene (**B**), and (1,1,4-trimethyl-hex-2-enyl)-benzene (**C**) (Fig. 4). However, product **A** only formed in 46% yield, which is insufficient for ADMET chemistry, again illustrating the difficulty associated with the homodimerization of this class of olefins. Products **B** and **C**, formed by reaction of one molecule

Fig. 2. Synthesis of monomer **11**.



^a Monomer:catalyst ratios: 1500:1 for **1**, 450:1 for **2**

Fig. 3. ADMET reaction of **11**.

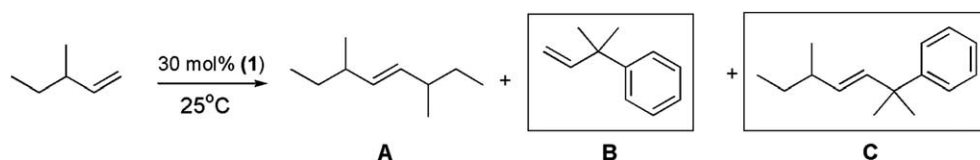


Fig. 4. Cross-metathesis of 3-methyl-1-pentene catalyzed by **1**.

of substrate with the original molybdenum catalyst (and therefore present in catalytic quantities), normally are not observed. They are visible here because of the use of high catalyst concentrations.

Fig. 5 depicts the catalytic cycle involved in the formation of each products presented in Fig. 4. For clarity, note that single arrows are drawn instead of equilibrium arrows, but according to the metathesis mechanism it is implied that each step actually exists as an equilibrium. Further, it should be noted that steps 3', 7 and 8 do not represent equilibrium conditions, but rather the non-productive metathesis cycle.

As the reaction starts, the first feature we observe is the major production of $\text{CH}_2=\text{C}(\text{CH}_3)_2\text{Ph}$ (**B**) compared to the alternate product **C**, which indicates that formation of the 2,4-metallacyclobutane is largely favored when 3-methyl-1-pentene coordinates to the original Schrock's alkylidene (Step 1 in Fig. 5). The two doublets at δ 13.18 and 13.23 ppm ($^2J_{\text{H,H}} = 5.6$ Hz) confirm the presence of the new alkylidene $\text{Mo}=\text{CHCH}(\text{CH}_3)\text{Et}$, each signal corresponding to one enantiomer of the racemic mixture (Fig. 6(a)) [2a]. Two metallacyclobutanes can form from this intermediate, the 2,3-addition leading to productive metathesis (step 3), and the 2,4-addition leading to non-productive

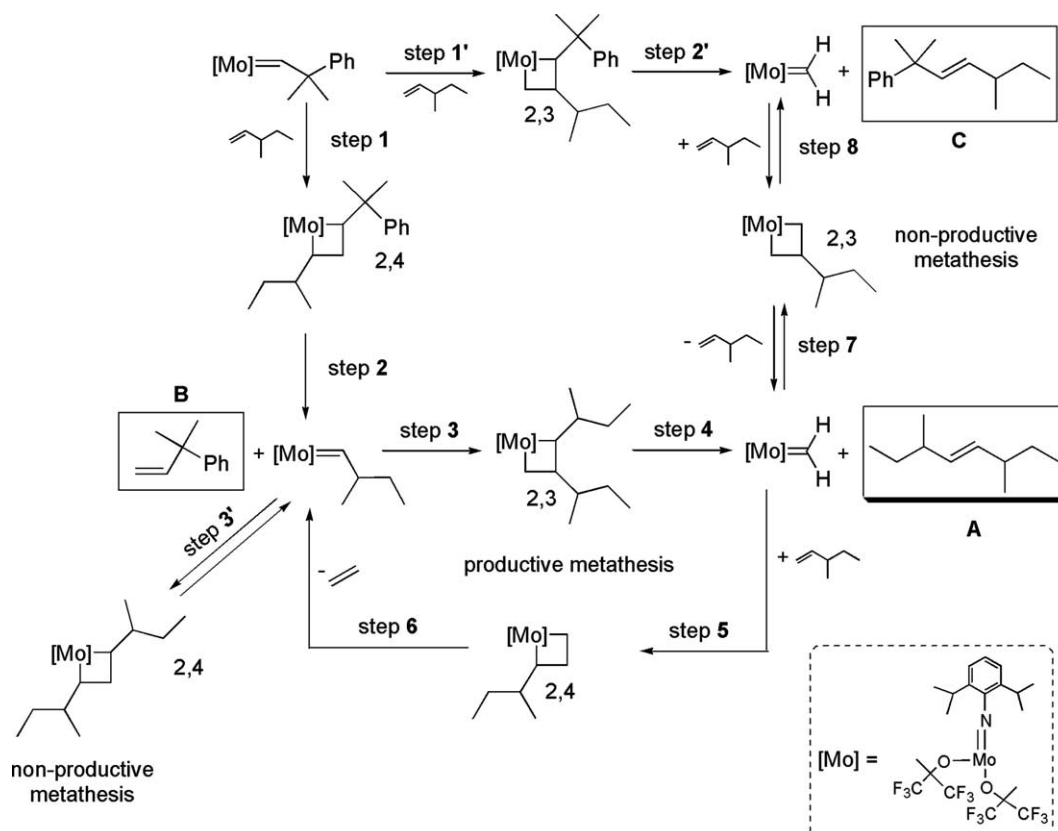


Fig. 5. Catalytic cycle for the metathesis of 3-methyl-1-pentene with a molybdenum carbene catalyst.

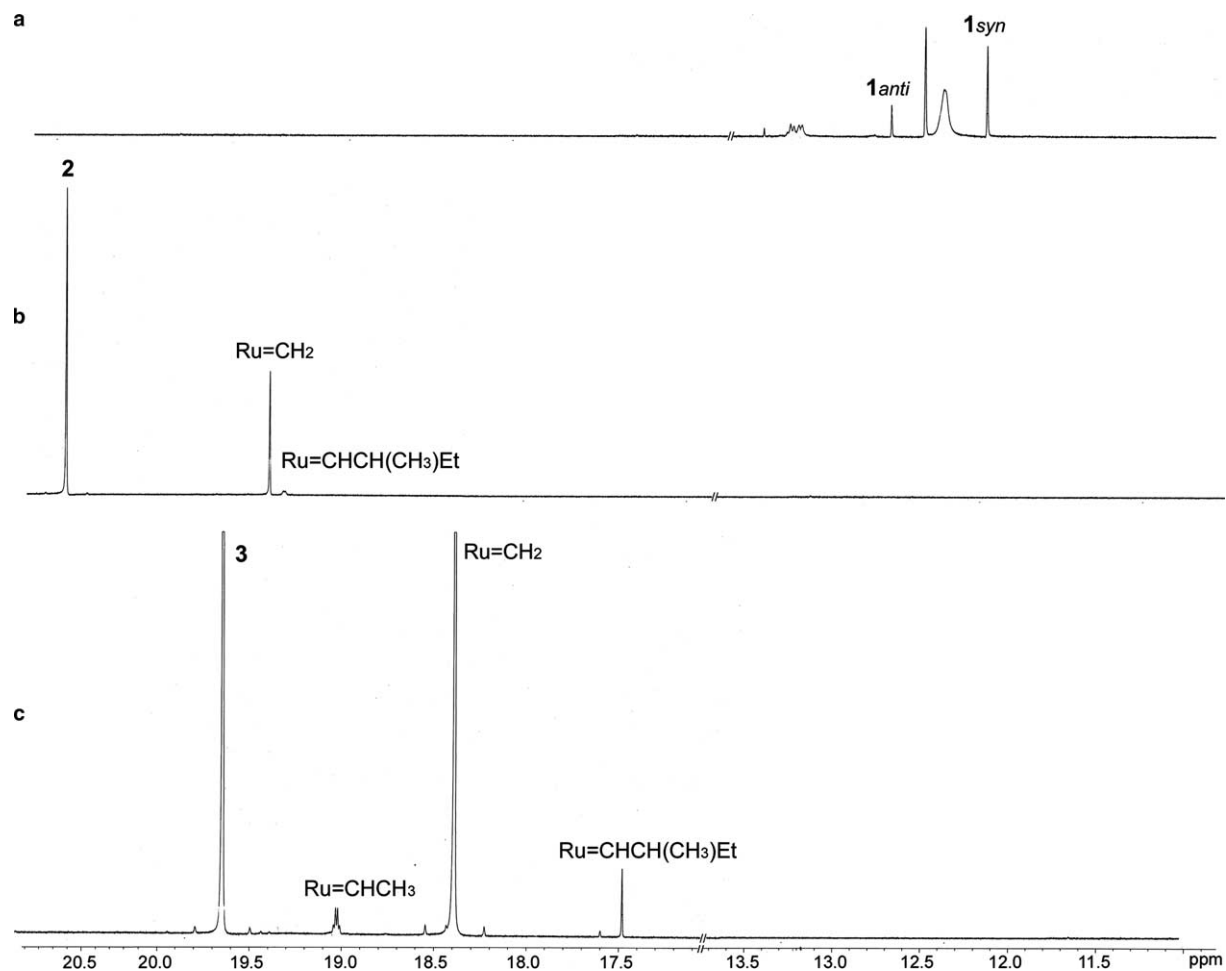


Fig. 6. ^1H NMR alkylidene region for the reaction of 3-methyl-1-pentene with catalyst (a) **1**; (b) **2**; (c) **3**.

metathesis (step 3'). After 10 min, two broad singlets appear in equal ratios at -0.17 and -1.06 ppm, characteristic of the two β protons of a trigonal-bipyramidal metallacyclobutane ring, therefore implying the formation of the 2,4-metallacyclobutane, further confirmed by the two α protons singlets at 5.10 and 4.84 ppm [2a]. The 2,3-metallacyclobutane would have given rise to a single signal in the upper field region. The fact that it is undetectable by NMR may be simply a result of its instability, forcing the metallacyclobutane intermediate to decompose quickly into the methyldiene and the metathesis product (step 4), as proven by the internal olefin resonance at 5.32 ppm. Because the methyldiene complex is highly unstable, we cannot unambiguously assign its signals. Moreover, the few methyldiene complexes that were ever observable by NMR were adducts stabilized by a polar solvent such as dme or THF, which is not possible here [2c,18]. The most common decomposition routes for high oxidation state ("d⁰") alkylidene complexes in the presence of olefins are rearrangement of metallacyclobutanes complexes by β -hydride mechanism and bimolecular coupling, methyldienes being the most susceptible to bimolecular decomposition [18]. However, the broad singlet at δ 12.36 ppm, assigned to the NH proton of an amido alkylidene complex, indicates yet another substantial decomposi-

tion pathway. This kind of proton transfer reaction from carbon to nitrogen was observed by Shrock et al. [19] during the preparation of $\text{Mo}(\text{NAr}_{\text{Cl}})(\text{CHCMe}_2\text{Ph})[\text{Biphen}]$. In any case, the metathesis reaction only reaches 46% conversion after 30 minutes, while the 2,4-metallacyclobutane already constitutes 50% of the catalyst mixture, which highlights the significant extent of non-productive metathesis.

The product distribution is similar when 3-methyl-1-pentene is substituted with monomer **11**, although ADMET conversions are slightly lower probably because of the substrate's longer carbon chain.

4. Grubbs' ruthenium catalysts

The NMR experiments with 3-methyl-1-pentene (CM conditions) and monomer **11** (ADMET conditions) were repeated using ruthenium catalysts **2** and **3**. Unlike what is observed in the case of early transition metals, the ruthenium metallacyclobutane is highly unstable, and it is still debated whether it is an intermediate or a transition state in the metathesis catalytic cycle [20]. As had been done before, an NMR tube was loaded with a 0.2 M solution of 3-methyl-1-pentene in C_6D_6 and 30 mol% of complex **2**.

After 30 min at 45 °C, the proton NMR spectrum indicates the presence of the metathesis product 3,6-dimethyloct-4-ene (**A**) in low yields and products of the catalyst initiation: styrene (**D**), and (3-methyl-pent-1-enyl)-benzene (**E**) that are formed by reaction of one molecule of substrate with the ruthenium benzylidene (Fig. 7). Product **A** is formed in 5% and 30% yields with catalyst **2** and **3**, respectively, again too low to be useful in ADMET step-growth polymerization. As before, products **D** and **E** are only visible because of the high catalyst concentrations.

Fig. 8 depicts the catalytic cycle involved in each product formation. Downfield in the NMR spectrum, we observe the steady disappearance of ruthenium benzylidene while the methylidene resonance at δ 19.40 ppm appears almost at a comparable rate. At the end of the experiment, three times more $\text{Ru}=\text{CH}_2$ (15%) is present than the expected $\text{Ru}=\text{CHCH}(\text{CH}_3)\text{Et}$ (5% of the catalyst mixture), evidenced by a doublet at δ 19.28 ppm (Fig. 6(b)).

As observed with the molybdenum catalyst, styrene is produced in much larger quantities than product **E**, which indicates the preferred formation of the 2,4-metallacyclob-

utane from the ruthenium benzylidene (steps 1 and 1' in Fig. 8). Theoretically, the amount of styrene released corresponds to the amount of catalyst activated for productive metathesis, $\text{Ru}=\text{CHCH}(\text{CH}_3)\text{Et}$. Since this alkylidene is not detected by NMR, it must react quickly with a substrate molecule through the intermediate of a 2,3-metallacyclobutane to afford the metathesis product **A** and the methylidene (steps 3 and 4). This analysis is further supported by the fact that the amount of **A** equals the amount of styrene generated. At this point, the methylidene continues to increase in concentration, while the metathesis reaction seems to cease, indicating that upon coordination of a new olefin molecule, the 2,3-metallacyclobutane is formed preferentially to regenerate the methylidene through step 7. Step 1' and 2' could also generate the methylidene, but this would involve a build-up of product **E**, which we do not observe. Further, the saturation of the reaction vessel with ethylene cannot be held entirely responsible for the methylidene build-up either, since little ethylene is present in solution compared to the excess of starting material.

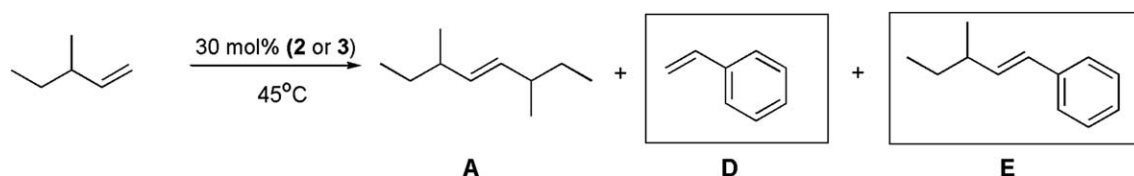


Fig. 7. CM of 3-methyl-1-pentene catalyzed by **2** or **3**.

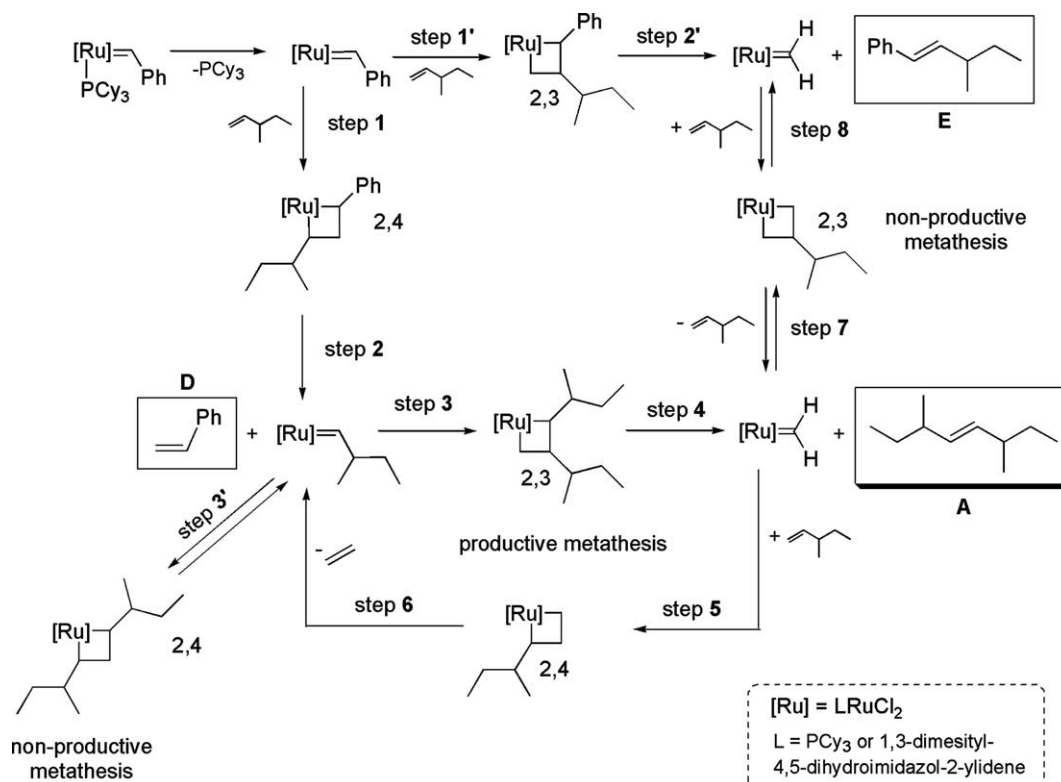


Fig. 8. Catalytic cycle for the metathesis of 3-methyl-1-pentene with ruthenium carbene catalyst **2** or **3**.

In any case, after 30 min, only 5% of starting material has reacted even though more than 20% of the benzylidene precatalyst has been consumed, mostly forming the highly unstable ruthenium methylidene. Apparently, decomposition of the catalyst system occurs at a faster rate than the metathesis reaction.

Hence, complex **2** cannot be regarded as a suitable catalyst for the homodimerization of 3-methyl-1-pentene, and probably not for any other olefin containing allylic methyls [16]. Indeed, when the reaction was repeated with the corresponding ADMET diene, we observed similar patterns; in fact, conversions were even lower. Metathesis products **A** and **E** were undetectable, and half less styrene was produced compared to the CM experiment, implying that less metallacyclobutane had formed. After 30 min, the methylidene constitutes 13% of the catalyst mixture and seems to be the only species besides the original benzylidene. These data indicate that with the ADMET monomer the rate of formation of any metallacyclobutane is slower, more likely because of the larger olefin.

Catalyst **3** was subjected to scrutiny under the same conditions. At room temperature, approximately the same amounts of styrene and **E** are detected at room temperature, while at 45 °C styrene seems to be in slight excess. Phosphine dissociation is so slow at low temperatures that an equilibrium between the 2,3- and 2,4-metallacyclobutane is created. When the dissociation event becomes faster, a greater amount of active catalyst is generated and the rate difference between formation of the 2,3- or 2,4-metallacyclobutane becomes evident because of the higher catalyst concentration.

After 30 min the methylidene represents about 30% of the catalyst mixture whereas $\text{Ru}=\text{CHCH}(\text{CH}_3)\text{Et}$ is only present in 1%, appearing as a doublet at δ 17.48 ppm (Fig. 6(c)). A quadruplet at 19.0 ppm also indicates the presence of $\text{Ru}=\text{CHCH}_3$ formed from the metathesis of isomerized starting material. Indeed, ruthenium catalysts, particularly those containing N-heterocyclic carbene ligands (NHC), can isomerize olefins by migration of the double bond along the backbone [13b,13c,13d]. The appearance of a multiplet at δ 5.19 ppm confirms the presence of 3-methyl-2-pentene by structural isomerization of the starting material. Traces of 2-methyl-1-butene also become visible at δ 4.67 ppm, formed by reaction of 3-methyl-2-pentene with the ruthenium methylidene. Nevertheless, the expected metathesis product **A**, 3,6-dimethyl-oct-4-ene, constitutes only 30% of the olefinic mixture, while 50% of starting material still remains. This level of conversion obviates any ADMET chemistry. The reaction does proceed, albeit at slow rates. Noteworthy, 34% of the original precatalyst **3** has already been consumed at this point, which is equivalent to a 10 mol% catalyst loadings, already surpassing the typical catalytic quantities.

Since $\text{Ru}=\text{CHCH}(\text{CH}_3)\text{Et}$ is not detected in significant amounts, we can still assume that the 2,3-metallacyclo-

tane is preferred during step 3. However, the amount of metathesis product formed far exceeds the amount of styrene detected, which implies that productive metathesis does occur, unlike what was observed with catalyst **2**. This observation is consistent with the higher reactivity of NHC-containing complexes towards olefinic substrates, attributed to the stabilizing effect of the NHC ligand on the metallacyclobutane [20b]. The ligand sphere may also allow a better arrangement of the alkyl bulk during the formation of the 2,4-metallacyclobutane.

As seen with 1st generation complex **2**, the reaction profile of catalyst **3** with the ADMET monomer **11** is identical to the CM reaction, but affords much lower conversions. Under the same conditions as CM chemistry, 70% of starting material remains even though more catalyst has been activated (46%). The amount of methylidene formed is also higher than during the CM reaction, which suggests that non-productive metathesis occurs to a larger extent through the preferred formation of a 2,3-metallacyclobutane. This favored conformation is likely a direct result of the additional sterics brought about by the larger diene monomer. In addition, four hydride complexes have formed during the course of the reaction indicating the start of the catalytic decomposition process, accelerated by the accumulation of the unstable methylidene complex.

5. Discussion

Although the conditions used in this study do not reflect exact polymerization conditions (where the metathesis equilibrium is driven by removal of ethylene) these experiments reflect a general catalytic behavior, since they demonstrate a steric conflict rather than a rate problem.

In the case of the Schrock's molybdenum catalyst, 3-methyl-1-pentene (or its diene analog, monomer **11**) seem to consistently coordinate to the metal in order to minimize steric interactions between the alkyl branches, hence forming the 2,4-metallacyclobutane, which, during step 3' (Fig. 5), only leads to non-productive metathesis. Moreover, this somewhat stable intermediate traps the catalyst in an inactive form. Even though productive metathesis occurs to some extent, it is insufficient to promote ADMET polymerization, a step-growth process that requires high conversions (>99%) in order to reach high molecular weight polymer.

A different mechanism operates with ruthenium catalysts to prevent the metathesis of allylic methyl-containing substrates. The ruthenium methylidene accumulates when catalyst **2** is used with either 3-methyl-1-pentene or the corresponding ADMET monomer, through the consecutive steps 1–4 in Fig. 8. The original benzylidene first forms a 2,4-metallacyclobutane upon olefin coordination to create a new alkylidene complex (steps 1 and 2 in Fig. 8), which then forms the 2,3-metallacyclobutane by reacting with another olefin (steps 3 and 4) [21]. From this point on, the methylidene complex only reacts with incoming olefins to

promote non-productive metathesis and regenerate itself (step 7), even though formation of the methylidene is not kinetically favored [16].

It has been suggested that the steric effects orient the bulk away from the crowded ruthenium metal center, while the electronic effects favor alkyl substituents adjacent to the metal [16]. Consequently, when the olefin reacts with the benzylidene complex, the benzene ring adjacent to ruthenium may be sufficiently electron-withdrawing to place the alkyl group next to the metal center, minimizing in the same time the steric repulsions between the alkyl branch and the phenyl group (step 1). On the other hand, when the methylidene complex is involved, no electronic effect directs the coordination of the olefin, which positions its steric bulk *away* from the metal center to form the 2,3-ruthenacyclobutane (step 7). The fact that the same reaction with linear olefins affords the inverse conformation [16] reveals the directing effect of allylic methyls, more likely by steric interactions with the ligand sphere of the complex.

These conclusions also apply to catalyst **3**, although the steric directing effects seem to be diminished in the presence of the NHC ligand. This could be due to a different arrangement of the ligand sphere reducing steric interactions, or to the propensity of the NHC ligand to stabilize the ruthenacyclobutane. Despite better yields, we could not achieve the conditions required by ADMET polycondensation. In addition, we observed a significant amount of olefin isomerization interfering with the metathesis process that render this 2nd generation of catalysts unsuitable for the modeling of precise molecules.

6. Conclusion

ADMET polymerization of dienes possessing allylic methyl groups is not possible, principally due to interaction of this methyl group with the metathesis catalyst. A series of NMR spectroscopy experiments conducted with both the diene monomer (**11**) and model compound 3-methyl-1-pentene, the corresponding mono-olefin, demonstrated that the reaction limitations depend on catalyst selection. With Schrock's molybdenum catalyst **1**, the reaction led to an accumulation of metallacyclobutane, trapping the catalyst into an inactive form. With Grubbs' ruthenium catalysts **2** and **3**, the substrate coordinates to the metal center only to yield non-productive metathesis, which results in a build-up of the methylidene complex, more prompt to decomposition. Although the NHC-containing complex **3** affords better yields than its phosphine analog, our experiments also illustrate the competitive nature of double-bond isomerization during olefin metathesis. These results are dictated by the steric arrangement of the substrate within the catalyst ligand sphere during the metallacyclobutane formation, the alkyl branch being adjacent to the metal center for the molybdenum **1**, and opposite to it in the case of ruthenium catalysts **2** and **3**.

7. Experimental

7.1. General

¹H NMR (300 MHz) and ¹³C NMR (75 Hz) spectra were recorded on either a Mercury series or Varian VXR-300 NMR superconducting spectrometer for small molecule structure determination. Chemical shifts were referenced to residual C₆H₆ (7.15 for ¹H and 128.39 for ¹³C) or CHCl₃ (7.27 for ¹H and 77.23 for ¹³C), and the NMR solvents were distilled, degassed by three freeze–pump–thaw cycles, and stored in an argon-filled drybox prior to use. Thin layer chromatography (TLC) was performed on EMD silica gel coated (250 μm thickness) glass plates cut to custom sizes. Developed TLC plates were stained with iodine absorbed on silica to produce a visible signature. Reaction conversions and relative purity of crude products were monitored by TLC chromatography and NMR. High-resolution mass spectral (HRMS) data were obtained on a Finnegan 4500 gas chromatograph/mass spectrometer using either the chemical ionization (CI) or electrospray ionization (ESI) mode.

7.2. Materials and methods

All materials were purchased from Aldrich chemical and used as received unless otherwise specified. Complex **1** [2a,2b,2c], and **3** [3a] were synthesized according to literature procedure. Complex **2** was a gift from Materia Inc., and was used as received. Catalysts were stored in an argon-filled drybox prior to use.

7.3. Bulk polymerization experiment

Monomer **4** (1.5 g, 77 mmol) was vacuum transferred from potassium mirror into a schlenk flask and taken into an argon-filled glove box. The catalyst (monomer:catalyst ratio is 1500:1 for **1**, 450:1 for **2**) was added to the monomer in a 50 ml round-bottom flask equipped with a magnetic stirbar, and allowed to react approximately 15 min before sealing the reactor with a schlenk adaptor and connecting to high vacuum line. Vacuum was applied intermittently for the first 2 h, then polymerization was heated at 40 °C and put under full vacuum (10⁻³ Torr) for 4 days. NMR samples were taken in *d*-chloroform directly from the reactor with no purification. Conversions were calculated by the ratio of integral values of the internal olefin (δ 5.20 ppm, m, 2H) to the terminal olefin (δ 4.95 ppm, m, 2H).

7.4. NMR catalyst experiments

NMR spectra were recorded on a Varian Inova spectrometer equipped with a 5 mm indirect detection probe, operating at 500 MHz for ¹H and at 125 MHz for ¹³C. The solvent was *d*₆-benzene and the temperature was

25 °C for catalyst **1** and 45 °C for catalysts **2** and **3**. Chemical shifts were referenced to residual C₆H₆ (7.15 for ¹H and 128.39 for ¹³C). In the drybox, 0.036 mmol of catalyst was introduced in an NMR tube equipped with a Teflon valve. Approximately 0.8 ml of C₆D₆ was added to the tube so as not to dissolve the catalyst extensively, and 0.119 mmol of substrate (3-methyl-1-pentene or monomer **11**) was carefully layered on top of the mixture. The NMR tube was sealed and shaken right before being introduced in the spectrometer. Proton spectra were recorded every 5 min, and quantitation was obtained by integration of the appropriate peaks against the solvent peak, which served as internal standard.

7.5. Synthesis of EP3 monomer (4–11)

7.5.1. 3-Methyl-4-pentene-1-ol (4)

Under an argon atmosphere a solution of 3-methyl-4-pentenoic acid (30.0 g, 263 mmol) in diethyl ether (100 mL) was added dropwise to a suspension of LAH (12.0 g, 342 mmol) in diethyl ether (350 mL) over 45 min at 0 °C. When the addition was complete, the slurry was stirred cold for 15 min, then the reaction was warmed to room temperature for 2 h. The reaction was then cooled to 0 °C and quenched by addition of water (200 mL) and concentrated HCl (~30 mL) until the aqueous layer was pH 3. The organic layer was collected, combined with a second ether wash (200 mL), and dried with brine and MgSO₄. Filtration, followed by distillation of the filtrate yielded a 21.5 g of colorless oil. 81.6% yield. b.p. = 149 °C, 760 mmHg. ¹H NMR matched reported spectral data [22]. ¹³C NMR (300 MHz, CDCl₃): δ (ppm) 20.61, 35.10, 39.48, 61.41, 113.32, 144.45.

7.5.2. 3-Ethenyl-1-butanol tosylate (5)

To a stirred solution of **4** (21.45 g, 214 mmol) in pyridine (100 mL) at 0 °C was added tosyl chloride (53.06 g, 278 mmol). The suspension was stirred cold for 10 min, then the viscous slurry was warmed to room temperature for 2 h. Addition of water (200 mL) and diethyl ether (200 mL) produced a biphasic mixture. The organic phase was isolated and combined with a second diethyl ether wash. Washing twice with 1 N HCl (200 mL), followed by drying over MgSO₄, and column chromatography (15% diethyl ether in hexane) afforded 53.6 g of colorless oil. 98.3% yield. ¹H NMR (300 MHz, CDCl₃): δ (ppm) 0.96 (d, 3H), 1.64 (m, 2H), 2.24 (m, 1H), 2.46 (s, 3H), 4.04 (m, 2H), 4.90 (m, 2H), 5.55 (m, 1H), 7.35 (d, 2H), 7.79 (d, 2H). ¹³C NMR (300 MHz, CDCl₃): δ (ppm) 20.27, 21.84, 34.34, 35.40, 69.01, 114.31, 128.10, 130.00, 133.40, 142.70, 144.86.

7.5.3. Diethyl 2,2-bis(3-methyl-4-pentenyl) malonate (6)

A solution of diethyl malonate (15.7 g, 98 mmol) in THF (100 mL) was added to a stirred solution of **5** (53.6 g, 210 mmol) and sodium hydride (5.6 g, 233 mmol) in THF (100 mL) over 30 min at 0 °C. The mixture was

stirred cold for 1 h, then warmed to room temperature for 18 h. The reaction was quenched by addition of water (250 mL), extracted with diethyl ether (300 mL), and dried with brine. Column chromatography (10% diethyl ether in hexane) afforded 18.9 g of colorless oil. 59.5% yield. ¹H NMR (300 MHz, CDCl₃): δ (ppm) 0.95 (d, 6H), 1.14 (q, 4H), 1.24 (t, 6H), 1.85 (m, 4H), 2.08 (m, 2H), 4.17 (q, 4H), 4.96 (m, 4H), 5.64 (m, 2H). ¹³C NMR (300 MHz, CDCl₃): δ (ppm) 14.33, 20.35, 29.96, 30.87, 38.10, 57.51, 61.16, 113.35, 144.11, 172.06. Elemental Anal. Calc. for C₁₉H₃₂O₄: C, 70.33; H, 9.94. Found: C, 69.93; H, 9.54%.

7.5.4. 2,2-Bis(3-methyl-4-pentenyl)malonic acid (7)

Potassium hydroxide (26.3 g, 470 mmol) was added to a solution of **6** (18.9 g, 58 mmol) in ethanol (100 mL) and water (20 mL) which was then brought to reflux for 3 h. The reaction was cooled, quenched with water (150 mL) and conc. HCl (until pH 3), and washed twice with diethyl ether (200 mL). The ether phase was dried with brine and concentrated to 15.0 g of a white solid with no further purification necessary. 95.7% yield. ¹H NMR (300 MHz, CDCl₃): δ (ppm) 1.01 (d, 6H), 1.25 (m, 4H), 1.83 (m, 4H), 2.11 (m, 2H), 4.98 (m, 4H), 5.65 (m, 2H), 11.18 (br, 2H). ¹³C NMR (300 MHz, CDCl₃): δ (ppm) 20.40, 31.18, 32.09, 38.14, 57.85, 113.73, 143.75, 177.96. CI/HRMS: [M + H]⁺ Cacl. for C₁₅H₂₅O₄: 269.1753. Found: 269.1749. Elemental Anal. Calc. for C₁₅H₂₅O₄: C, 67.14; H, 9.01. Found: C, 66.98; H, 8.89%.

7.5.5. 5-Methyl-2-(3-methyl-4-pentenyl)-6-heptenoic acid (8)

Decalin™ (15 mL, 1:1 wt%) was added to **7** (14.5 g, 54 mmol) and heated to 185 °C in a 250 mL round bottom flask equipped with an air cooled condenser under nitrogen. Production of CO₂ was monitored with a mineral oil bubbler, and the reaction was stirred vigorously until gas evolution ceased after about 30 min. Upon cooling, Decalin™ was removed via rotary evaporation affording crude acid. Column chromatography (20% ethyl acetate in hexane) afforded 11.4 g colorless oil. 94.0% yield. ¹H NMR (300 MHz, CDCl₃): δ (ppm) 1.01 (d, 6H), 1.33 (m, 4H), 1.50 (m, 2H), 1.61 (m, 2H), 2.12 (m, 2H), 2.31 (m, 1H), 4.96 (m, 4H), 5.67 (m, 2H). ¹³C NMR (300 MHz, CDCl₃): δ (ppm) 20.34, 20.51, 29.96, 30.06, 34.25, 34.36, 37.96, 38.08, 45.70, 45.86, 46.05, 113.13, 113.17, 144.38, 144.45, 183.01. CI/HRMS: [M + H]⁺ Cacl. for C₁₄H₂₅O₂: 225.1855. Found: 225.1845. Elemental Anal. Calc. for C₁₄H₂₅O₂: C, 74.95; H, 10.78. Found: C, 74.89; H, 10.68%.

7.5.6. 5-Methyl-2-(3-methyl-4-pentenyl) hept-6-en-1-ol (9)

Same procedure as for **4** using **8** as starting material. 8.6 g of colorless oil was isolated with no further purification needed. 84% yield. ¹H NMR (300 MHz, CDCl₃): δ (ppm) 1.00 (d, 6H), 1.20–1.41 (br, 9H), 1.66 (br, 1H), 2.09 (m, 2H), 3.53 (d, 2H), 4.95 (m, 4H), 5.69 (m, 2H). ¹³C NMR (300 MHz, CDCl₃): δ (ppm) 20.44, 20.47, 28.55, 28.58, 28.65, 33.97, 38.35, 40.94, 40.99, 65.74, 65.78, 112.78,

144.92, 144.94. CI/HRMS: $[M + H]^+$ Calcd. for $C_{14}H_{27}O$: 211.2062. Found: 211.2062. Elemental Anal. Calc. for $C_{14}H_{26}O$: C, 79.94; H, 12.46. Found: C, 79.71; H, 12.31%.

7.5.7. 5-Methyl-2-(3-methyl-4-pentenyl)-6-heptenyl tosylate (10)

Same procedure for **5** with **9** as starting material, 103% crude yield after concentration. No further purification performed. 1H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.93 (d, 6H), 1.15 (m, 4H), 1.22 (m, 4H), 1.56 (br, 1H), 1.99 (m, 2H), 2.45 (s, 3H), 3.90 (d, 2H), 4.91 (m, 4H), 5.60 (m, 2H), 7.34 (d, 2H), 7.78 (d, 2H). ^{13}C NMR (300 MHz, $CDCl_3$): δ (ppm) 20.31, 20.39, 21.79, 28.29, 28.36, 28.40, 33.38, 33.41, 33.49, 37.97, 38.08, 38.10, 72.81, 112.94, 112.97, 128.11, 129.97, 133.25, 144.81, 144.43, 144.46. CI/HRMS: $[M + H]^+$ Calcd. for $C_{21}H_{33}O_3S$: 365.2150. Found: 365.2143. Elemental Anal. Calc. for $C_{21}H_{33}O_3S$: C, 69.19; H, 8.85. Found: C, 68.93; H, 8.58%.

7.5.8. 3,6,9-Trimethylundeca-1,10-diene (11)

Same procedure as for **9** with **10** as starting material. Isolated 2.5 g of a colorless oil after column chromatography (hexane). 81.1% yield. 1H NMR (300 MHz, C_6D_6): δ (ppm) 0.87 (d, 3H), 0.98 (d, 6H), 1.12 (m, 2H), 1.30 (7H), 2.03 (m, 2H), 4.97 (m, 4H), 5.68 (2H). ^{13}C NMR (300 MHz, C_6D_6): δ (ppm) 19.85, 19.92, 19.98, 20.40, 20.64, 33.34, 33.42, 33.54, 34.48, 34.89, 34.92, 34.99, 35.01, 38.54, 112.65, 112.75, 144.96, 145.07. CI/HRMS: $[M + H]^+$ Calcd. for $C_{14}H_{26}O$: 194.2035. Found: 194.2037. Elemental Anal. Calc. for $C_{14}H_{26}O$: C, 86.52; H, 13.48. Found: C, 86.32; H, 13.51%.

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