Development of new olefin metathesis reactions via substrate modification:

Alkyne and olefin metathesis

Thesis by

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Abstract

Olefin metathesis (OM) reaction is a facile reaction to synthesize various molecules through carbon-carbon double bond rearrangement. With the development of more reactive yet functional group tolerant catalysts, OM proved its usefulness and became one of the most important reaction in modern organic chemistry. Among the various olefins that can subjected to OM, alkynes have special characteristic. As OM only exchanges carbon-carbon double bonds, reaction between alkyne and metal carbene catalyst does not completely cleave carbon-carbon triple bond: instead, new metal 1,3-dienylidene is formed, which can undergo further metathesis reactions, such as enyne metathesis or conjugated polyene synthesis. This thesis will describe about the various application of OM with alkynes, from synthesis of small molecules to high-molecular-weighted conjugated polyenes.

Chapter 2 describes synthesis of multicyclic compounds through selective tandem dienyne ring-closing metathesis (RCM) reaction and Diels-Alder reaction. Dienyne RCM reaction is a useful reaction to synthesize fused bicyclic compounds, but due to the lack of catalyst selectivity between olefins with same structures, dienyne RCM reaction tend to produce two different isomers with different ring sizes. Also, product of conventional dienyne RCM reaction was restricted to the bicyclic compounds containing small or medium sized rings only. Thus, conformation of 1,3-diene functional group in bicyclic compound was fixed to *s-trans* conformation, thus further modification such as Diels-Alder reaction was impossible. By modifying the dienyne substrate to contain long tether to synthesize bicyclic compound comprising small (5-7 membered) and large (14-17 membered) rings, both problems could be solved. As cyclization rate of small ring and catalyst exchange rate between alkenes were significantly faster than that of large ring, single isomer could be synthesized from dienyne RCM reaction. Also, due to the flexible macrocycle chain, 1,3-diene functional group could form

s-cis conformation, which could undergo Diels-Alder reaction to synthesize multicyclic compound.

Chapter 3 describes tandem ring-opening/ring-closing metathesis (RO/RCM) polymerization of monomers containing cycloalkene and alkyne. Although cycloalkenes with low ring strain and alkynes were not suitable for metathesis polymerization, mixing those two functional groups in one monomer facilitated efficient tandem RO/RCM reaction to perform ultrafast living polymerization. Living characteristic of tandem polymerization could also synthesize block copolymers. Also, 1,3-diene functional groups in the polymer backbone could undergo further modification by cycloadditionr reactions. By changing monomer structures, we found out that monomers with certain combinations of cycloalkene, alkyne, and linker group could undergo efficient polymerization, while monomers with other combinations did not. In order to increase polymerization efficiency, two strategies were proposed. Firstly, monomer structures were modified to increase intramolecular RO/RCM with enhanced Thorpe-Ingold effect, which allowed the synthesis of challenging dendronized polymer. Secondly, reaction concentration was reduced to suppress intermolecular side reactions, which could effectively polymerize monomers without structural modifications. In order to further broaden the monomer scope, monomers containing internal alkynes were also studied, and surprisingly, monomers with internal alkynes tend to undergo non-selective α- and β-addition to form two different polymer units with different ring structures. Further studies revealed that steric and electronic effects of internal alkyne substituents changed polymer unit ratio, polymerization reactivity, and even polymerization kinetics. Thorough mechanism study revealed that the rate-determining step of monomers containing certain internal alkyne was six-membered ring cyclization step *via* β-addition, whereas that for monomers containing other alkynes was the conventional intermolecular propagation step, as observed in other chain-growth polymerization reactions.

Last chapter describes about fast cyclopolymerization of 1,7-octadiyne derivatives. Although cyclopolymerization was effective for the synthesis of conjugated polyenes, cyclopolymerization of 1,7-octadiyne was rarely studied, due to the slow polymerization rate by slow six-membered ring cyclization rate. Although this polymerization rate could be increased by using bulky substituents in side chains, simply increasing substituent bulkiness could not effectively increase polymerization rate. Thus, we proposed two strategies to increase polymerization rate. Firstly, dimethyl substitution was introduced to α-position of side chains. This strategy effectively increased polymerization rate by enhanced Thorpe-Ingold effect, and synthesis of 50-mer polymer could be done within 1 hour, instead of previous 24 hours. However, in order to achieve controlled polymerization, reaction temperature should be decreased and polymerization time was increased to 6 hours. To solve this problem, second strategy was applied: by changing substituent position from 4,4-disubstitution to 4,5-disubstitution, polymerization rate was significantly increased, and even living polymerization with narrow PDI and well-predictable molecular weight was possible within 1 hours, and even challenging synthesis of dendronized polymer could be possible. All those polymers were analyzed by UV-Vis, NMR, and IR spectroscopy to observe polymer backbone structures, such as conjugation length of polymer and *cis*/*trans* conformation of polymer backbone.

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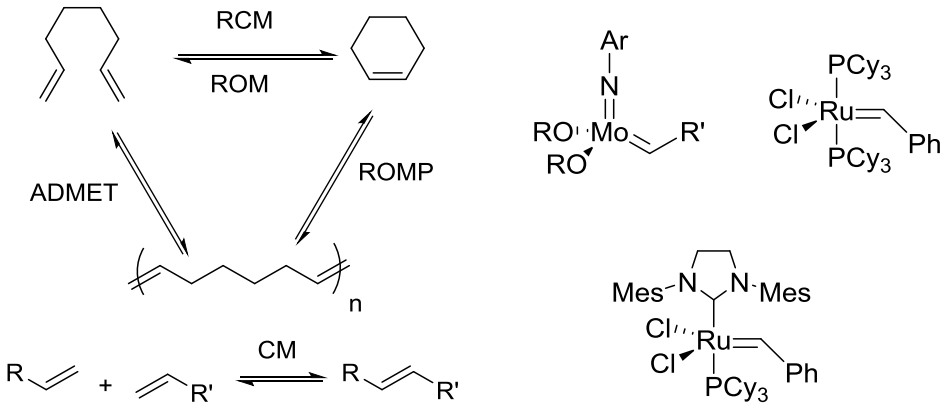
Chapter 1

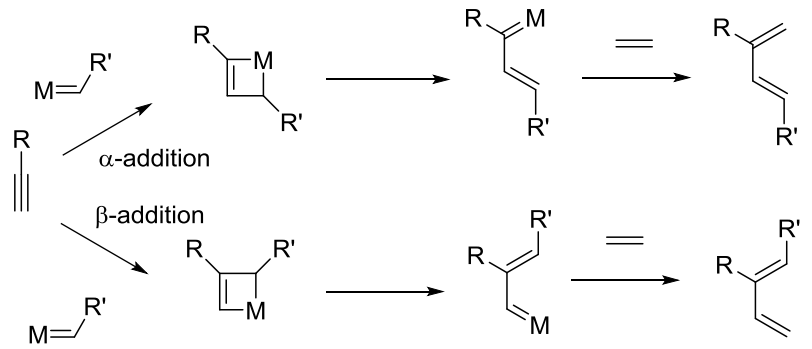
Olefin metathesis reaction with alkyne

Brief History of olefin metathesis with alkyne



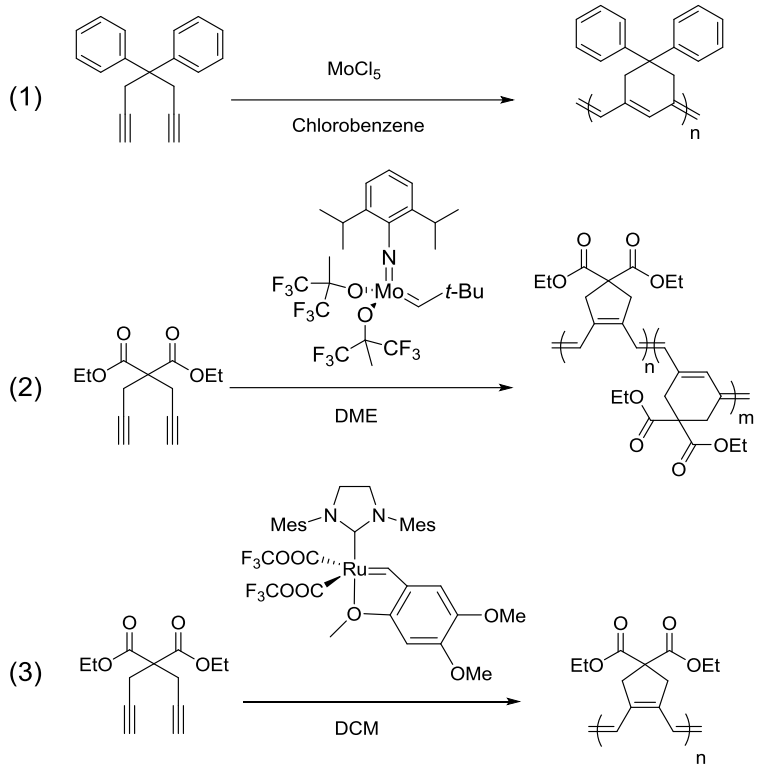
Scheme 1. Olefin metathesis reaction and notable catalysts

Olefin metathesis reaction is carbon-carbon double bond rearrangement between olefins to form new carbon-carbon double bond.[1] Since the discovery of olefin metathesis reactions at 1960's,[2] chemists developed various olefin metathesis techniques to provide three main reaction systems known as ring-opening metathesis (ROM)[3], cross metathesis (CM)[4], and ring-closing metathesis (RCM)[5]. Due to their usefulness, olefin metathesis reaction was further applied to polymerization to develop ring-opening metathesis polymerization (ROMP)[6] and acyclic diene metathesis polymerization (ADMET)[7] systems (Scheme 1). With the development of olefin metathesis reactions, olefin metathesis catalyst was also developed to increase their efficiencies. Starting from ill-defined transition metal salts (WCl_6, $MoCl_5$, etc.) with low functional group tolerance,[8] Schrock and Grubbs reported well-defined catalysts with molybdenum[9] and ruthenium[10] metal carbene system.



Scheme 2. Possible reaction pathway of alkyne reacting with metal carbene catalyst

Among the various olefin metathesis reaction substrates, alkyne shows interesting characteristics. When alkyne is reacted with olefin metathesis catalyst, it may undergo two different modes of α-, or β-additions to result in two different products (Scheme 2).[11] This mechanism was not well studied until Schrock's discovery of two different addition modes of molybdenum carbene catalyst toward 1,6-heptadiyne to form two different polymer units.[12] If catalyst undergoes α-addition, a sterically hindered 1,1-disubstituted metal alkylidene is obtained. On the other hands, if catalyst undergoes β-addition, more reactive monosubstituted metal alkylidene is formed. Wu's group explained this result with computational calculation that the steric effects of ligands affect to α-, and β-addition selectivity, suggesting large steric effect of alkoxyl ligand would disfavor α-addition, and large steric effect of alkylidene ligand would disfavor β-addition.[13] On the other hands, Grubbs catalysts tend to undergo highly selective α-addition, which is explained that steric effect between alkylidene ligand and alkyne substituent disfavors β-addition.[14] The most important feature of olefin metathesis reaction with alkyne is the formation of conjugated 1,3-dienylidene intermediate, which provides access to new synthetic methodologies such as conjugated polyene synthesis and tandem enyne metathesis reaction.

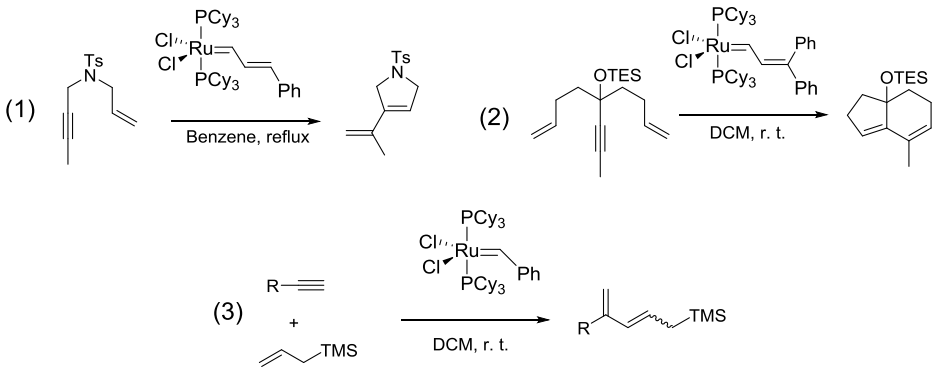


Scheme 3. Diyne cyclopolymerizations using metathesis catalysts

Initially, alkyne was introduced to metathesis reaction as a monomer for the synthesis of conjugated polyenes. Since the first acetylene polymerization by Natta and co-workers at 1958[15] and Shirakawa's report about electronical conductivity characteristic of conjugated polyene at 1974,[16] acetylene polymerization has been widely studied for the preparation of conducting polymers. The first acetylene metathesis polymerization was reported by Masuda and co-workers at 1974, which used WCl_6 or $MoCl_5$ olefin metathesis catalysts.[17] Further development acetylene polymerization allowed the living polymerization of polyacetylene via Ta[18], Mo[19], and Ru[20] based catalysts. However, acetyelene

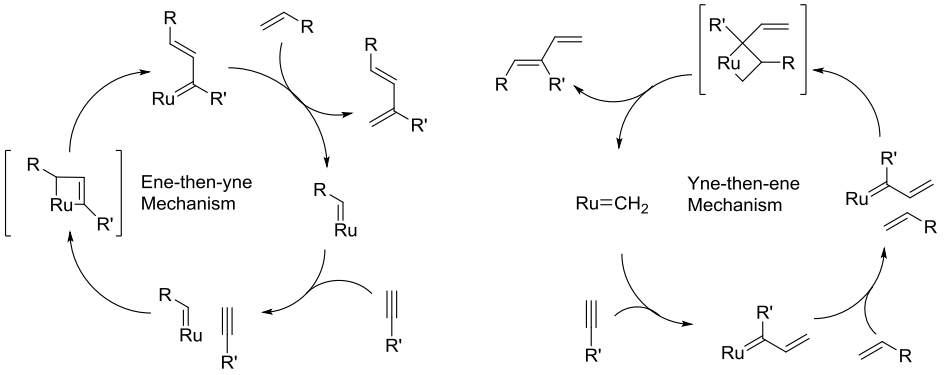
metathesis polymerization required harsh condition and polymerization efficiency was not good.

As an alternative pathway, diyne cyclopolymerization was used for polyene synthesis. First report of polymerization of non-conjugated diyne substrate to synthesize conjugated polyene used Zigger catalyst, which was done by Stille and co-workers at 1961, using 1,6-heptadiyne.[21] However, metathesis polymerization of 1,6-heptadiyne was overlooked until 1990, due to the low molecular weight of oligomer, insolubility of products, and low tolerance to air oxidation.[22] Those problems were solved with the introduction of substitution groups on 4-position of 1,6-heptadiyne. Starting from diphenyldipropargylmethane (DPDPM) and diethyldipropargylmalonate (DEDPM) monomer, various 4,4-disubstituted 1,6-heptadiyne monomers were polymerized with metathesis catalysts using $MoCl_5$ catalyst and opened renaissance of polyene synthesis through olefin metathesis reaction (Scheme 3).[23] At that time, polymer units from metathesis reactions were exclusively six-membered ring unit, derived from β-addition. In 1992, Schrock used well-defined molybdenum carbene complex for the living polymerization of 4,4-disubstitute 1,6-heptadiyne monomer.[24] Although the polymerization efficiency was high and well-controlled in both molecular weight and PDI, a mixture of five- and six-membered ring polymer units were formed due to the low selectivity between α-addition and β-addition (Scheme 3). Diyne cyclopolymerization using ruthenium based catalyst was studied a decade later, when Buchmeiser and co-workers polymerized 1,6-heptadiynes using modified Hoveyda-Grubbs catalyst at 2003 (Scheme 3).[25] Due to the high α-addition selectivity of ruthenium based catalyst to synthesize five-membered ring polymer unit exclusively, ruthenium based catalysts became widely used for cyclopolymerization along with the good tolerances toward air and moisture.[26]



Scheme 3. Notable enyne metathesis reactions.

Unlike polymer chemistry, organic chemists used enyne metathesis reaction to synthesize small molecules.[27] Enyne metathesis reaction is carbon-carbon double bond exchange between alkyne and alkene to form 1,3-diene functional group. First enyne metathesis reaction used Fischer carbene catalysts using tungsten or chromium metal, but they suffered high amount of catalyst loading, bad functional group tolerances, and low product yield due to the formation of various isomers.[28] The breakthrough for enyne metathesis reaction was started with the development of ruthenium based catalyst with good functional group tolerance. First enyne metathesis reaction with ruthenium based catalysts was reported by Mori and co-workers, who discovered ring-closing enyne metathesis reaction using ruthenium carbene catalyst at 1992.[29] Concurrently, Grubbs and co-workers reacted dienyne compound with ruthenium carbene catalyst to perform tandem ring-closing enyne metathesis reaction to synthesize bicyclic compound, which was the first example of tandem enyne metathesis.[30] At 1997, Blechert and co-workers reported intermolecular enyne cross metathesis reaction using ruthenium carbene catalysts.[31] Starting from those discoveries, enyne metathesis reaction could be applied to the preparation of various organic molecules.



Scheme 4. Two reaction pathways for enyne metathesis reaction

Although enyne metathesis reaction has been developed by many chemists, reaction mechanism of enyne metathesis reaction was in dispute for past decades. As both alkyne and alkene can react with metal carbene catalyst, both ene-then-yne mechanism and yne-then-ene mechanism could be possible (Scheme 4). In 2010, Sohn and co-workers reported fluorescence resonance energy transfer (FRET) based quenching experiment, which provided important clue on the reaction mechanism.[32] They reacted various kinds of metathesis catalysts containing on Mo and Ru metal carbenes with their substrate containing fluorescence dye and different olefins including terminal alkene and terminal alkyne. When catalysts reacted with olefin, catalyst will quench fluorescence of dye. According to their experiment, ruthenium catalysts containing *N*-heterocyclic (NHC) ligands reacted with alkyne faster, while catalysts without NHC ligands reacted with alkene faster. Their reports suggested that for olefins with same steric and electronic effects, catalysts without NHC ligand such as first-generation Grubbs catalyst undergoes ene-then-yne mechanism and catalysts with NHC ligand such as second-generation Grubbs catalyst undergoes yne-then-ene mechanism.

Thesis Research

As described above, many chemists studied metathesis reaction with alkyne to increase organic synthesis methodologies. However, due to the limitation of metathesis reactions such as low selectivity between olefins, reaction methodologies are not universal to various kinds of substrates. In the thesis research, we looked forward to further expand the scope of metathesis reactions from small molecule to polymers.

Chapter 2 describes synthesis of multicyclic compounds containing small and large rings through selective tandem dienyne ring-closing metathesis reaction and Diels-Alder reaction. Due to the slow cyclization rate of macrocycles, 'small ring first' cyclization product could be exclusively synthesized. Also, flexible macrocycle allowed *s-cis* conformation of 1,3-diene functional group within the ring, which could undergo Diels-Alder post-modification reaction to selectively form single multicyclic compound.

Chapter 3 discuss about tandem ring-opening/ring-closing metathesis polymerization of monomer containing cycloalkene with low ring strain and alkyne. Fusing those two unreactive monomers for metathesis polymerization to single monomer resulted ultrafast polymerization reaction, due to the fast alkyne addition and irreversible cyclization step. With this observations basic polymerization mechanism was studied. Reaction mechanism study provided new polymerization strategy to increase polymerization efficiencies for monomers with low reactivity. Lastly, monomers containing internal alkyne were polymerized to observe steric and electronic effect of alkyne substituents toward polymer reactivity, polymer microstructure, and polymerization kinetics.

Last Chapter demonstrates fast cyclopolymerization of 1,7-octadiyne monomers. Unlike 1,6-heptadiynes which undergo fast polymerization, 1,7-octadiyne

suffered from slow polymerization rate due to the slow cyclization rate. This chapter describes two monomer modification strategies to significantly increase polymerization rate. Firstly, dimethyl substituents were introduced to α-position of side chain, in order to induce greater Thorpe-Ingold effect toward 1,7-octadiyne tether. Secondly, monomer structure was changed from 4,4-disubstitution to 4,5-disubstitution. Monomer design, monomer synthesis, polymerization optimization, and detailed polymer characteristic studies are described in this chapter.

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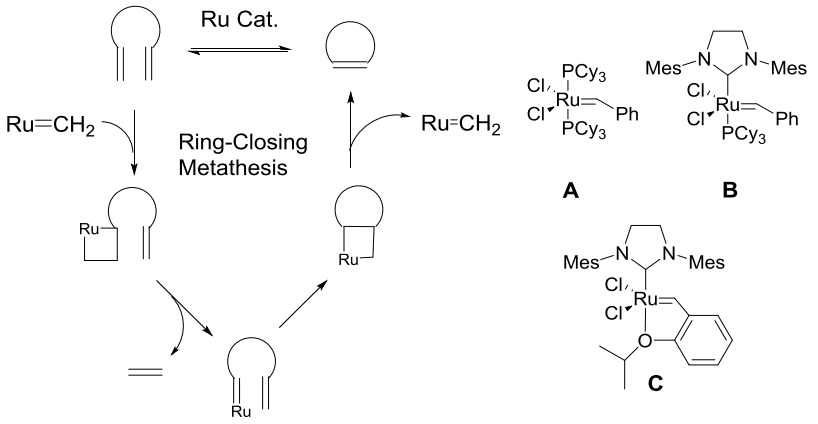
Chapter 2

Synthesis of fused multicyclic compound through dienyne ring-closing metathesis and Diels-Alder reaction

Abstract

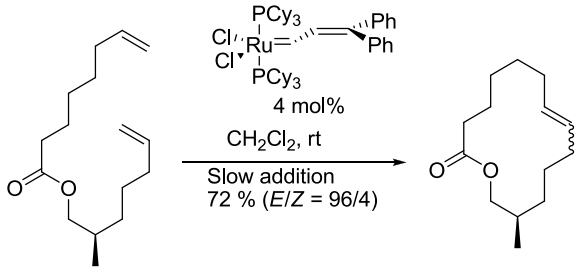
Fused multicyclic compound was synthesized through selective dienyne ring-closing metathesis (RCM) reaction and Diels-Alder reaction. The major drawback of tandem dienyne RCM reaction was the formation of two isomers with different ring structures, due to the low selectivity of catalyst toward terminal alkenes. In order to solve this problem, dienyne substrates with one short tether and one long tether were synthesized. Thanks to the fast small ring cyclization-catalyst exchange rate and slower large ring cyclization-dimerization rate, single isomer of fused bicyclic compound could be synthesized. Furthermore, flexible macrocycle chain allowed the formation of *s-cis* conformation of 1,3-diene functional group in bicyclic compound, which could be modified with cycloaddition reaction, and detailed structural analysis suggested that the resulting structure had single regiochemistry. Lastly, sequential one-pot reaction was performed to synthesize multicyclic compound without purification step.

Background



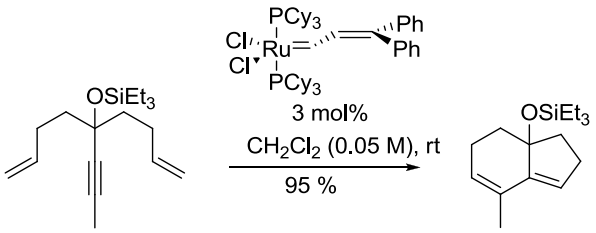
Scheme 1. Reaction pathway of RCM reaction and notable ruthenium based catalysts.

Synthesis of cyclic compound was one of the most important reaction in organic chemistry. Various methods were used for the synthesis of various ring structures like simple small sized rings, macrocyclic compounds, or cholesterol-like fused multicyclic compounds. Among the various methodologies to synthesize cyclic compounds, ring-closing metathesis (RCM) was one of the most powerful reaction (Scheme 1).[1] With the development of highly active ruthenium based catalysts with good functional group tolerances, RCM reaction provided easy access to the synthesis of various cyclic compounds with high productivity.[2]



Scheme 2. Macrocyclic RCM reaction using Grubbs catalyst.

Macrocyclization took great advantage by the development of RCM reaction.[3] Previously, macrocyclic compounds were synthesized by conventional organic reactions based on radical-mediated cyclization[4], Prins macrocyclization[5] or Yamaguchi macrolactonization[6]. However, those reactions showed relatively low productivity and suffered by the use of toxic reagents or excess chemical reagents. RCM reaction was good alternative method for macrocyclization due to their high productivity, low toxicity of reagent, and catalytic amount of reagent use (Scheme 2).



Scheme 3. Tandem dienyne RCM reaction for synthesis of bicyclic molecule.

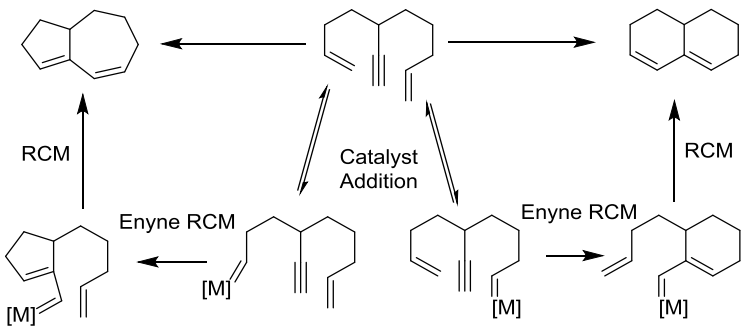
Also, RCM reaction was used as an effective protocol for the synthesis of multicyclic compounds.[7] Organic chemists used tandem radical cyclization reaction for the synthesis of various fused multicyclic compounds.[8] This method could be used to synthesize many complex molecules including complex cholesterol analogues, but controlling reactive intermediate to give the desired product can be difficult, and toxic residues are generated as a side-product. However, since Grubbs' first report on the synthesis of fused bicyclic compound by tandem dienyne metathesis reaction, RCM reaction has been recognized as an alternative method (Scheme 3).[9]

As new substrates had been synthesized by various RCM reactions, further post-modification reaction could provide the methods to synthesize more complex molecules. One of the good candidate is 1,3-diene functional group, which could be generated from enyne metathesis reaction. Using appropriate dienophiles, various cycloaddition reactions such as Diels-Alder reaction could be used as a good candidate for post-modification.[10] However, examples of Diels-Alder reaction on bicyclic compounds produced by tandem dienyne RCM were quite rare.[11]

In this chapter, selective synthesis of multicyclic compound using selective tandem dienyne RCM reaction and Diels-Alder post-modification will be described.

Introduction

Since the first tandem dienyne RCM reaction by Grubbs and co-workers, tandem dienyne RCM has been used as a versatile method for the synthesis of fused bicyclic compounds containing 1,3-diene functional group.[9] However, previously studied tandem dienyne RCM reaction had two limitations. First, due to the low selectivity of catalyst between olefins, two isomers containing different ring sizes were synthesized. In order to undergo selective RCM reaction, chemists used an additional protection to one alkene to decrease reactivity.[12] Second, due to the limitation of substrate scope to synthesize only small to medium sized ring containing products, resulting 1,3-diene functional group in the ring was restricted to form *s-trans* structures only, and further modification was not possible.[13] (Scheme 4)



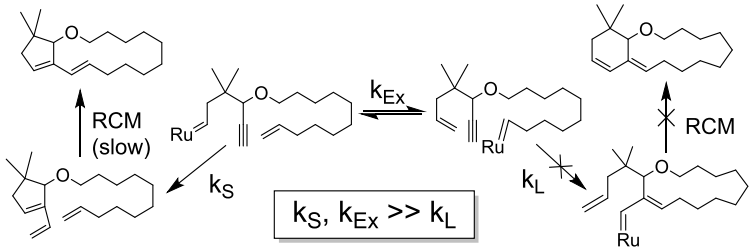
Scheme 4. Possible reaction pathways for tandem dienyne RCM reaction

Follwing the development of highly active olefin metathesis catalysts containing *N*-heterocyclic carbene (NHC) ligand[2], synthesis of more challenging substrates through RCM could be performed, including macrocyclic RCM reaction. This development further expanded the scope of substrates for RCM, including tandem dienyne RCM reaction. First, macrocyclization rate is significantly slower than the cyclization of small rings, which makes good candidate for selective tandem

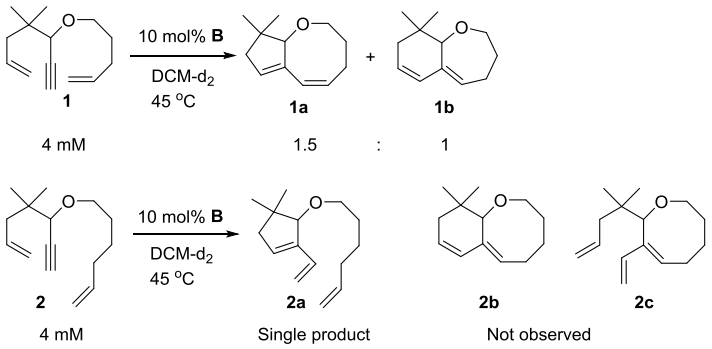
dienyne RCM reaction. Second, flexibility of macrocycle can form *s-cis* diene functional group after dienyne RCM reaction, which can be used for post-functionalization with cycloaddition reactions. Herein, we introduce the synthesis of multicyclic compound with tandem dienyne RCM reaction and Diels-Alder post functionalization reaction. Tandem dienyne RCM could produce single isomer containing small sized rings (5-7) and macrocycles (14-18), with the use of different cyclization rate between small and large rings.[14]

Result and Discussion

One potential problem of asymmetric dienyne RCM reaction was that dienyne substrates with different lengths of tethers give two isomers with different ring sizes.[9] This was due to the catalyst to react with both terminal alkenes with no preference. To achieve selective dienyne RCM reaction, one terminal alkene should have protected as a disubstituted internal alkene, allowing catalyst to react with less sterically hindered alkene first.[12] On the other hand, increasing reaction concentration also enhanced the selectivity by increasing the exchange rate between metal carbenes,[15] but this strategy is not suitable for macrocyclization because low concentration is required to prevent oligomerization.



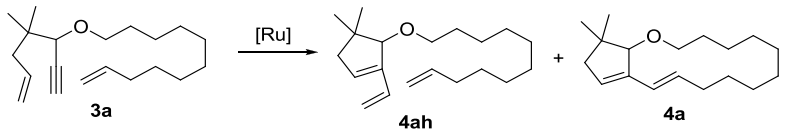
Scheme 5. Proposed reaction pathway for dienyne tandem RCM reaction.



Scheme 6. Tandem dienyne metathesis reaction for bicyclic compound containing small rings.

For the synthesis of bicyclic compound containing small and large rings, we expected that the selectivity issue will be eliminated if the rate of initial RCM to form a small ring (k_S) and metal carbene exchange rate (k_{Ex}) was far greater than the the rate of RCM to form a large ring (k_L) (Scheme 5). In order to confirm this proposal, two substrates **1** and **2** were prepared, in order to estimate the relative rate of k_S, k_{Ex}, and k_L. When **1** was reacted with second-generation Grubbs catalyst (**B**) under diluted concentration of 4 mM DCM, two products with a 1.5 : 1 ratio of **1a** and **1b** from non-selective RCM were observed during crude NMR analysis (Scheme 6). This suggests that five- and seven-membered ring cyclization rate was almost equal at low concentration, implying that the cyclization rate of five-, six-, and seven-membered ring cyclization rates were faster than the k_{Ex} between two different terminal alkenes. However, when substrate **2** reacted at low concentration, **2a** with a five-membered ring was observed exclusively during crude NMR analysis without the presence of **2b** or **2c** containing eight-membered ring. This suggests that eight-membered ring cyclization rate was slower than the k_{Ex} between two different terminal alkenes, resulting in complete selectivity. However, desired fused bicyclic compound was not observed due to the congested structure of medium-sized ring.

Table 1. Dienyne RCM reaction optimization[a]

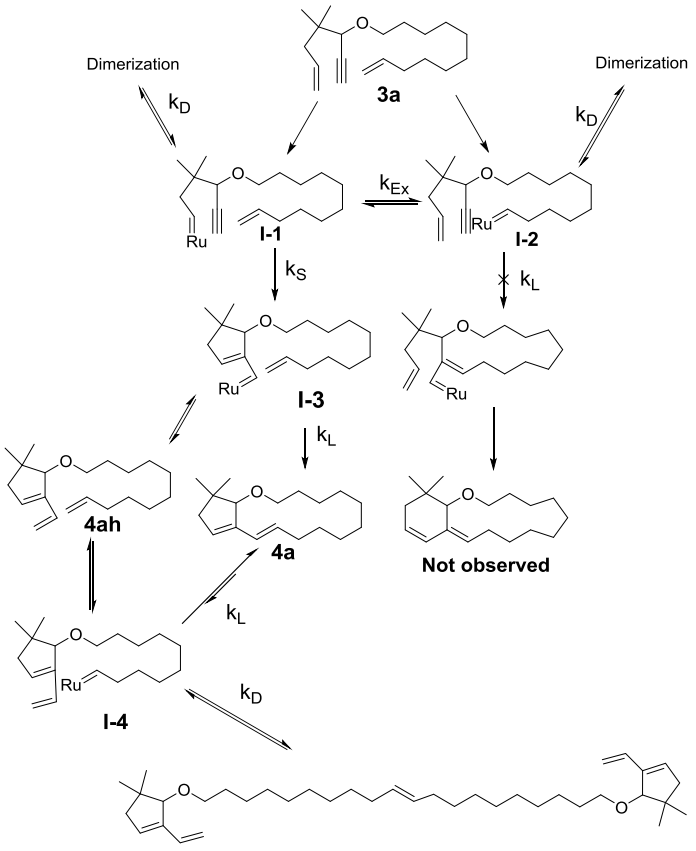


Entry	Catalyst	Solvent	Temp.	Yield of **4a**	**4ah**:**4a**[b]
1	**B**	DCM	45 ℃	N/A	1 : 2
2	**C**	DCM	45 ℃	N/A	1 : 2
3	**B**	1, 2-DCE	55 ℃	N/A	1 : 1.2
4	**B**	Toluene	55 ℃	73 %	1 : 12
5	**B**	Toluene	70 ℃	82 %	1 : 14

[a] General reaction condition : Under Ar atmosphere, 5 mol% catalyst was added to a substrate in 4 mM degassed solvent. Solution was heated for 24 hours under reflux condition. [b] Ratio was determined by ^{1}H NMR analysis.

With this result, we expected that selective dienyne RCM to synthesize bicyclic compound with small and large ring would be possible, as RCM rate of macrocycle would be significantly slower than the RCM rate of small ring. Also, desired bicyclic compound could be synthesized easily due to the flexible alkene tether to easily perform macrocyclization with carbene intermediate. In order to confirm this observation, substrate **3a** was synthesized and reacted with second-generation Grubbs catalyst at 4 mM concentration. When **3a** was reacted under 45 ℃ DCM solvent for 24 hours, 1 : 2 mixture of **4ah** and **4a** was observed, without the formation of macrocyclization-first product (Table 1, entry 1). This suggests that k_S and k_{Ex} were indeed faster than k_L for macrocycles to perform selective dienyne RCM reaction. In order to promote complete cyclization, various reaction conditions were tried. Initially, catalyst was changed to second-generation Hoveyda-Grubbs catalyst (**C**), but macrocyclization was not promoted

(Entry 2). In order to raise reaction temperature to 55 ℃ to promote macrocyclization, 1,2-DCE was used as a solvent instead, but it was less favorable to for macrocyclization, giving almost equal amount of **4ah** and **4a** (1 : 1.2) (Entry 3). However, switching the solvent to toluene greatly improve the conversion, forming the desired product in 73 % yield (Entry 4). Further increasing the temperature to 70 ℃ increased catalyst activity, giving **4a** with 82 % yield (Entry 5). Also, the product showed only the *trans*-isomer on the macrocyclic alkene. This selectivity is noteworthy because *E*/*Z* stereoselectivity in macrocyclic RCM remains a serious issue.[16]

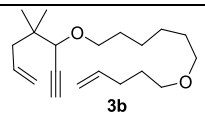
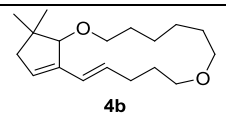
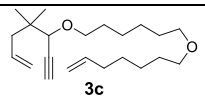
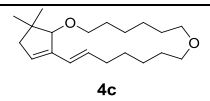
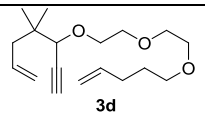
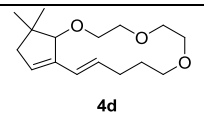
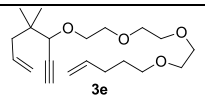
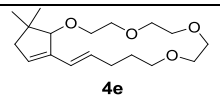
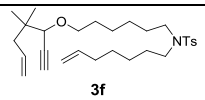
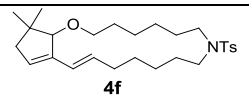


Scheme 7. Detailed reaction mechanism of tandem dienyne RCM

In order to observe details of reaction mechanism, substrate **3a** was reacted with catalyst **B** under diluted condition to check initial intermediate product. When reaction was performed for only 3 hours, only intermediate product **4ah** was observed, which would undergo complete cyclization to form **4a**. This provided important insight to the reaction mechanism (Scheme 7). Initially, catalyst will react with two terminal alkenes non-selectively to form intermediate **I-1** or **I-2**. Those metal carbenes may undergo RCM with alkyne, carbene exchange between **I-1** and **I-2**, or dimerization of **3a** through cross metathesis reaction. Here, only intermediate **I-1** underwent RCM reaction due to the fast k_S. On the other hand, cyclization product of **I-2** or dimerization product of **3a** were not observed, due to the much slower k_L and k_D. Instead, **I-2** underwent exchange reaction to form **I-1** again rapidly, which then produce **4ah** immediately. After the initial enyne RCM reaction that formed small rings exclusively, intermediate **I-3** or **I-4** underwent final macrocyclization to form fused bicyclic product. Overall, this process (k_S, $k_{Ex} > k_L$, k_D) pushed the equilibrium to one pathway, leading to the selective synthesis of **4a**.

Previously, Fogg and co-workers reported that during the macrocyclization of dienes, the dimer and oligomers formed initially as kinetic products and then reacted further to yield macrocycles.[17] However, we only observed **4ah** and **4a**, and any formation of dimer or oligomers were not observed during NMR monitoring studies. We believe that due to the fast RCM reaction to form **4ah**, the substrate contained one reactive terminal alkene and one less reactive conjugated olefin with a bulky substituent. This might reduce the chance of dimerization compared to the substrates with two reactive terminal alkenes. Also, the cyclopentyl moiety might have induced a biased structure favoring macro RCM over dimerization.

Table 2. Dienyne RCM reaction of various substrates[a]

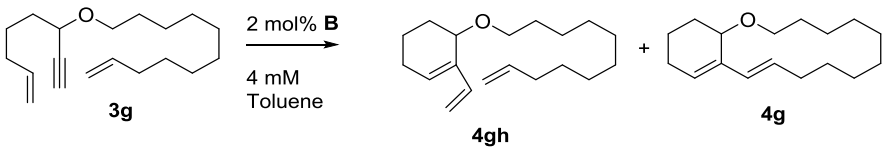
Entry	Substrate	Product	Temp.	Yield
1	 **3b**	 **4b**	55 ℃	95 %
2	 **3c**	 **4c**	55 ℃	85 %
3	 **3d**	 **4d**	55 ℃	91 %
4	 **3e**	 **4e**	55 ℃	85 %
5	 **3f**	 **4f**	70 ℃	87 %

[a] General reaction condition : Under Ar atmosphere, 5 mol% catalyst **B** was added to substrates in 4 mM toluene. Solution was heated for 24 hours under reflux condition.

In order to expand the reaction scope, various substrates with different tether structures were subjected to tandem RCM reaction to synthesize [n.3.0] (n = 12-15) bicyclic compounds. Under reflux condition, bicyclic compounds with 14- to 17-membered rings were synthesized with 85-95 % isolated yields using 5 mol% of catalyst **B**. Due to the enhanced Thorpe-Ingold effect by pseudo *gem*-dialkyl effect by lone pair electrons of oxygen atoms in long tethers, carbon-oxygen-carbon bond angle becomes smaller than the carbon-carbon-carbon bond angle.[18] Thus, product yields were relatively higher than **4a** with pure carbon tether (Table 2, entries 1-4).[19] Substrate **3f** with nitrogen atom also resulted in good productivity, although slightly higher reaction temperature (70 ℃) was required for effective

macrocylclization (Entry 5).

Table 3. Synthesis of six-membered ring containing fused bicycle[a]

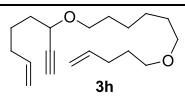
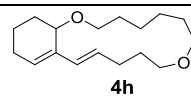
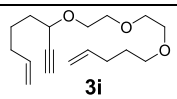
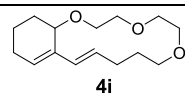
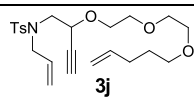
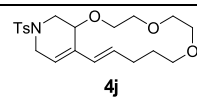
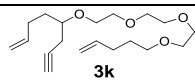
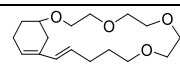


Entry	Catalyst	Temp.	Yield of **4g**	**4gh :4g**[b]
1	5 mol%	55 ℃	N/A	1 : 0
2	10 mol%	55 ℃	N/A	1 : 1.5
3	10 mol%	70 ℃	59 %	1 : 8
4	10 mol%	90 ℃	87 %	1 : 28

[a] General reaction condition : Under Ar atmosphere, 5 mol% catalyst **B** was added to substrates in 4 mM toluene. Solution was heated for 24 hours under reflux condition. Additional 5 mol% catalyst was added and the solution was heated for another 24 hours. [b] Ratio was determined by ^{1}H NMR analysis.

In order to further expand the substrate scope, bicyclic compounds with six-membered ring unit was synthesized. Initially, substrate **3g** was reacted with 5 mol% of catalyst **B**. Initially, the same reaction condition with the previous cyclopentene-containing substrates, but only a small amount of **4gh** was synthesized without the formation of bicyclic compound **4g** (Table 3, entry 1). When 10 mol% of catalyst was used instead, 1:1.5 mixture of **4gh** and **4g** was obtained (Entry 2). In order to increase macrocyclization efficiency, reaction temperature was increased up to 90 ℃ to get 87 % isolated yield of of **4g** (Entries 2-3). Since the initial cyclization of six-membered ring completed almost immediately after the catalyst addition, I could expect that the macrocyclization rate of **3g** was relatively slower than substrates with cyclopentene moieties.

Table 4. Synthesis of various six-membered ring containing fused bicycles[a]

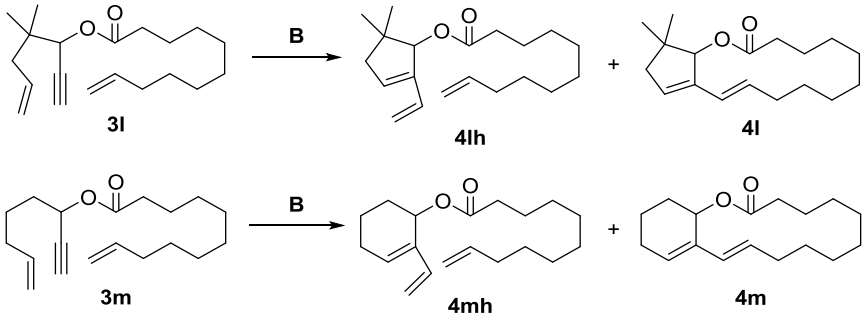
Entry	Substrate	Product	Catalyst	Temp.	Yield
1	 **3h**	 **4h**	5 mol%	100 ℃	75 %
2	 **3i**	 **4i**	5 mol%	55 ℃	71 %
3[b]	 **3j**	 **4j**	8 mol%	90 ℃	71 %
4[b]	 **3k**	 **4k**	10 mol%	70 ℃	69 %

[a] General reaction condition : Under Ar atmosphere, 5 mol% catalyst **B** was added to substrates in 4 mM toluene. Solution was heated for 24 hours under reflux condition. [b] Additional 3-5 mol% catalyst was added and the solution was heated for another 24 hours.

Similar to the fused bicyclic compounds with five-membered ring unit, substrate with oxygen atoms in the long tether resulted higher yield in tandem RCM reaction. Introducing one oxygen atom to the long tether resulted in 75 % yield of **4h**, even with the use of 5 mol% catalyst **B** (Table 4, entry 1). Adding more oxygen further improved macrocyclization reactivity so that the desired bicyclic compound was synthesized under milder condition at lower temperature (Entry 2). When nitrogen was introduced in the small ring, substrate **3j** underwent cyclization to form bicyclic compound with 71 % yield, but it required higher temperature and higher catalyst loading for efficient reaction (Entry 3). Furthermore, Bridgehead fused bicyclic compound was also synthesized by dienyne RCM reaction (Entry 4). Although bicyclic compolund contained an anti-Bredt olefin which is not easily formed in small molecules, long flexible chain of

macrocycle reduced ring strain to allow the formation of desired bicyclic compound in 69 % yield.

Table 5. Synthesis of fused bicycles containing ester group[a]



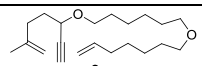
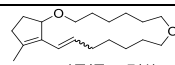
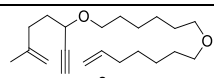
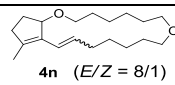
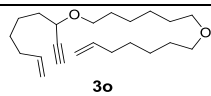
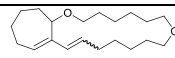
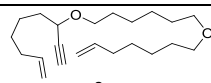
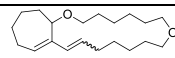
Entry	Substrate	Catalyst	Solvent	Temp.	Yield of **4x**	**4xh : 4x**[b]
1	**3l**	5 mol%	Toluene	55 ℃	19 %	1 : 0.23
2	**3l**	5 mol%	1,2-DCE	55 ℃	73 %	1 : 10
3	**3m**	5 mol%	1,2-DCE	55 ℃	N/A	1 : 1
4[c]	**3m**	10 mol%	1,2-DCE	70 ℃	83 %	1 : 10

[a] General reaction condition : : Under Ar atmosphere, 5 mol% catalyst was added to substrates in 4 mM solvent. Solution was heated for 24 hours under reflux condition. [b] Ratio was determined by ^{1}H NMR analysis. [c] Additional 5 mol% catalyst was added and the solution was heated for another 24 hours.

Synthesis of bicyclic compounds containing macrolactones was also investigated. Interestingly, substrate containing ester group showed low reactivity under toluene solvent condition, which was used in other tandem RCM reactions (Table 5, entry 1). However, when the solvent was changed to 1,2-DCE, macrocyclization reactivity was significantly increased to yield 73 % of **4l** (Entry 2). It seemed that polar solvent 1,2-DCE induced faster macrocyclization to yield **4l** with ester group. Synthesis of six-membered ring containing fused bicyclic

compound was also synthesized with the use of 1,2-DCE as a solvent. Similar to the previous case, **3m** required higher catalyst loading and higher reaction temperature to induce effective macrocyclization (Entries 3 and 4).

Table 6. Synthesis of fused bicycles with mixture of stereoisomers[a]

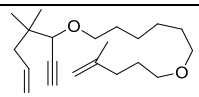
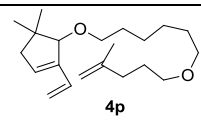
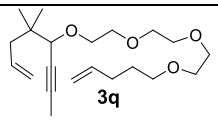
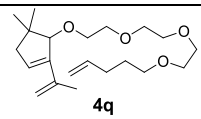
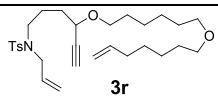
Entry	Substrate	Product	Catalyst	Temp.	Yield
1	 **3n**	 **4n** (*E*/*Z* = 5/1)	5 mol%	55 ℃	63 %
2	 **3n**	 **4n** (*E*/*Z* = 8/1)	5 mol%	90 ℃	87 %
3[b]	 **3o**	 **4o** (*E*/*Z* = 5/1)	10 mol%	70 ℃	27 %
4[b]	 **3o**	 **4o** (*E*/*Z* = 25/1)	15 mol%	100 ℃	63 %

[a] General reaction condition : Under Ar atmosphere, 5 mol% catalyst **B** was added to substrates in 4 mM toluene. Solution was heated for 24 hours under reflux condition. *E*/*Z* ratio was determined by ^{1}H NMR analysis. [b] Additional 5-10 mol% catalyst was added and the solution was heated for another 24-48 hours in 2 mM toluene.

Although most macro-RCM reactions produced *E*-olefins on the macrocyclic alkenes, mixtures of *E*/*Z* isomers were observed in some cases. One case was tandem RCM of **3n** with 1,1-disubstituted alkene on short tether undergoes, which yielded fused bicyclic compound with synthetically challenging tetrasubstituted alkene (Table 6, entries 1 and 2). Under 55 ℃ reaction condition, yield of **4n** was 63 % and *E*/*Z* ratio was 5/1. When reaction temperature was increased, not only product yield was increased (87 %), but also stereoselectivity was improved (*E*/*Z* = 8/1). Another case was the synthesis of fused bicyclic compound containing

seven-membered ring, which is more challenging for RCM reaction than bicyclic compounds containing five- or six-membered rings. Thus, tandem RCM reaction of substrate **3o** required 100 ℃ temperature and high catalyst loading (15 mol%) to achieve 63 % yield. Increasing the reaction temperature and catalyst loading changed *E*/*Z* ratio from 5/1 to 25/1 (Entries 3 and 4). In both examples, *E*/*Z* selectivity was increased with higher substrate conversion due to the enhanced catalyst activity. As more catalysts remain active, reversible *E*/*Z* isomerization on the macrocyclic alkene occurred more frequently to form more stable *E* isomer.

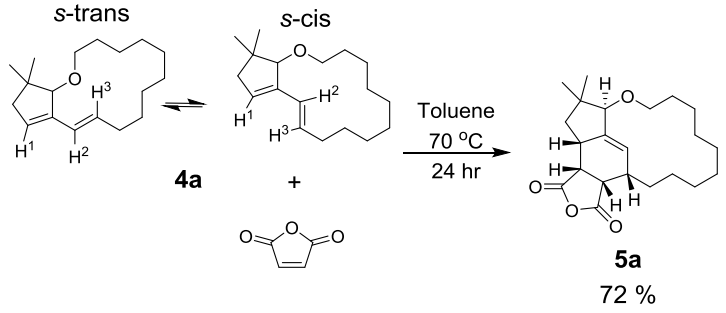
Table 7. Unsuccessful examples of tandem RCM[a]

Entry	Substrate	Product	Catalyst	Temp.	Yield
1	 **3p**	 **4p**	5 mol%	55 ℃	66 %
2	 **3q**	 **4q**	5 mol%	55 ℃	74 %
3[b]	 **3r**	Complex mixture	10 mol%	100 ℃	N/A

[a] General reaction condition : Under Ar atmosphere, 5 mol% catalyst **B** was added to substrates in 4 mM toluene. Solution was heated for 24 hours under reflux condition. [b] Additional 5 mol% catalyst was added and the solution was heated for another 24 hours

Although the substrate scope for fused bicyclic macrocyclization was quite broad as seen in the previous tables, several substrates did not lead to desired products. Unlike the previous example, in which the fused bicyclic compound with an additional methyl substituted olefin on the small ring was successfully prepared (Table 6, entry 2), synthesizing fused cyclic compounds containing an additional

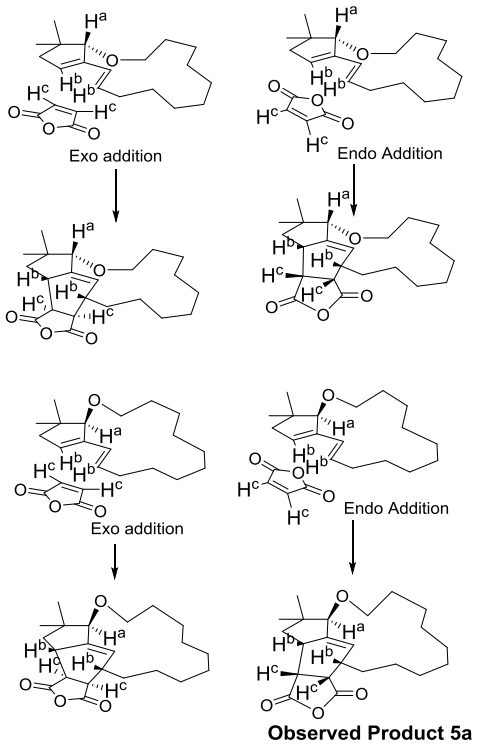
substitution on the alkene of the macrocycles to make trisubstituted alkenes failed, giving only molecules with incomplete cyclisation (Table 7, entries 1 and 2). Because the additional substitution made it harder for the catalyst to perform effective metathesis reaction, the macrocyclization rate became even slower, leaving only small ring-closed products. Synthesis of eight-membered ring containing fused cyclic compounds was even more challenging (Table 7, entry 3) due to intrinsically low reactivity of RCM toward the formation of eight-membered rings. Even with high catalyst loading at an elevated temperature, this reaction gave a complex mixture of molecules, and not even clean conversion to the initial eight-membered ring was observed.



Scheme 8. Diels–Alder reaction of a fused cyclic compound synthesized by the dienyne RCM reaction

So far, we have demonstrated that the fused bicyclic compounds comprising small and large rings were efficiently prepared by tandem dienyne RCM reactions. This method would be more useful if further manipulation on the RCM products would be possible giving more diversity. For a typical dienyne RCM reaction, 1, 3-diene, a potential functional group for Diels–Alder reaction, is formed at the end of the reaction. However, there have been no previous reports of Diels–Alder reactions on the dienes of fused bicycles formed by dienyne RCM reactions because the products were composed of two small or medium rings. Thus, there was no

chance of forming *s-cis* dienes but *s-trans* dienes only, which cannot participate in Diels–Alder reactions.[13] On the other hand, we reasoned that dienes on the bicycles containing small and large rings might adopt the *s-trans* conformation as well due to the presence of flexibile chains on macrocycles. The first evidence for this came from a nuclear Overhauser effect (NOE) study on substrate **4a**, which showed interaction between vinyl proton H^1 with both proton H^2 and H^3 (Scheme 8). These suggested that substrate **4a** might adopt both *s*-trans and *s*-cis conformations, implying that these dienes could undergo Diels–Alder reactions with dienophiles. Indeed, when treated with maleic anhydride at 70 ℃, a cycloaddition product **5a** with a single diastereomer was obtained in 76 % isolated yield.



Scheme 9. Origin of stereochemistry for the Diels-Alder reaction

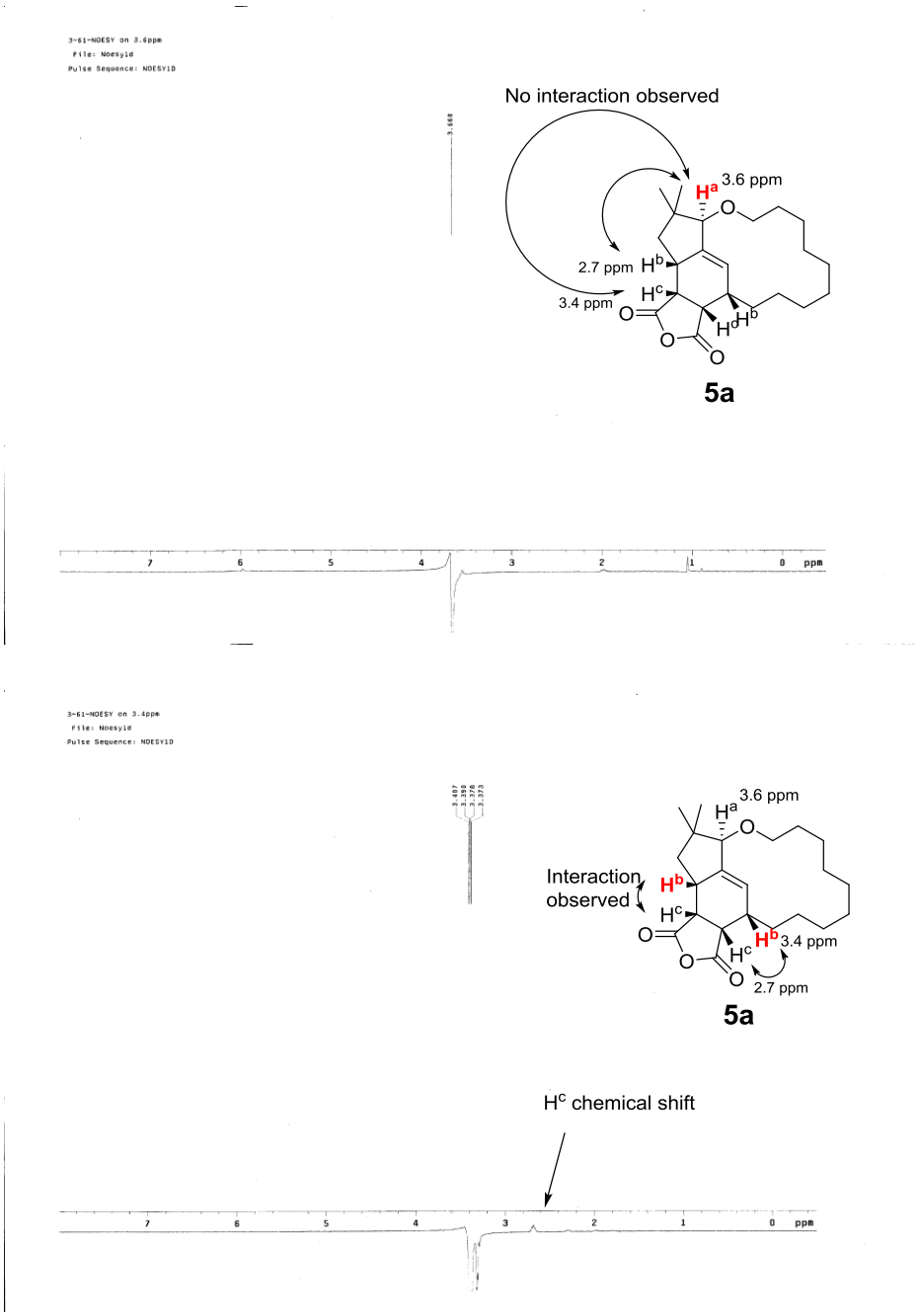
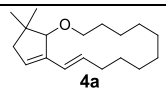
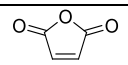
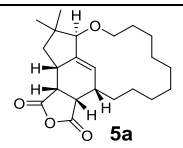
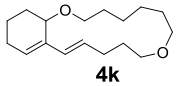
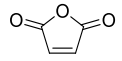
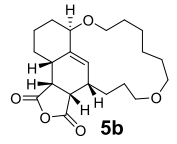
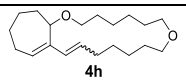
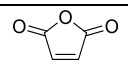
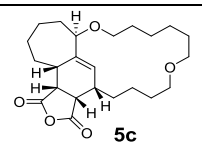
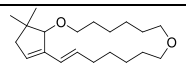
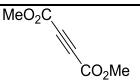
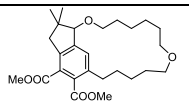
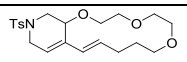
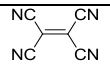
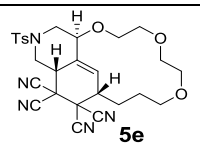


Figure 1. 1D NOE spectrum analysis of **5a**

As shown in Scheme 9, the Diels–Alder reaction could give four different diastereomers depending on how the dienophile approached the fused bicyclic diene molecule. First, the dienophile could add to the diene from two different sides, but the dienophile would preferentially approach from the less sterically hindered side, H^a, and away from the more sterically hindered ether linkage. Second, the dienophile could approach the diene with *endo* orientation over *exo*. To determine the molecular structure of the adduct, 1D NOE study was conducted and showed that H^a interact with neither H^b or H^c, suggesting that they were *anti* to one another (Scheme 9).[20] Also, the NOE study showed that H^b interacted with H^c, confirming that the product isolated was the predicted **5a** isomer due to *endo* selective addition of the dienophile from the less hindered side of the fused cyclic diene (Figure 1).

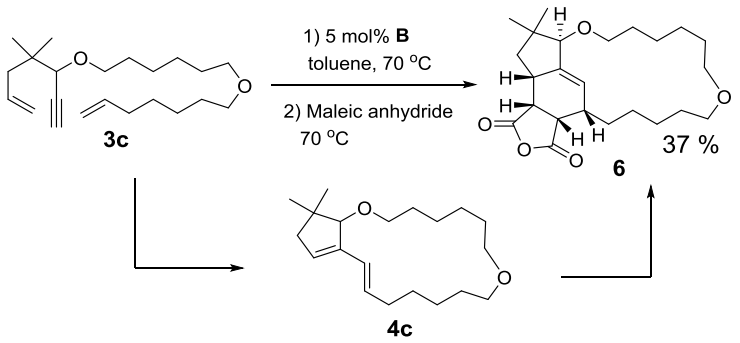
Table 8. Diels–Alder reaction on the dienyne RCM products[a]

Entry	Diene	Dienophile	Product	Yield
1	 **4a**		 **5a**	76 %
2	 **4k**		 **5b**	74 %
3	 **4h**		 **5c**	75 %
4[b]	 **4c**		 **5d**	66 %

5[c]	 **4l**		 **5e**	83 %

[a] General information : Under Ar atmosphere, 2 equiv. dienophiles was added to dienes in 0.3 M toluene. Reaction flask was heated to 70 ℃ for 4 hours. [b] Reaction flask was heated to 100 ℃ for 48 hours. [c] Reaction proceeded at room temperature for 24 hours.

Reactions between maleic anhydride and various dienyne RCM products containing five- to seven-membered rings in toluene at 70 ℃ gave good yields of Diels–Alder products (74–76%) comprising tetracyclic compounds (Table 8, entries 1–3). In all cases, single diastereomers with the predicted stereochemistry were obtained. To test dienophiles other than maleic anhydride, dimethyl acetylenedicarboxylate was reacted with **4a**. Even at higher temperature, this Diels-Alder reaction was much slower than the previous cases with maleic anhydride as a dienophile. We expected to obtain the Diels–Alder product with a 1, 4-cyclohexadiene moiety, but **5d** with an aromatic ring was the only isolated product. Presumably, the initial Diels–Alder product of 1, 4-cyclohexadiene, quickly underwent aromatization under the reaction conditions, giving a tricyclic compound with the aromatic ring (Enry 4).[21] Since the Diels–Alder reactions were conducted at elevated temperatures, it was unclear whether equilibrium between *s*-cis and *s*-trans isomers of the dienes was possible at room temperature. Thus, a stronger dienophile, tetracyanoethylene, was added to **4l** at room temperature, and the product **5e** was isolated with excellent yield (Table 8, entry 5). This confirmed our initial assumption that the fused cyclic compounds containing macrocycles could adopt the *s*-cis diene conformation at room temperature due to the flexible chains on the macrocycles.



Scheme 11. Sequential RCM–Diels–Alder reaction in one-pot reaction

As the Diels–Alder reactions were performed under the same solvent and the same temperature, dienyne RCM and Diels–Alder reactions could be conducted sequentially in a one-pot reaction. Substrate **3c** was treated with catalyst **B** at 70 ℃, and after 24 hours, addition of two equiv. of maleic anhydride produced the fused tetracyclic compound **6** with 37% isolated yield (Scheme 11). Although the yield was low, this result demonstrated that the complexity of the molecules could be rapidly built up by the combination of one-pot tandem dienyne RCM and Diels–Alder reactions, producing the tetracycle from an acyclic substrate.

Conclusions

In here, we described on the synthesis of multicyclic compounds comprising small and large rings through selective dienyne RCM reaction and Diels-Alder reaction to produce single isomer with high selectivity, generality, and predictability. Because the cyclisation rate was significantly faster for the small rings compared with the macrocycles, the synthetic pathway was driven to produce single isomers. This methodology efficiently produced fused bicycles with small rings from 5- to 7-membered rings and macrocycles from 14- to 17-membered rings, demonstrating the versatility of the reactions. Generally, higher

conversion to complete macrocyclization was achieved with higher temperature or higher catalyst loading. Also, the RCM reaction products underwent Diels–Alder reactions with exclusive stereo-control. The combination of tandem dienyne RCM and Diels–Alder reactions provided a powerful method to rapidly build complex molecules, especially those multicyclic compounds containing macrocycles.

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Chapter 3

Tandem ring-opening/ring-closing metathesis polymerization

Abstract

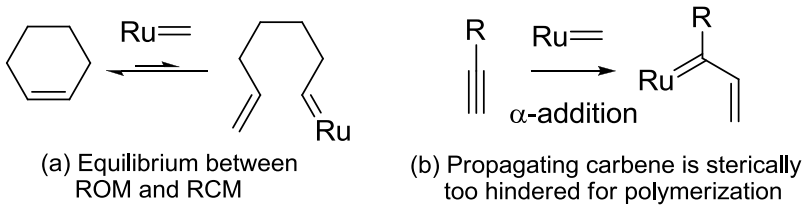
Tandem ring-opening/ring-closing metathesis polymerization has been studied. Cycloalkenes with low ring strain and alkynes were not good monomer for metathesis polymerization, due to their lack of driving force for polymerization against depolymerization. However, by fusing two unreactive functional groups in single monomer, we could achieve ultrafast living polymerization, using third-generation Grubbs catalyst. This reactive polymerization could be used to synthesize block copolymer. Also, polymer backbone could be modified with Diels-Alder post modification to prepare polymers with more complex structure. Reaction mechanism study of tandem polymerization revealed that the polymerization followed alkyne-first pathway to synthesize polymer with extremely good regioregularity. With this observations, monomers with various combinations of cycloalkenes, alkynes, and linker groups were studied, but monomers with certain combinations did not undergo efficient polymerization. In order to promote efficient polymerization, two strategies were used. Firstly, monomers were modified to contain bulky substituent groups to accelerate RO/RCM cyclization rate by enhanced Thorpe-Ingold effect, and this strategy could synthesize monomers with various structures, even challenging dendronized polymers. Secondly, reaction concentration was reduced to suppress intermolecular side reaction, which could effectively synthesize monomers which cannot change their structures. In order to expand monomer scope further, monomers containing internal alkyne was also studied. Polymerization of monomers containing internal alkyne revealed that steric, electronic effects of alkyne substituents affected to various features in polymerization, such as polymer unit ratio between five- and six-membered ring unit, polymerization reactivity, and polymerization kinetics. Detailed mechanistic study revealed that the rate determining step of polymerization of monomers with certain internal

alkyne substituents was tandem RO/RCM cyclization step, while that of other monomers was propagation step, which is common for conventional chain-growth polymerization.

Background

Olefin metathesis (OM) reaction has been used as a versatile method for the synthesis of various organic molecules.[1] With the development catalysts with high reactivity and good functional group tolerance based on molybdenum[2] and ruthenium metals[3], reaction scope for olefin metathesis reaction has been significantly broadened. With these catalysts, chemists developed various olefin metathesis reactions based on three systems; ring-opening metathesis (ROM), cross metathesis (CM), and ring-closing metathesis (RCM). Application of OM was not limited to the small molecule synthesis, but also applied to polymer chemistry. These three systems were applied to polymer synthesis as ring-opening metathesis polymerization (ROMP)[4], acyclic diene metathesis polymerization (ADMET)[5], and cyclopolymerization[6].

As metathesis reactions undergo thermodynamically equilibrium reactions, metathesis polymerizations need good strategies to drive the equilibrium toward polymerization against depolymerization pathway. ROMP takes advantage of reliving ring strain of highly strained cyclic alkene monomers. Thus, highly strained cycloalkenes such as norbornene or cyclooctenes are frequently used as ROMP monomers. ADMET release ethylene gas as a side product, and removing this ethylene gas eventually drives equilibrium toward polymerization. Lastly, cyclopolymerization of diyne monomers undergoes irreversible generation of stable conjugated polyenes to achieve effective polymerization. In short, three polymerization methods become useful when thermodynamics of the reactions favors polymerization over depolymerization.



(a) Equilibrium between ROM and RCM

(b) Propagating carbene is sterically too hindered for polymerization

Scheme 1. Unreactive monomers for metathesis polymerization

On the other hand, monomers without thermodynamically driving forces cannot undergo effective polymerization. Cyclohexene is a good example for this; due to the extremely low ring strain, cyclohexene tends to easily undergoes depolymerization. Although metathesis reaction of cyclohexene under extremely low temperature could yield oligomers of cyclohexene, synthesis of high molecular weighted polymer using cyclohexene as a single monomer has not been studied.[7] Furthermore, cycloalkenes with subsitutiton groups tend to reduce ring strain, such as cyclopentenes with 3- or 4- substitution.[8] Currently, only a small number of reports used cyclohexene as a co-monomer for alternating metathesis polymerizations.[9]

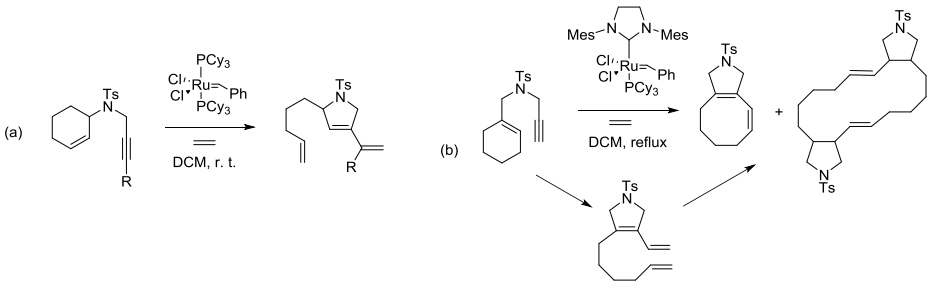
Another example is CM polymerization of alkynes. Although CM of alkyne will generate conjugated olefins which will favor enthalpic gains during the reaction, propagating carbene complexes are not reactive enough to undergo polymerization.[10] When terminal alkyne is reacted with ruthenium based catalyst, catalyst tend to undergo α-addition to form 1,1-disubstituted alkylidene, and resulting bulky carbene complex is not reactive enough to undergo desired polymerization. Although Masuda and co-workers could achieve CM polymerization of alkynes with Grubbs catalyst, harsh condition was required and polymerization was not controlled.[10]

In organic chemistry, chemists use tandem metathesis reactions to synthesize various kinds of complex molecules.[11] These methods were well used to synthesize the core skeletons of various natural products.[12] For example, tandem relay metathesis reaction has been used to promote ring rearrangement reactions *via* enyne ROM and RCM reaction.[13] On the other hand, conventional metathesis polymerizations use single metathesis reaction system, only simple polymer microstructures are expected. Application of tandem metathesis reactions to polymerization can synthesize polymers with complex structures, and provide new field of monomer scopes.

This chapter will describe about tandem ring-opening/ring-closing metathesis (RO/RCM) polymerization using monomers containing cycloalkene with low ring strain and terminal alkynes. With the use of two unreactive functional groups in single monomer, miraculously highly reactive polymerization has been possible. With the development of new polymerization reaction, various optimization trials and mechanistic studies for the polymerization are also reported.

Part A. Tandem RO/RCM of monomers containing nitrogen linker group

Introduction



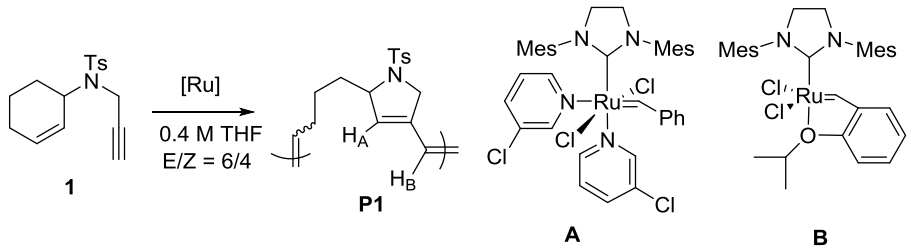
Scheme 1. Tandem enyne ring rearrangement reaction

Since metathesis polymerization of cycloalkenes with low ring strain (ex – cyclohexene) and terminal alkynes were not efficient enough to synthesize polymers with high molecular weight, these functional groups were overlooked as a monomer for metathesis polymerization. However, with the help of tandem relay-type metathesis reaction, they may have a good chance to act as a polymerization monomer. Previously, Mori and co-workers studied tandem enyne metathesis reaction using substrate containing cycloalkene and alkyne.[14] When those substrates reacted with first-generation Grubbs catalyst under ethylene atmosphere, they tend to undergo efficient ring rearrangement reaction through tandem ring-opening/ring-closing metathesis reaction (Scheme 1a). Furthermore, when those substrates reacted with highly reactive second-generation Grubbs catalyst, they tend to undergo dimerization or internal RCM reaction after initial ring rearrangement reaction (Scheme 1b). These results suggest valuable informations: first, substrate containing cycloalkene and alkyne is reactive enough to undergo intramolecular ring rearrangement reaction. Second, with the

use of reactive Grubbs catalysts containing *N*-heterocyclic (NHC) ligand, substrate may undergo further reaction after ring rearrangement to form dimer, or bigger oligomers and polymers from newly generated terminal alkenes.

Results and Discussions

Table 1. Tandem metathesis polymerization of **1**



Entry	Solvent	Cat.	M/I	Temp.	Time	M_n[a]	PDI[a]	Conv.[b]
1	DCM	**B**	100	r. t.	1 hr	15000	1.46	60 %
2	THF	**B**	100	r. t.	1 hr	30000	1.88	100 %
3	THF	**A**	100	r. t.	1 min	26000	1.86	100 %
4	THF	**A**	100	-10 ℃	2 min	31000	1.18	100 %
5	THF	**A**	100	-30 ℃	10 min	31000	1.18	100 %
6	THF	**A**	30	-30 ℃	3 min	8000	1.17	100 %
7	THF	**A**	50	-30 ℃	5 min	18000	1.18	100 %
8	THF	**A**	150	-30 ℃	20 min	41000	1.21	90 %

[a] Determined by THF SEC calibrated using polystyrene standards. [b] Conversion determined by crude ^{1}H-NMR analysis.

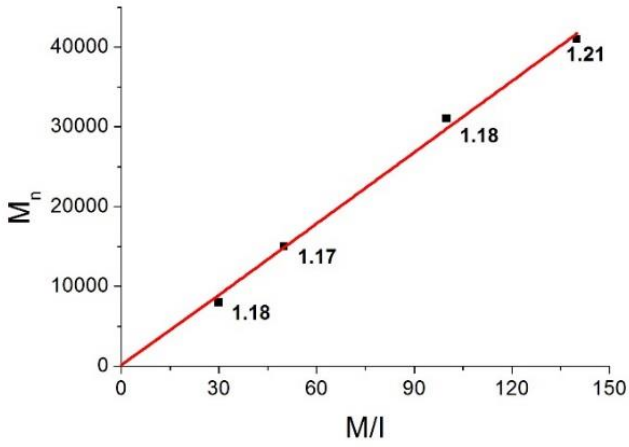


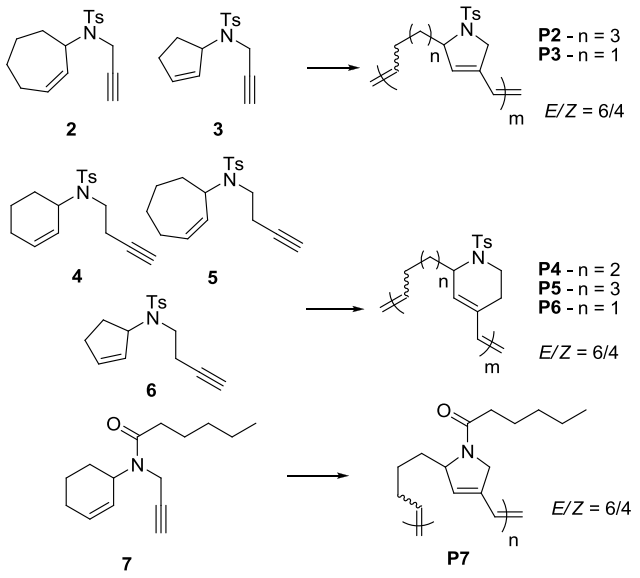
Figure 1. Plot of M_n versus M/I for **P1**. Numbers on the line indicate PDI values.

In order to prove this observation, monomer **1** was prepared and reacted with metathesis catalysts. Initially, monomer **1** was reacted with second-generation Hoveyda-Grubbs catalyst (**B**) in 0.4 M concentration of DCM solvent, which resulted only 60 % monomer conversion (Table 1, entry 1). Polymerization reactivity was enhanced by changing solvent to THF, which could perfectly convert monomers to polymer (Entry 2). However, polydispersity index (PDI) of polymer was quite broad with 1.88. With this observation, we reasoned two factors which increased PDI. One is the slow initiation rate of catalyst **B**, and the other is chain transfer reaction during long reaction time. Thus, catalyst was changed to third-generation Grubbs catalyst (**A**), which have extremely fast initiation rate, and reaction time was decreased to 1 minute (Entry 3). Polymerization of **1** was surprisingly fast to achieve full conversion within 1 minute under monomer to initiator (M/I) ratio at 100, but PDI was still broad with 1.86. With this observation, reaction temperature was decreased to -10 ℃ to suppress chain transfer reaction, and perfect conversion of monomer was achieved within 2 minutes to synthesize polymer with PDI narrower than 1.2

(Entry 4). To ensure controlled polymerization with M/I ratio higher than 100, the reaction temperature was further lowered to -30 ℃. Regardless of the choice of catalysts, solvents, and temperatures, an *E/Z* ratio of 6:4 for the newly formed olefins on the polymer backbone remained unchanged. This ratio was easily determined by crude ^{1}H-NMR analysis because each peak corresponding to *E/Z* isomers for olefinic H_A and H_B (with the correct coupling constants of 16 and 8 Hz for *E* and *Z* isomers. For detail, see Figure 4) was clearly resolved, allowing for reliable integration.

Polymers having various molecular weights were synthesized by varying M/I, and controlled polymerization was achieved with the degree of polymerization (DP) ranging from 30 to 135 (Table 1, entries 5–8), resulting in a linear increase in molecular weights (Figure 1). In addition, PDI was controlled to be less than or equal to 1.2.

Table 2. Tandem metathesis polymerization of various monomers with different ring sizes and linker alkynes



Entry	Mono	Cat.	M/I	Temp.	Time	Conv.[a]	M_n[b]	PDI[b]
1	**2**	**A**	15	-30 ℃	3 min	100 %	5000	1.28
2	**2**	**A**	30	-30 ℃	5 min	100 %	9100	1.28
3	**2**	**A**	50	-30 ℃	10 min	100 %	12500	1.25
4	**3**	**A**	100	r. t.	12 h	30 %	11400	1.70
5	**3**	**B**	50	50 ℃	2 h	98 %	13500	1.62
6	**4**	**B**	50	50 ℃	12 h	<20 %	-	-
7	**5**	**B**	50	50 ℃	12 h	0 %	-	-
8	**6**	**B**	50	50 ℃	12 h	82 %	12000	1.54
9	**6**	**B**	50	65 ℃	2 h	100 %	15000	1.79
10	**7**	**A**	50	-10 ℃	5 min	90 %	13100	1.23

[a] Conversion determined by crude ^{1}H-NMR. [b] Determined by THF SEC calibrated using polystyrene (PS) standards.

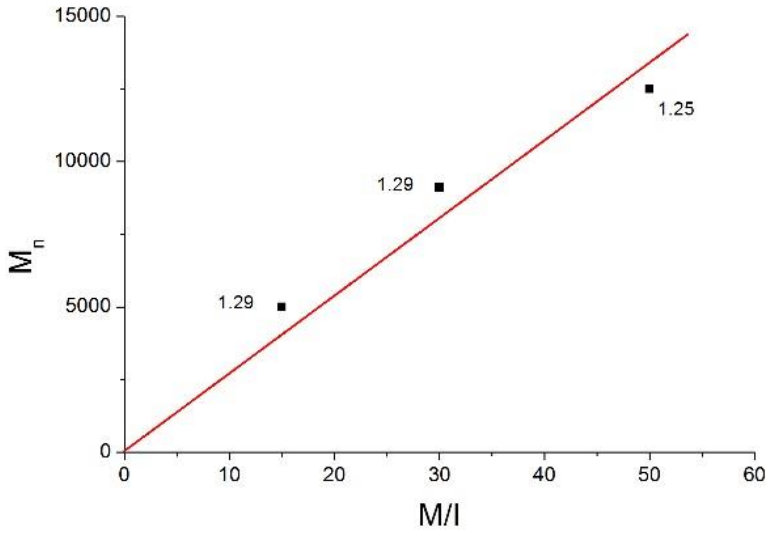


Figure 2. Plot of M_n versus M/I for **P2**. Numbers on the line indicate PDI values.

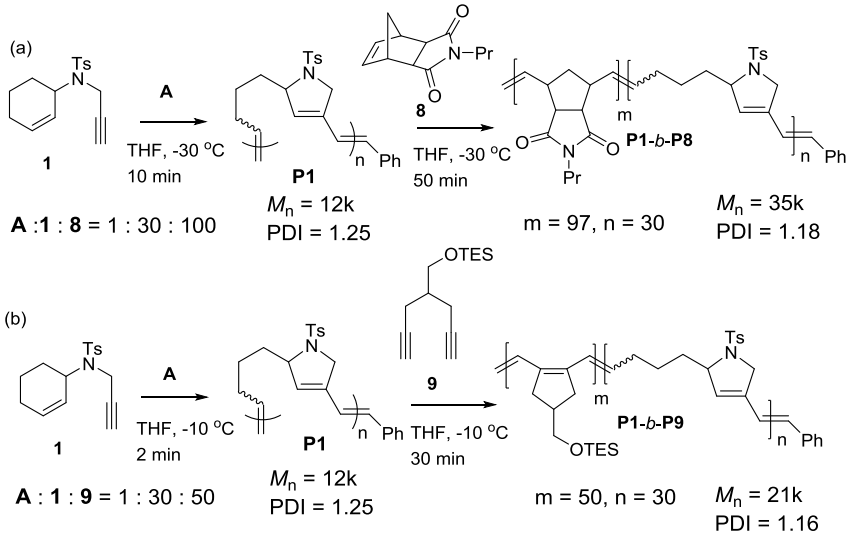
With the successful polymerization of monomer **1** containing cyclohexene and propargyl group, we started to broaden the monomer scope for tandem

polymerization. Initially, ring size of cycloalkene was modified to broaden the monomer scope. As cyclohexene has the lowest ring strain among cycloalkenes, we expected that other cycloalkenes with relatively higher ring strain should undergo tandem polymerization as well. Monomer **2** containing cycloheptene rapidly underwent tandem polymerization at room temperature with reactivity comparable to that of **1**. In order to suppress the chain transfer reaction, reaction temperature was lowered to -30 ℃ and polymerization of **2** also showed fast propagation and controlled polymerization as PDIs of the polymers were narrower than 1.3, and a linear relationship between M/I ratio and molecular weight was observed (Table 2, entries 1-3, Figure 2). Unlike monomers containing cyclohexene and cycloheptene, tandem polymerization of monomer **3** containing cyclopentene was not efficient, yielding only 30 % conversion after 12 hours of polymerization at room temperature (Entry 4). In order to facilitate polymerization, thermally more stable catalyst **B** was used and almost complete conversion of monomer was achieved at 50 ℃ polymerization, although PDI broadening was occurred due to the slow initiation rate and chain transfer reactions (Entry 5). Similar to **P1**, the polymer microstructure showed excellent regiochemistry and the *E*/*Z* ratio on **P2** and **P3** were 6/4.

Secondly, alkyne structure was changed from propargyl group to homopropargyl group. If homopropargyl group was used instead of propargyl group, the polymer unit structure changed from five-membered ring to six-membered ring, which is expected to be less reactive toward tandem RO/RCM reaction. Initial trial was done on a monomer **4** containing cyclohexene. However, the polymerization hardly occurred even at 50 ℃, and polymer was not obtained (Entry 6). Even monomer **5** containing cycloheptene was unreactive and did not undergo polymerization at all (Entry 7). However, monomer **6** containing cyclopentene underwent tandem RO/RCM polymerization with 82 % conversion at 50 ℃ and

full conversion at 65 ℃ in 2 hours (Entries 8 and 9). This result was unexpected, as monomer **1**, **2** and **3** containing propargyl analogs showed higher reactivity for monomers containing cyclohexene and cyclopentene, but monomers containing homopropargyl group showed an opposite result. Overall, monomers containing homopropargyl group showed decreased reactivity due to the slower six-membered ring cyclization rate compared to the five-membered ring cyclization rate as expected.[15]

Lastly, *N*-toluenesulfonyl linker structure was changed to amide linker structure. When monomer **7** containing amide group was reacted with catalyst **A**, it showed high reactivity and well controlled polymerization to yield perfect conversion within 5 minutes and narrow PDI (Entry 10). Nevertheless, the reactivity of **7** was slightly lower than those of monomer **1**, as polymerization required relatively higher temperature (-10 ℃ vs. -30 ℃) to achieve high conversion.



Scheme 2. Block copolymerization via tandem polymerization by (a) ROMP or (b) cyclopolymerization.

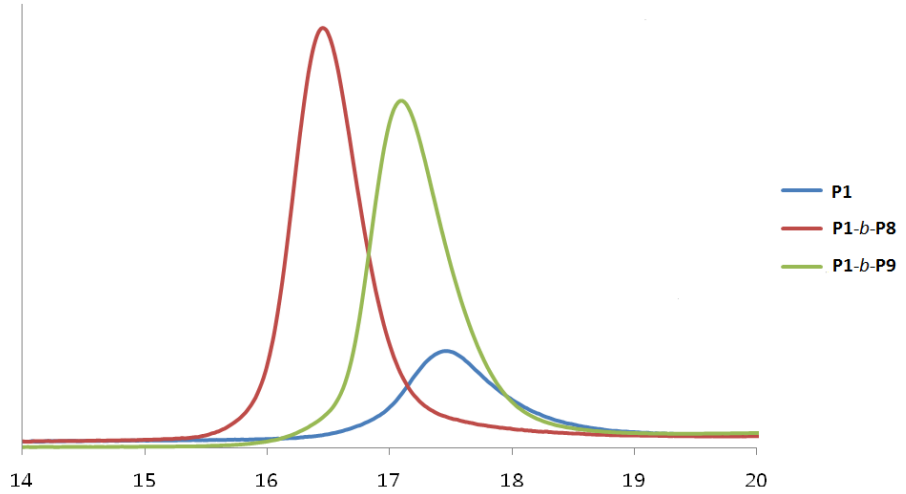
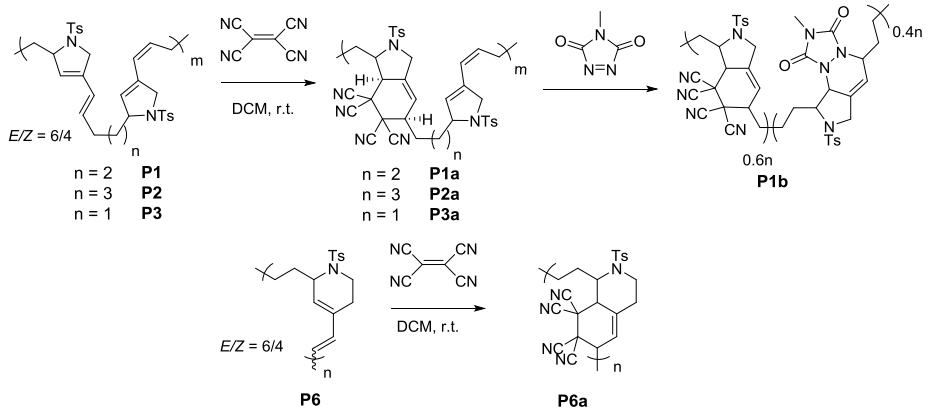


Figure 3. THF SEC trace of **P1**, **P1**-*b*-**P8**, and **P1**-*b*-**P9**.

Since the tandem metathesis polymerization promoted living polymerization, block copolymers could also be prepared by this method. To demonstrate this, conventional living ROMP and cyclopolymerization was combined with tandem metathesis polymerization for block copolymerization (Scheme 2, Figure 3). First, a diblock copolymer was prepared using the most optimized monomer **1** as the first block and ROMP monomer **8** as the second block. The diblock copolymer structure was confirmed by the total shift of the size exclusion chromatography (SEC) trace from the first block of **1** (M_n = 12k, PDI = 1.25) to a high molecular weight, while retaining the narrow PDI (M_n = 35k, PDI = 1.18). Similarly, another diblock copolymer, in which the second block was prepared by the cyclopolymerization of **9** at -10 ℃, was successfully synthesized and characterized by SEC analysis (M_n = 21k, PDI = 1.16).

Table 3. Post-functionalization of polymers by Diels-Alder reaction

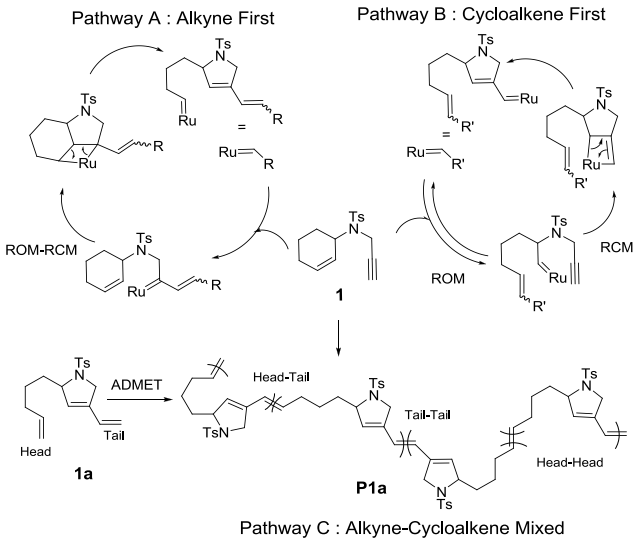


Entry	Substrate	M_n[a]	PDI[a]	Time	Conv.[b]	Product	M_n[a]	PDI[a]
1[c]	**P1**	16.0 k	1.22	48 h	60 %[e]	**P1a**	11.0 k	1.28
2	**P2**	12.3 k	1.21	48 h	60 %[e]	**P2a**	14.3 k	1.28
3[d]	**P3**	12.0 k	1.56	16 h	60 %[e]	**P3a**	14.0 k	1.64
4[c]	**P1a**	11.0 k	1.28	1.5 h	100 %	**P1b**	14.0 k	1.24
5	**P6**	8.9 k	1.65	8 h	100 %	**P6a**	11.0 k	1.69

[a] Determined by THF SEC calibrated using PS standards. [b] Conversion determined by crude ^{1}H-NMR. [c] Molecular weights and PDIs determined by chloroform SEC calibrated using PS standards. [d] Reaction was done at 60 ℃ in 1,2-dichloroethane as a solvent due to low reactivity. [e] Only the *trans* diene underwent Diels-Alder reaction while all the *cis* diene remained.

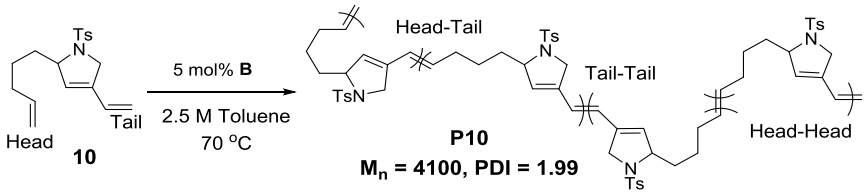
As a result of enyne metathesis reaction during polymerization, 1,3-diene moiety is generated in the polymer backbone. These backbones could be further functionalized by Diels-Alder reaction. Polymer **P1**, **P2** and **P3** containing pyrrolidine units have dienes with different stereoisomers (*E*/*Z* = 6/4), and when the polymer was reacted with tetracyanoethylene as a dienophile, only diene containing *trans*-alkene was fully converted by cycloaddition reaction, while diene containing *cis*-alkene did not react at all (Table 3, entries 1-3). Diels-Alder

reaction on **P3** required slightly higher temperature of 60 ℃ for complete conversion, possibly due to the congested structure of polymer backbone by the lack of methylene in polymer unit. Those dienes containing *cis*-alkene did not react with dienophiles, even at high temperature (up to 100 ℃). However, a more reactive dienophile, 4-methyl-1,2,4-triazole-3,5-dione underwent facile aza-Diels-Alder reaction with the remaining *cis*-isomers in **P1a** to form **P1b**, resulting in the quantitative conversion of all the dienes in **P1** (Entry 4). For **P6** containing six-membered ring structure, Diels-Alder post-modification with tetracyanoethylene underwent more rapidly, as both *E* or *Z* isomers were converted by cycloaddition reaction within just 8 hours (Entry 5). Although all the Diels-Alder post-modification caused total shift of polymer SEC trace while maintaining PDI, surprisingly, **P1a** showed decreased molecular weight after initial Diels-Alder reaction on **P1**, possibly due to the relationship between backbone tether length and hydrodynamic volume (See supporting informations for detail (Figure S1-S4)).



Scheme 3. Possible mechanisms of tandem metathesis polymerization

Since this relay-type tandem RO/RCM polymerization is unique and unprecedented, it would be worthwhile to investigate its mechanism in detail. There are three possible pathways: first, catalyst initiating from the alkyne selectively (Pathway **A**: Alkyne First); second, catalyst initiating from the cycloalkene selectively (Pathway **B**: Cycloalkene First); and last, random initiation of catalyst on either alkyne or cycloalkene non-selectively (Pathway **C**: Alkyne–Cycloalkene Mixed) (Scheme 3). If the catalyst selectively initiated and propagated on a single functional group such as in pathways **A** or **B**, the polymer unit structure would always have head-to-tail structure and as a result, the polymer would have a regular microstructure. On the other hand, non-selective pathway **C** would produce polymers comprising mixture junctions of head-to-tail, head-to-head, and tail-to-tail, and polymer structure would be completely random.



Scheme 4. ADMET polymerization of monomer **10**

To elucidate the mechanism of tandem metathesis polymerization, the synthesis of **P1** by ADMET polymerization was attempted as a comparison (Scheme 4). Monomer **10**, a product of the ring rearrangement reaction of **1** with ethylene ga s, was subjected to ADMET polymerization, yielding **P10** with low molecular w eight (M_n = 4100, PDI = 1.99) in 83% yield. In this process, new alkene signals that were not present in **P1** were observed by ^{1}H-NMR (Figure 4). These signals could be attributed to the *regio*-random cross coupling reaction occurring in this process. As the catalyst reacted with two different terminal alkenes with low selectivity, ADMET polymerizati

on gave all the possible mixtures of head-to-head, head-to-tail, and tail-to-tail junctions, whereas only *regio*-regular head-to-tail junction was observed for **P1**. In addition, only *trans*-alkenes were obtained by ADMET polymerization because this polymerization, which is essentially the repetition of the CM reaction, produced thermodynamically more stable *trans*-olefins, while the *regio*-regular polymer obtained by the kinetically controlled process contained olefins with an *E/Z* ratio of 6:4. These observations indicated that *regio*-regular **P1** resulting from tandem polymerization was formed by a single kinetically controlled reaction pathway, which rules out Pathway **C**.

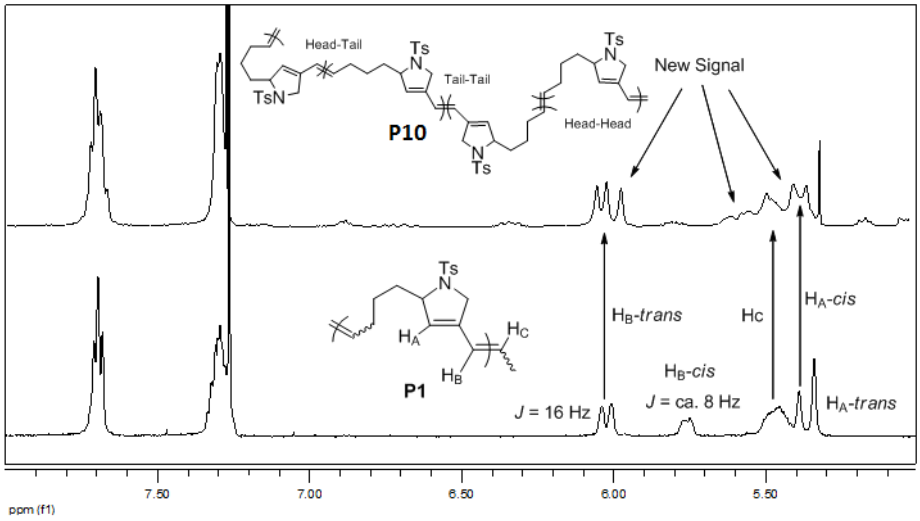
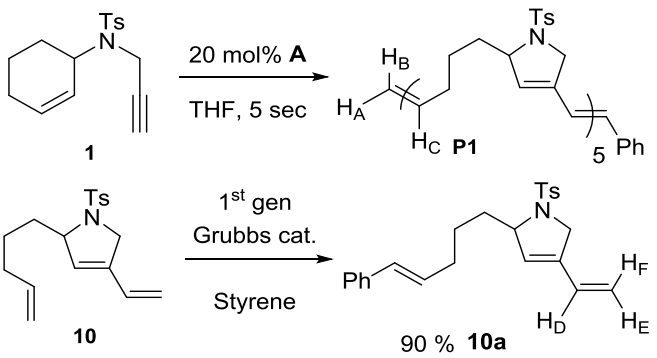


Figure 4. ^{1}H-NMR comparison between **P1** and **P10**



Scheme 5. Comparison between **P1** and CM product **10a**

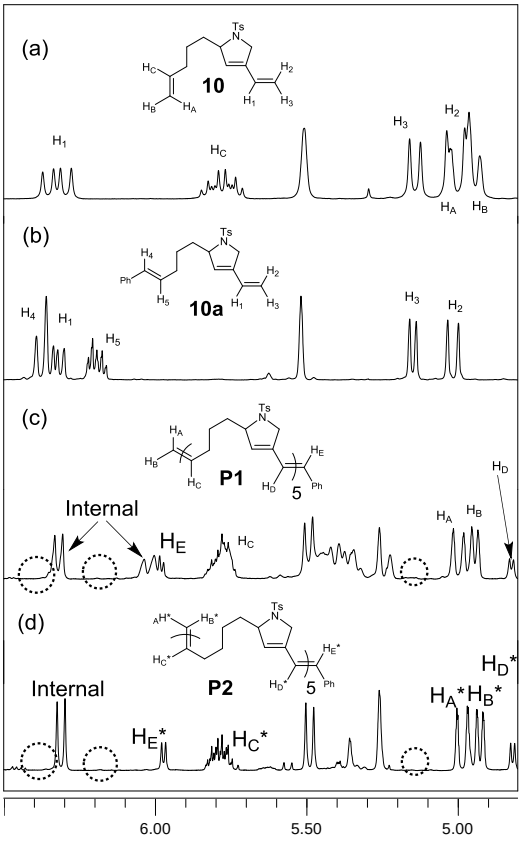
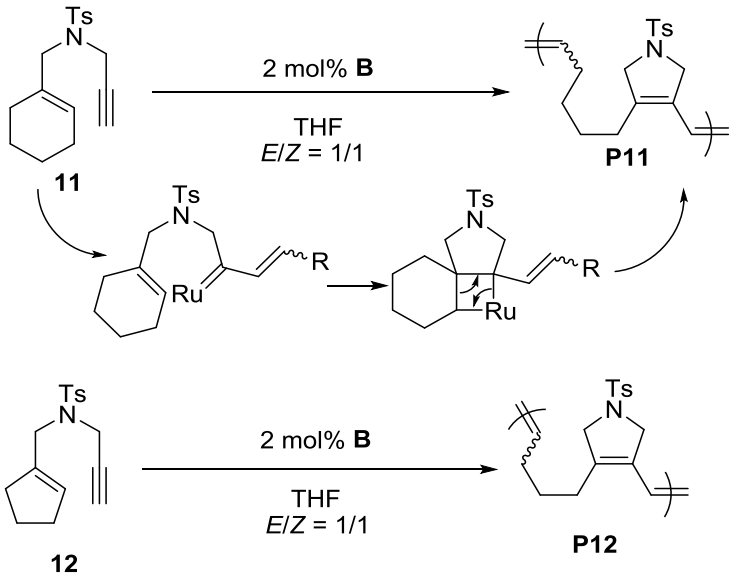


Figure 5. NMR spectra of (a) **10**, (b) **10a**, (c) oligo-**P1**, and (d) oligo-**P2**.

In order to confirm which mechanism was correct for the tandem polymerization, we performed mechanistic studies on monomers **1** and **2**. If the polymerization followed pathway **A**, the styryl group on the catalyst would be transferred onto the conjugated diene group and the chain-end group would be the terminal non-conjugated alkene obtained after quenching with ethyl vinyl ether. On the other hand, if the catalyst initiated on the cycloalkene first (pathway **B**), the styryl group would be transferred to the non-conjugated alkene and the chain-end group would be conjugated diene. Therefore, we could determine the actual mechanism for the tandem RO/RCM polymerization by conducting end-group analysis using ^{1}H-NMR analysis. Firstly, we prepared oligomeric **P1** by treating **1** with 20 mol% **A** and quenching the polymerization by adding ethyl vinyl ether so that its end-groups could be analyzed in detail. For a comparison study, **10a** was independently prepared by selective CM between styrene and the more reactive non-conjugated terminal alkene on **10** (Scheme 5). When the ^{1}H-NMR spectra of three substrates (**10**, **10a**, and oligo-**P1**) were compared, peaks for all the terminal olefins could be unambiguously assigned (Figure 5 (a-c)). From these data, we observed that oligo-**P1** vividly showed non-conjugated terminal alkene proton signals as H_A, H_B, and H_C, whereas chemical shifts corresponding to $H_{1\text{-}5}$ of **10a** were totally absent. This confirmed that tandem RO/RCM polymerization of **1** followed pathway **A** exclusively. We also conducted a similar mechanistic study on **2**, because the monomer containing cycloalkenes with higher ring strains might follow different pathway. A similar chemical shifts—H_A*, H_B*, and H_C* without $H_{1\text{-}5}$—were observed for the oligomeric **P2** as well, suggesting that the polymerization pathway was not altered by the ring strain of cycloalkenes (Figure 5d). All these observations proved that the mechanism of tandem RO/RCM polymerization follows pathway **A** exclusively (Scheme 4).

Table 4. Tandem metathesis polymerization of monomers with trisubstituted cycloalkenes

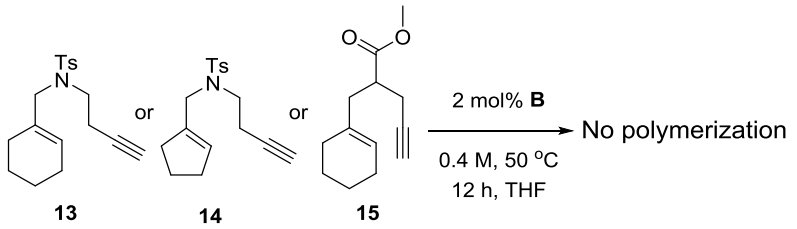


Entry	Mono.	Temp.	Conc.	Time	Conv.[a]	M_n[b]	PDI[b]
1	**11**	r. t.	0.4 M	3 h	0 %	-	-
2	**11**	50 ℃	0.4 M	6 h	37 %	4400	1.61
3	**11**	60 ℃	0.8 M	12 h	50 %	3900	1.25
4	**12**	50 ℃	0.4 M	12 h	65 %	8000	1.93
5	**12**	60 ℃	0.6 M	12 h	100 %	6000	1.57

[a] Conversion determined by crude ^{1}H-NMR. [b] Determined by THF SEC calibrated using PS standards.

Up to now, sterically hindered trisubstituted cycloalkenes with low ring strain, such as 1-methylcyclopentene or 1-methylcyclohexene, has not been polymerized by ROMP.[16] However, we envisioned that utilizing the relay sequence of this efficient RO/RCM process, monomers containing extremely challenging

trisubstituted cycloalkenes might undergo tandem polymerization just as 3-substituted cycloalkenes underwent efficient tadem RO/RCM polymerization. Initially, monomer **11** containing trisubstituted cyclohexene and propargyl group was subjected to 2 mol% of catalyst **B** at room temperature, but no polymer was obtained because of severe steric hindrance of trisubstituted olefin (Table 4, entry 1). In order to enhance the reactivity, reaction temperature was increased to 50 ℃ to yield **P11** containing tetrasubstituted cyclopentene moiety in 37 % conversion (Entry 2) and further to 60 ℃ to achieve 50 % conversion, with M_n of 3.9 k (Entry 3). To our delight, monomer **12** containing trisubstituted cyclopentene showed 65 % conversion at 50 ℃ and 100 % conversion at 60 ℃, implying that **12** was more reactive monomer than **11** at the same reaction condition (Entries 4 and 5). These results were contrast to the previous results which showed that the monomer containing propargyl group and cyclohexene (**1**) was more reactive than its cyclopentene derivative (**3**). In both cases, *E*/*Z* ratio on the newly generated olefin was 1/1, similar to the previous results.



Scheme 6. Unsuccessful tandem metathesis polymerization of monomers with trisubstituted cycloalkenes

On the other hand, monomers containing trisubstituted cycloalkenes and 1-butynyl moieties, **13** and **14**, were totally inactive for the tandem polymerization (Scheme 6). At least, polymerization result of **14** was rather disappointing because its 3-substituted cyclopentene derivative, **6**, showed good reactivity

toward the tandem polymerization to give the polymer having a six-membered ring repeat unit (Table 2, entries 8 and 9). Also, **15** with carbon linker failed to give any polymer (Scheme 6). This suggested that monomers with sterically hindered trisubstituted cycloalkenes were much more challenging to undergo the tandem polymerization compared to the disubstituted cycloalkene derivatives, and their reactivities were also sensitive to the monomer structures presumably.

Conclusion

In conclusion, we demonstrated ultrafast efficient tandem RO/RCM polymerization using monomers consisted with unreactive functional groups: cycloalkenes with low ring strain, and terminal alkyne. With the help of efficient tandem relay type metathesis reaction, those two unreactive monomers underwent metathesis reaction with high efficiency. By changing the structures of cycloalkene and alkyne functional groups, we could provide that broad scope of monomers could be used as a monomer for tandem polymerization. This polymerization method could be also used to block copolymerization thanks to its living polymerization characteristic, and polymer backbone could be modified with Diels-Alder cycloaddition reaction. Also, we studied reaction mechanism of tandem polymerization to reveal that the polymerization undergoes single pathway starting from the initiation on alkyne.

Part B. Strategies and deeper mechanistic study of monomers with low reactivity

Introduction

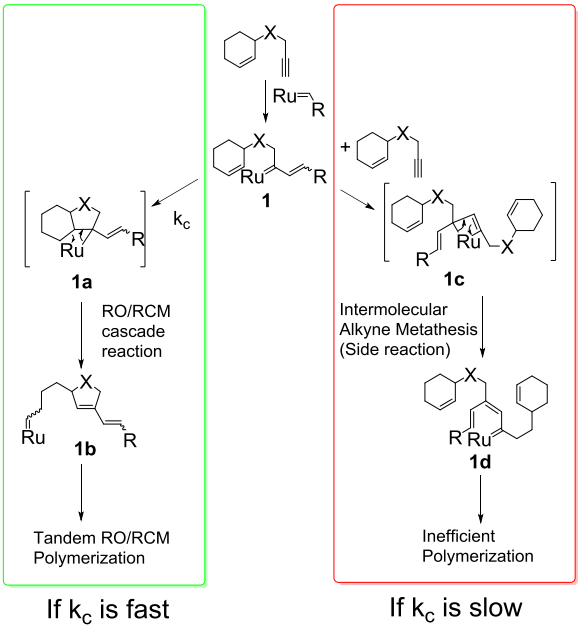
Development of tandem ring-opening/ring-closing metathesis (RO/RCM) polymerization allowed us to synthesize polymers from terminal alkyne and cycloalkene, which are known as a bad monomer, through selective cascade reaction.[17] Although various monomer scopes were studied for the polymerization, the monomer scope for tandem polymerization were not perfectly generalized, as monomers containing certain combinations of functional groups could undergo efficient polymerization, while other combinations did not, such as monomers containing homopropargyl group. Also, monomers containing more diverse functional groups should be studied, including monomers containing carbon or oxygen linker instead of optimized nitrogen linker, or internal alkyne instead of terminal alkynes. This chapter will describe about the strategies to greatly improve tandem RO/RCM polymerization and broaden the monomer scope to provide general polymerization method. In this regard, two strategies – modifying the monomers to enhance the Thorpe-Ingold effect and lowering the reaction concentration – successfully directed the reaction pathway toward effective polymerization. Also, detailed kinetic analysis was performed to observe reaction mechanism to explain the polymerization behavior and to validate our logic.

Results and Discussion

Previously, we successfully demonstrated tandem RO/RCM polymerization of monomers containing nitrogen linker groups, cycloalkenes, and propargyl groups. These optimized monomers exhibited extremely fast polymerization, with full

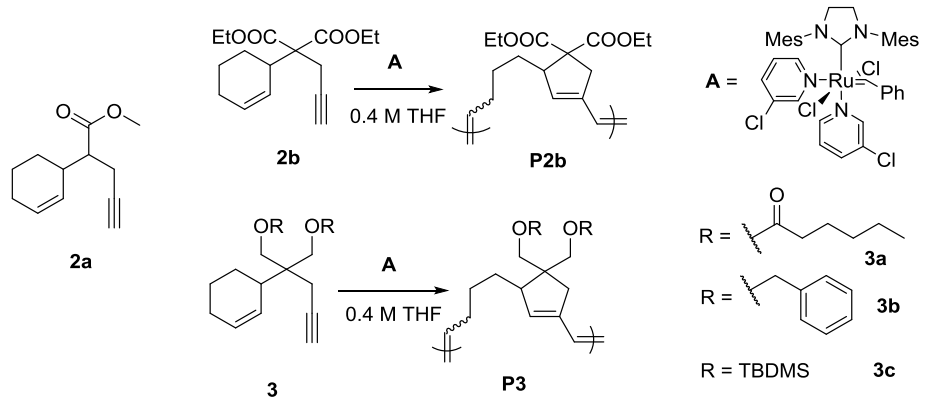
conversion within 1 minute at room temperature or 10 minutes at −30 ℃.[17] However, polymerization of certain monomers were very inefficient or totally inactive, such as monomer containing an analogous homopropargyl group. In order to explain this low reactivity, we proposed reaction mechanism. During tandem polymerization, the initiator reacted with an alkyne in α-addition manner to form a 1,1-disubstituted metal carbene intermediate (**1**); the resulting intermediate underwent intramolecular tandem RO/RCM reaction (**1a**) to form a propagating species (**1b**).[17] However, if this intramolecular cyclization rate (k_c) was relatively slow, metal carbene intermediate **1** would undergo side reactions such as intermolecular CM (**1c**), which would then afford inactive propagating species (**1d**). On the basis of this proposal, we devised with two strategies to favor cyclization selectivity, thereby enhancing the tandem polymerization reaction pathway.

Scheme 1. Possible competing reaction during the tandem RO/RCM process.



We first focused on designing new monomers to accelerate the intramolecular RO/RCM reaction by enhancing the Thorpe–Ingold effect. Thus, we focused on the monomers containing carbon linker group, as side chain modification is much easier than monomers with other kind of linker structure. Firstly, monoester substituted **2a** was subjected to the polymerization, but it did not undergo polymerization possibly due to the lack of Thorpe-Ingold effect by small monosubstitution. To improve polymerization, we added an additional ester substituent to the monomer to enhance the Thorpe–Ingold effect; as a result, disubstituted monomer **2b** underwent successful tandem polymerization in the presence of a third-generation Grubbs catalyst (**A**) to yield a high-molecular-weight polymer, with 80 % monomer conversion after 90 minutes at room temperature (Table 1, Entry 1).[18] Although this strategy appeared to be successful, polymerization of **2b** was still slow when compared to polymerization of the previously reported sulfonamide monomers that exhibited complete conversion within 1 minute under the same reaction conditions.[17] We reasoned that the relatively low reactivity of monomer **2b** was due to the small size of the ester substituent (A-value of -COOR: 1.27 kcal/mol)[19] and that changing the substituents to larger methoxy derivatives would increase the polymerization reactivity (A-value of -CH_2OH: 1.8 kcal/mol).[19]

Table 1. Polymerization of monomer with disubstituted carbon linker



Entry	Mono	M/I	Time	Temp.	Conv.[a]	M_n[b]	PDI[b]
1	**2a**	50	12 h	50 ℃	0 %	-	-
2	**2b**	50	90 min	r. t.	80 %	20000	1.49
3	**3a**	50	20 min	r. t.	100 %	33000	1.99
4	**3a**	50	15 min	-10 ℃	100 %	26000	1.17
5	**3a**	100	30 min	-10 ℃	87 %	48000	1.79
6	**3b**	50	1 min	r. t.	96 %	16000	1.18
7	**3b**	75	1.5 min	r. t.	100 %	26000	1.11
8	**3b**	100	2 min	r. t.	100 %	33000	1.32
9	**3b**	150	3 min	r. t.	80 %	37000	1.35
10	**3c**	50	30 sec	r. t.	100 %	27000	1.25
11	**3c**	100	30 sec	r. t.	95 %	50000	1.37
12	**3c**	75	8 min	0 ℃	100 %	34000	1.14
13	**3c**	100	10 min	0 ℃	100 %	50000	1.27
14	**3c**	150	20 min	0 ℃	100 %	84000	1.44

[a] Conversion determined by crude ^{1}H-NMR. [b] Determined by THF SEC, calibrated using polystyrene (PS) standards.

Tandem polymerization of monomer **3a** with hexanoyl groups underwent complete conversion within 20 minutes at room temperature to give a high-molecular-weight polymer; however, the polydispersity index (PDI) of this polymer was disappointingly broad because of the chain transfer reaction (Entry 2).[17] The chain transfer reaction was suppressed when the reaction temperature was reduced to −10 ℃ (Entry 3), but the PDI was still broad for polymerization at a higher monomer-to-initiator (M/I) ratio (Entry 4). To achieve living polymerization, monomers containing even larger substituents are necessary to enhance polymerization reactivity and suppress the chain transfer reaction. Thus, monomer **3b** containing bulkier benzyl ether substituents was synthesized, and the polymerization of **3b** yielded 96% monomer conversion within 1 minute; in addition, the PDI was narrower than 1.2 (Entry 5). The molecular weights of **P3b** were linearly controlled by increasing the M/I ratio such that the degree of polymerization (DP) was 120 and the PDIs remained relatively narrow (Entries 5–8, Figure 1). A monomer with bulkier *tert*-butyldimethylsilyl (TBDMS) substituents (**3c**) exhibited even higher reactivity, with complete monomer conversion within 30 seconds to give **P3c** with a narrow PDI (Entry 9). This monomer appeared to be more reactive than the previously reported amide analogues.[17] To ensure controlled polymerization, we decreased the reaction temperature to 0 ℃ to give **P3c** with a narrower PDI; the molecular weight was well controlled to a DP of 150 (Entries 10–13, Figure 1). These data suggested that the modification of monomer structures to enhance the Thorpe–Ingold effect was indeed a successful strategy to increase tandem polymerization reactivity and to achieve living polymerization.

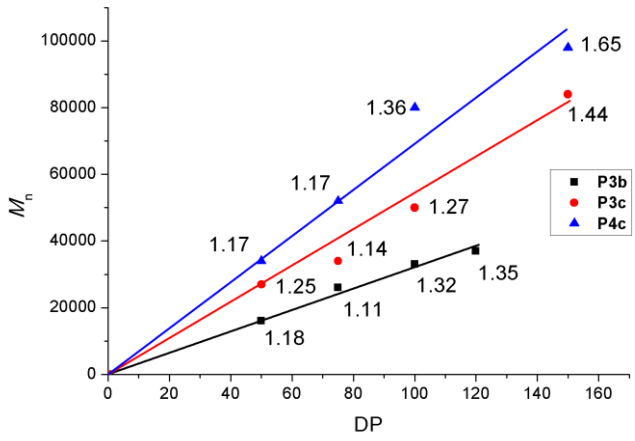
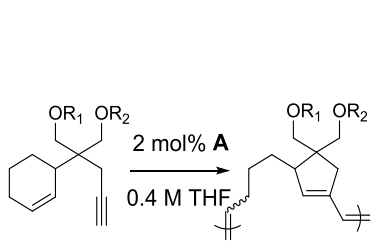
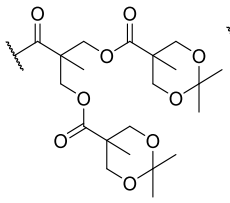
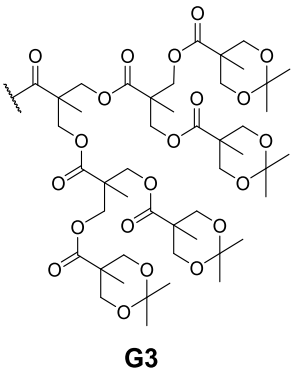


Figure 1. Plot of M_n versus DP for **P3b**, **P3c**, and **P4c**. The PDI values are shown as labels.

Table 2. Polymerization of monomer with dendronized substituent







4a - R_1, R_2 = **G2**
4b - R_1, R_2 = **G3**
4c - R_1 = TIPS, R_2 = **G3**

Entry	Mono	M/I	Time	Temp.	Conv.[a]	M_n[b]	PDI[b]
1	**4a**	50	2 h	r. t.	100 %	33000	1.39
2	**4b**	50	8 h	r. t.	0 %	-	-
3	**4c**	50	1 h	r. t.	100 %	34000	1.17
4	**4c**	75	1.75 h	r. t.	100 %	52000	1.17

5	**4c**	100	2.5 h	r. t.	100 %	80000	1.36
6	**4c**	150	3.5 h	r. t.	100 %	98000	1.65

[a] Conversion determined by crude ^{1}H-NMR. [b] Determined by THF SEC, calibrated using polystyrene (PS) standards.

To demonstrate the effectiveness of this strategy, we attempted tandem polymerization of even more challenging monomers to synthesize dendronized polymers *via* a macromonomer approach.[20] Although the macromonomer approach to dendronized polymers was extremely challenging because of the highly bulky dendron substituents, these dendrons could also induce a strong Thorpe–Ingold effect to increase polymerization reactivity. Initially, **4a** containing bis-substituted second-generation ester dendrons (**G2**)[21] was tested and resulted in complete conversion to polymer after 2 hour (M/I = 50) (Table 2, Entry 1). However, monomer **4b** containing two larger third-generation dendrons (**G3**) did not polymerize at all after long reaction times (Entry 2). The excessively bulky **G3** bis-substituents likely blocked the catalyst approach to the alkyne. To solve this problem, we substituted one of the **G3** dendron substituents to a smaller triisopropylsilyl (TIPS) substituent; as a result, monomer **4c** was completely converted into a 50-mer dendronized polymer with a narrow PDI within 1 hour (Entry 3). Furthermore, the controlled polymerization of **4c** was successful for M/I ratios up to 150 (Entries 3–6, Figure 1).

A substantial advantage of the dendronized polymer having bulky side chains was that it allowed us to clearly observe a single chain of the polymer by atomic force microscopy (AFM). Indeed, Figure 2 shows the relatively stretched chains of **P4c** for the 100-mer polymer whose length and height were approximately 75 nm and 0.3 nm, respectively. The rigidity of **P4c** was similar to that of polynorbornene-based dendronized polymers[20a] but was certainly less than that of polymers prepared by cyclopolymerization[18] or ROMP of *endo*-tricyclo[4.2.2.0]deca-3,9-

diene[20b] with the same dendron structure and dendron generation. This was due to the presence of flexible methylenes polymer backbone, which increased the conformational freedom of the polymer chain.

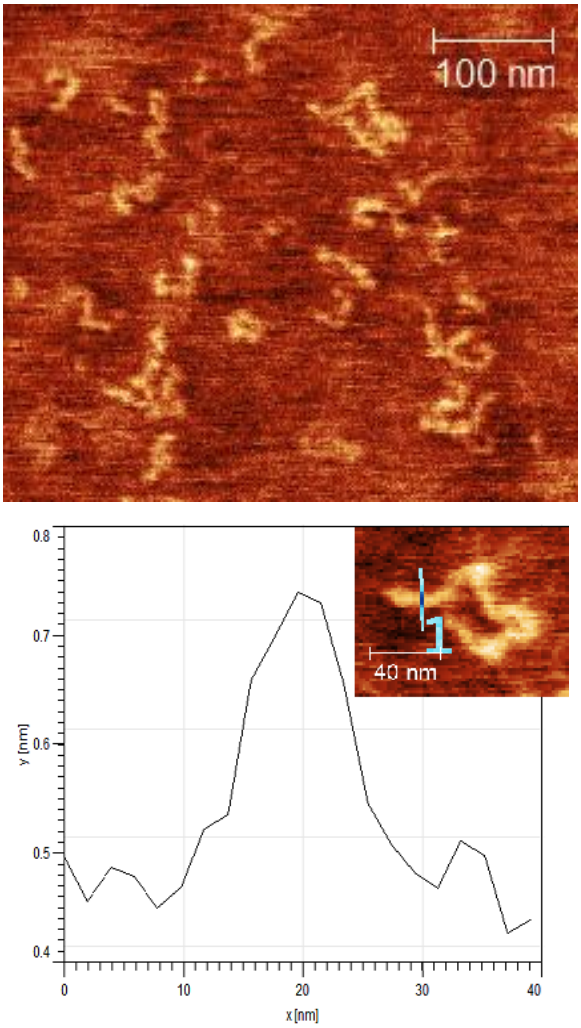
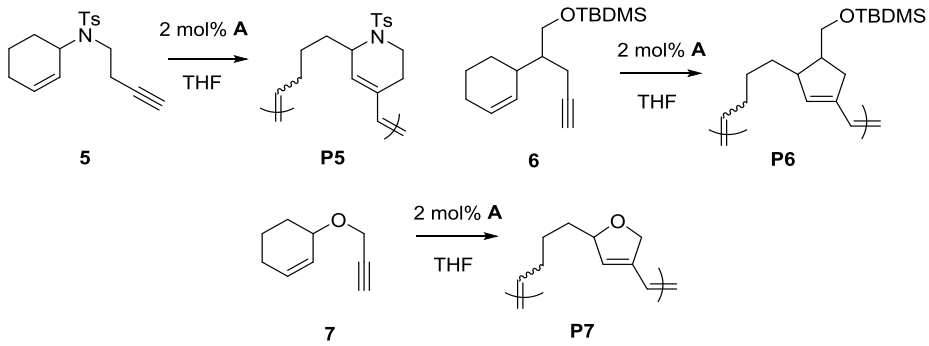


Figure 2. AFM image of **P4c** in phase mode and single-chain height profile in height mode. The polymer solution in DCM (1.25 mg/L) was spin-coated onto a mica surface.

Table 3. Polymerization of monomers with low reactivity



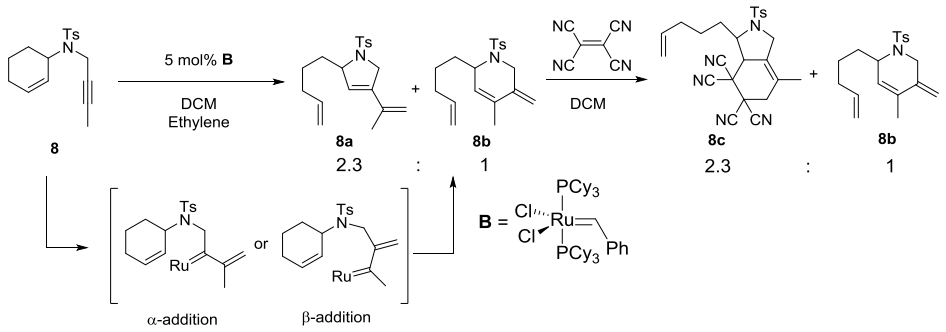
Entry	Mono	Conc.	Time	Temp.	Conv.[a]	M_n[b]	PDI[b]
1	**5**	0.4 M	12 h	r. t.	10 %	-	-
2	**6**	0.4 M	12 h	r. t.	16 %	-	-
3	**7**	0.4 M	12 h	r. t.	0 %	-	-
4	**5**	0.03 M	3 h	40 ℃	100 %	26000	1.50
5	**6**	0.03 M	3 h	r. t.	100 %	7700	2.88
6	**7**	0.03 M	30 min	r. t.	100 %	3600	1.51

[a] Conversion determined by crude ^{1}H-NMR. [b] Determined by THF SEC calibrated using polystyrene (PS) standards.

Although modifying monomer structures was an effective strategy to increase polymerization reactivity, an alternate strategy was required in cases where the monomer structures could not be modified. In such cases, we applied the second strategy of suppressing intermolecular side reactions by reducing the monomer concentration (Scheme 1). Previously, we reported that monomers containing a homopropargyl group (**5**), which could not undergo tandem polymerization (Table 3, Entry 1).[17] Similarly, monomers with monosubstituted carbon (**6**), or oxygen linker (**7**) did not yield polymers at 0.4 M concentration, which is the concentration typically used for this tandem polymerization (Table 3, Entries 2

and 3).[17] However, when the monomer concentration was decreased from 0.4 M to 0.03 M, all three monomers underwent complete conversion at room temperature or at slightly elevated temperature (40 °C for **5**) (Entries 4–6). These results indicate that the intramolecular RO/RCM reaction was indeed slow for these monomers (Scheme 1) and that consequently the competing side reaction stopped the tandem polymerization. Gratifyingly, simple dilution solved this problem. However, the polymerization reactions at low concentrations were inevitably much slower and the PDIs also broadened (Table 3).

Scheme 2. Ring rearrangement of a monomer containing internal alkyne **8** by ethylene.



With these successful strategies to promote efficient polymerization of various monomers, we focused on even broader monomer scope by using monomers with internal alkynes instead of terminal alkynes. Polymerization of the internal alkynes was even more challenging because of steric hindrance from the additional substituent. Moreover, unlike terminal alkynes, which exclusively undergo α-addition,[17] internal alkynes undergo both α-addition and β-addition non-selectively, thereby forming complex polymer microstructures.[22] As a control experiment, we tested the ring rearrangement reaction of **8** by performing ethenolysis with a first-generation Grubbs catalyst (**B**) and obtained a mixture of

two different products, **8a** and **8b**, which could be separated to **8c** and **8b** upon sequential Diels-Alder reaction, in a 2.3:1 ratio (Scheme 2, Figure 3). This result suggested that tandem polymerization of monomers containing internal alkynes would also form both five- and six-membered-ring repeating units as a result of non-selective α- and β-addition (Scheme 3).

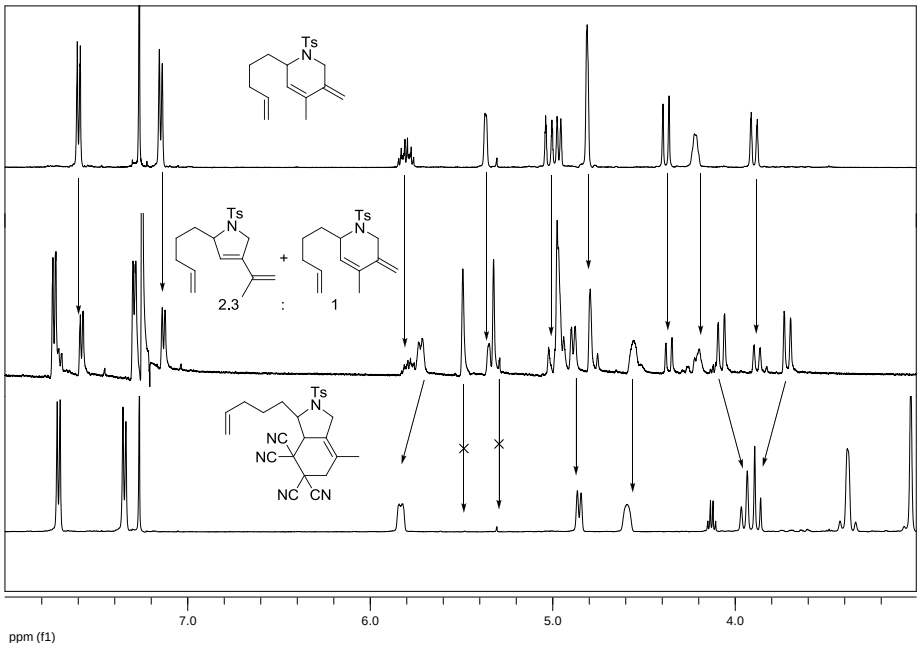


Figure 3. ^{1}H-NMR spectrum of ethenolysis products of **8**.

Scheme 3. Possible reaction mechanism of a monomer with internal alkyne

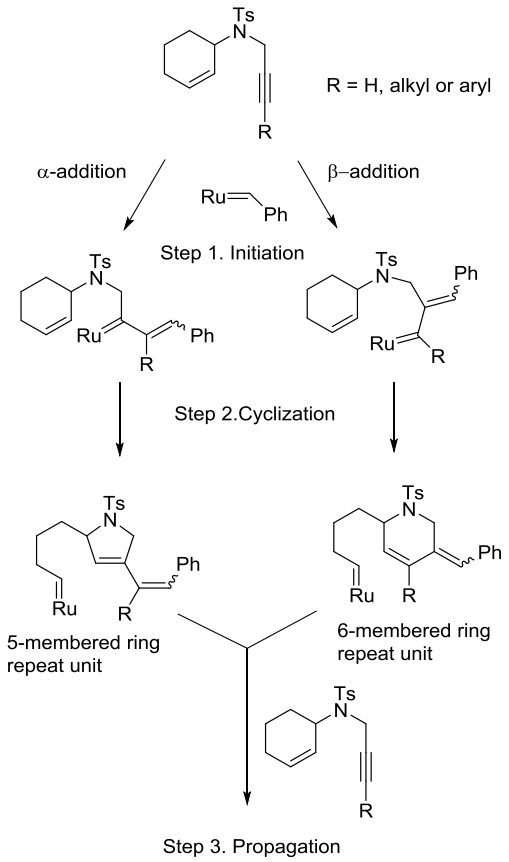
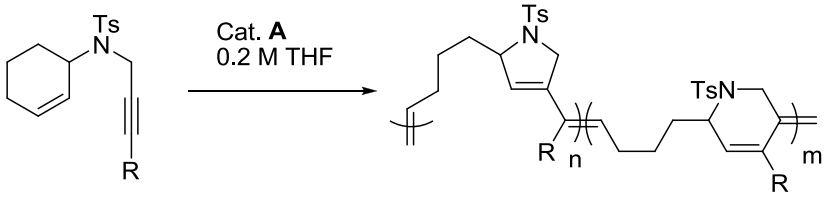


Table 4. Tandem polymerization of monomers containing an internal alkyne



8 - R = Me
9 - R = Et
10 - R = CF_3

P8 - R = Me
P9 - R = Et
P10 - R = CF_3

Entry	Mono	M/I	Time	Temp.	Conv.[a]	M_n[b]	PDI[b]	n : m[a]
1[c]	**8**	50	2 hr	r. t.	50 %	15000	1.50	2.3 : 1
2	**8**	50	5 min	r. t.	93 %	30000	1.20	2.3 : 1
3	**8**	50	10 min	15 ℃	93 %	20000	1.08	2.3 : 1
4	**8**	100	14 min	15 ℃	92 %	39000	1.24	2.3 : 1
5	**8**	150	15 min	15 ℃	95 %	65000	1.20	2.3 : 1
6	**8**	200	20 min	15 ℃	95 %	82000	1.31	2.3 : 1
7	**9**	25	5 min	10 ℃	85 %	10000	1.04	1.7 : 1
8	**9**	50	25 min	10 ℃	92 %	20000	1.07	1.7 : 1
9	**9**	100	30 min	10 ℃	92 %	36000	1.10	1.7 : 1
10	**9**	150	40 min	10 ℃	80 %	44000	1.36	1.7 : 1
11	**10**	50	10 min	r. t.	100 %	16000	1.06	1 : 0
12	**10**	100	1.5 h	15 ℃	89 %	42000	1.15	1 : 0
13	**10**	150	2.5 h	15 ℃	80 %	49000	1.44	1 : 0

[a] Determined by crude ^{1}H-NMR. [b] Determined by THF SEC calibrated using polystyrene (PS) standards. [c] Reaction concentration was 0.4 M.

Initially, we attempted the tandem polymerization of monomer **8** at a concentration of 0.4 M, but it only yielded 50% monomer conversion after 2 h, with a broad PDI (Table 4, Entry 1). We subsequently used the dilution strategy and observed that reducing the concentration to 0.2 M increased the conversion to 93% within just 5 min. Notably, this polymerization occurred rapidly and the resulting PDI was 1.2 (Entry 2). ^{1}H-NMR analysis of **P8** showed two different sets of signals corresponding to five- and six-membered-ring repeating units with an identical ratio of 2.3:1, favoring α-addition (Scheme 2). When the reaction temperature was lowered to 15 ℃, the chain-transfer reaction was further suppressed and the PDI became narrower than 1.1 (Entry 3). Again, we observed well-controlled polymerization behavior, where the molecular weight and DP exhibited a linear relationship up to a DP of 190 and the PDIs were narrow

(Entries 3–6, Figure 4). Similarly, controlled polymerization of monomer **9**, which contained an ethyl-substituted alkyne, was successful at 10 ℃ (Entries 7–10, Figure 4). A slight increase in steric bulkiness provided by an ethyl substituent (A-value: 1.75 kcal/mol)[19] in place of the methyl substituent (A-value: 1.70 kcal/mol)[19] decreased the selectivity between α-addition and β-addition to give a 1.7:1 ratio.

Lastly, we studied the polymerization of monomer **10**, which contained an electron-withdrawing trifluoromethyl (CF_3) substituent. For an M/I ratio of 50, monomer **10** was completely converted to a polymer with a PDI narrower than 1.1 (Entry 11). For high M/I ratios, a decrease in the reaction temperature to 15 ℃ appeared to result in greater polymerization efficiency (Entries 12 and 13). Interestingly, although the A-value of the CF_3 substituent is greater than that of a methyl or ethyl substituent (A-value: 2.1 kcal/mol)[19], only a five-membered-ring polymer unit was observed for **P10**, implying that α-addition occurred exclusively. These results suggested that the regioselectivity was not only dependent on the steric bulk but also the electronic effects of the alkyne substituent.

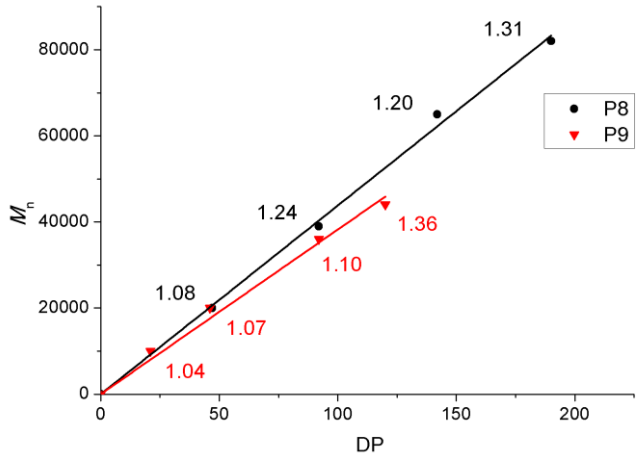


Figure 4. Plot of M_n versus DP for **P8** and **P9**. Numbers on the line indicate PDIs.

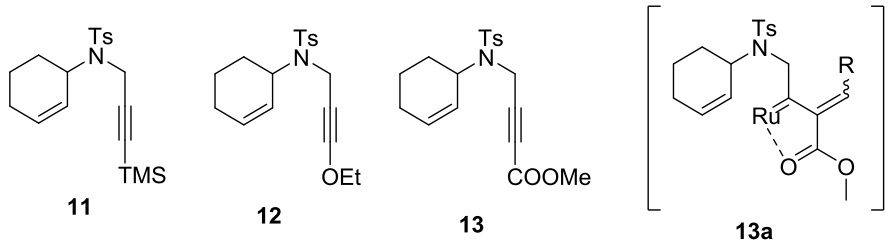
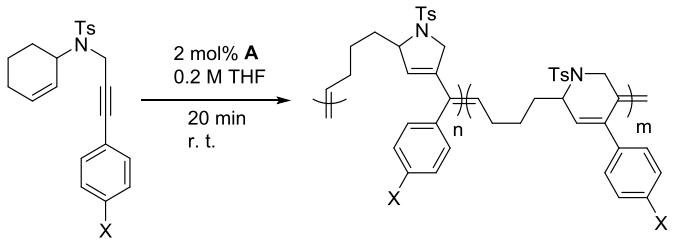


Figure 5. Unreactive monomers for tandem RO/RCM polymerization

However, monomers containing certain alkyne substituents were not suitable for tandem polymerization (Figure 5). For examples, bulky trimethylsilyl (TMS) group in monomer **11** blocked catalyst approach toward alkyne, and polymerization could not take place. Monomer **12** containing electron-rich ethoxy substituent also did not undergo polymerization. Surprisingly, monomer **13** containing electron-poor methyl ester substituent also did not undergo polymerization, unlike monomer **10** containing trifluoromethyl substituent. It seems that coordination effect from ester carboxyl group formed five-membered ring intermediate (**13a**), which suppressed catalyst activity. Thus, in order to perform polymerization, choice of alkyne substituent based on steric, electronic, and coordination effect is important for the polymerization.

Table 5. Polymerization of monomer with phenyl derivatives



11a - X = OMe
11b - X = Me
11c - X = H
11d - X = F
11e - X = CF_3

P11a - X = OMe
P11b - X = Me
P11c - X = H
P11d - X = F
P11e - X = CF_3

Entry	Mono	Conv.[a]	M_n[b]	PDI[b]	n : m[c]
1	**11a**	22 %	-	-	-
2[d]	**11b**	33 %	27000	1.31	-
3	**11c**	73 %	22000	1.25	2 : 1
4	**11d**	85 %	34000	1.31	2.7 : 1
5	**11e**	85 %	30000	1.48	1 : 1

[a] Conversion determined by crude ^{1}H-NMR. [b] Determined by THF SEC calibrated using polystyrene (PS) standards. [c] Ratio determined by ^{13}C-NMR. [d] SEC measurement was performed with crude polymerization sample because purification of polymer failed.

To investigate the electronic effects of the substituent toward the polymerization, we investigated the structure–reactivity relationship of monomers containing internal alkyne substituents with the same steric effect but different electronic effects. Therefore, we prepared several monomers containing 4-substituted phenyl substituents (**11a–e**) and tested for tandem polymerization with 2 mol% of catalyst **A** for 20 min. Monomer **11c**, which contained a neutral phenyl substituent, exhibited 73% conversion, whereas monomers with electron-donating groups (**11a**, **11b**) showed less than 40% conversion (Table 5, Entries 1–3) and monomers with electron-withdrawing groups (**11d**, **11e**) showed 85% conversion (Entries 4 and 5). Although the steric effects of phenyl substituents are quite high (A-value: 3.00 kcal/mol)[19], the ratio between five- and six-membered-ring units varied from 1:1 to 2.7:1 for **P11c–e**, as determined by ^{13}C-NMR experiments (see Supporting Information for details (Figure S5 and S6)). This complex α- and β-addition selectivity appears to originate by electronic effects of phenyl substituents.

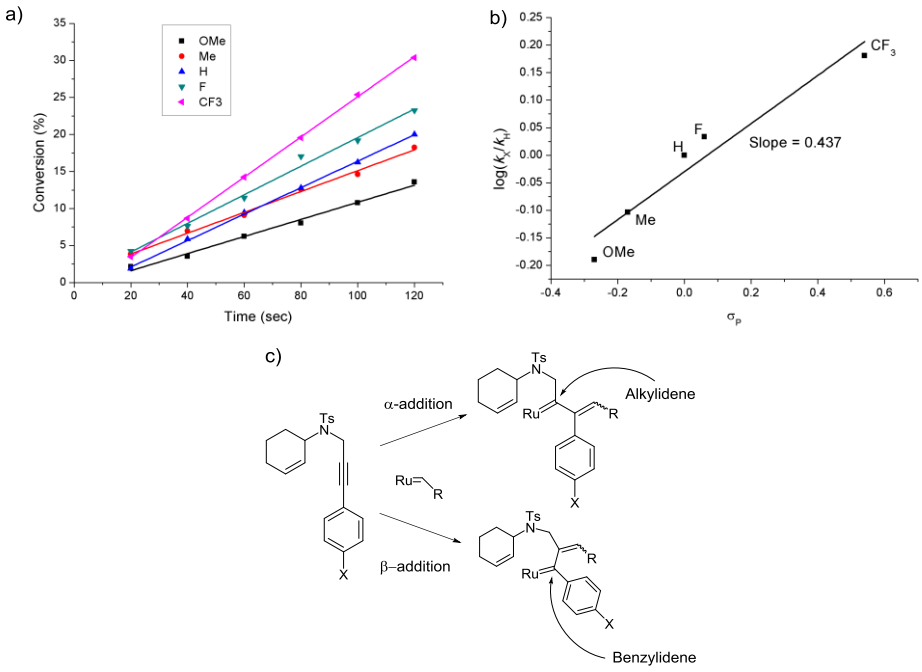


Figure 6. a) Plot of the polymerization rate of phenyl derivative monomers. b) Hammett plot of phenyl derivative monomers. c) Possible intermediates from the alkyne initiation step.

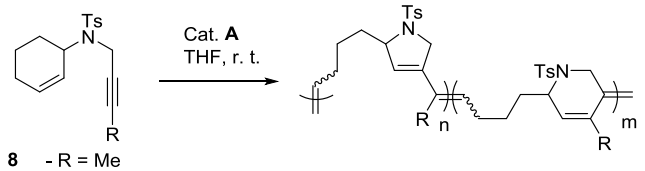
Table 6. Hammett plot data for reaction rate of monomer **11**.

Entry	X	[Mono]	[Cat]	*k*(obs)	log(k_D/k_H)	Sigma(σ_P)
1	OMe	0.02 M	0.4 mM	0.11541 M/sec	-0.18998	-0.27
2	Me	0.02 M	0.4 mM	0.14079 M/sec	-0.10365	-0.17
3	H	0.02 M	0.4 mM	0.17874 M/sec	0	0
4	F	0.02 M	0.4 mM	0.26933 M/sec	0.03363	0.06
5	CF3	0.02 M	0.4 mM	0.27113 M/sec	0.18096	0.54

To further elucidate the electronic effects of various phenyl substituents, we monitored the polymerization kinetics by ^{1}H-NMR and constructed Hammett plots (Figures 6a and 6b) from the propagation rate constants. The plots showed positive linear relationships between the Hammett constant and log(k_D/k_H) (ρ = 0.55), indicating that the polymerization rate was accelerated by electron-

withdrawing groups on the phenyl substituent. Similar ρ values were reported by Chen et al., who investigated the structure–reactivity relationship in olefin metathesis reactions involving benzylidenes with various electronic effects.[23] They explained that electron-deficient ruthenium benzylidenes reacted faster than electron-rich benzylidenes because electron-deficient benzylidenes were destabilized to a greater extent. For the tandem RO/RCM polymerization, β-addition of propagating carbene to alkynes formed a benzylidene intermediate (not an alkylidene intermediate formed after α-addition), whose reactivity was directly governed by the electronic effects of phenyl substituents, similar to the results reported by Chen et al. (Figure 6c).[23] On the basis of the kinetics data, we concluded that the rate-determining step involves intermediates that would show the electronic effect on phenyl substituents to affect the polymerization rate.(Similar relationship could be observed during initiation step. For detailed data, see Supporting Informations (Figure S7).)[24]

Table 6. Kinetics study of tandem RO/RCM monomers



8 - R = Me
10 - R = CF_3
11e - R = 4-CF_3-C_6H_4
12 - R = H

Entry	Monomer	[Monomer]	[**A**]	Rate[a] (M/sec)
1[b]	**12**	0.02 M	0.13 mM	$8.90X10^{-4}$
2[b]	**12**	0.01 M	0.13 mM	$4.85X10^{-4}$
3	**11e**	0.03 M	0.2 mM	$1.37X10^{-5}$
4	**11e**	0.02 M	0.2 mM	$1.57X10^{-5}$
5	**11e**	0.01 M	0.2 mM	$1.36X10^{-5}$
6	**10**	0.02 M	0.4 mM	$8.40X10^{-5}$

7	**10**	0.01 M	0.4 mM	$4.04X10^{-5}$
8	**8**	0.02 M	0.4 mM	$1.52X10^{-5}$
9	**8**	0.01 M	0.4 mM	$1.76X10^{-5}$

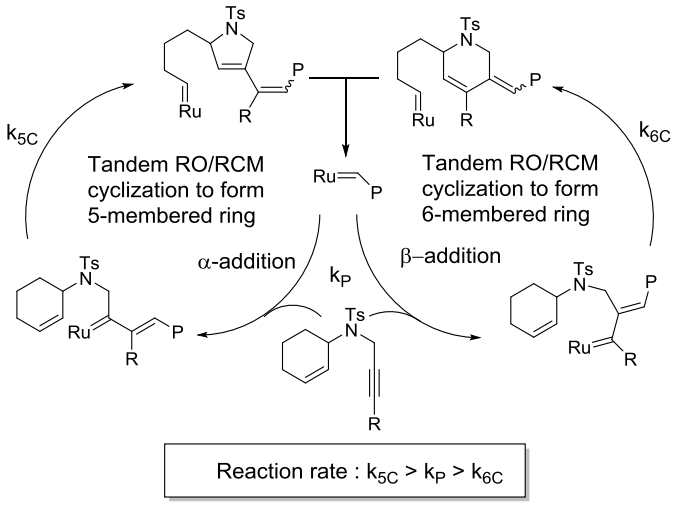
[a] Reaction rate is the linear slope of monomer disappearance versus time, as measured by ^{1}H-NMR. [b] The reaction temperature was −10 ℃.

Detailed understanding of the mechanism would require determination of the rate-determining step of tandem polymerization through a series of kinetics studies. Tandem RO/RCM polymerization fundamentally consists of two steps: the intermolecular propagation step between a growing active alkylidene and other monomers, followed by the intramolecular RO/RCM cyclization step forming the ring structure. Polymerization kinetics became more complex for monomers containing internal alkynes because depending on the selectivity of α- or β-addition, two different intermediates could form and undergo five- or six-membered-ring cyclization with different reaction rates (Schemes 1 and 3). With these polymerization pathways in mind, we performed kinetics studies for tandem RO/RCM polymerization at monomer concentrations ranging from 0.01 to 0.03 M to exclude any possible side reactions.

Initially, this kinetics study was performed with a highly reactive monomer **12** containing a terminal alkyne. Under a constant concentration of catalyst **A**, a twofold increase in the monomer concentration resulted in a doubling of the reaction rate, indicating that the reaction was first order in monomer **12** (Table 6, Entries 1 and 2). This result suggested that the rate-determining step was the intermolecular propagation step, as observed for typical living polymerization reactions, and that five-membered-ring cyclization was indeed fast. However, in the case of monomer **11e**, which contained an internal alkyne with a 4-CF_3-phenyl substituent, the kinetics study revealed that the reaction was zeroth order in monomer concentration (i.e., changing the monomer concentration did not

change the reaction rate) (Entries 3–5). This result suggested that the rate-determining step for the polymerization of **11e** was the intramolecular RO/RCM step. At this point, which cyclization step was the actual rate-determining step remained unclear because the two different cyclizations were possible for the internal alkyne.[18] We therefore performed a kinetics study on monomer **10**, which possesses an internal alkyne with a CF_3 substituent; and **10** only underwent five-membered-ring cyclization, and confirmed the first-order relationship in the monomer concentration, unlike **11e** with similar electron-withdrawing substituent (Entries 6 and 7). This result implies that the propagation step was the rate-determining step and that the five-membered-ring cyclization was still fast for monomer **10**. Unlike monomer **10**, kinetics study of monomer **8** containing methyl substituent with lower A-value confirmed the zero-order relationship in the monomer concentration (Entries 8 and 9). In conclusion, rate-determining step of tandem polymerization is affected by the presence of six-membered cyclization step from β-addition, not by the steric or electronic effects of alkyne substituents.

Scheme 4. Reaction kinetics of tandem RO/RCM polymerization



On the basis of the series of kinetics data, we drew several conclusions. The kinetics study suggested that the five-membered-ring cyclization (k_{5C}) after α-addition was the fastest step, which logically led us to believe that six-membered-ring cyclization (k_{6C}) from β-addition was, surprisingly, the slowest step, becoming the rate-determining step for monomers containing internal alkynes (Scheme 4). This conclusion also agreed with the interpretation of ρ values obtained from the Hammett plot, which suggested that the rate-determining step involved the olefin metathesis reactions from benzylidenes after β-addition (Figure 5). These results are unusual because the rate-determining step of conventional chain-growth polymerization reactions is typically the propagation step. Notably, with this understanding of the mechanism, where the cyclization step could be the rate-determining step, our previous failures, new proposals, and new strategies all became logically consistent. In short, controlling the intramolecular tandem RO/RCM cyclization is the key for the successful polymerization.

CONCLUSION

In this chapter, we studied the reaction mechanism of tandem RO/RCM polymerization to enhance polymerization efficiency for various challenging monomers. The previous unsuccessful polymerization was because of relatively slow intramolecular RO/RCM that led to the acceleration of competing side reactions such as intermolecular CM reactions. To this end, two strategies successfully solved this problem and greatly enhanced polymerization reactivity. First, we modified the monomer structures to accelerate the cyclization by enhancing the Thorpe–Ingold effect; this strategy also allowed living polymerization. Furthermore, the synthesis of dendronized polymers containing as large as third-generation dendrons was possible, and the resulting single polymer chain was visualized *via* AFM. The second strategy was to reduce the

reaction concentration to favor the intramolecular RO/RCM step over competing side reactions. The monomer scope was then further expanded to those containing internal alkynes, and polymerization of these monomers was more challenging because the selectivity issue between α- and β-addition resulted in the formation of more complex polymer microstructures comprising five- and six-membered-ring units. Nonetheless, polymerization of internal-alkyne-containing monomers was successful under dilute conditions, and their regioselectivity was governed by steric and electronic effects of the substituents. Lastly, the polymerization kinetics study and Hammett-plot analysis revealed the unique kinetics of tandem RO/RCM polymerization. As expected, the rate-determining step of the reactive monomers was the intermolecular propagation step. However, for challenging monomers containing internal alkynes, the intramolecular six-membered ring cyclization step was the rate-determining step. This observation agrees well with all the data we obtained and validates our strategies. In conclusion, studying the mechanism in detail not only provided deep insights into the polymerization pathway but also provided clues to greatly improve the polymerization efficiency and broaden the monomer scope.

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Chapter 4

Fast diyne cyclopolymerization of 1,7-octadiynes

Abstract

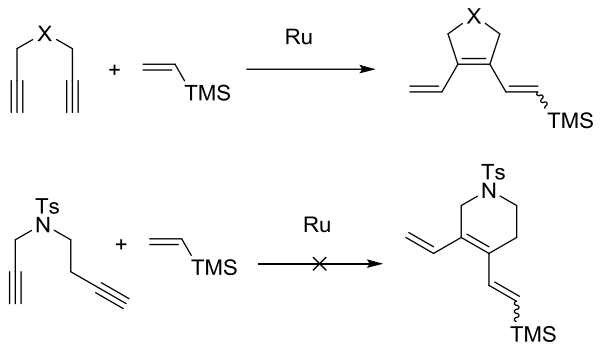
Fast cyclopolymerization of 1,7-octadiyne derivatives has been achieved. Cyclopolymerization of 1,7-octadiyne has been rarely studied due to the slow ring-closing metathesis reaction rate to form six-membered ring unit. Although 1,7-octadiyne could undergo cyclopolymerization by modifying monomer structure to contain sterically bulky substituent, which increase Thorpe-Ingold effect to accelerate cyclization rate, polymerization rate was too slow compared to that of 1,6-heptadiyne derivatives. In order to solve this problem, two monomer modification strategies were proposed. Firstly, dimethyl substituent was introduced to the α-position of side chain, which would be sterically bulky enough to induce Thorpe-Ingold effect to diyne tether in close proximity. Secondly, position of substituent groups were changed from 4,4-disubstitution to 4,5-disubstitution. Both strategies significantly increased cyclopolymerization rate and allowed controlled polymerization with narrow polydispersity index (PDI) and predictable molecular weight which has linear relationship with monomer-to-initiator (M/I) ratio. With this highly reactive controlled polymerization, block copolymerization and challenging dendronized polymer synthesis could be achieved. Resulting polymer was analyzed with various methods including UV-Vis spectroscopy to thoroughly study the structure of polymers.

Background

Acetylene polymerization is one of the most widely studied conjugated polymer synthesis method. Since the first polyene synthesis by Natta and co-workers,[1] various methodologies were developed to synthesize polyenes, such as Ziegler-Natta catalysis system, radical polymerization using radical initiator, and ionic polymerizations using anionic or cationic initiators.[2] Acetylene olefin metathesis reaction was one of the polyene synthesis methodology, which forms new carbon-

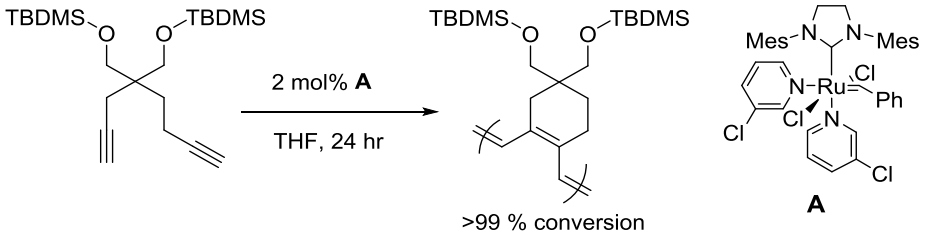
carbon double bonds between acetylene monomers through [2+2] reaction between metal carbene initiator and acetylene. Since the first polymerization of phenylacetylene by Masuda and co-workers,[3] various metals including tungsten[4], tantalum[5], molybdenum[6], and ruthenium[7] were used for metathesis polymerization. However, acetylene polymerization suffered from harsh reaction condition and low productivity, due to the formation of 1,1-disubstituted alkylidene intermediate with low reactivity from α-addition.

Instead of acetylene polymerization, chemists took notice on the cyclopolymerization of non-conjugated diynes.[8] Due to the fast ring-closing metathesis (RCM) reaction, 1,1-disubstituted alkylidene could rapidly undergo intramolecular cyclization to form monosubstituted alkylidene, which can undergo fast intermolecular propagation. However, initial cyclopolymerization suffered several problems, such as low molecular weighted polymer, insolubility of product, and low stability toward air oxidation. In 1990, chemists added substitution to diyne tether to solve these problems.[9] Starting from diphenyldipropargylmethane (DPDPM) and diethyldipropargylmalonate (DEDPM) monomers, various 4,4-disubstituted 1,6-heptadiyne monomers were polymerized with metathesis catalyst to yield polymers with high molecular weight and good solubility. This simple monomer modification allowed effective cyclopolymerization, and well controlled polymerization could be achieved with well-defined catalysts based on molybdenum[10] and ruthenium metal.[11]



Scheme 1. Diyne cycloisomerization-cross metathesis study

Theoretically, all non-conjugated α,ω-diyne substrates could act as a monomer for cyclopolymerization. However, only cyclopolymerization of 1,6-heptadiyne has been thoroughly studied, while other diyne substrates such as 1,7-octadiyne was rarely studied. This was due to the slow cyclization rate of 1,7-octadiyne to form six-membered ring unit compared to the fast cyclization rate of 1,6-heptadiyne to form five-membered ring unit. This tendency was studied by Blechert and co-workers at 1999.[12] When they reacted 1,7-octadiyne and allyltrimethylsilane with Grubbs catalyst to achieve enyne reaction and cycloisomerization, they could not observe any cyclization product, while the same reaction using 1,6-heptadiyne resulted efficient enyne reaction and cycloisomerization. (Scheme 1)



Scheme 2. Cyclopolymerization of 4,4-disubstituted 1,7-octadiyne with bulky substituents

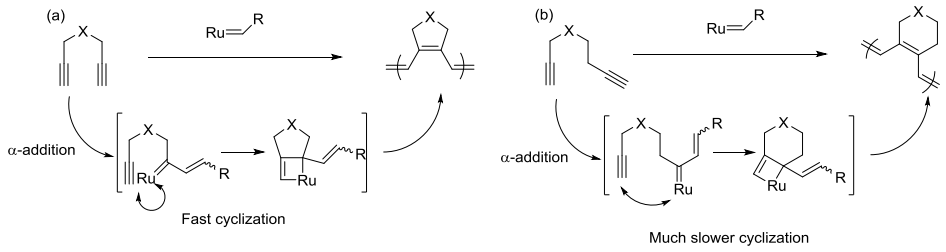
Recently, our group reported cyclopolymerization of 4,4-disubstituted 1,7-octadiyne by increasing the steric effect of substituents to enhance Thorpe-Ingold effect and increased cyclization rate (Scheme 2).[13] By changing the substituent group from less sterically bulky malonate group to sterically bulky *tert*-butyldimethylsilyl (TBDMS) group, well-controlled polymerization with narrow polydispersity index (PDI) and predictable molecular weight could be achieved. However, the polymerization rate was still too slow compared to the polymerization of 1,6-heptadiyne monomers, as polymerization of 50-mer 1,7-octadiyne required 24 hours, while 1,6-heptadiynes required less than 1 hour.

From the polymerization of DPDPM to 1,7-octadiynes, modification of monomer structures broadened monomer scope for cyclopolymerization. In this chapter, I suggest further modification of 1,7-octadiyne derivatives to achieve efficient cyclopolymerization comparable to the cyclopolymerization of 1,6-heptadiyne derivatives. In the first chapter, 1,1-dimethyl substitution was introduced to the substituent side chain, in order to induce Thorpe-Ingold effect more closely to diyne tether. In the second chapter, 4,5-disubstituted 1,7-octadiyne was polymerized instead of conventional 4,4-disubstituted 1,7-octadiyne to achieve even more efficient cyclopolymerization.

Part A. Cyclopolymerization of 1,7-octadiynes containing dimethyl substituents in α-position of side chain

Introduction

Diyne cyclopolymerization is a powerful method for the synthesis of conjugated polyenes via ring-closing metathesis (RCM) reactions using non-conjugated α,ω-diyne monomers. Since the development of polymerization, various catalyst systems using tungsten and molybdenum salt, or Schrock catalysts have been used for cyclopolymerization.[8-10] With the development of ruthenium based Grubbs catalyst,[14] monomer scope for cyclopolymerization was expanded due to the higher stability and functional group tolerances. Also, Grubbs catalyst underwent selective α-addition on terminal alkynes to form regioselective polymers containing five-membered ring unit exclusively.[11] Recent development of third-generation Grubbs catalyst[15] allowed the preparation of polymers with well-controlled molecular weight and narrow polydispersity index (PDI) value, due to the fast initiation rate of catalyst.

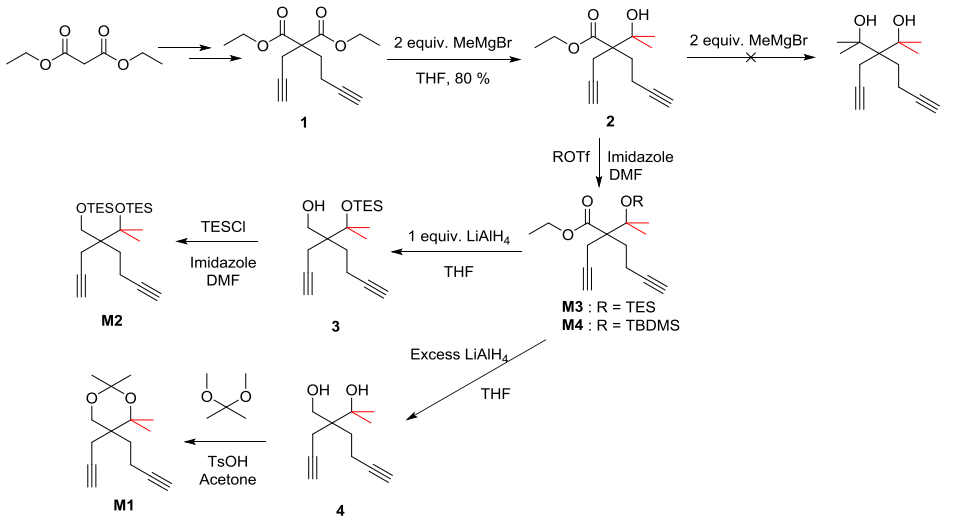


Scheme 1. Cyclopolymerization schemes for (a) 1,6-heptadiyne and (b) 1,7-octadiyne

Although cyclopolymerization has been studied thoroughly, polymerization of 1,6-heptadiyne was well studied, while polymerization of 1,7-octadiyne was

rarely studied.[13,16] It is because polymerization rate, or the cyclization rates of 1,7-octadiyne derivatives to produce cyclohexene moieties are significantly slower thant that of 1,6-heptadiyne derivatives, making them unsuitable for cyclopolymerization (Scheme 1). Our group previously reported cyclopolymerization of 4,4-disubstituted 1,7-octadiyne monomers using third-generation Grubbs catalyst. Among the various monomers, monomer with the bulky tert-butyldimethylsilyl (TBDMS) group showed high conversion toward polymer, with living polymerization characteristics.[13] This successful polymerization was due to the enhanced cyclization rate by Thorpe-Ingold effect.[17] However, even with this bulky substituent, polymerization rate was still low, as TBDMS group containing monomer required 24 hours for preparation of a polymer with degree of polymerization (DP) of 50. Simple solution to further accerelate cyclization rate is to further increase the substituent size. However, as TBDMS substituent is already sterically bulky, introducing even bulkier substituent could be challenging, and other methods should be tried. This chapter will discuss about the accelerated cyclopolymerization of 4,4-disubstituted 1,7-octadiyne monomers, as a result of an enhanced Thorpe-Ingold effect by introduction of dimethyl groups on the side chain α-position near the main chain. This introduction of additional bulky moieties in proximity to the octadiyne tether effectively enhanced Thorpe-Ingold effect and significantly increased polymerization rate.

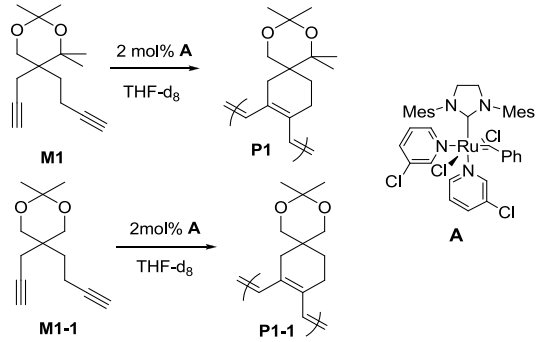
Results and discussions



Scheme 2. Introduction of dimethyl substitution to a 4,4-disubstituted 1,7-octadiyne monomer.

In order to accelerate polymerization rate of 1,7-octadiynes, monomers with faster cyclization rate should be designed with enhanced Thorpe-Ingold effect. Thus, new monomers with dimethyl substitution on α-position of the side chain at the 4-position of the main chain was designed, so that it can influence greater steric effect toward diyne tethers to accelerate cyclization rate. Also, this new group would be small enough not to block the catalyst approach toward alkynes, while effectively large enough to accelerate cyclization rate. In order to introduce dimethyl substitution onto the α-position of the side chain, 1,7-octadiyne substrate was prepared from diethyl malonate (Scheme 2). Then, **1** was treated with 2 equivalent of methyl magnesium bromide to yield tertiary alcohol **2**. From this alcohol, various monomers containing dimethyl substitution were prepared by simple organic chemistry reactions. Unfortunately, tetramethyl substituted

monomer was not prepared with this methodology, as excess amount of Grignard reagent caused retro-Aldol reaction to remove tertiary alcohol group to produce monosubstituted substrate. Also, similar reactions using other kinds of Grignard reagents (ex – ethyl magnisum bromide) or malonates (ex – dimethyl malonate) gave desired dimethyl substituted product with low yield, thus only ethyl malonate-methyl magnesium bromide combination was tried for monomer synthesis.



Scheme 3. Cyclopolymerization of acetal-protected monomers with and without dimethyl substitution

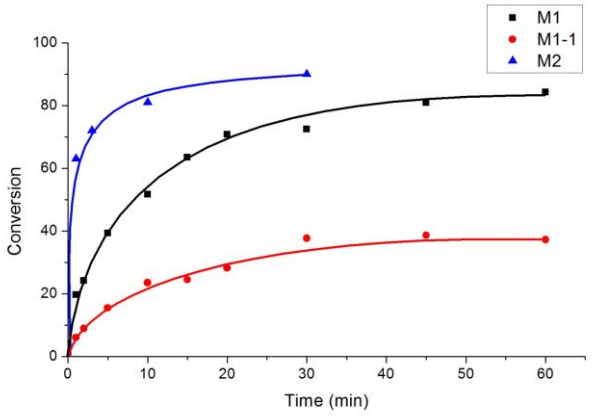
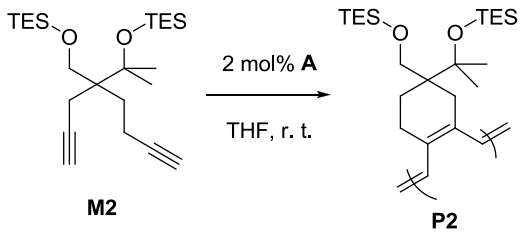


Figure 1. Kinetic study for polymerization of **M1**, **M1-1**, and **M2**

In the previous report by our group, 1,7-octadiyne monomer containing bulky silyl ether groups was reactive toward polymerization, while monomers containing smaller ester groups did not. Although the previous report reasoned that Thorpe-Ingold effect affected to the successful polymerization, but possible coordination effect from ester groups to ruthenium catalyst might slowed down the polymerization. Thus, previous studies could not separate steric effect from coordination effect to explain the faster cyclopolymerization of bulky, non-coordinating silylated monomers compared to smaller, coordinating ester-containing monomers. In order to confirm that Thorpe-Ingold effect was crucial for the cyclopolymerization rate, monomers with non-coordinating cyclic acetal-protected monomers were designed. Those acetal protected monomers **M1** (containing dimethyl substitution) and **M1-1** (without dimethyl substitution) were subjected to the polymerization kinetics study using ^{1}H-NMR experiment (Scheme 3, Figure 1). When the monomers were reacted with third-generation Grubbs catalyst **A**, initial propagation rate of **M1** containing dimethyl substitution was much faster than that of **M1-1** without dimethyl substitution. Also, conversion of **M1** was 80 % after 1 hour, while **M1-1** reached only 35 % conversion. This result support our proposal that introducing dimethyl substitution to side chains indeed accelerated the cyclopolymerization through enhanced Thorpe-Ingold effect.



Scheme 4. Cyclopolymerization of TES-1,7-octadiyne monomer

With the conclusion that the dimethyl substitution indeed accelerated the cyclopolymerization of 1,7-octadiynes, we investigated polymerization of monomer **M2** containing two bulky triethylsilyl (TES) ether groups (Scheme 4). The monomer structure was similar to the previously optimized monomer structure with the exception of additional dimethyl substitution.[13] ^{1}H-NMR kinetics experiment of **M2** polymerization with 2 mol% of catalyst **A** suggested that **M2** containing bulky side chain showed even faster propagation than **M1**, giving 90 % conversion within 30 minutes (Figure 1). This also matches our proposal that monomer with bulkier side chain undergoes faster cyclopolymerization due to the enhanced Thorpe-Ingold effect.

Table 1. Cyclopolymerization of **M2**

Entry	M/I	Time	Temp	Conv.[a]	M_n[b]	PDI[b]
1	50	1 hr	r. t.	>95 %	24000	1.36
2	15	3 hr	5 ℃	>99 %	7200	1.18
3	30	4.25 hr	5 ℃	>99 %	13300	1.22
4	50	6 hr	5 ℃	>99 %	22000	1.18
5[c]	100	3.75 hr	5 ℃	80 %	38000	1.28

[a] Conversion determined by crude ^{1}H-NMR. [b] Determined by THF SEC calibrated using polystyrene (PS) standards. [c] Monomer concentration was 0.8 M.

Polymerization of **M2** conducted at room temperature produced **P2** with an excellent convertion and a relatively narrow PDI of 1.36 within 1 hour. This result is much faster than the optimized result of previous report, which did not contain dimethyl substitution (Table 1, entry 1). In order to obtain polymers with narrower PDI, the reaction temperature was lowered to suppress chain transfer reaction. Although the reaction time was increased from 1 hour to 6 hours by reducing the reaction temperature from 25 ℃ to 5 ℃, **M2** showed high reactivity toward

cyclopolymerization due to the dimethyl substitution, and its polymerization could proceeded at a reasonable rate. Lowering the temperature successfully suppressed chain transfer reaction to reduce PDI narrower than 1.3 and molecular weight showed linear relationship with the monomer-to-initiator ratio (M/I) between 15 to 80 (Entries 2-5 and Figure 2).

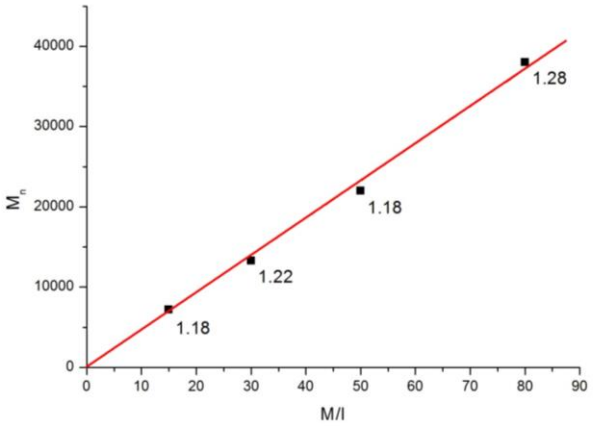
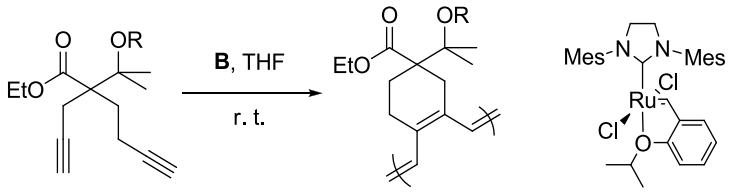


Figure 2. Plot of M_n versus M/I for **M2**. Numbers on the line indicate PDI values.

Table 2. Cyclopolymerization of monomers containing an ester group



M3 : R = TES
M4 : R = TBDMS

P3 : R = TES
P4 : R = TBDMS

B

Entry	Monomer	Catalyst	Time	Conv.[a]	M_n[b]	PDI[b]
1[c]	**M3**	2 mol%	1 hr	100 %	17000	1.43
2[c, d]	**M3**	2 mol%	8 hr	69 %	22000	1.39

3	**M3**	1 mol%	4 hr	93 %	31000	2.38
4[c]	**M4**	2 mol%	50 min	100 %	20000	1.48
5[c, d]	**M4**	2 mol%	5 hr	82 %	15000	1.38
6	**M4**	1 mol%	1 hr	96 %	32000	2.34
7	**M4**	0.5 mol%	3 hr	99 %	39000	1.87
8	**M4**	0.33 mol%	4.5 hr	80 %	40000	2.34

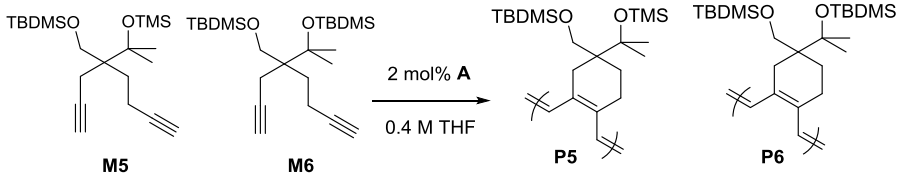
[a] Conversion determined by crude ^{1}H-NMR. [b] Determined by THF SEC calibrated using PS standards. [c] Catalyst **A** was used instead of **B**. [d] Reaction was performed at -10 ℃ instead of room temperature.

In the previous report, cyclopolymerization of 1,7-octadiyne monomers containing bis-ester substitution showed less than 60 % conversion, presumably due to the lack of Thorpe-Ingold effect. As newly introduced dimethyl substitution promoted efficient cyclopolymerization, it was expected that monomer containing ester groups with dimethyl substitution might also undergo efficient cyclopolymerization. Thus, monomer **M3** containing TES ether and ethyl ester substituents was prepared and subjected to the polymerization. Cyclopolymerization at room temperature resulted full conversion of **M3** within 1 hour, but a broad PDI of 1.43 was observed (Table 2, entry 1). In order to obtain **P3** with narrow PDI, reaction temperature was further decreased to -10 ℃. However, PDI was not narrowed enough and conversion was less than 70 %. (Entry 2). This phenomena was presumably due to the low steric effect of ester group in **M3**, which cannot provide enough shielding effect to protect olefins on the polymer backbone to suppress chain transfer reaction. Thus, instead of achieving controlled polymerization, we attempted to maximize the polymerization turn-over number (TON) to obtain high molecular weighted polymers. By using the more stable second-generation Hoveyda-Grubbs catalyst **B**, polymerization of **M3** showed TON up to 93 (Entry 3). PDI inevitably

increased over 2.0, because of the intrinsically slow initiation of catalyst **B**, as well as higher chance of chain transfer reaction at room temperature.

Monomer **M4** containing TBDMS substituent showed greater polymerization efficiency, resulting in full conversion within 50 minutes with 2 mol% of catalyst **A** at room temperature, although PDI was still over 1.4 (Entry 4). Again, **M4** was subjected to polymerization at -10 ℃ temperature in order to obtain polymer with narrow PDI, but PDI was still broader than 1.3 (Entry 5). However, as **M4** generally showed higher reactivity than **M3**, providing higher monomer conversions with shorter reaction times. Thus, higher molecular weighted **P4** could be synthesized with lower catalyst loading of **B**, with a maximum TON up to 240 and molecular weight up to 40 k obtained (Entries 6-8). This result implied that dimethyl substitution induced high Thorpe-Ingold effect for the efficient cyclization of 4,4-disubstituted 1,7-octadiyne monomers, as maximum TON of monomers without dimethyl substitution was only 75.[13]

Table 3. Cyclopolymerization of less reactive monomers



Entry	Mono	Time	Temp	Conv.[a]	M_n[b]	PDI[b]
1	**M5**	3.5 hr	r. t.	50 %	10000	1.53
2	**M6**	30 min	r. t.	>99 %	18000	1.46
3	**M6**	4 hr	5 ℃	60 %	14000	1.27

[a] Conversion determined by crude ^{1}H-NMR. [b] Determined by THF SEC calibrated using PS standards.

When **M5** with trimethylsilyl (TMS) and TBDMS group was reacted with catalyst **A**, only 50 % of monomer was converted to polymer, even at room temperature condition (Entry 1). We expect that less sterically hindered TMS group could not provide enough Thorpe-Ingold effect to accelerate cyclopolymerization, so that the polymerization efficiency was significantly decrease compared to **M2** study. **M6** with two TBDMS group, which have the same structure with the previously reported optimized monomer except of dimethyl group, showed excellent polymerization efficiency, with full monomer conversion within only 30 minutes, although PDI was broad. In order to suppress the chain transfer reaction and obtain **P6** with narrow PDI, **M6** was reacted under 5 ℃ condition. Surprisingly, reactivity of **M6** was significantly decreased, giving only 60 % conversion, while PDI of polymer was nearly 1.3.

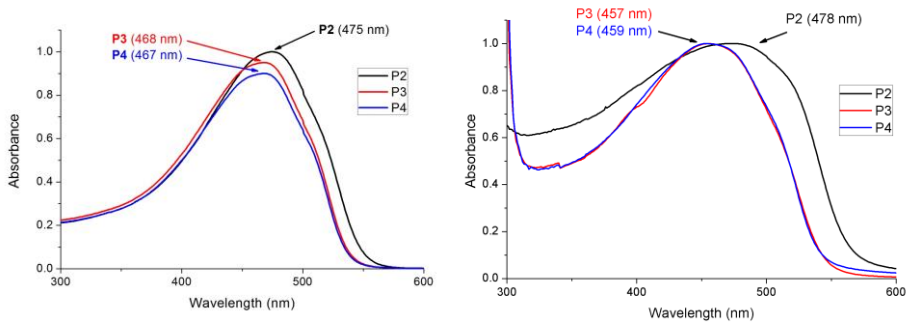
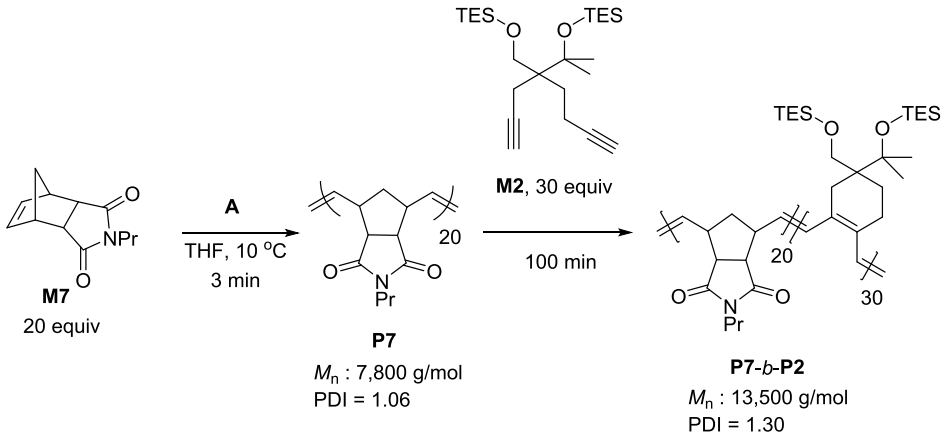


Figure 3. Solution (left) and film (right) state UV-Vis spectra of **P2**, **P3**, and **P4**: λ_{max} of each polymer is indicated.

Conjugated polymers containing a six-membered ring repeat unit were analyzed by UV-Vis spectroscopy. In both solution state and film state, all conjugated polymers (**P2**, **P3**, and **P4**) showed a bathochromic shift as the molecular weight of polymers increased, as a result of an increase in conjugation length (See supporting information for details (Figure S8-S10)). Bis-TES substituted polymer

P2 showed λ_{max} of 475 nm and 478 nm in THF solution and thin film state respectively (Figure 3, see SI for film state UV-Vis spectrum). Polymers **P3** and **P4** with ester side chains showed λ_{max} of 468 nm and 467 nm respectively in THF solution, and λ_{max} of 457 nm and 459 nm for film state, which are lower than those of **P2**. Notably, all these values were lower than λ_{max} of 1,7-octadiyne cyclopolymer without dimethyl substitution (λ_{max} of 486 nm and 482 nm for solution and film state).[13] Moreover, bandgaps of polymers with dimethyl substitution were slightly higher than that of 1,7-octadiyne cyclopolymer without dimethyl substitution (2.20 eV), showing 2.25 eV for **P2** and 2.28 eV for both **P3** and **P4**. These results implied that the polymers containing dimethyl substitution adjacent to the polymer backbone of the cyclohexene ring showed a slight twist in the polymer backbone, resulting in a slight decrease in polymer coplanarity and conjugation length.[18]



Scheme 5. Block copolymerization of **M2** with norbornene monomer **M7**

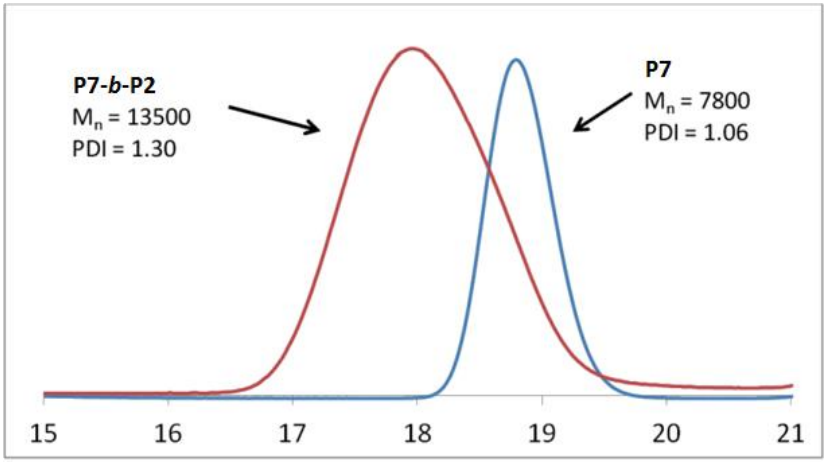


Figure 4. THF SEC trace of **P7** and block copolymer **P7**-*b*-**P2**.

As the dimethyl substitution increased the rate of cyclopolymerization for 1,7-octadiyne derivatives, it was thought that synthesis of diblock copolymers could also be made more efficiently by this method compared to the lengthy polymerization times of previous monomers without dimethyl substitution (24 hours).[5] Block copolymerization was carried with **M7** as a first block and **M2** as a second block with M/I = 20:30 (Scheme 5). Initially, **M7** was reacted with catalyst **A** at 10 ℃ for 3 minutes to produce **P7** with a very narrow PDI with 1.06. Then, **M2** was added to the reaction flask and after 100 min, the final diblock copolymer **P7**-*b*-**P2**, with PDI of 1.30, was isolated in 90% yield. The block microstructure was confirmed by the total shift of the SEC trace to left demonstrating the increase in molecular weight from 7,800 g/mol (**P7**) to 13,500 g/mol (**P7**-*b*-**P2**) (Figure 4). In short, a diblock polymer could be prepared in less than 2 hours rather than 24 hours, as previously reported.

Conclusion

In this chapter, we have introduced additional dimethyl substitution as an

activating group to a 4,4-disubstituted 1,7-octadiyne monomer skeleton. Using ^{1}H-NMR kinetic studies, we could unambiguously confirm that the presence of dimethyl substitution accelerated cyclopolymerization by maximizing the Thorpe-Ingold effect, such that full conversion of the monomer was achieved with 2 mol% catalytic loading in one hour at room temperature. With the newly designed monomer containing bulky silyl ether groups and dimethyl substitution, even controlled polymerization could be achieved, yielding polymers with narrow PDIs. Use of the bulky bis-TES group was also advantageous as it served to block chain transfer reactions. In addition, monomers containing ester groups on one side chain and dimethyl substitution on the other side chain showed high activities toward cyclopolymerization, giving TON values up to 240. Lastly, using the more reactive 1,7-octadiyne monomer **M2**, synthesis of the diblock copolymer was successfully carried out in a much shorter reaction time. This work demonstrates that optimal monomer design is crucial to achieve efficient polymerization of a seemingly challenging polymerization process.

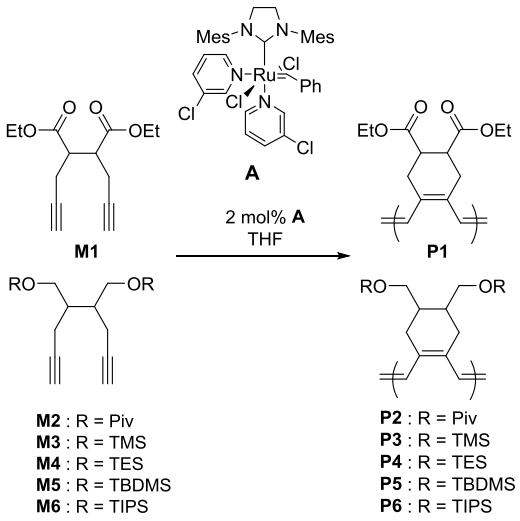
Part B. Cyclopolymerization of 4,5-disubstituted 1,7-octadiyne

Introduction

Introduction of 1,1-dimethyl substituent on the α-position of side chain on 4-position significantly increased cyclopolymerization of 1,7-octadiyne deriatives.[19] This simple modification decreased reaction time from 24 hours to 1 hour at room temperature to synthesize polymer with a degree of polymerization (DP) of 50. However, to achieve a well-controlled polymerization by suppressing the chain transfer reaction, reaction temperature was lowered to 5 ℃, and this increased the reaction time up to 6 hours. While we designing new monomer structures, Buchmeiser and co-workers reported cyclopolymerization of 4,5-disubstituted 1,7-octadiyne monomers using modified Hoveyda-Grubbs catalyst and Schrock catalysts.[16] Although the polymerization with the modified Hoveyda-Grubbs catalyst was unsuccessful,[16a] controlled polymerization with Schrock catalysts was successful.[16b] This 4,5-disubstitution might induce higher reactivity toward cyclopolymerization than conventional 4,4-disubstitution because of the effectively larger Thorpe-Ingold effect toward diyne tether.[17] Also, as molybdenum catalysts are less tolerant to air or functional groups, cyclopolymerization with much stable Grubbs catalyst would expand the scope of the monomers. This chapter will describe about the controlled polymerization of 4,5-disubstituted 1,7-octadiyne monomers using third-generation Grubbs catalyst. With high reactivity, various conjugated polyenes such as a diblock copolymer and challenging dendronized polymer containing exclusively six-membered ring polymer units were successfully prepared.

Result and Discussions

Table 1. Cyclopolymerization of 4,5-disubstituted 1,7-octadiyne monomers



Entry	Mono	Temp.	Time	Conv.[a]	M_n[b]	PDI[b]
1	**M1**	r. t.	50 min	>99 %	22000	1.82
2	**M2**	r. t.	30 min	>99 %	15000	1.86
3	**M3**	r. t.	45 min	>99 %	20000	1.49
4	**M4**	r. t.	50 min	>99 %	17000	1.36
5	**M5**	r. t.	50 min	>99 %	18000	1.28
6	**M6**	r. t.	40 min	>99 %	21000	1.25
7	**M1**	-20 ℃	5 h	90 %	13000	1.23
8	**M2**	-10 ℃	2 h	83 %	21000	1.17
9	**M3**	5 ℃	70 min	90 %	18000	1.28
10	**M4**	5 ℃	2 h	>99 %	14000	1.28

[a] Conversion determined by crude ^{1}H-NMR. [b] Determined by THF SEC calibrated using polystyrene (PS) standards.

Initially, 4,5-bis(ethyl ester) monomer **M1** was prepared and subjected to polymerization with 2 mol% of third-generation Grubbs catalyst (**A**)[15] in THF at room temperature. Within 50 minutes, the monomer was completely consumed (Table 1, Entry 1). As ruthenium-based catalysts react with terminal alkynes *via* regioselective α-addition[11,13], Grubbs catalysts tend to selectively give polymers with either five-membered or six-membered rings as repeat units from 1,6-heptadiynes or 1,7-octadiynes, respectively. In order to confirm whether the same trend would hold for **M1**, the ^{13}C NMR spectrum of **P1** was analyzed. Signals for two ester carbonyls (174.2, 172.8 ppm), two backbone olefins (131.8, 125.2 ppm), two methines in a six-membered ring (41.4, 39.8 ppm), and two methylenes in a six-membered ring (29.2, 27.4 ppm) were observed (Figure 1). These data match with those reported by Buchmeiser, who produced the same polyenes containing six-membered rings from the same monomer using a molybdenum catalyst,[16b] and this suggests that the polymerization of 4,5-disubstiuted 1,7-octadiyne derivatives with a Grubbs catalyst indeed promotes regioselective α-addition to give polymers with six-membered ring repeat units.

One would notice that the monomer **M1** is a mixture of two diastereomers, a *meso* and a *racemic* (1 : 1 mixture of (*R*, *R*) and (*S*, *S*) enantiomers) compound. From ^{1}H-NMR study of the monomer **M1**, the ratio of *meso* to *racemic* compounds were measured to 4 : 6. As the reactivity of each diastereomer towards cyclopolymerization may differ, we monitored the kinetics by ^{1}H-NMR on each diastereomer by treating them with 10 mol% of the catalyst **A** in deuterated DCM. When we compared the reaction rate of two diastereomers in 1st order kinetics, reaction rate of the *meso* compound was 0.50 min^{-1}, while reaction rate of the *racemic* compound was 0.31 min^{-1} (Figure 2). Overall, both diastereomers showed a comparable reactivity with slightly higher reactivity for the *meso* monomer, similar to the previous report by Buchmeiser.[16b]

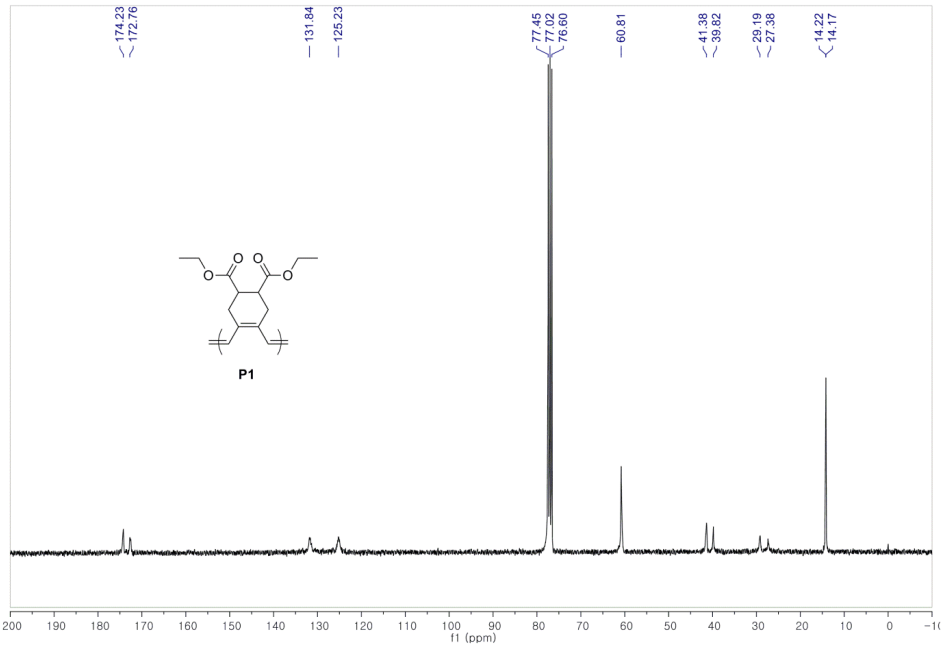


Figure 1. ^{13}C-NMR spectrum of **P1**

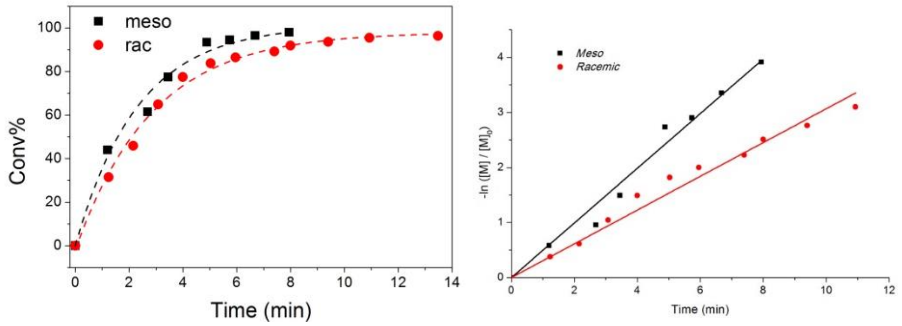
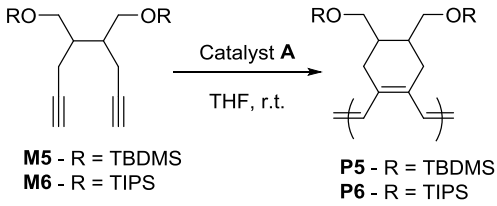


Figure 2. Plot of conversion vs. time (left) and -*ln* ([M]/[M]$_0$) vs. time (right) for *meso* and *racemic* diastereomer of monomer **M1** with M/I = 10 at room temperature.

Despite using the ultrafast initiating catalyst **A**, a broad PDI of 1.82 was observed for **P1**, presumably due to the facile chain transfer reaction at room temperature.

Thus, monomers with bulkier substituents were prepared to increase the shielding effect to protect the prepared polyenes and suppress the chain transfer reaction. Monomer **M2** with pivalate group was fully converted to **P2** within 30 min, but the PDI was still broad (1.86, Entry 2). To our delight, we observed that narrower PDIs were obtained for monomers having bulkier silyl protecting groups (1.49 for **P3** containing trimethylsilyl (TMS) and 1.36 for **P4** containing triethylsilyl (TES), Entries 3 and 4). Monomers with even bulkier groups such as TBDMS and triisopropylsilyl (TIPS) produced **P5** and **P6** with PDIs narrower than 1.3 even at room temperature (Entries 5 and 6). This implied that the shielding effect from the bulky substituents hindered the chain transfer reaction. For the monomers with smaller substituents (**M1**–**4**), the chain transfer reaction was suppressed at lower temperature (-20 to 5 ℃), and polymers with narrower PDIs (<1.3) were produced despite the longer reaction times (Entries 7–10).

Table 2. Cyclopolymerization of **M5** and **M6**



Entry	Mono	M/I	Time	Conv.[a]	M_n[b]	PDI[b]
1	**M5**	15	15 min	>99 %	6500	1.17
2	**M5**	30	28 min	>99 %	11000	1.23
3	**M5**	50	50 min	>99 %	18000	1.28
4 [c]	**M5**	100	120 min	90 %	25000	1.43
5	**M6**	20	8 min	92 %	7700	1.20
6	**M6**	30	23 min	>99 %	10000	1.29

7	**M6**	50	40 min	>99 %	21000	1.25
8	**M6**	75	60 min	99 %	33000	1.31
9	**M6**	100	70 min	>99 %	40000	1.57

[a] Conversion determined by crude ^{1}H-NMR. [b] Determined by THF SEC calibrated using PS standards. [c] The polymerization was conducted at 5 ℃.

Although the cyclopolymerization of many 4,5-disubstituted 1,7-octadiyne monomers produced polymers with narrow PDIs, we focused our study on the controlled polymerization of **M5** and **M6**, because **P5** and **P6** with narrow PDIs were prepared at room temperature. First, **M5** was polymerized with various monomer to initiator (M/I) ratios ranging from 15 to 100. At M/I ratios between 15 and 50, **P5** with a narrower PDI (<1.3) was produced at room temperature (Table 2, Entries 1–3), and a linear relationship between the M/I ratio and the molecular weight was observed (Figure 3a). At an M/I ratio of 100, the polymerization was conducted at 5 ℃ to obtain optimal results (Table 2, Entry 4). Cyclopolymerization of **M6**, containing the even bulkier TIPS group, showed a similar result as **M5**. By changing the M/I ratio from 20 to 100, the molecular weight of **P6** increased proportionally, and the PDI remained narrow in most cases, except when the M/I ratio was 100 (Entries 5–9, Figure 3b).

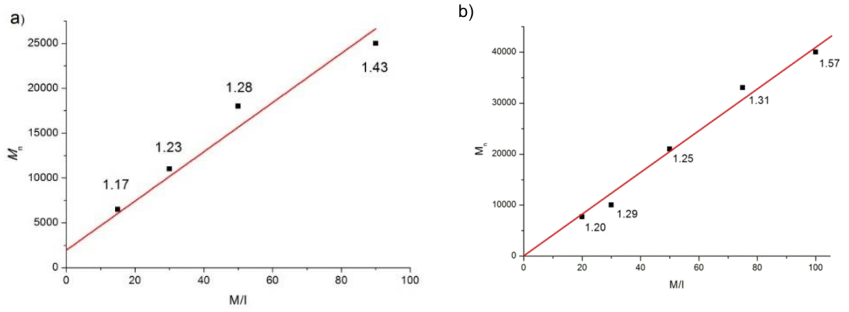
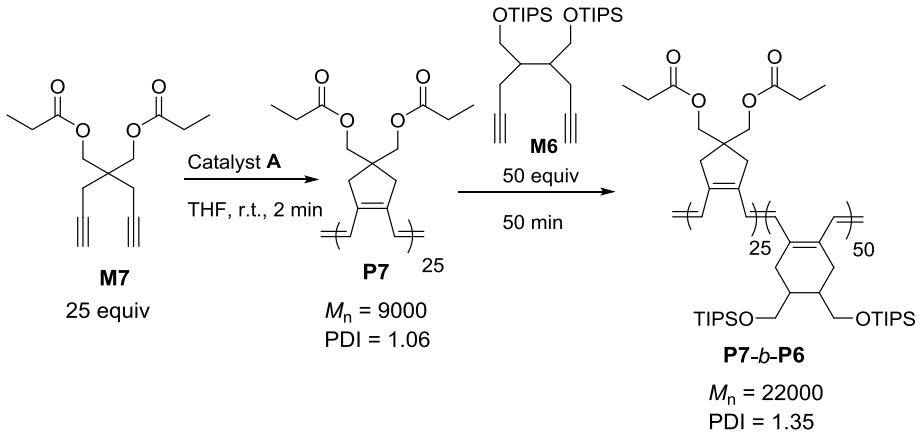


Figure 3. Plot of M_n versus M/I for a) **P5** and b) **P6**. The PDI values are shown as labels.



Scheme 1. Block copolymerization of **M6** with 1,6-heptadiyne monomer **M7**.

With the successful controlled polymerization of 4,5-disubstituted 1,7-octadiyne monomers in hand, we carried out the synthesis of a fully conjugated diblock copolymer from **M6** and 1,6-heptadiyne monomer **M7** (Scheme 1). Initially, 25 equiv of **M7** was added to the solution of catalyst **A**, and after 2 min, 50 equiv of **M6** was added. After 50 min at room temperature, monomers **M6** and **M7** were fully converted to diblock copolymer **P7**-*b*-**P6**. From size exclusion chromatography (SEC) analysis, the trace of the block copolymer was shifted to a higher molecular weight region (22000) from the 1st block of **P7** (9000), and the PDI of the block copolymer remained low (1.35) (Figure 4). Compared to our previous block copolymerization of a 1,6-heptadiyne monomer and a 4,4-disubstituted 1,7-octadiyne monomer that required 24 hours of reaction time, this new copolymerization using the 4,5-disubstituted monomer showed a significant improvement with a much shorter reaction time.[13] Buchmeiser and co-workers also reported a similar block copolymerization using a molybdenum catalyst, but their cyclopolymerization of a 1,6-heptadiyne monomer produced a small portion of six-membered rings as a defect, because the regioselectivity of the molybdenum catalyst was not exclusive and resulted in some β-addition.[16b]

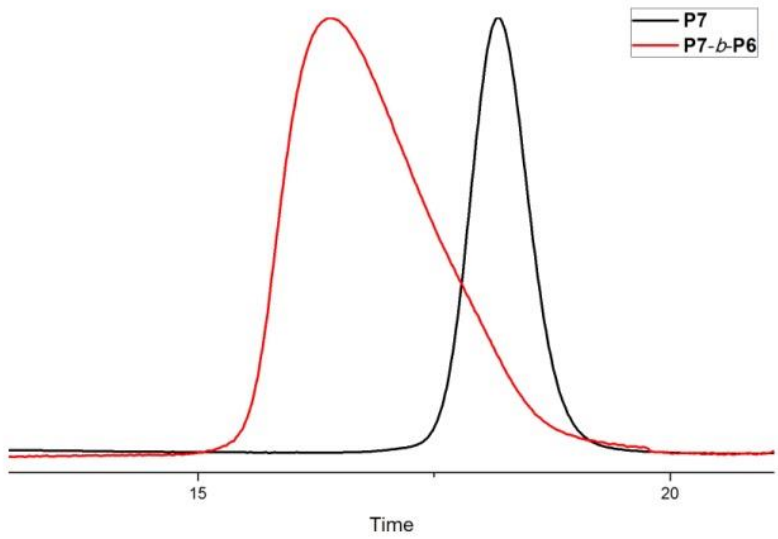


Figure 4. THF SEC traces for **P7** and **P7**-*b*-**P6**.

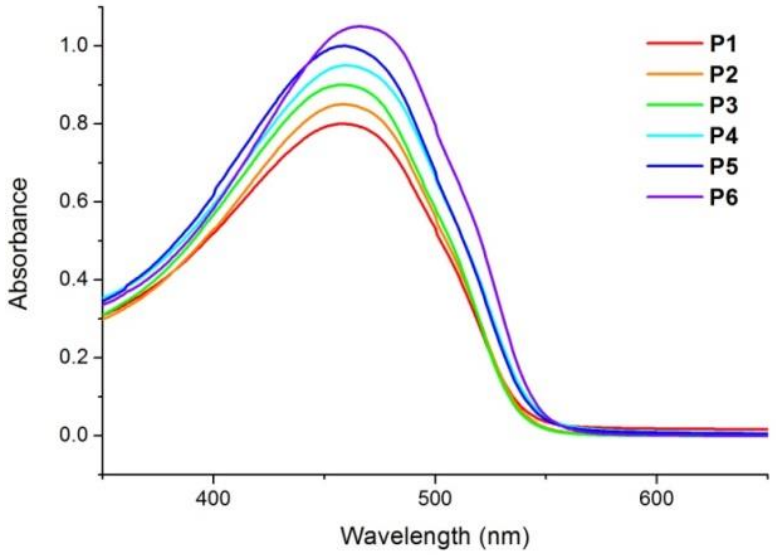


Figure 5. UV-Vis spectra of **P1**–**P6** in THF (0.25 mg/ml).

The newly synthesized conjugated polymers were characterized by UV-Vis

spectroscopy. In THF, λ_{max} of **P1** to **P6** was at 460–466 nm (Figure 5). As expected, when the molecular weights of polymers increased, λ_{max} of the polymers also increased because of the increased conjugation length (See supporting informations for details (Figure S11)). For the UV-Vis spectra of the thin films, λ_{max} of **P1** with the small ester substituent increased to 468 nm, while λ_{max} of **P2**–**P6** with bulkier substituents decreased to 452–458 nm (See supporting informations for details (Figure S12 and S13). This tendency is presumably due to the bulky substituents distorting the backbone planarity of the polymers in the film state, effectively decreasing the conjugation length of the polymers.[18]

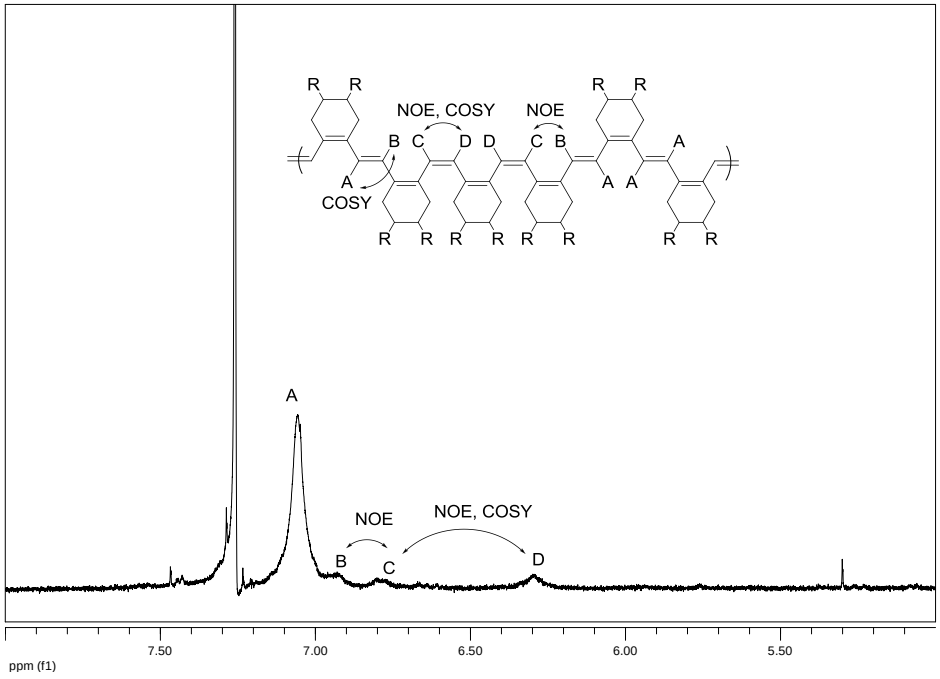


Figure 6. ^{1}H-NMR (500 MHz) spectrum of **P5** prepared from 4,5-disubstituted 1,7-octadiyne. Arrows indicate corresponding COSY correlation or NOE effect.

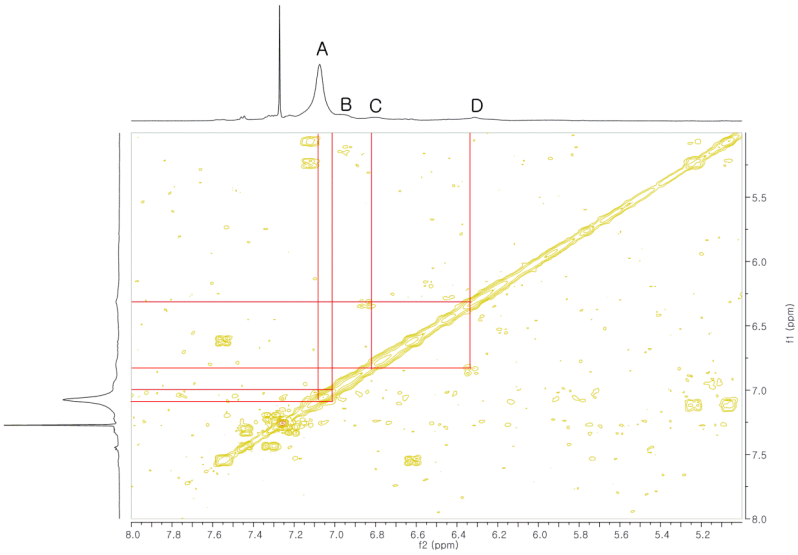


Figure 7. 2D ^{1}H-COSY correlation spectrum of **P5**. Red lines indicate COSY correlation.

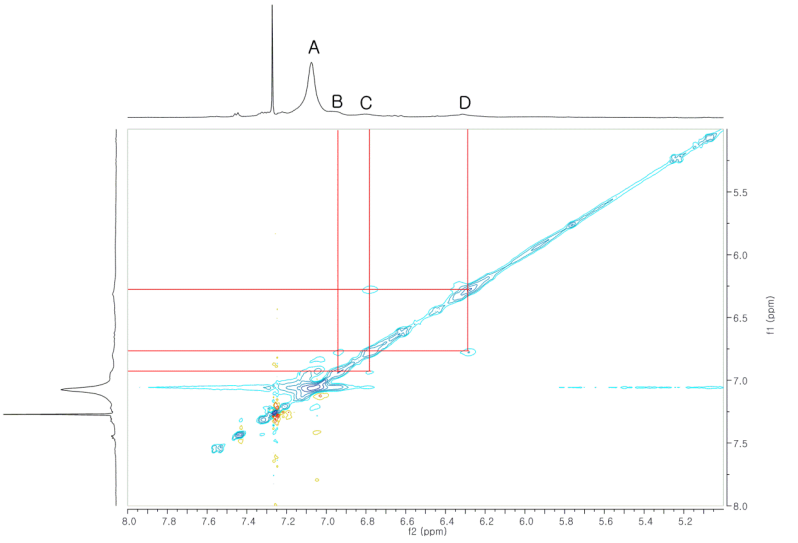


Figure 8. 2D ^{1}H-NOESY spectrum of **P5**. Red lines indicate NOE effect

Compared to the previously reported polymers from 4,4-disubstituted 1,7-octadiynes, the polymers from 4,5-disubstituted 1,7-octadiynes showed lower λ_{max} values. For example, λ_{max} of the polymer from 4,4-TBDMS disubstituted 1,7-octadiyne in solution and as a thin film were 486 and 482 nm, respectively, while λ_{max} of **P5** containing 4,5-TBDMS substituents in solution and as a thin film were 459 nm and 453 nm.[11] In order to explain the difference, the polymer structure was analyzed in detail by various ^{1}H-NMR techniques. As shown in Figure 6, the ^{1}H-NMR spectrum for **P5** showed one major signal, A, and three minor signals, B, C, and D. From 2D correlation spectroscopy (COSY) (Figure 7) and 2D nuclear Overhauser effect spectroscopy (NOESY) NMR experiments (Figure 8), A and B showed a COSY correlation, and B and C showed NOE effects, while C and D showed both NOE effects and a COSY correlation (See SI for details). Based on these observations, signals A and B corresponded to protons of a *trans* olefin, while signals C and D corresponded to protons of a *cis* olefin. From the NOESY correlation, signals B and C corresponded to protons where *trans* and *cis* olefins were adjacent to each other (Figure 6). A very similar assignment was achieved for the polymers from 1,6-heptadiyne monomers.[20] Based on the NMR analysis, one could conclude that the stereochemistry of the polymer backbone from 4,4-disubstituted 1,7-octadiyne was almost exclusively *trans*, while **P5** contained 74 % *trans* olefin. **P1**–**P6** showed similar ratios of 70–78 % *trans* olefin. This suggested that the lower λ_{max} of **P1** to **P6** was due to the presence of *cis* olefin, which decreased the conjugation length or the backbone planarity.

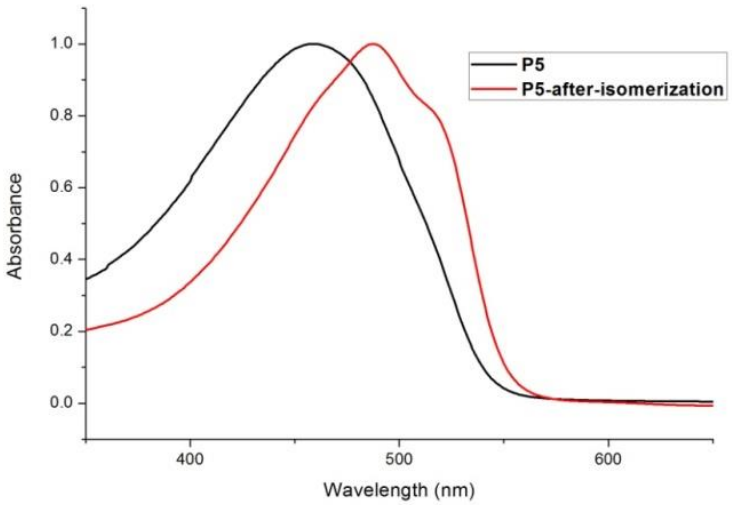
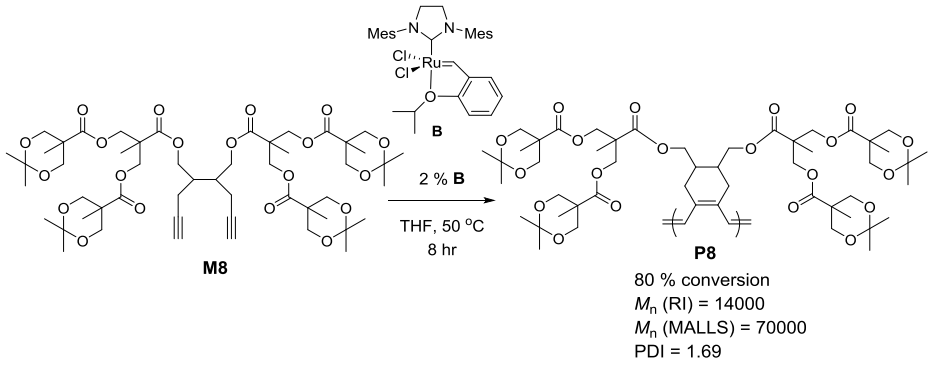


Figure 9. UV-Vis spectra of **P5** before isomerization (black) and after isomerization (red) in THF (0.25 mg/ml) (left) and NMR.

If λ_{max} of the UV-Vis spectrum depends on the ratio of *trans* olefin in the backbone, isomerization of *cis* olefin to *trans* will increase λ_{max} of the polymer. Therefore, **P5** in dichloromethane (1 mg/mL) was exposed to 480 nm blue LED irradiation for 1 hour,[20] and this completely isomerized the remaining *cis* olefin to *trans*, as confirmed by ^{1}H-NMR spectroscopy (See supporting informations for details (Figure S14)). Also, IR spectroscopy verified that the *cis* olefin stretching at 740 cm^{-1} disappeared after isomerization, while the *trans* stretching at 950 cm^{-1} remained (See supporting informations for details (Figure S15 and S16).[16b] As a result, λ_{max} of fully isomerized **P5** increased from 459 nm to 487 nm, which is similar to that of the polymer containing 4,4-disubstitution (Figure 9).[13] This suggests that the stereochemistry of the polyene backbone affects the conjugation length.[20]



Scheme 2. Synthesis of dendronized polymer **P8** from macromonomer **M8**.

To show that this enhanced cyclopolymerization could be applicable to prepare more complex molecules, we turned our attention to the synthesis of dendronized polymers. The study of dendronized polymers is interesting because they show an extended rod-like conformation because of the steric repulsion between the dendrons. However, their synthesis is quite challenging, especially via a macromonomer approach, because the propagation of bulky macromonomers becomes extremely slow. As monomers with bulky substituents such as TBDMS or TIPS group were successfully polymerized, we attempted a challenging cyclopolymerization of a macromonomer containing two dendrons at the 4 and 5 positions. Macromonomer **M8** containing two 2nd generation ester dendrons (equivalent to a 3rd generation dendron)[21] was synthesized and tested for polymerization.[22] Initially, **M8** was treated with 2 mol% of catalyst **A** at room temperature, but the reactivity of the monomer was too low with only 40 % conversion. Because the reactivity of **M8** was much lower than that of other monomers, the reaction temperature was raised to 50 ℃. However, catalyst **A** could not survive the long reaction time at 50 ℃. Therefore, 2 mol% of thermally stable 2nd generation Hoveyda-Grubbs catalyst (**B**) was used. After 8 hours, **P8** with an absolute molecular weight of 70k, as determined by multi-angle laser

light scattering (MALLS) analysis, was prepared in 80% yield (Scheme 2). Its PDI was inevitably broad (1.69) because of the slow initiating catalyst and reaction condition that enabled chain transfer reactions. This demonstrated that the reactivity of 4,5-substituted 1,7-octadiynes was high enough to produce dendronized polymers via a macromonomer approach.

P8 was imaged using atomic force microscopy (AFM). Although **P8** contained low-generation ester dendrons, and the molecular weight was not very high, clear images of a single polymer chain were obtained. As shown in Figures 7 and 8, **P8** showed an extended rod-like conformation approximately 50 nm in length and 0.4 nm in height. This single polymer chain can find potential application as an insulated molecular wire because the conjugated polymer backbone is covered by an insulating dendron.[23]

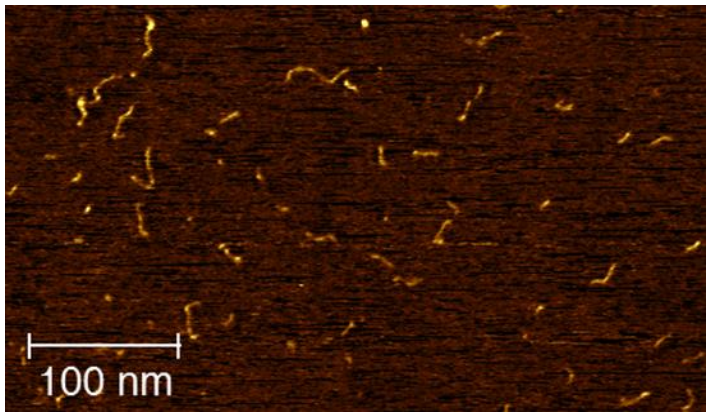


Figure 7. AFM image of **P8** in phase mode. The polymer solution in DCM (0.25 mg/L) was spin-coated onto mica.

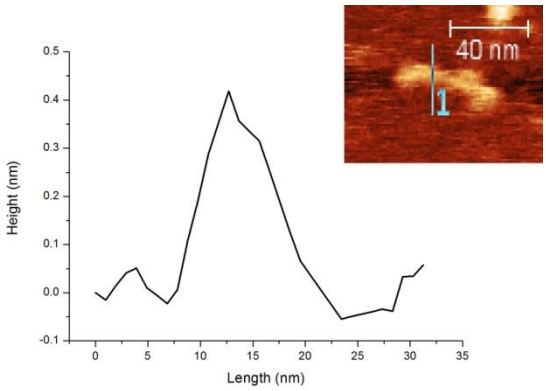


Figure 8. Single chain AFM image of **P8** in height mode with height profile. The average height of polymer chain was 0.4 nm.

Conclusions

In summary, we performed cyclopolymerization of various 4,5-disubstituted 1,7-octadiynes using a 3rd generation Grubbs catalyst to produce polyenes containing six-membered rings. These monomers showed higher reactivity than 4,4-disubstituted 1,7-octadiynes, and the corresponding polymers had narrow PDIs. Among the monomers tested, those with bulky substituents such as TBDMS and TIPS underwent controlled polymerization at room temperature within 1 h. With this high reactivity, a block copolymer was prepared more efficiently from **M6** and a 1,6-heptadiyne monomer. Finally, we applied this improved polymerization to the synthesis of a dendronized polymer from a macromonomer containing two 2nd generation ester dendrons, and AFM imaging revealed a rod-like conformation.

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Supporting Information

SEC trace of Diels-Alder modified polymers (Chapter 3A)

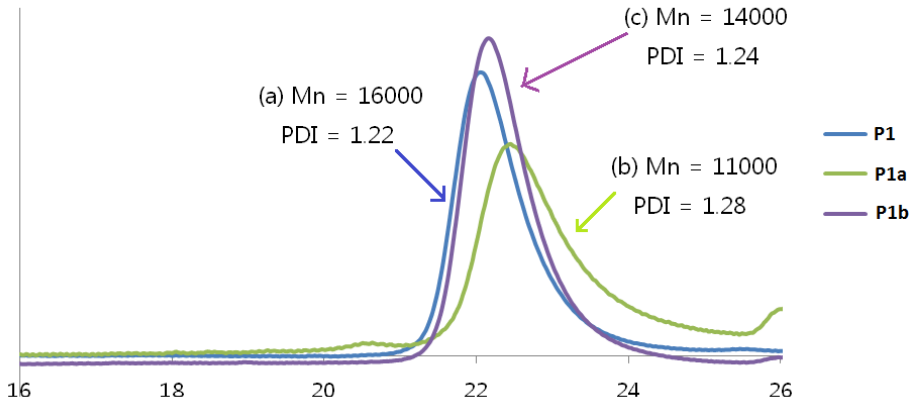

Figure S1. THF SEC trace of (a) **P1**, (b) **P1a**, and (c) **P1b**

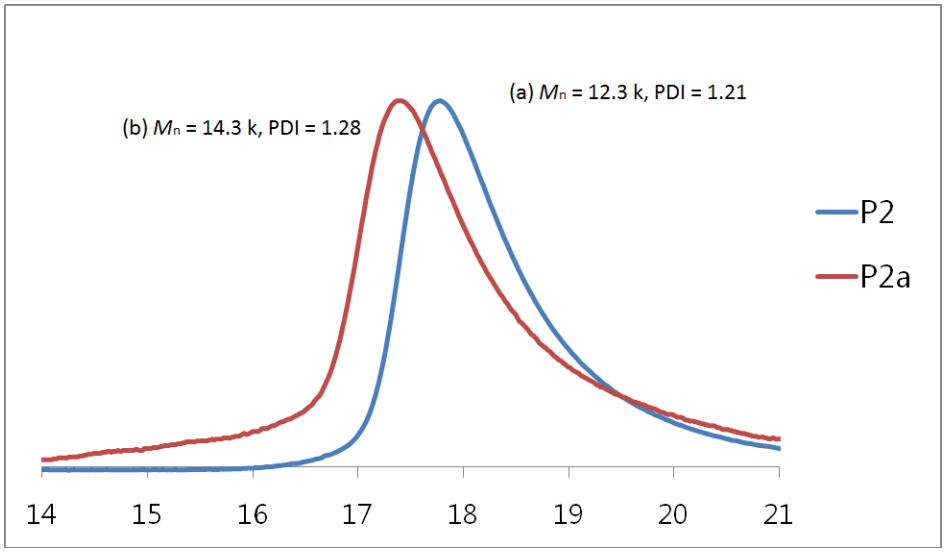

Figure S2. THF SEC trace of (a) **P2**, (b) **P2a**

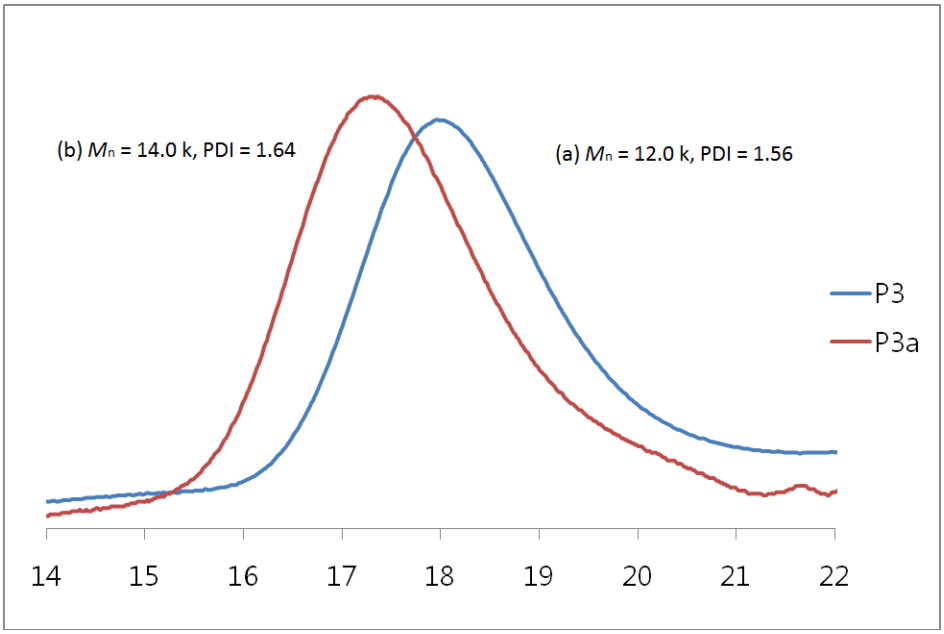

Figure S3. THF SEC trace of (a) **P3**, (b) **P3a**

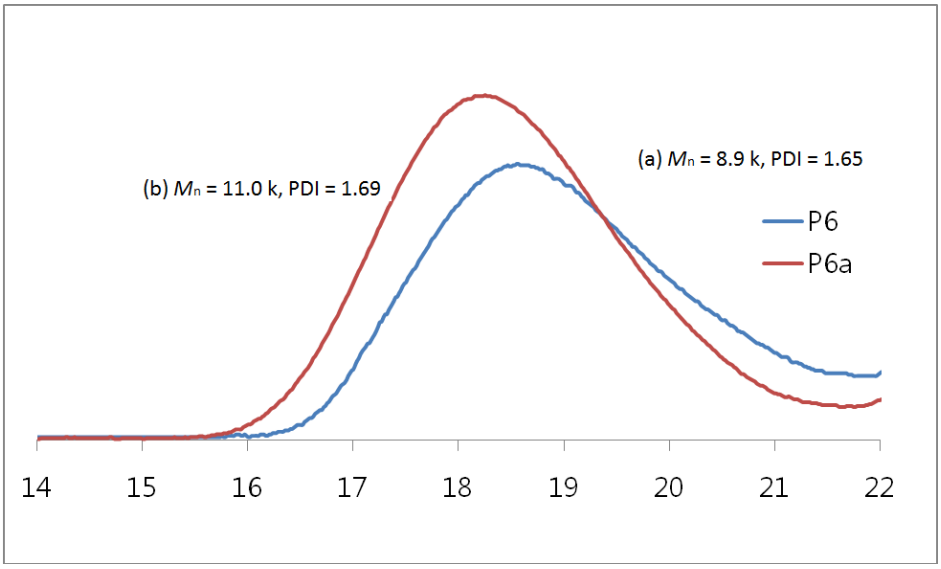

Figure S4. THF SEC trace of (a) **P4**, (b) **P4a**

Polymer unit ratio determination of Phenyl substituted polymers (Chapter 3B)

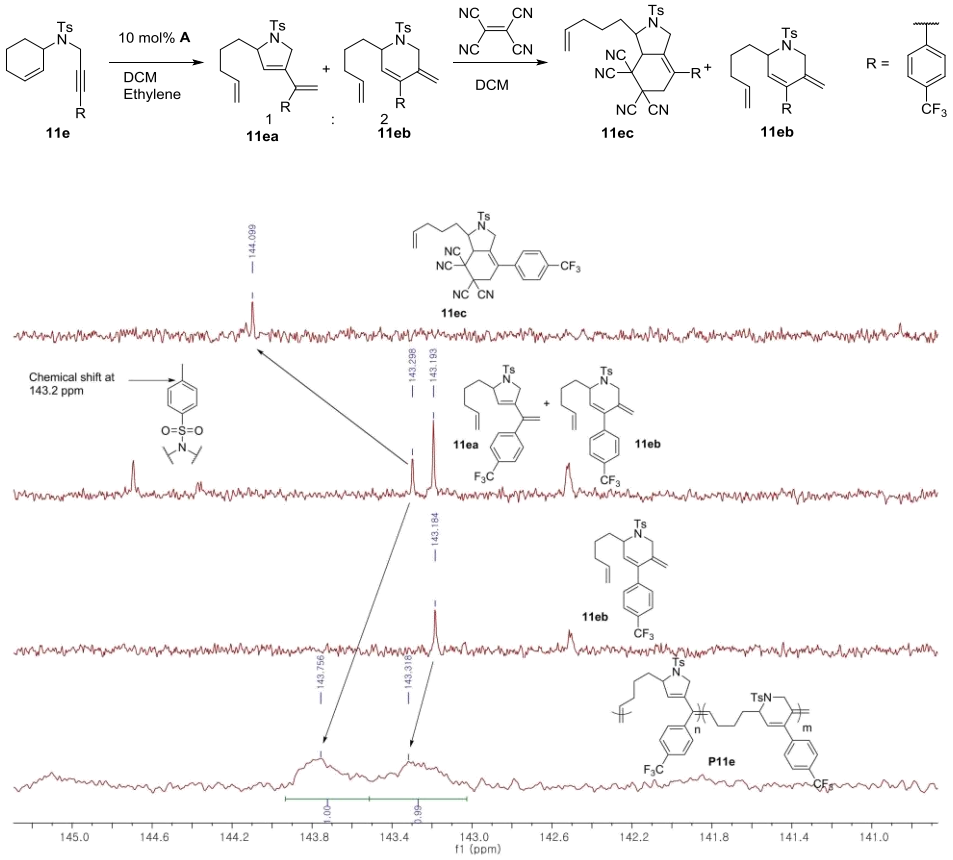

Figure S5. ^{13}C-NMR spectrum of ethenolysis products of **11e** and **P11e**.

Ethenolysis of monomer **11e** with 10 mol% of second-generation Grubbs catalyst **A** resulted the mixture of two molecules. Those inseparable mixture was reacted with 2 equivalent of tetracyanoethylene in 0.3 M DCM solvent. After 1 hour, DCM was evaporated and column chromatography (ethyl acetate : hexane = 1 : 5) resulted 2 products, **11eb** (R_f = 0.4) and **11ec** (R_f = 0.1) with 2 : 1 ratio. Presence of **11ec** suggests the formation of five-membered ring molecule **11ea** during initial ethenolysis, which was converted to **11ec** after Diels-Alder reaction.

By comparing the ^{13}C-NMR chemical shift of substrates and polymers, we observed that toluene chemical shift is different for each structures. **11ea** showed one peaks at 143.30 ppm, and **11eb** showed one peak at 143.19 ppm. **11ec** showed one peak at 144.10 ppm. Based on the observation, chemical shift at 143.30 ppm indicates five-membered ring structure, and chemical shift at 143.19 ppm indicates six-membered ring structure. With this observation, we analyzed the ^{13}C-NMR of **P11e** and observed two peaks at 143.76 ppm, and 143.32 ppm, which are slightly different from small molecules. This is possibly due to the chemical shift change during polymerization, similar to the ^{13}C-NMR chemical shift of **P8** (143.52, 143.38 ppm) and small molecule counterparts (142.99 ppm for **P8b**, and 144.25 ppm for **P8c**) cases. The integration ratio between two peaks of **P11e** showed almost 1 : 1 ratio, suggesting the polymeric unit ratio between five- and six-membered ring is 1 : 1.

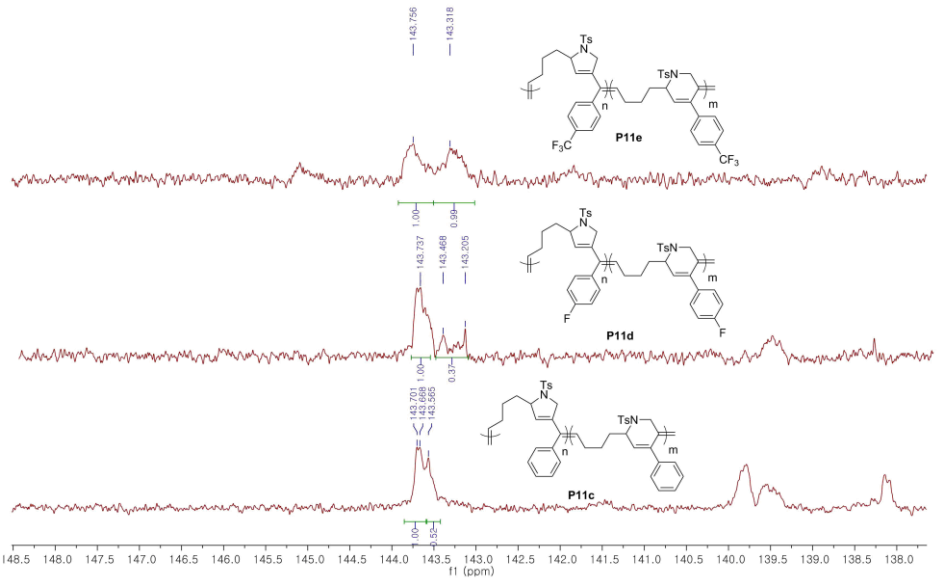

Figure S6. ^{13}C-NMR spectrum of **P11c-e**.

With this observation, tandem polymers with phenyl substituents were also observed to calculate the ratio between five- and six-membered ring units. **P11d** with 4-fluorophenyl substituent showed one large peak at 143.74 ppm and two small peaks at 143.47 and 143.21 ppm, possibly due to the cis/trans splitting. Ratio between those peaks are 2.7 : 1, suggesting the ratio between five- and six-membered ring units are 2.7 : 1. **P11c** with phenyl substituent showed two peaks at 143.70 ppm and 143.57 ppm, which showed 2 : 1 ratio upon integration, suggesting that the ratio between five- and six-membered ring units are 2 : 1.

Initiation rate kinetics study of monomer 11 with phenyl substituents (Chapter 3B)

To a 5 ml vial, catalyst **A** (27.85 mg, 0.000725 mmol) was added and purged with Ar gas. The catalyst was dissolved by 0.125 ml of THF-d^8 and 0.5 drop of hexamethyldisilane (HMDS) was added as a standard. 0.025 ml of mixture was injected to an Ar-purged NMR tube and diluted with 0.475 ml of THF-d^8 to calculate initial ratio between initiator carbene and standard. To another NMR tube, monomer **11** (0.06 mmol) and 0.5 ml THF-d^8 were added. After monomer was fully dissolved to NMR solvent, NMR tube was inserted into 400 MHz NMR. After obtaining initial NMR spectrum of monomer, 0.1 ml solution of catalyst **A** in THF-d^8 (0.01 mM) was quickly injected. After solution is fully mixed with quick shakes, NMR tube was inserted and both monomer conversion and carbene signal was monitored. Initiation rate was obtained by ratio between proton chemical shifts of initiator carbene (19.1 ppm) and internal standard (0.21 ppm). NMR data was collected up to 20 minutes, which were plotted as a function of time. After plotting the reaction rate, initial monomer/initiator ratio was extrapolated to remove errors from catalyst decomposition before injection. Reaction rates data showed zero order relation to monomer concentration. Obtained rate data was used to derive the Hammett plot.

Entry	X	[Mono] (M)	[I] (mM)	Corrected [I] (mM)	*k*(obs) (M/sec)	$\log(k_X/k_H)$	Sigma (ρ)
1	OMe	0.06	0.6	0.4332	0.01683	-0.13263	-0.27
2	Me	0.06	0.6	0.5148	0.01759	-0.11242	-0.17
3	H	0.06	0.6	0.4302	0.02278	0	0
4	F	0.06	0.6	0.387	0.02863	0.09843	0.06
5	CF3	0.06	0.6	0.3822	0.03761	0.21725	0.54

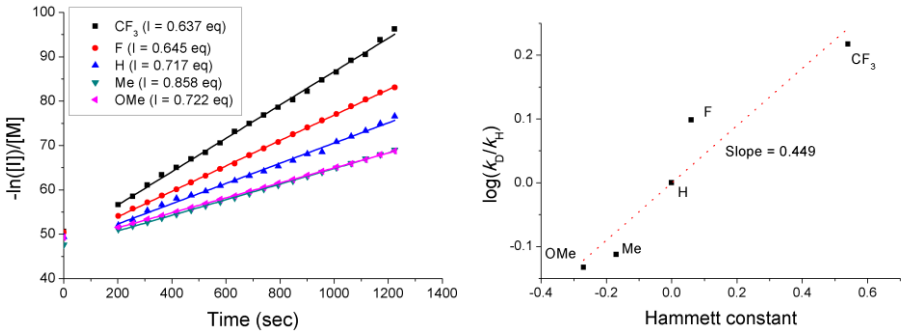

Figure S7. Initiation rate study result (left) and Hammett plot (right) of monomer **11a-11e** with phenyl substituents.

UV-Vis spectra of conjugated polymers (Chapter 4A)

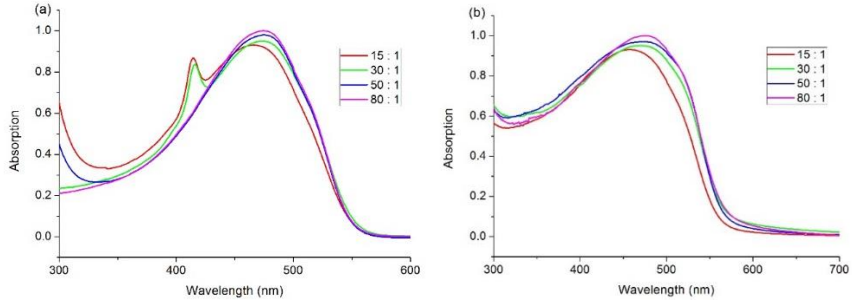

Figure S8. UV-Vis spectra of **P2** (a) in THF solution and (b) in thin film with different DPs (n = 15-80)

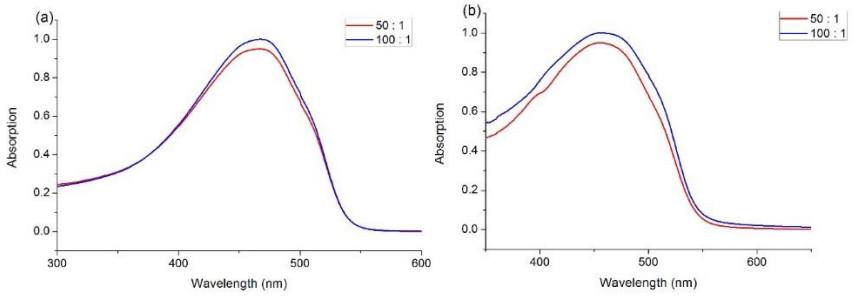

Figure S9. UV-Vis spectra of **P3** (a) in THF solution and (b) in thin film with different DPs (n = 50 and 100)

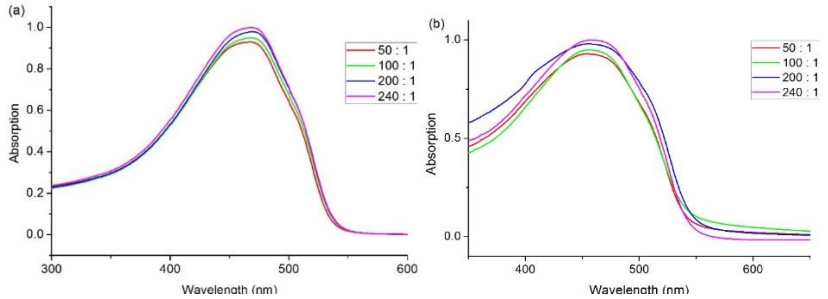

Figure S10. UV-Vis spectra of **P4** (a) in THF solution and (b) in thin film with different DPs (n = 50-240)

UV-Vis spectra of conjugated polymers (Chapter 4B)

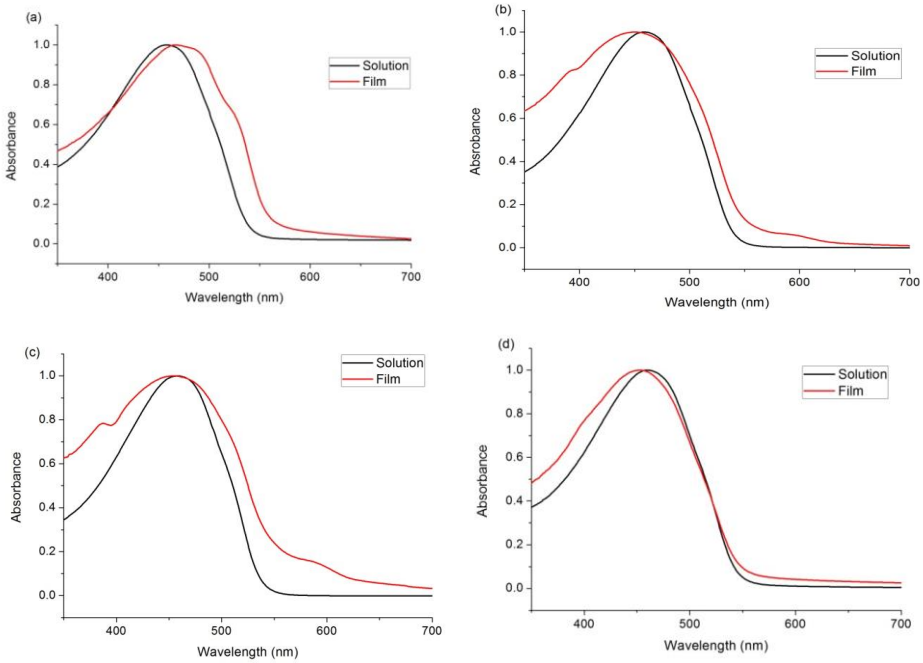

Figure S11. UV-Vis spectra of a) **P1**, b) **P2**, c) **P3**, and d) **P4** in THF solution and in thin film.

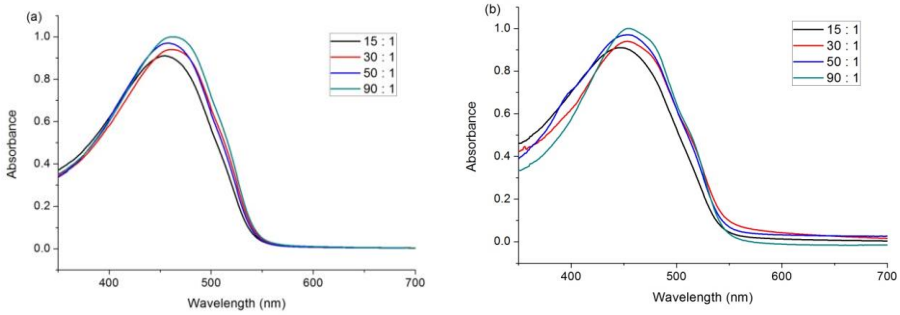

Figure S12. UV-Vis spectra of **P5** a) in THF solution and b) in thin film with different DPs (n = 15-90).

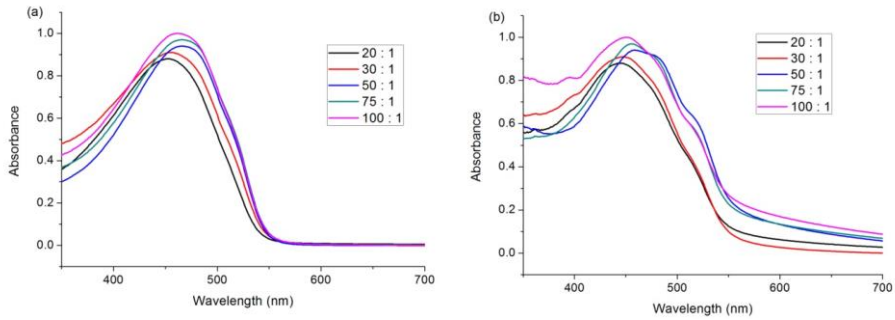

Figure S13. UV-Vis spectra of **P6** a) in THF solution and b) in thin film with different DPs (n = 20-100).

Isomerization data of P5

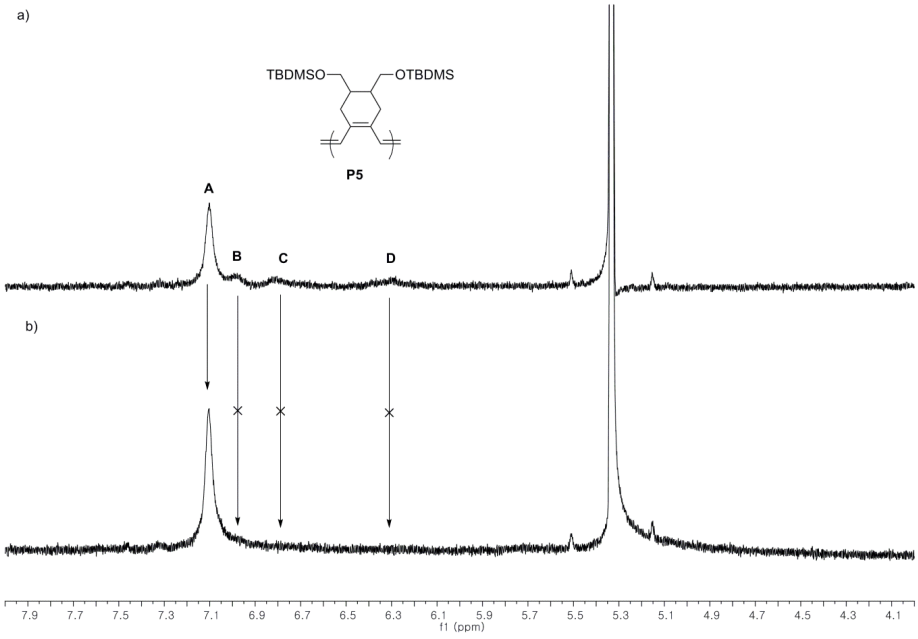

Figure S14. ^{1}H NMR spectrum of **P5** a) before isomerization and b) after isomerization in CD_2Cl_2. **P5** (0.4 mg) was put into NMR tube and dissolved in deuterated DCM (0.4 ml). The solution was irradiated by 480 nm blue LED light for 60 minutes.

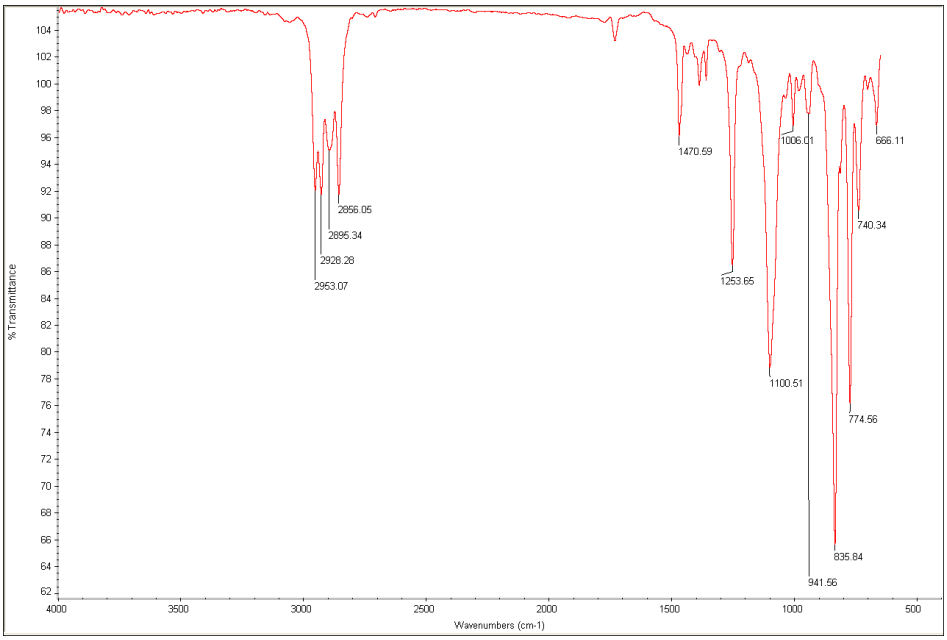

Figure S15. IR spectrum of **P5** before isomerization.

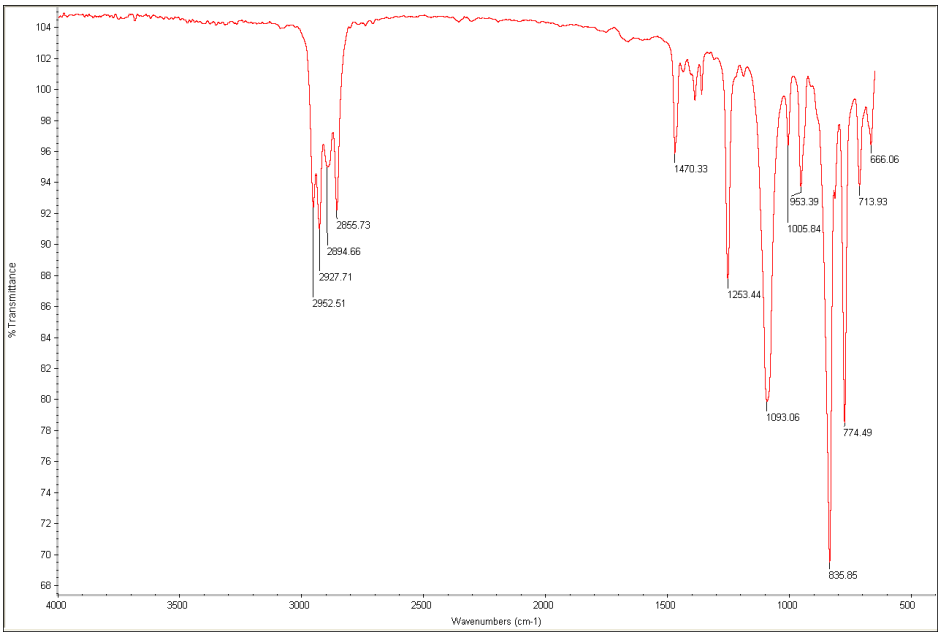

Figure S16. IR spectrum of **P5** after isomerization.

국문 초록

올레핀 메타테시스 반응은 탄소간 이중결합 위치를 변화시키는 반응으로, 이를 이용해서 다양한 종류의 유기 물질을 합성할 수 있다. 반응성이 높고 작용기에 대해 안정성이 높은 올레핀 메타테시스 촉매들이 개발 되면서 이 반응은 현대 유기화학에서 가장 중요한 반응 중 하나로 존재하게 되었다. 올레핀 메타테시스 반응에 사용되는 작용기 중에서도 알카인 물질의 경우, 촉매와 반응할 경우 1,3-다이인 형태의 작용기를 형성하게 되며, 이 작용기는 탠덤 반응을 통한 새로운 물질의 합성이나 전도성 고분자의 합성에 사용할 수 있다. 이 논문에서는 알카인을 이용한 올레핀 메타테시스 반응을 통해서 기존의 방법으로는 합성할 수 없었던 다양한 종류의 유기 화합물과 전도성 고분자를 합성하는 과정에 대해서 서술하였다.

제 2 장에서 다이인아인 물질에 대한 탠덤 고리 닫음 메타테시스 반응과 디엘스-알더 반응을 이용해서 다중고리 화합물을 합성하는 과정에 대해서 서술하였다. 일반적으로 탠덤 고리 닫음 메타테시스 반응을 통해서 이중고리 화합물을 합성하는 경우에는 촉매의 올레핀에 대한 반응 선택성이 없다는 단점 때문에 2 가지의 다른 종류의 물질이 형성되는 것이 일반적이다. 하지만 생성되는 고리의 크기 차이를 크게 해줄 경우, 고리화 반응의 속도 차이가 매우 커지기 때문에 하나의 물질만을 선택적으로 형성하는 것이 가능하다. 또한 이렇게 해서 형성된 1,3-다이인 작용기의 경우, 디엘스-알더 반응을 통해서 다중고리 화합물의 합성이 가능하게 되었다.

제 3 장에서 탠덤 고리 염/고리 닫음 메타테시스 반응을 이용해서 알카인과 사이클로알킨 물질을 가진 단분자의 고분자 중합을 진행한 것에 대한 연구를 서술하였다. 일반적으로 알카인과 사이클로알킨 작용기는 메타테시스 반응을 통한 고분자 중합이 매우 힘든 물질로 알려져 있다. 하지만 이 두 작용기를 하나의 단분자로 합칠 경우, 빠르고 비가역적인

탠덤 반응을 일으키면서 매우 빠른 속도로 분자량이 조절된 고분자를 합성하는 것이 가능하다. 이러한 새로운 반응을 개발하면서, 그에 따른 반응 메커니즘, 단분자 구조의 변경으로 인한 반응성의 변화, 그리고 반응 역학적인 연구를 같이 진행하였다.

제 4 장에서 1,7-옥타다이아인 물질에 대한 빠른 속도의 고리화 고분자 중합을 통한 전도성 고분자의 합성 과정을 서술하였다. 기존에 1,7-옥타다이아인 물질은 고리화 반응의 속도가 느린 편에 속해서 일반적으로 전도성 고분자를 합성하는데 적합하지 않았다. 이 문제를 해결하기 위해 단분자에 크기가 큰 작용기들을 도입하거나 작용기들의 위치를 바꿔 주는 것으로 짧은 시간 안에 원하는 고분자를 합성하는 것이 가능하게 되었다.

주요어 : 메타테시스, 고분자중합, 알카인

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Development of new olefin metathesis reactions via substrate modification:

Alkyne and olefin metathesis

Thesis by

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In Partial Fullfillment of the Requirements

For the Degree of Doctor of Philosophy

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Abstract

Olefin metathesis (OM) reaction is a facile reaction to synthesize various molecules through carbon-carbon double bond rearrangement. With the development of more reactive yet functional group tolerant catalysts, OM proved its usefulness and became one of the most important reaction in modern organic chemistry. Among the various olefins that can subjected to OM, alkynes have special characteristic. As OM only exchanges carbon-carbon double bonds, reaction between alkyne and metal carbene catalyst does not completely cleave carbon-carbon triple bond: instead, new metal 1,3-dienylidene is formed, which can undergo further metathesis reactions, such as enyne metathesis or conjugated polyene synthesis. This thesis will describe about the various application of OM with alkynes, from synthesis of small molecules to high-molecular-weighted conjugated polyenes.

Chapter 2 describes synthesis of multicyclic compounds through selective tandem dienyne ring-closing metathesis (RCM) reaction and Diels-Alder reaction. Dienyne RCM reaction is a useful reaction to synthesize fused bicyclic compounds, but due to the lack of catalyst selectivity between olefins with same structures, dienyne RCM reaction tend to produce two different isomers with different ring sizes. Also, product of conventional dienyne RCM reaction was restricted to the bicyclic compounds containing small or medium sized rings only. Thus, conformation of 1,3-diene functional group in bicyclic compound was fixed to *s-trans* conformation, thus further modification such as Diels-Alder reaction was impossible. By modifying the dienyne substrate to contain long tether to synthesize bicyclic compound comprising small (5-7 membered) and large (14-17 membered) rings, both problems could be solved. As cyclization rate of small ring and catalyst exchange rate between alkenes were significantly faster than that of large ring, single isomer could be synthesized from dienyne RCM reaction. Also, due to the flexible macrocycle chain, 1,3-diene functional group could form

s-cis conformation, which could undergo Diels-Alder reaction to synthesize multicyclic compound.

Chapter 3 describes tandem ring-opening/ring-closing metathesis (RO/RCM) polymerization of monomers containing cycloalkene and alkyne. Although cycloalkenes with low ring strain and alkynes were not suitable for metathesis polymerization, mixing those two functional groups in one monomer facilitated efficient tandem RO/RCM reaction to perform ultrafast living polymerization. Living characteristic of tandem polymerization could also synthesize block copolymers. Also, 1,3-diene functional groups in the polymer backbone could undergo further modification by cycloadditionr reactions. By changing monomer structures, we found out that monomers with certain combinations of cycloalkene, alkyne, and linker group could undergo efficient polymerization, while monomers with other combinations did not. In order to increase polymerization efficiency, two strategies were proposed. Firstly, monomer structures were modified to increase intramolecular RO/RCM with enhanced Thorpe-Ingold effect, which allowed the synthesis of challenging dendronized polymer. Secondly, reaction concentration was reduced to suppress intermolecular side reactions, which could effectively polymerize monomers without structural modifications. In order to further broaden the monomer scope, monomers containing internal alkynes were also studied, and surprisingly, monomers with internal alkynes tend to undergo non-selective α- and β-addition to form two different polymer units with different ring structures. Further studies revealed that steric and electronic effects of internal alkyne substituents changed polymer unit ratio, polymerization reactivity, and even polymerization kinetics. Thorough mechanism study revealed that the rate-determining step of monomers containing certain internal alkyne was six-membered ring cyclization step *via* β-addition, whereas that for monomers containing other alkynes was the conventional intermolecular propagation step, as observed in other chain-growth polymerization reactions.

Last chapter describes about fast cyclopolymerization of 1,7-octadiyne derivatives. Although cyclopolymerization was effective for the synthesis of conjugated polyenes, cyclopolymerization of 1,7-octadiyne was rarely studied, due to the slow polymerization rate by slow six-membered ring cyclization rate. Although this polymerization rate could be increased by using bulky substituents in side chains, simply increasing substituent bulkiness could not effectively increase polymerization rate. Thus, we proposed two strategies to increase polymerization rate. Firstly, dimethyl substitution was introduced to α-position of side chains. This strategy effectively increased polymerization rate by enhanced Thorpe-Ingold effect, and synthesis of 50-mer polymer could be done within 1 hour, instead of previous 24 hours. However, in order to achieve controlled polymerization, reaction temperature should be decreased and polymerization time was increased to 6 hours. To solve this problem, second strategy was applied: by changing substituent position from 4,4-disubstitution to 4,5-disubstitution, polymerization rate was significantly increased, and even living polymerization with narrow PDI and well-predictable molecular weight was possible within 1 hours, and even challenging synthesis of dendronized polymer could be possible. All those polymers were analyzed by UV-Vis, NMR, and IR spectroscopy to observe polymer backbone structures, such as conjugation length of polymer and *cis*/*trans* conformation of polymer backbone.

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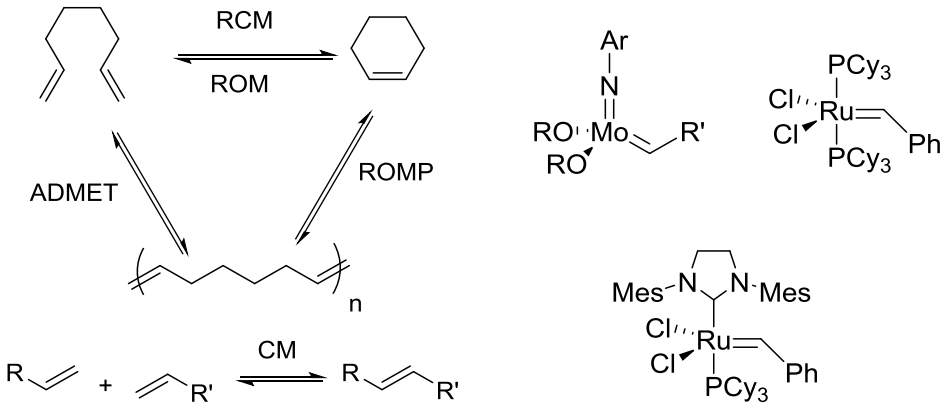
Chapter 1

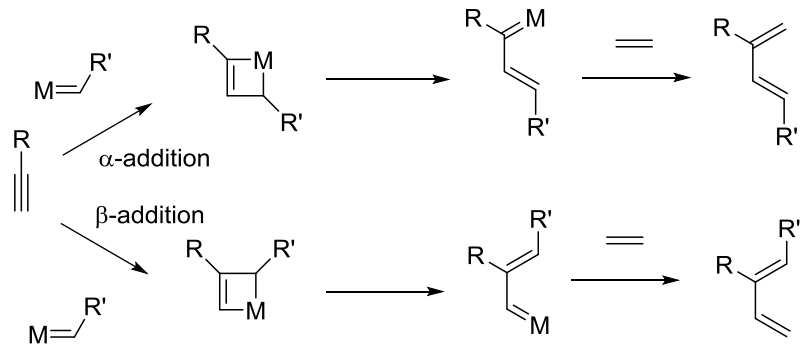
Olefin metathesis reaction with alkyne

Brief History of olefin metathesis with alkyne



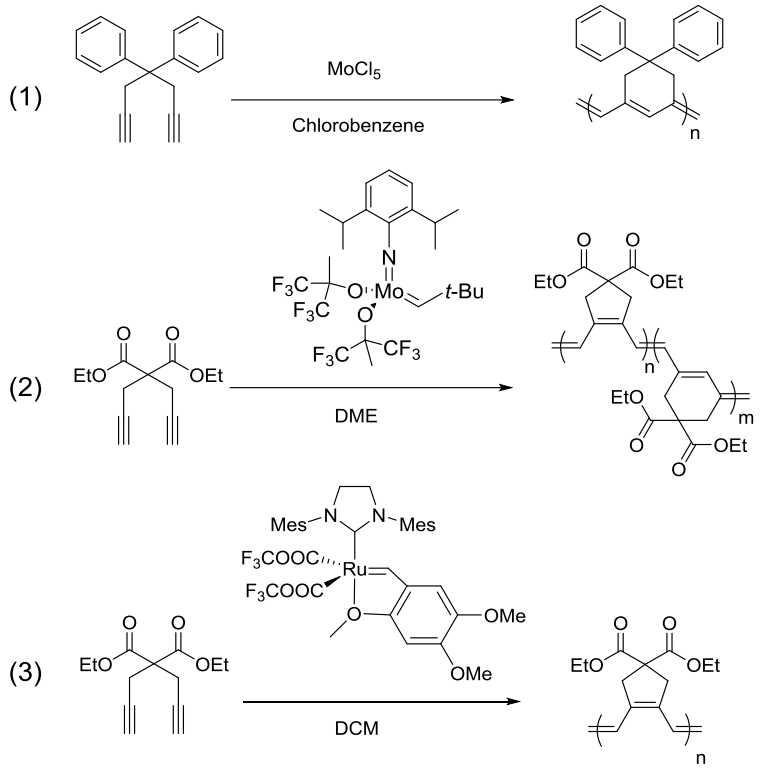
Scheme 1. Olefin metathesis reaction and notable catalysts

Olefin metathesis reaction is carbon-carbon double bond rearrangement between olefins to form new carbon-carbon double bond.[1] Since the discovery of olefin metathesis reactions at 1960's,[2] chemists developed various olefin metathesis techniques to provide three main reaction systems known as ring-opening metathesis (ROM)[3], cross metathesis (CM)[4], and ring-closing metathesis (RCM)[5]. Due to their usefulness, olefin metathesis reaction was further applied to polymerization to develop ring-opening metathesis polymerization (ROMP)[6] and acyclic diene metathesis polymerization (ADMET)[7] systems (Scheme 1). With the development of olefin metathesis reactions, olefin metathesis catalyst was also developed to increase their efficiencies. Starting from ill-defined transition metal salts (WCl_6, $MoCl_5$, etc.) with low functional group tolerance,[8] Schrock and Grubbs reported well-defined catalysts with molybdenum[9] and ruthenium[10] metal carbene system.



Scheme 2. Possible reaction pathway of alkyne reacting with metal carbene catalyst

Among the various olefin metathesis reaction substrates, alkyne shows interesting characteristics. When alkyne is reacted with olefin metathesis catalyst, it may undergo two different modes of α-, or β-additions to result in two different products (Scheme 2).[11] This mechanism was not well studied until Schrock's discovery of two different addition modes of molybdenum carbene catalyst toward 1,6-heptadiyne to form two different polymer units.[12] If catalyst undergoes α-addition, a sterically hindered 1,1-disubstituted metal alkylidene is obtained. On the other hands, if catalyst undergoes β-addition, more reactive monosubstituted metal alkylidene is formed. Wu's group explained this result with computational calculation that the steric effects of ligands affect to α-, and β-addition selectivity, suggesting large steric effect of alkoxyl ligand would disfavor α-addition, and large steric effect of alkylidene ligand would disfavor β-addition.[13] On the other hands, Grubbs catalysts tend to undergo highly selective α-addition, which is explained that steric effect between alkylidene ligand and alkyne substituent disfavors β-addition.[14] The most important feature of olefin metathesis reaction with alkyne is the formation of conjugated 1,3-dienylidene intermediate, which provides access to new synthetic methodologies such as conjugated polyene synthesis and tandem enyne metathesis reaction.

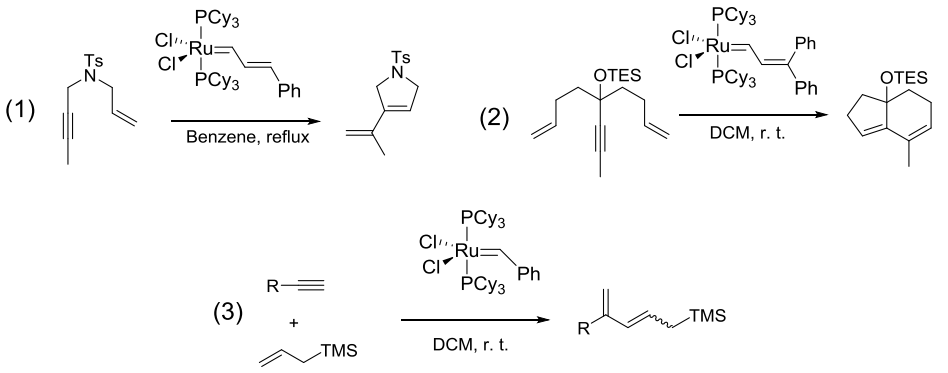


Scheme 3. Diyne cyclopolymerizations using metathesis catalysts

Initially, alkyne was introduced to metathesis reaction as a monomer for the synthesis of conjugated polyenes. Since the first acetylene polymerization by Natta and co-workers at 1958[15] and Shirakawa's report about electronical conductivity characteristic of conjugated polyene at 1974,[16] acetylene polymerization has been widely studied for the preparation of conducting polymers. The first acetylene metathesis polymerization was reported by Masuda and co-workers at 1974, which used WCl_6 or $MoCl_5$ olefin metathesis catalysts.[17] Further development acetylene polymerization allowed the living polymerization of polyacetylene via Ta[18], Mo[19], and Ru[20] based catalysts. However, acetyelene

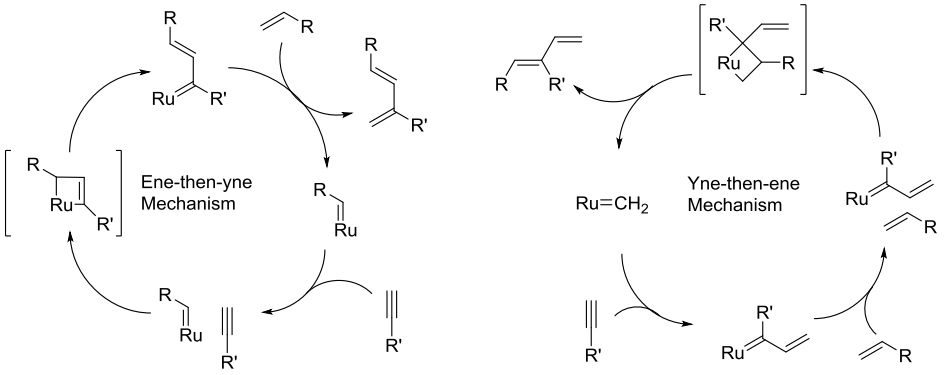
metathesis polymerization required harsh condition and polymerization efficiency was not good.

As an alternative pathway, diyne cyclopolymerization was used for polyene synthesis. First report of polymerization of non-conjugated diyne substrate to synthesize conjugated polyene used Zigger catalyst, which was done by Stille and co-workers at 1961, using 1,6-heptadiyne.[21] However, metathesis polymerization of 1,6-heptadiyne was overlooked until 1990, due to the low molecular weight of oligomer, insolubility of products, and low tolerance to air oxidation.[22] Those problems were solved with the introduction of substitution groups on 4-position of 1,6-heptadiyne. Starting from diphenyldipropargylmethane (DPDPM) and diethyldipropargylmalonate (DEDPM) monomer, various 4,4-disubstituted 1,6-heptadiyne monomers were polymerized with metathesis catalysts using $MoCl_5$ catalyst and opened renaissance of polyene synthesis through olefin metathesis reaction (Scheme 3).[23] At that time, polymer units from metathesis reactions were exclusively six-membered ring unit, derived from β-addition. In 1992, Schrock used well-defined molybdenum carbene complex for the living polymerization of 4,4-disubstitute 1,6-heptadiyne monomer.[24] Although the polymerization efficiency was high and well-controlled in both molecular weight and PDI, a mixture of five- and six-membered ring polymer units were formed due to the low selectivity between α-addition and β-addition (Scheme 3). Diyne cyclopolymerization using ruthenium based catalyst was studied a decade later, when Buchmeiser and co-workers polymerized 1,6-heptadiynes using modified Hoveyda-Grubbs catalyst at 2003 (Scheme 3).[25] Due to the high α-addition selectivity of ruthenium based catalyst to synthesize five-membered ring polymer unit exclusively, ruthenium based catalysts became widely used for cyclopolymerization along with the good tolerances toward air and moisture.[26]



Scheme 3. Notable enyne metathesis reactions.

Unlike polymer chemistry, organic chemists used enyne metathesis reaction to synthesize small molecules.[27] Enyne metathesis reaction is carbon-carbon double bond exchange between alkyne and alkene to form 1,3-diene functional group. First enyne metathesis reaction used Fischer carbene catalysts using tungsten or chromium metal, but they suffered high amount of catalyst loading, bad functional group tolerances, and low product yield due to the formation of various isomers.[28] The breakthrough for enyne metathesis reaction was started with the development of ruthenium based catalyst with good functional group tolerance. First enyne metathesis reaction with ruthenium based catalysts was reported by Mori and co-workers, who discovered ring-closing enyne metathesis reaction using ruthenium carbene catalyst at 1992.[29] Concurrently, Grubbs and co-workers reacted dienyne compound with ruthenium carbene catalyst to perform tandem ring-closing enyne metathesis reaction to synthesize bicyclic compound, which was the first example of tandem enyne metathesis.[30] At 1997, Blechert and co-workers reported intermolecular enyne cross metathesis reaction using ruthenium carbene catalysts.[31] Starting from those discoveries, enyne metathesis reaction could be applied to the preparation of various organic molecules.



Scheme 4. Two reaction pathways for enyne metathesis reaction

Although enyne metathesis reaction has been developed by many chemists, reaction mechanism of enyne metathesis reaction was in dispute for past decades. As both alkyne and alkene can react with metal carbene catalyst, both ene-then-yne mechanism and yne-then-ene mechanism could be possible (Scheme 4). In 2010, Sohn and co-workers reported fluorescence resonance energy transfer (FRET) based quenching experiment, which provided important clue on the reaction mechanism.[32] They reacted various kinds of metathesis catalysts containing on Mo and Ru metal carbenes with their substrate containing fluorescence dye and different olefins including terminal alkene and terminal alkyne. When catalysts reacted with olefin, catalyst will quench fluorescence of dye. According to their experiment, ruthenium catalysts containing *N*-heterocyclic (NHC) ligands reacted with alkyne faster, while catalysts without NHC ligands reacted with alkene faster. Their reports suggested that for olefins with same steric and electronic effects, catalysts without NHC ligand such as first-generation Grubbs catalyst undergoes ene-then-yne mechanism and catalysts with NHC ligand such as second-generation Grubbs catalyst undergoes yne-then-ene mechanism.

Thesis Research

As described above, many chemists studied metathesis reaction with alkyne to increase organic synthesis methodologies. However, due to the limitation of metathesis reactions such as low selectivity between olefins, reaction methodologies are not universal to various kinds of substrates. In the thesis research, we looked forward to further expand the scope of metathesis reactions from small molecule to polymers.

Chapter 2 describes synthesis of multicyclic compounds containing small and large rings through selective tandem dienyne ring-closing metathesis reaction and Diels-Alder reaction. Due to the slow cyclization rate of macrocycles, 'small ring first' cyclization product could be exclusively synthesized. Also, flexible macrocycle allowed *s-cis* conformation of 1,3-diene functional group within the ring, which could undergo Diels-Alder post-modification reaction to selectively form single multicyclic compound.

Chapter 3 discuss about tandem ring-opening/ring-closing metathesis polymerization of monomer containing cycloalkene with low ring strain and alkyne. Fusing those two unreactive monomers for metathesis polymerization to single monomer resulted ultrafast polymerization reaction, due to the fast alkyne addition and irreversible cyclization step. With this observations basic polymerization mechanism was studied. Reaction mechanism study provided new polymerization strategy to increase polymerization efficiencies for monomers with low reactivity. Lastly, monomers containing internal alkyne were polymerized to observe steric and electronic effect of alkyne substituents toward polymer reactivity, polymer microstructure, and polymerization kinetics.

Last Chapter demonstrates fast cyclopolymerization of 1,7-octadiyne monomers. Unlike 1,6-heptadiynes which undergo fast polymerization, 1,7-octadiyne

suffered from slow polymerization rate due to the slow cyclization rate. This chapter describes two monomer modification strategies to significantly increase polymerization rate. Firstly, dimethyl substituents were introduced to α-position of side chain, in order to induce greater Thorpe-Ingold effect toward 1,7-octadiyne tether. Secondly, monomer structure was changed from 4,4-disubstitution to 4,5-disubstitution. Monomer design, monomer synthesis, polymerization optimization, and detailed polymer characteristic studies are described in this chapter.

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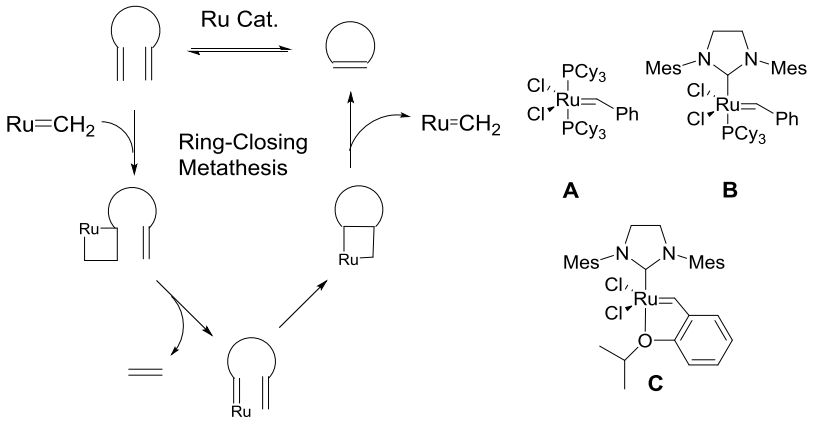
Chapter 2

Synthesis of fused multicyclic compound through dienyne ring-closing metathesis and Diels-Alder reaction

Abstract

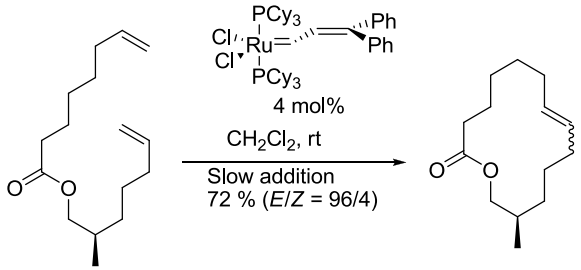
Fused multicyclic compound was synthesized through selective dienyne ring-closing metathesis (RCM) reaction and Diels-Alder reaction. The major drawback of tandem dienyne RCM reaction was the formation of two isomers with different ring structures, due to the low selectivity of catalyst toward terminal alkenes. In order to solve this problem, dienyne substrates with one short tether and one long tether were synthesized. Thanks to the fast small ring cyclization-catalyst exchange rate and slower large ring cyclization-dimerization rate, single isomer of fused bicyclic compound could be synthesized. Furthermore, flexible macrocycle chain allowed the formation of *s-cis* conformation of 1,3-diene functional group in bicyclic compound, which could be modified with cycloaddition reaction, and detailed structural analysis suggested that the resulting structure had single regiochemistry. Lastly, sequential one-pot reaction was performed to synthesize multicyclic compound without purification step.

Background



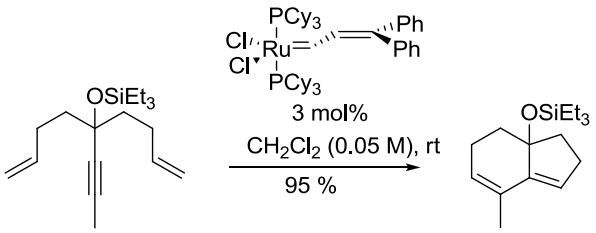
Scheme 1. Reaction pathway of RCM reaction and notable ruthenium based catalysts.

Synthesis of cyclic compound was one of the most important reaction in organic chemistry. Various methods were used for the synthesis of various ring structures like simple small sized rings, macrocyclic compounds, or cholesterol-like fused multicyclic compounds. Among the various methodologies to synthesize cyclic compounds, ring-closing metathesis (RCM) was one of the most powerful reaction (Scheme 1).[1] With the development of highly active ruthenium based catalysts with good functional group tolerances, RCM reaction provided easy access to the synthesis of various cyclic compounds with high productivity.[2]



Scheme 2. Macrocyclic RCM reaction using Grubbs catalyst.

Macrocyclization took great advantage by the development of RCM reaction.[3] Previously, macrocyclic compounds were synthesized by conventional organic reactions based on radical-mediated cyclization[4], Prins macrocyclization[5] or Yamaguchi macrolactonization[6]. However, those reactions showed relatively low productivity and suffered by the use of toxic reagents or excess chemical reagents. RCM reaction was good alternative method for macrocyclization due to their high productivity, low toxicity of reagent, and catalytic amount of reagent use (Scheme 2).



Scheme 3. Tandem dienyne RCM reaction for synthesis of bicyclic molecule.

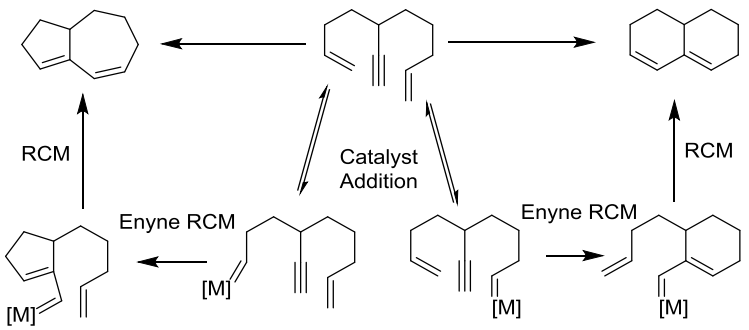
Also, RCM reaction was used as an effective protocol for the synthesis of multicyclic compounds.[7] Organic chemists used tandem radical cyclization reaction for the synthesis of various fused multicyclic compounds.[8] This method could be used to synthesize many complex molecules including complex cholesterol analogues, but controlling reactive intermediate to give the desired product can be difficult, and toxic residues are generated as a side-product. However, since Grubbs' first report on the synthesis of fused bicyclic compound by tandem dienyne metathesis reaction, RCM reaction has been recognized as an alternative method (Scheme 3).[9]

As new substrates had been synthesized by various RCM reactions, further post-modification reaction could provide the methods to synthesize more complex molecules. One of the good candidate is 1,3-diene functional group, which could be generated from enyne metathesis reaction. Using appropriate dienophiles, various cycloaddition reactions such as Diels-Alder reaction could be used as a good candidate for post-modification.[10] However, examples of Diels-Alder reaction on bicyclic compounds produced by tandem dienyne RCM were quite rare.[11]

In this chapter, selective synthesis of multicyclic compound using selective tandem dienyne RCM reaction and Diels-Alder post-modification will be described.

Introduction

Since the first tandem dienyne RCM reaction by Grubbs and co-workers, tandem dienyne RCM has been used as a versatile method for the synthesis of fused bicyclic compounds containing 1,3-diene functional group.[9] However, previously studied tandem dienyne RCM reaction had two limitations. First, due to the low selectivity of catalyst between olefins, two isomers containing different ring sizes were synthesized. In order to undergo selective RCM reaction, chemists used an additional protection to one alkene to decrease reactivity.[12] Second, due to the limitation of substrate scope to synthesize only small to medium sized ring containing products, resulting 1,3-diene functional group in the ring was restricted to form *s-trans* structures only, and further modification was not possible.[13] (Scheme 4)



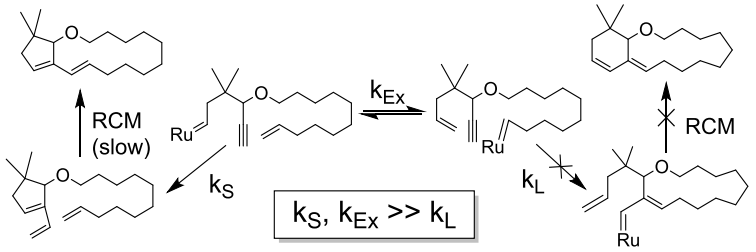
Scheme 4. Possible reaction pathways for tandem dienyne RCM reaction

Follwing the development of highly active olefin metathesis catalysts containing *N*-heterocyclic carbene (NHC) ligand[2], synthesis of more challenging substrates through RCM could be performed, including macrocyclic RCM reaction. This development further expanded the scope of substrates for RCM, including tandem dienyne RCM reaction. First, macrocyclization rate is significantly slower than the cyclization of small rings, which makes good candidate for selective tandem

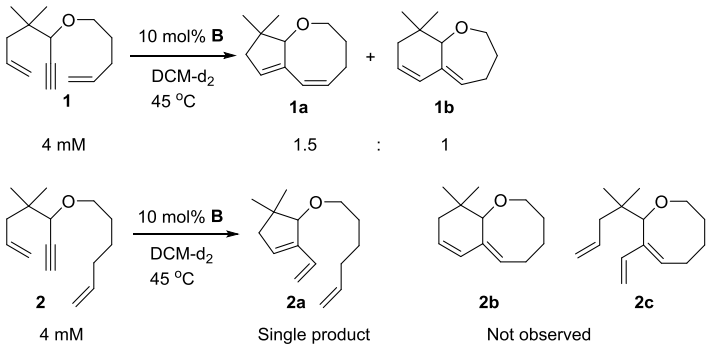
dienyne RCM reaction. Second, flexibility of macrocycle can form *s-cis* diene functional group after dienyne RCM reaction, which can be used for post-functionalization with cycloaddition reactions. Herein, we introduce the synthesis of multicyclic compound with tandem dienyne RCM reaction and Diels-Alder post functionalization reaction. Tandem dienyne RCM could produce single isomer containing small sized rings (5-7) and macrocycles (14-18), with the use of different cyclization rate between small and large rings.[14]

Result and Discussion

One potential problem of asymmetric dienyne RCM reaction was that dienyne substrates with different lengths of tethers give two isomers with different ring sizes.[9] This was due to the catalyst to react with both terminal alkenes with no preference. To achieve selective dienyne RCM reaction, one terminal alkene should have protected as a disubstituted internal alkene, allowing catalyst to react with less sterically hindered alkene first.[12] On the other hand, increasing reaction concentration also enhanced the selectivity by increasing the exchange rate between metal carbenes,[15] but this strategy is not suitable for macrocyclization because low concentration is required to prevent oligomerization.



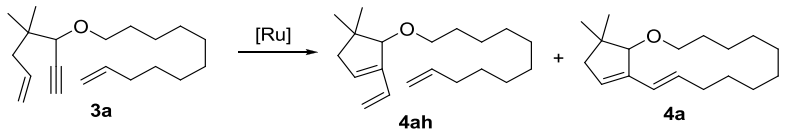
Scheme 5. Proposed reaction pathway for dienyne tandem RCM reaction.



Scheme 6. Tandem dienyne metathesis reaction for bicyclic compound containing small rings.

For the synthesis of bicyclic compound containing small and large rings, we expected that the selectivity issue will be eliminated if the rate of initial RCM to form a small ring (k_S) and metal carbene exchange rate (k_{Ex}) was far greater than the the rate of RCM to form a large ring (k_L) (Scheme 5). In order to confirm this proposal, two substrates **1** and **2** were prepared, in order to estimate the relative rate of k_S, k_{Ex}, and k_L. When **1** was reacted with second-generation Grubbs catalyst (**B**) under diluted concentration of 4 mM DCM, two products with a 1.5 : 1 ratio of **1a** and **1b** from non-selective RCM were observed during crude NMR analysis (Scheme 6). This suggests that five- and seven-membered ring cyclization rate was almost equal at low concentration, implying that the cyclization rate of five-, six-, and seven-membered ring cyclization rates were faster than the k_{Ex} between two different terminal alkenes. However, when substrate **2** reacted at low concentration, **2a** with a five-membered ring was observed exclusively during crude NMR analysis without the presence of **2b** or **2c** containing eight-membered ring. This suggests that eight-membered ring cyclization rate was slower than the k_{Ex} between two different terminal alkenes, resulting in complete selectivity. However, desired fused bicyclic compound was not observed due to the congested structure of medium-sized ring.

Table 1. Dienyne RCM reaction optimization[a]

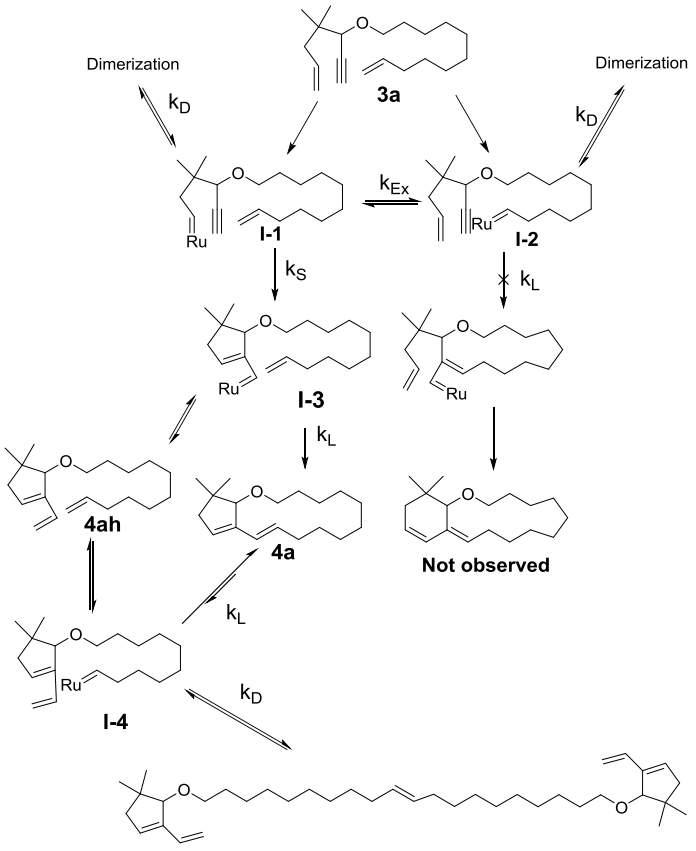


Entry	Catalyst	Solvent	Temp.	Yield of **4a**	**4ah**:**4a**[b]
1	**B**	DCM	45 ℃	N/A	1 : 2
2	**C**	DCM	45 ℃	N/A	1 : 2
3	**B**	1, 2-DCE	55 ℃	N/A	1 : 1.2
4	**B**	Toluene	55 ℃	73 %	1 : 12
5	**B**	Toluene	70 ℃	82 %	1 : 14

[a] General reaction condition : Under Ar atmosphere, 5 mol% catalyst was added to a substrate in 4 mM degassed solvent. Solution was heated for 24 hours under reflux condition. [b] Ratio was determined by ^{1}H NMR analysis.

With this result, we expected that selective dienyne RCM to synthesize bicyclic compound with small and large ring would be possible, as RCM rate of macrocycle would be significantly slower than the RCM rate of small ring. Also, desired bicyclic compound could be synthesized easily due to the flexible alkene tether to easily perform macrocyclization with carbene intermediate. In order to confirm this observation, substrate **3a** was synthesized and reacted with second-generation Grubbs catalyst at 4 mM concentration. When **3a** was reacted under 45 ℃ DCM solvent for 24 hours, 1 : 2 mixture of **4ah** and **4a** was observed, without the formation of macrocyclization-first product (Table 1, entry 1). This suggests that k_S and k_{Ex} were indeed faster than k_L for macrocycles to perform selective dienyne RCM reaction. In order to promote complete cyclization, various reaction conditions were tried. Initially, catalyst was changed to second-generation Hoveyda-Grubbs catalyst (**C**), but macrocyclization was not promoted

(Entry 2). In order to raise reaction temperature to 55 ℃ to promote macrocyclization, 1,2-DCE was used as a solvent instead, but it was less favorable to for macrocyclization, giving almost equal amount of **4ah** and **4a** (1 : 1.2) (Entry 3). However, switching the solvent to toluene greatly improve the conversion, forming the desired product in 73 % yield (Entry 4). Further increasing the temperature to 70 ℃ increased catalyst activity, giving **4a** with 82 % yield (Entry 5). Also, the product showed only the *trans*-isomer on the macrocyclic alkene. This selectivity is noteworthy because *E*/*Z* stereoselectivity in macrocyclic RCM remains a serious issue.[16]

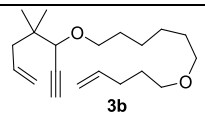
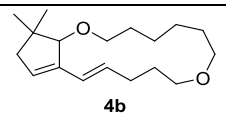
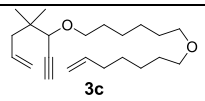
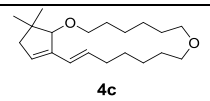
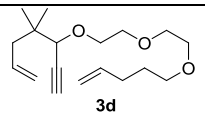
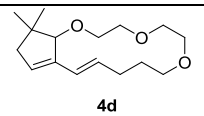
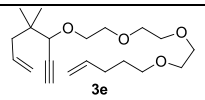
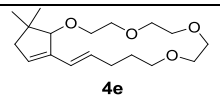
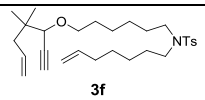
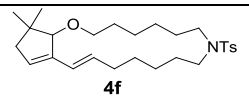


Scheme 7. Detailed reaction mechanism of tandem dienyne RCM

In order to observe details of reaction mechanism, substrate **3a** was reacted with catalyst **B** under diluted condition to check initial intermediate product. When reaction was performed for only 3 hours, only intermediate product **4ah** was observed, which would undergo complete cyclization to form **4a**. This provided important insight to the reaction mechanism (Scheme 7). Initially, catalyst will react with two terminal alkenes non-selectively to form intermediate **I-1** or **I-2**. Those metal carbenes may undergo RCM with alkyne, carbene exchange between **I-1** and **I-2**, or dimerization of **3a** through cross metathesis reaction. Here, only intermediate **I-1** underwent RCM reaction due to the fast k_S. On the other hand, cyclization product of **I-2** or dimerization product of **3a** were not observed, due to the much slower k_L and k_D. Instead, **I-2** underwent exchange reaction to form **I-1** again rapidly, which then produce **4ah** immediately. After the initial enyne RCM reaction that formed small rings exclusively, intermediate **I-3** or **I-4** underwent final macrocyclization to form fused bicyclic product. Overall, this process (k_S, $k_{Ex} > k_L$, k_D) pushed the equilibrium to one pathway, leading to the selective synthesis of **4a**.

Previously, Fogg and co-workers reported that during the macrocyclization of dienes, the dimer and oligomers formed initially as kinetic products and then reacted further to yield macrocycles.[17] However, we only observed **4ah** and **4a**, and any formation of dimer or oligomers were not observed during NMR monitoring studies. We believe that due to the fast RCM reaction to form **4ah**, the substrate contained one reactive terminal alkene and one less reactive conjugated olefin with a bulky substituent. This might reduce the chance of dimerization compared to the substrates with two reactive terminal alkenes. Also, the cyclopentyl moiety might have induced a biased structure favoring macro RCM over dimerization.

Table 2. Dienyne RCM reaction of various substrates[a]

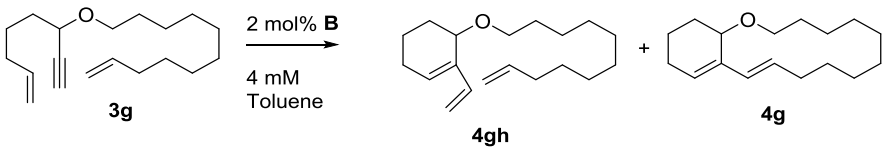
Entry	Substrate	Product	Temp.	Yield
1	 **3b**	 **4b**	55 ℃	95 %
2	 **3c**	 **4c**	55 ℃	85 %
3	 **3d**	 **4d**	55 ℃	91 %
4	 **3e**	 **4e**	55 ℃	85 %
5	 **3f**	 **4f**	70 ℃	87 %

[a] General reaction condition : Under Ar atmosphere, 5 mol% catalyst **B** was added to substrates in 4 mM toluene. Solution was heated for 24 hours under reflux condition.

In order to expand the reaction scope, various substrates with different tether structures were subjected to tandem RCM reaction to synthesize [n.3.0] (n = 12-15) bicyclic compounds. Under reflux condition, bicyclic compounds with 14- to 17-membered rings were synthesized with 85-95 % isolated yields using 5 mol% of catalyst **B**. Due to the enhanced Thorpe-Ingold effect by pseudo *gem*-dialkyl effect by lone pair electrons of oxygen atoms in long tethers, carbon-oxygen-carbon bond angle becomes smaller than the carbon-carbon-carbon bond angle.[18] Thus, product yields were relatively higher than **4a** with pure carbon tether (Table 2, entries 1-4).[19] Substrate **3f** with nitrogen atom also resulted in good productivity, although slightly higher reaction temperature (70 ℃) was required for effective

macrocylclization (Entry 5).

Table 3. Synthesis of six-membered ring containing fused bicycle[a]

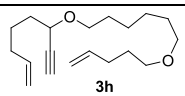
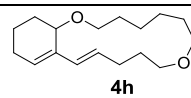
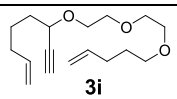
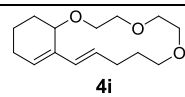
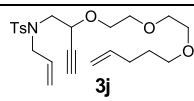
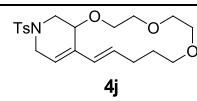
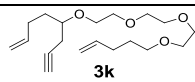
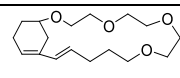


Entry	Catalyst	Temp.	Yield of **4g**	**4gh :4g**[b]
1	5 mol%	55 ℃	N/A	1 : 0
2	10 mol%	55 ℃	N/A	1 : 1.5
3	10 mol%	70 ℃	59 %	1 : 8
4	10 mol%	90 ℃	87 %	1 : 28

[a] General reaction condition : Under Ar atmosphere, 5 mol% catalyst **B** was added to substrates in 4 mM toluene. Solution was heated for 24 hours under reflux condition. Additional 5 mol% catalyst was added and the solution was heated for another 24 hours. [b] Ratio was determined by ^{1}H NMR analysis.

In order to further expand the substrate scope, bicyclic compounds with six-membered ring unit was synthesized. Initially, substrate **3g** was reacted with 5 mol% of catalyst **B**. Initially, the same reaction condition with the previous cyclopentene-containing substrates, but only a small amount of **4gh** was synthesized without the formation of bicyclic compound **4g** (Table 3, entry 1). When 10 mol% of catalyst was used instead, 1:1.5 mixture of **4gh** and **4g** was obtained (Entry 2). In order to increase macrocyclization efficiency, reaction temperature was increased up to 90 ℃ to get 87 % isolated yield of of **4g** (Entries 2-3). Since the initial cyclization of six-membered ring completed almost immediately after the catalyst addition, I could expect that the macrocyclization rate of **3g** was relatively slower than substrates with cyclopentene moieties.

Table 4. Synthesis of various six-membered ring containing fused bicycles[a]

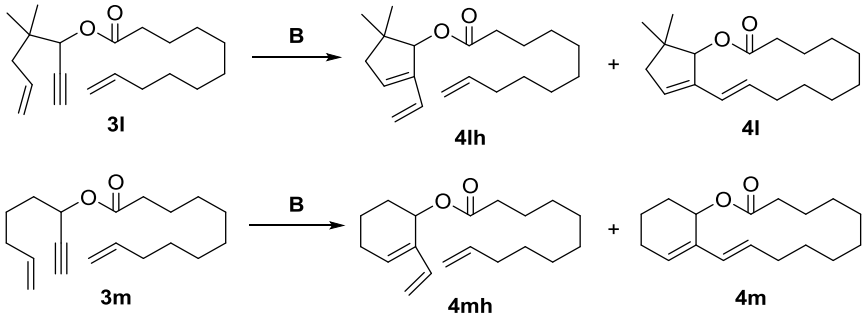
Entry	Substrate	Product	Catalyst	Temp.	Yield
1	 **3h**	 **4h**	5 mol%	100 ℃	75 %
2	 **3i**	 **4i**	5 mol%	55 ℃	71 %
3[b]	 **3j**	 **4j**	8 mol%	90 ℃	71 %
4[b]	 **3k**	 **4k**	10 mol%	70 ℃	69 %

[a] General reaction condition : Under Ar atmosphere, 5 mol% catalyst **B** was added to substrates in 4 mM toluene. Solution was heated for 24 hours under reflux condition. [b] Additional 3-5 mol% catalyst was added and the solution was heated for another 24 hours.

Similar to the fused bicyclic compounds with five-membered ring unit, substrate with oxygen atoms in the long tether resulted higher yield in tandem RCM reaction. Introducing one oxygen atom to the long tether resulted in 75 % yield of **4h**, even with the use of 5 mol% catalyst **B** (Table 4, entry 1). Adding more oxygen further improved macrocyclization reactivity so that the desired bicyclic compound was synthesized under milder condition at lower temperature (Entry 2). When nitrogen was introduced in the small ring, substrate **3j** underwent cyclization to form bicyclic compound with 71 % yield, but it required higher temperature and higher catalyst loading for efficient reaction (Entry 3). Furthermore, Bridgehead fused bicyclic compound was also synthesized by dienyne RCM reaction (Entry 4). Although bicyclic compolund contained an anti-Bredt olefin which is not easily formed in small molecules, long flexible chain of

macrocycle reduced ring strain to allow the formation of desired bicyclic compound in 69 % yield.

Table 5. Synthesis of fused bicycles containing ester group[a]



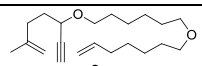
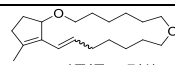
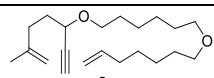
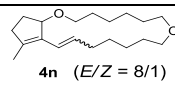
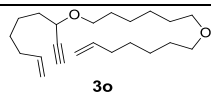
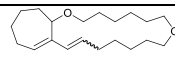
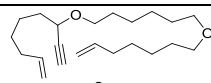
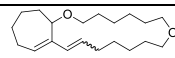
Entry	Substrate	Catalyst	Solvent	Temp.	Yield of **4x**	**4xh : 4x**[b]
1	**3l**	5 mol%	Toluene	55 ℃	19 %	1 : 0.23
2	**3l**	5 mol%	1,2-DCE	55 ℃	73 %	1 : 10
3	**3m**	5 mol%	1,2-DCE	55 ℃	N/A	1 : 1
4[c]	**3m**	10 mol%	1,2-DCE	70 ℃	83 %	1 : 10

[a] General reaction condition : : Under Ar atmosphere, 5 mol% catalyst was added to substrates in 4 mM solvent. Solution was heated for 24 hours under reflux condition. [b] Ratio was determined by ^{1}H NMR analysis. [c] Additional 5 mol% catalyst was added and the solution was heated for another 24 hours.

Synthesis of bicyclic compounds containing macrolactones was also investigated. Interestingly, substrate containing ester group showed low reactivity under toluene solvent condition, which was used in other tandem RCM reactions (Table 5, entry 1). However, when the solvent was changed to 1,2-DCE, macrocyclization reactivity was significantly increased to yield 73 % of **4l** (Entry 2). It seemed that polar solvent 1,2-DCE induced faster macrocyclization to yield **4l** with ester group. Synthesis of six-membered ring containing fused bicyclic

compound was also synthesized with the use of 1,2-DCE as a solvent. Similar to the previous case, **3m** required higher catalyst loading and higher reaction temperature to induce effective macrocyclization (Entries 3 and 4).

Table 6. Synthesis of fused bicycles with mixture of stereoisomers[a]

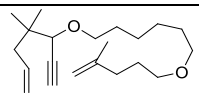
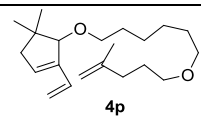
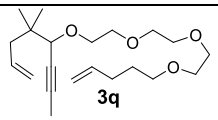
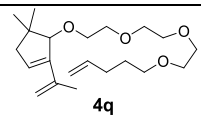
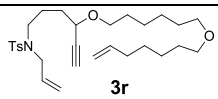
Entry	Substrate	Product	Catalyst	Temp.	Yield
1	 **3n**	 **4n** (*E*/*Z* = 5/1)	5 mol%	55 ℃	63 %
2	 **3n**	 **4n** (*E*/*Z* = 8/1)	5 mol%	90 ℃	87 %
3[b]	 **3o**	 **4o** (*E*/*Z* = 5/1)	10 mol%	70 ℃	27 %
4[b]	 **3o**	 **4o** (*E*/*Z* = 25/1)	15 mol%	100 ℃	63 %

[a] General reaction condition : Under Ar atmosphere, 5 mol% catalyst **B** was added to substrates in 4 mM toluene. Solution was heated for 24 hours under reflux condition. *E*/*Z* ratio was determined by ^{1}H NMR analysis. [b] Additional 5-10 mol% catalyst was added and the solution was heated for another 24-48 hours in 2 mM toluene.

Although most macro-RCM reactions produced *E*-olefins on the macrocyclic alkenes, mixtures of *E*/*Z* isomers were observed in some cases. One case was tandem RCM of **3n** with 1,1-disubstituted alkene on short tether undergoes, which yielded fused bicyclic compound with synthetically challenging tetrasubstituted alkene (Table 6, entries 1 and 2). Under 55 ℃ reaction condition, yield of **4n** was 63 % and *E*/*Z* ratio was 5/1. When reaction temperature was increased, not only product yield was increased (87 %), but also stereoselectivity was improved (*E*/*Z* = 8/1). Another case was the synthesis of fused bicyclic compound containing

seven-membered ring, which is more challenging for RCM reaction than bicyclic compounds containing five- or six-membered rings. Thus, tandem RCM reaction of substrate **3o** required 100 ℃ temperature and high catalyst loading (15 mol%) to achieve 63 % yield. Increasing the reaction temperature and catalyst loading changed *E*/*Z* ratio from 5/1 to 25/1 (Entries 3 and 4). In both examples, *E*/*Z* selectivity was increased with higher substrate conversion due to the enhanced catalyst activity. As more catalysts remain active, reversible *E*/*Z* isomerization on the macrocyclic alkene occurred more frequently to form more stable *E* isomer.

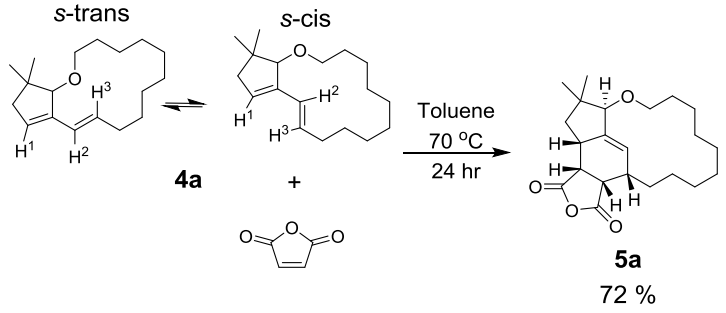
Table 7. Unsuccessful examples of tandem RCM[a]

Entry	Substrate	Product	Catalyst	Temp.	Yield
1	 **3p**	 **4p**	5 mol%	55 ℃	66 %
2	 **3q**	 **4q**	5 mol%	55 ℃	74 %
3[b]	 **3r**	Complex mixture	10 mol%	100 ℃	N/A

[a] General reaction condition : Under Ar atmosphere, 5 mol% catalyst **B** was added to substrates in 4 mM toluene. Solution was heated for 24 hours under reflux condition. [b] Additional 5 mol% catalyst was added and the solution was heated for another 24 hours

Although the substrate scope for fused bicyclic macrocyclization was quite broad as seen in the previous tables, several substrates did not lead to desired products. Unlike the previous example, in which the fused bicyclic compound with an additional methyl substituted olefin on the small ring was successfully prepared (Table 6, entry 2), synthesizing fused cyclic compounds containing an additional

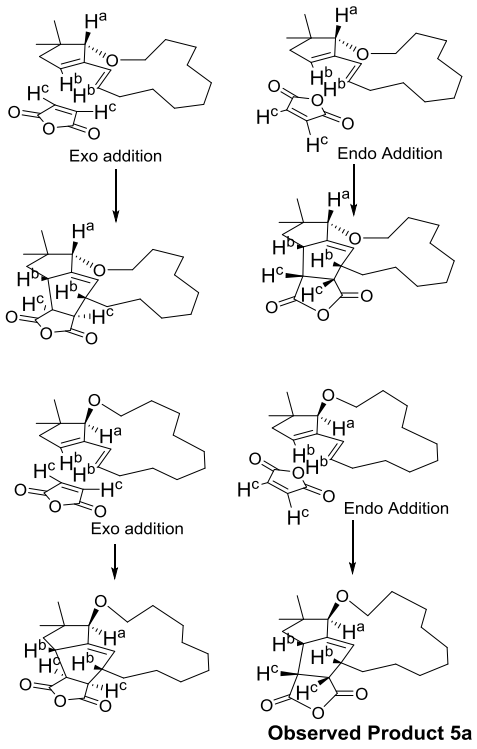
substitution on the alkene of the macrocycles to make trisubstituted alkenes failed, giving only molecules with incomplete cyclisation (Table 7, entries 1 and 2). Because the additional substitution made it harder for the catalyst to perform effective metathesis reaction, the macrocyclization rate became even slower, leaving only small ring-closed products. Synthesis of eight-membered ring containing fused cyclic compounds was even more challenging (Table 7, entry 3) due to intrinsically low reactivity of RCM toward the formation of eight-membered rings. Even with high catalyst loading at an elevated temperature, this reaction gave a complex mixture of molecules, and not even clean conversion to the initial eight-membered ring was observed.



Scheme 8. Diels–Alder reaction of a fused cyclic compound synthesized by the dienyne RCM reaction

So far, we have demonstrated that the fused bicyclic compounds comprising small and large rings were efficiently prepared by tandem dienyne RCM reactions. This method would be more useful if further manipulation on the RCM products would be possible giving more diversity. For a typical dienyne RCM reaction, 1, 3-diene, a potential functional group for Diels–Alder reaction, is formed at the end of the reaction. However, there have been no previous reports of Diels–Alder reactions on the dienes of fused bicycles formed by dienyne RCM reactions because the products were composed of two small or medium rings. Thus, there was no

chance of forming *s-cis* dienes but *s-trans* dienes only, which cannot participate in Diels–Alder reactions.[13] On the other hand, we reasoned that dienes on the bicycles containing small and large rings might adopt the *s-trans* conformation as well due to the presence of flexibile chains on macrocycles. The first evidence for this came from a nuclear Overhauser effect (NOE) study on substrate **4a**, which showed interaction between vinyl proton H^1 with both proton H^2 and H^3 (Scheme 8). These suggested that substrate **4a** might adopt both *s*-trans and *s*-cis conformations, implying that these dienes could undergo Diels–Alder reactions with dienophiles. Indeed, when treated with maleic anhydride at 70 ℃, a cycloaddition product **5a** with a single diastereomer was obtained in 76 % isolated yield.



Scheme 9. Origin of stereochemistry for the Diels-Alder reaction

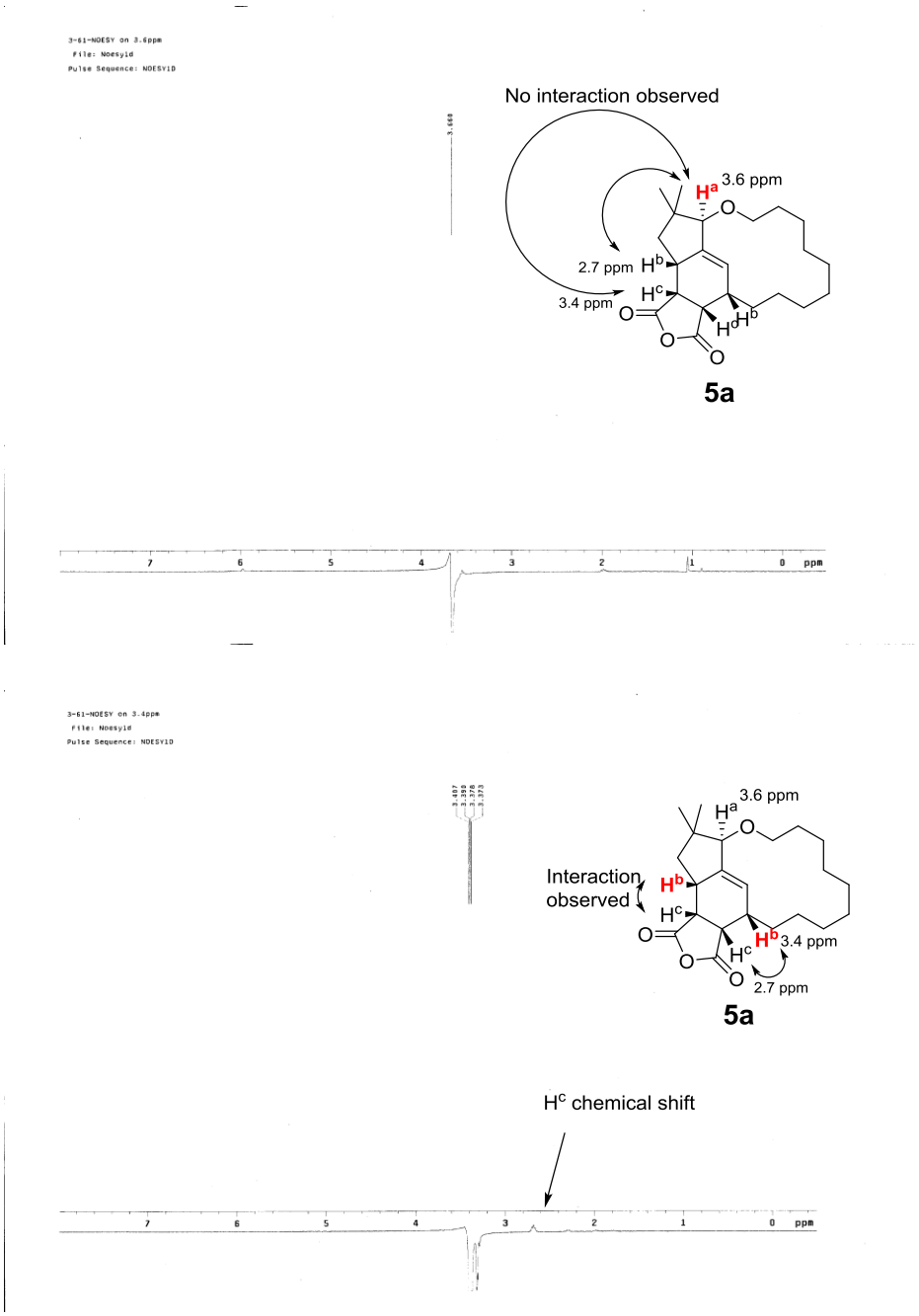
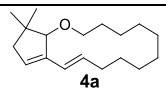
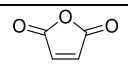
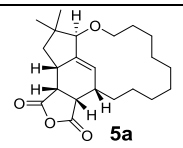
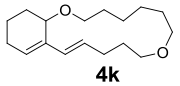
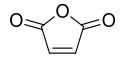
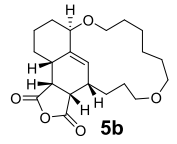
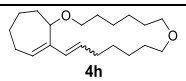
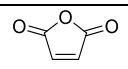
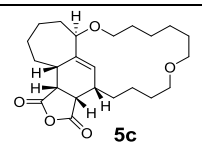
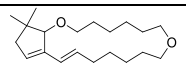
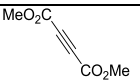
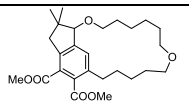
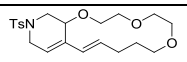
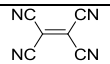
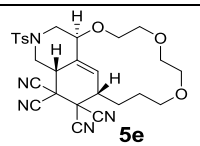


Figure 1. 1D NOE spectrum analysis of **5a**

As shown in Scheme 9, the Diels–Alder reaction could give four different diastereomers depending on how the dienophile approached the fused bicyclic diene molecule. First, the dienophile could add to the diene from two different sides, but the dienophile would preferentially approach from the less sterically hindered side, H^a, and away from the more sterically hindered ether linkage. Second, the dienophile could approach the diene with *endo* orientation over *exo*. To determine the molecular structure of the adduct, 1D NOE study was conducted and showed that H^a interact with neither H^b or H^c, suggesting that they were *anti* to one another (Scheme 9).[20] Also, the NOE study showed that H^b interacted with H^c, confirming that the product isolated was the predicted **5a** isomer due to *endo* selective addition of the dienophile from the less hindered side of the fused cyclic diene (Figure 1).

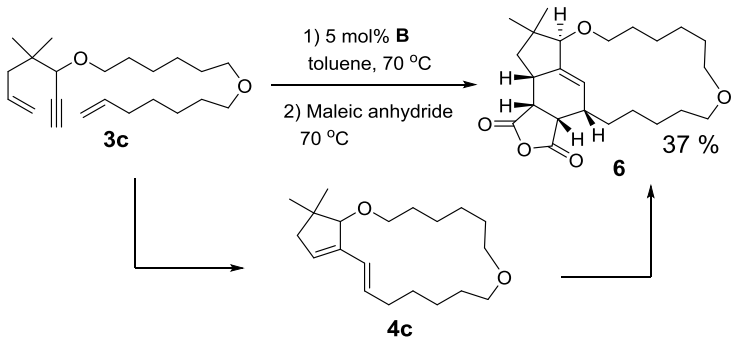
Table 8. Diels–Alder reaction on the dienyne RCM products[a]

Entry	Diene	Dienophile	Product	Yield
1	 **4a**		 **5a**	76 %
2	 **4k**		 **5b**	74 %
3	 **4h**		 **5c**	75 %
4[b]	 **4c**		 **5d**	66 %

5[c]	 **4l**		 **5e**	83 %

[a] General information : Under Ar atmosphere, 2 equiv. dienophiles was added to dienes in 0.3 M toluene. Reaction flask was heated to 70 ℃ for 4 hours. [b] Reaction flask was heated to 100 ℃ for 48 hours. [c] Reaction proceeded at room temperature for 24 hours.

Reactions between maleic anhydride and various dienyne RCM products containing five- to seven-membered rings in toluene at 70 ℃ gave good yields of Diels–Alder products (74–76%) comprising tetracyclic compounds (Table 8, entries 1–3). In all cases, single diastereomers with the predicted stereochemistry were obtained. To test dienophiles other than maleic anhydride, dimethyl acetylenedicarboxylate was reacted with **4a**. Even at higher temperature, this Diels-Alder reaction was much slower than the previous cases with maleic anhydride as a dienophile. We expected to obtain the Diels–Alder product with a 1, 4-cyclohexadiene moiety, but **5d** with an aromatic ring was the only isolated product. Presumably, the initial Diels–Alder product of 1, 4-cyclohexadiene, quickly underwent aromatization under the reaction conditions, giving a tricyclic compound with the aromatic ring (Enry 4).[21] Since the Diels–Alder reactions were conducted at elevated temperatures, it was unclear whether equilibrium between *s*-cis and *s*-trans isomers of the dienes was possible at room temperature. Thus, a stronger dienophile, tetracyanoethylene, was added to **4l** at room temperature, and the product **5e** was isolated with excellent yield (Table 8, entry 5). This confirmed our initial assumption that the fused cyclic compounds containing macrocycles could adopt the *s*-cis diene conformation at room temperature due to the flexible chains on the macrocycles.



Scheme 11. Sequential RCM–Diels–Alder reaction in one-pot reaction

As the Diels–Alder reactions were performed under the same solvent and the same temperature, dienyne RCM and Diels–Alder reactions could be conducted sequentially in a one-pot reaction. Substrate **3c** was treated with catalyst **B** at 70 ℃, and after 24 hours, addition of two equiv. of maleic anhydride produced the fused tetracyclic compound **6** with 37% isolated yield (Scheme 11). Although the yield was low, this result demonstrated that the complexity of the molecules could be rapidly built up by the combination of one-pot tandem dienyne RCM and Diels–Alder reactions, producing the tetracycle from an acyclic substrate.

Conclusions

In here, we described on the synthesis of multicyclic compounds comprising small and large rings through selective dienyne RCM reaction and Diels-Alder reaction to produce single isomer with high selectivity, generality, and predictability. Because the cyclisation rate was significantly faster for the small rings compared with the macrocycles, the synthetic pathway was driven to produce single isomers. This methodology efficiently produced fused bicycles with small rings from 5- to 7-membered rings and macrocycles from 14- to 17-membered rings, demonstrating the versatility of the reactions. Generally, higher

conversion to complete macrocyclization was achieved with higher temperature or higher catalyst loading. Also, the RCM reaction products underwent Diels–Alder reactions with exclusive stereo-control. The combination of tandem dienyne RCM and Diels–Alder reactions provided a powerful method to rapidly build complex molecules, especially those multicyclic compounds containing macrocycles.

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Chapter 3

Tandem ring-opening/ring-closing metathesis polymerization

Abstract

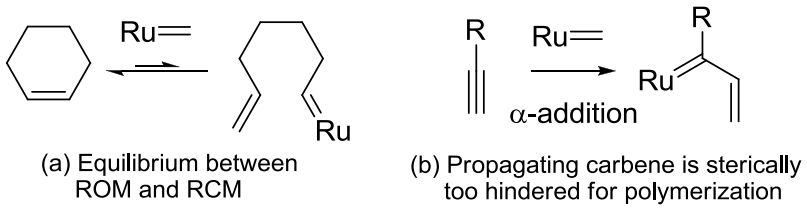
Tandem ring-opening/ring-closing metathesis polymerization has been studied. Cycloalkenes with low ring strain and alkynes were not good monomer for metathesis polymerization, due to their lack of driving force for polymerization against depolymerization. However, by fusing two unreactive functional groups in single monomer, we could achieve ultrafast living polymerization, using third-generation Grubbs catalyst. This reactive polymerization could be used to synthesize block copolymer. Also, polymer backbone could be modified with Diels-Alder post modification to prepare polymers with more complex structure. Reaction mechanism study of tandem polymerization revealed that the polymerization followed alkyne-first pathway to synthesize polymer with extremely good regioregularity. With this observations, monomers with various combinations of cycloalkenes, alkynes, and linker groups were studied, but monomers with certain combinations did not undergo efficient polymerization. In order to promote efficient polymerization, two strategies were used. Firstly, monomers were modified to contain bulky substituent groups to accelerate RO/RCM cyclization rate by enhanced Thorpe-Ingold effect, and this strategy could synthesize monomers with various structures, even challenging dendronized polymers. Secondly, reaction concentration was reduced to suppress intermolecular side reaction, which could effectively synthesize monomers which cannot change their structures. In order to expand monomer scope further, monomers containing internal alkyne was also studied. Polymerization of monomers containing internal alkyne revealed that steric, electronic effects of alkyne substituents affected to various features in polymerization, such as polymer unit ratio between five- and six-membered ring unit, polymerization reactivity, and polymerization kinetics. Detailed mechanistic study revealed that the rate determining step of polymerization of monomers with certain internal

alkyne substituents was tandem RO/RCM cyclization step, while that of other monomers was propagation step, which is common for conventional chain-growth polymerization.

Background

Olefin metathesis (OM) reaction has been used as a versatile method for the synthesis of various organic molecules.[1] With the development catalysts with high reactivity and good functional group tolerance based on molybdenum[2] and ruthenium metals[3], reaction scope for olefin metathesis reaction has been significantly broadened. With these catalysts, chemists developed various olefin metathesis reactions based on three systems; ring-opening metathesis (ROM), cross metathesis (CM), and ring-closing metathesis (RCM). Application of OM was not limited to the small molecule synthesis, but also applied to polymer chemistry. These three systems were applied to polymer synthesis as ring-opening metathesis polymerization (ROMP)[4], acyclic diene metathesis polymerization (ADMET)[5], and cyclopolymerization[6].

As metathesis reactions undergo thermodynamically equilibrium reactions, metathesis polymerizations need good strategies to drive the equilibrium toward polymerization against depolymerization pathway. ROMP takes advantage of reliving ring strain of highly strained cyclic alkene monomers. Thus, highly strained cycloalkenes such as norbornene or cyclooctenes are frequently used as ROMP monomers. ADMET release ethylene gas as a side product, and removing this ethylene gas eventually drives equilibrium toward polymerization. Lastly, cyclopolymerization of diyne monomers undergoes irreversible generation of stable conjugated polyenes to achieve effective polymerization. In short, three polymerization methods become useful when thermodynamics of the reactions favors polymerization over depolymerization.



(a) Equilibrium between ROM and RCM

(b) Propagating carbene is sterically too hindered for polymerization

Scheme 1. Unreactive monomers for metathesis polymerization

On the other hand, monomers without thermodynamically driving forces cannot undergo effective polymerization. Cyclohexene is a good example for this; due to the extremely low ring strain, cyclohexene tends to easily undergoes depolymerization. Although metathesis reaction of cyclohexene under extremely low temperature could yield oligomers of cyclohexene, synthesis of high molecular weighted polymer using cyclohexene as a single monomer has not been studied.[7] Furthermore, cycloalkenes with subsitutiton groups tend to reduce ring strain, such as cyclopentenes with 3- or 4- substitution.[8] Currently, only a small number of reports used cyclohexene as a co-monomer for alternating metathesis polymerizations.[9]

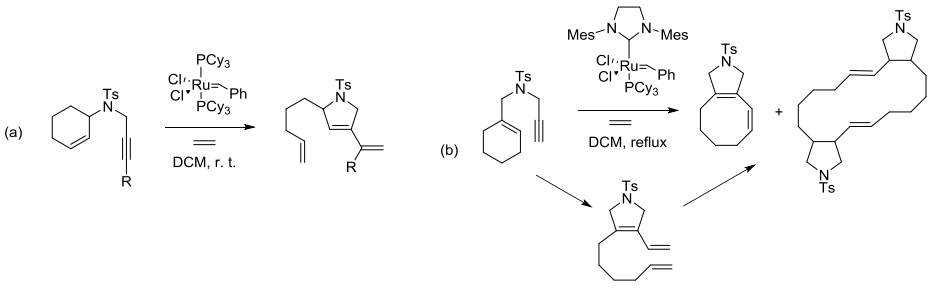
Another example is CM polymerization of alkynes. Although CM of alkyne will generate conjugated olefins which will favor enthalpic gains during the reaction, propagating carbene complexes are not reactive enough to undergo polymerization.[10] When terminal alkyne is reacted with ruthenium based catalyst, catalyst tend to undergo α-addition to form 1,1-disubstituted alkylidene, and resulting bulky carbene complex is not reactive enough to undergo desired polymerization. Although Masuda and co-workers could achieve CM polymerization of alkynes with Grubbs catalyst, harsh condition was required and polymerization was not controlled.[10]

In organic chemistry, chemists use tandem metathesis reactions to synthesize various kinds of complex molecules.[11] These methods were well used to synthesize the core skeletons of various natural products.[12] For example, tandem relay metathesis reaction has been used to promote ring rearrangement reactions *via* enyne ROM and RCM reaction.[13] On the other hand, conventional metathesis polymerizations use single metathesis reaction system, only simple polymer microstructures are expected. Application of tandem metathesis reactions to polymerization can synthesize polymers with complex structures, and provide new field of monomer scopes.

This chapter will describe about tandem ring-opening/ring-closing metathesis (RO/RCM) polymerization using monomers containing cycloalkene with low ring strain and terminal alkynes. With the use of two unreactive functional groups in single monomer, miraculously highly reactive polymerization has been possible. With the development of new polymerization reaction, various optimization trials and mechanistic studies for the polymerization are also reported.

Part A. Tandem RO/RCM of monomers containing nitrogen linker group

Introduction



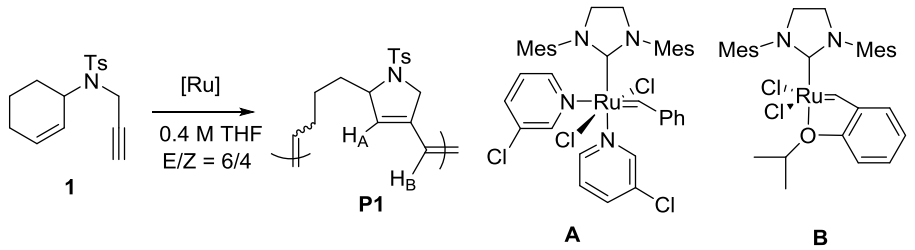
Scheme 1. Tandem enyne ring rearrangement reaction

Since metathesis polymerization of cycloalkenes with low ring strain (ex – cyclohexene) and terminal alkynes were not efficient enough to synthesize polymers with high molecular weight, these functional groups were overlooked as a monomer for metathesis polymerization. However, with the help of tandem relay-type metathesis reaction, they may have a good chance to act as a polymerization monomer. Previously, Mori and co-workers studied tandem enyne metathesis reaction using substrate containing cycloalkene and alkyne.[14] When those substrates reacted with first-generation Grubbs catalyst under ethylene atmosphere, they tend to undergo efficient ring rearrangement reaction through tandem ring-opening/ring-closing metathesis reaction (Scheme 1a). Furthermore, when those substrates reacted with highly reactive second-generation Grubbs catalyst, they tend to undergo dimerization or internal RCM reaction after initial ring rearrangement reaction (Scheme 1b). These results suggest valuable informations: first, substrate containing cycloalkene and alkyne is reactive enough to undergo intramolecular ring rearrangement reaction. Second, with the

use of reactive Grubbs catalysts containing *N*-heterocyclic (NHC) ligand, substrate may undergo further reaction after ring rearrangement to form dimer, or bigger oligomers and polymers from newly generated terminal alkenes.

Results and Discussions

Table 1. Tandem metathesis polymerization of **1**



Entry	Solvent	Cat.	M/I	Temp.	Time	M_n[a]	PDI[a]	Conv.[b]
1	DCM	**B**	100	r. t.	1 hr	15000	1.46	60 %
2	THF	**B**	100	r. t.	1 hr	30000	1.88	100 %
3	THF	**A**	100	r. t.	1 min	26000	1.86	100 %
4	THF	**A**	100	-10 ℃	2 min	31000	1.18	100 %
5	THF	**A**	100	-30 ℃	10 min	31000	1.18	100 %
6	THF	**A**	30	-30 ℃	3 min	8000	1.17	100 %
7	THF	**A**	50	-30 ℃	5 min	18000	1.18	100 %
8	THF	**A**	150	-30 ℃	20 min	41000	1.21	90 %

[a] Determined by THF SEC calibrated using polystyrene standards. [b] Conversion determined by crude ^{1}H-NMR analysis.

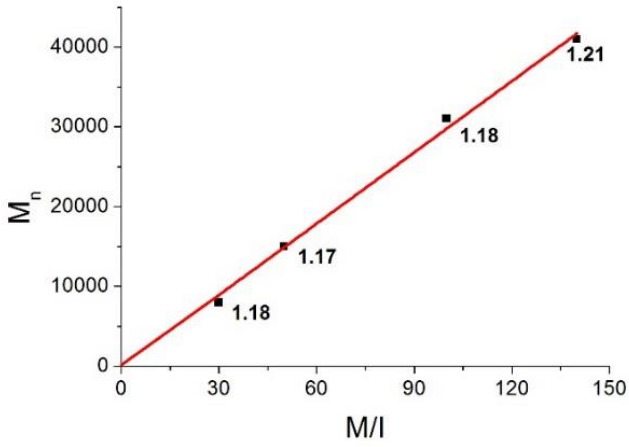


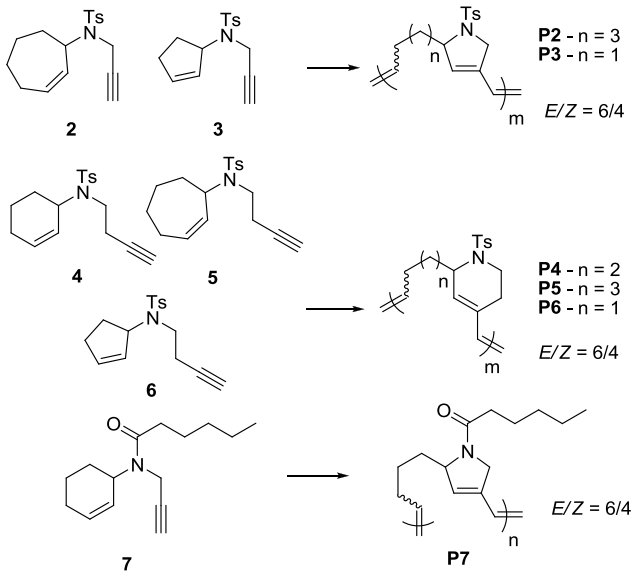
Figure 1. Plot of M_n versus M/I for **P1**. Numbers on the line indicate PDI values.

In order to prove this observation, monomer **1** was prepared and reacted with metathesis catalysts. Initially, monomer **1** was reacted with second-generation Hoveyda-Grubbs catalyst (**B**) in 0.4 M concentration of DCM solvent, which resulted only 60 % monomer conversion (Table 1, entry 1). Polymerization reactivity was enhanced by changing solvent to THF, which could perfectly convert monomers to polymer (Entry 2). However, polydispersity index (PDI) of polymer was quite broad with 1.88. With this observation, we reasoned two factors which increased PDI. One is the slow initiation rate of catalyst **B**, and the other is chain transfer reaction during long reaction time. Thus, catalyst was changed to third-generation Grubbs catalyst (**A**), which have extremely fast initiation rate, and reaction time was decreased to 1 minute (Entry 3). Polymerization of **1** was surprisingly fast to achieve full conversion within 1 minute under monomer to initiator (M/I) ratio at 100, but PDI was still broad with 1.86. With this observation, reaction temperature was decreased to -10 ℃ to suppress chain transfer reaction, and perfect conversion of monomer was achieved within 2 minutes to synthesize polymer with PDI narrower than 1.2

(Entry 4). To ensure controlled polymerization with M/I ratio higher than 100, the reaction temperature was further lowered to -30 ℃. Regardless of the choice of catalysts, solvents, and temperatures, an *E/Z* ratio of 6:4 for the newly formed olefins on the polymer backbone remained unchanged. This ratio was easily determined by crude ^{1}H-NMR analysis because each peak corresponding to *E/Z* isomers for olefinic H_A and H_B (with the correct coupling constants of 16 and 8 Hz for *E* and *Z* isomers. For detail, see Figure 4) was clearly resolved, allowing for reliable integration.

Polymers having various molecular weights were synthesized by varying M/I, and controlled polymerization was achieved with the degree of polymerization (DP) ranging from 30 to 135 (Table 1, entries 5–8), resulting in a linear increase in molecular weights (Figure 1). In addition, PDI was controlled to be less than or equal to 1.2.

Table 2. Tandem metathesis polymerization of various monomers with different ring sizes and linker alkynes



Entry	Mono	Cat.	M/I	Temp.	Time	Conv.[a]	M_n[b]	PDI[b]
1	**2**	**A**	15	-30 ℃	3 min	100 %	5000	1.28
2	**2**	**A**	30	-30 ℃	5 min	100 %	9100	1.28
3	**2**	**A**	50	-30 ℃	10 min	100 %	12500	1.25
4	**3**	**A**	100	r. t.	12 h	30 %	11400	1.70
5	**3**	**B**	50	50 ℃	2 h	98 %	13500	1.62
6	**4**	**B**	50	50 ℃	12 h	<20 %	-	-
7	**5**	**B**	50	50 ℃	12 h	0 %	-	-
8	**6**	**B**	50	50 ℃	12 h	82 %	12000	1.54
9	**6**	**B**	50	65 ℃	2 h	100 %	15000	1.79
10	**7**	**A**	50	-10 ℃	5 min	90 %	13100	1.23

[a] Conversion determined by crude ^{1}H-NMR. [b] Determined by THF SEC calibrated using polystyrene (PS) standards.

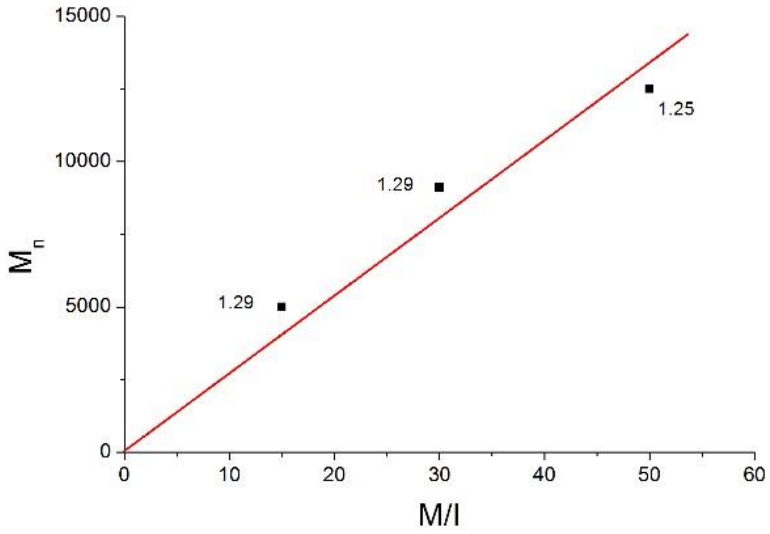


Figure 2. Plot of M_n versus M/I for **P2**. Numbers on the line indicate PDI values.

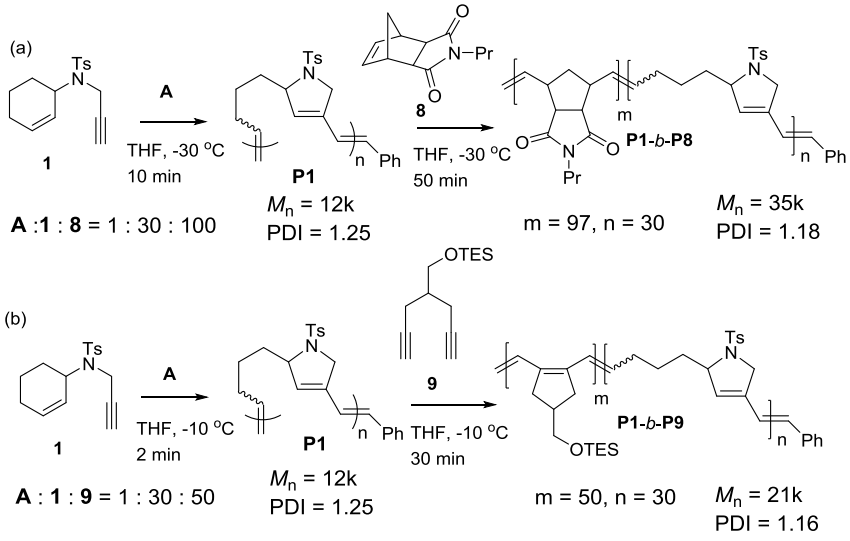
With the successful polymerization of monomer **1** containing cyclohexene and propargyl group, we started to broaden the monomer scope for tandem

polymerization. Initially, ring size of cycloalkene was modified to broaden the monomer scope. As cyclohexene has the lowest ring strain among cycloalkenes, we expected that other cycloalkenes with relatively higher ring strain should undergo tandem polymerization as well. Monomer **2** containing cycloheptene rapidly underwent tandem polymerization at room temperature with reactivity comparable to that of **1**. In order to suppress the chain transfer reaction, reaction temperature was lowered to -30 ℃ and polymerization of **2** also showed fast propagation and controlled polymerization as PDIs of the polymers were narrower than 1.3, and a linear relationship between M/I ratio and molecular weight was observed (Table 2, entries 1-3, Figure 2). Unlike monomers containing cyclohexene and cycloheptene, tandem polymerization of monomer **3** containing cyclopentene was not efficient, yielding only 30 % conversion after 12 hours of polymerization at room temperature (Entry 4). In order to facilitate polymerization, thermally more stable catalyst **B** was used and almost complete conversion of monomer was achieved at 50 ℃ polymerization, although PDI broadening was occurred due to the slow initiation rate and chain transfer reactions (Entry 5). Similar to **P1**, the polymer microstructure showed excellent regiochemistry and the *E*/*Z* ratio on **P2** and **P3** were 6/4.

Secondly, alkyne structure was changed from propargyl group to homopropargyl group. If homopropargyl group was used instead of propargyl group, the polymer unit structure changed from five-membered ring to six-membered ring, which is expected to be less reactive toward tandem RO/RCM reaction. Initial trial was done on a monomer **4** containing cyclohexene. However, the polymerization hardly occurred even at 50 ℃, and polymer was not obtained (Entry 6). Even monomer **5** containing cycloheptene was unreactive and did not undergo polymerization at all (Entry 7). However, monomer **6** containing cyclopentene underwent tandem RO/RCM polymerization with 82 % conversion at 50 ℃ and

full conversion at 65 ℃ in 2 hours (Entries 8 and 9). This result was unexpected, as monomer **1**, **2** and **3** containing propargyl analogs showed higher reactivity for monomers containing cyclohexene and cyclopentene, but monomers containing homopropargyl group showed an opposite result. Overall, monomers containing homopropargyl group showed decreased reactivity due to the slower six-membered ring cyclization rate compared to the five-membered ring cyclization rate as expected.[15]

Lastly, *N*-toluenesulfonyl linker structure was changed to amide linker structure. When monomer **7** containing amide group was reacted with catalyst **A**, it showed high reactivity and well controlled polymerization to yield perfect conversion within 5 minutes and narrow PDI (Entry 10). Nevertheless, the reactivity of **7** was slightly lower than those of monomer **1**, as polymerization required relatively higher temperature (-10 ℃ vs. -30 ℃) to achieve high conversion.



Scheme 2. Block copolymerization via tandem polymerization by (a) ROMP or (b) cyclopolymerization.

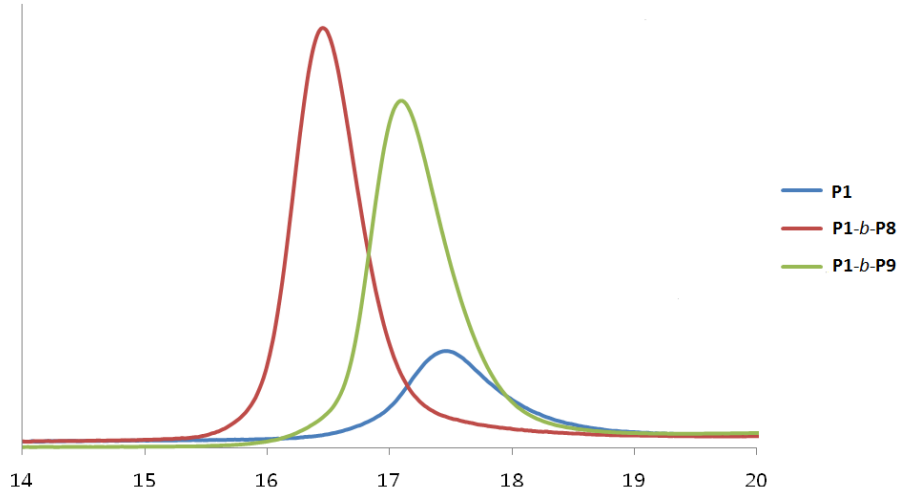
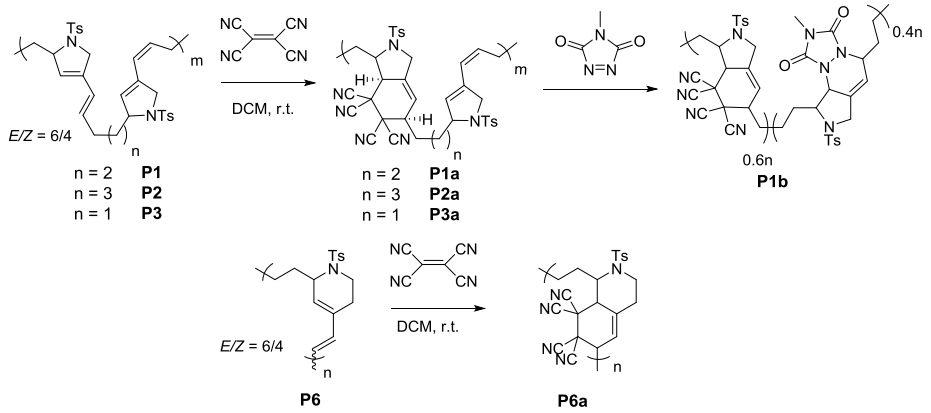


Figure 3. THF SEC trace of **P1**, **P1**-*b*-**P8**, and **P1**-*b*-**P9**.

Since the tandem metathesis polymerization promoted living polymerization, block copolymers could also be prepared by this method. To demonstrate this, conventional living ROMP and cyclopolymerization was combined with tandem metathesis polymerization for block copolymerization (Scheme 2, Figure 3). First, a diblock copolymer was prepared using the most optimized monomer **1** as the first block and ROMP monomer **8** as the second block. The diblock copolymer structure was confirmed by the total shift of the size exclusion chromatography (SEC) trace from the first block of **1** (M_n = 12k, PDI = 1.25) to a high molecular weight, while retaining the narrow PDI (M_n = 35k, PDI = 1.18). Similarly, another diblock copolymer, in which the second block was prepared by the cyclopolymerization of **9** at -10 ℃, was successfully synthesized and characterized by SEC analysis (M_n = 21k, PDI = 1.16).

Table 3. Post-functionalization of polymers by Diels-Alder reaction

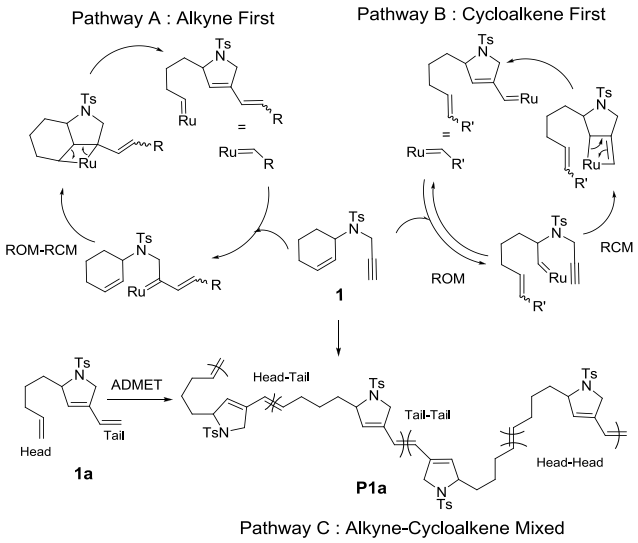


Entry	Substrate	M_n[a]	PDI[a]	Time	Conv.[b]	Product	M_n[a]	PDI[a]
1[c]	**P1**	16.0 k	1.22	48 h	60 %[e]	**P1a**	11.0 k	1.28
2	**P2**	12.3 k	1.21	48 h	60 %[e]	**P2a**	14.3 k	1.28
3[d]	**P3**	12.0 k	1.56	16 h	60 %[e]	**P3a**	14.0 k	1.64
4[c]	**P1a**	11.0 k	1.28	1.5 h	100 %	**P1b**	14.0 k	1.24
5	**P6**	8.9 k	1.65	8 h	100 %	**P6a**	11.0 k	1.69

[a] Determined by THF SEC calibrated using PS standards. [b] Conversion determined by crude ^{1}H-NMR. [c] Molecular weights and PDIs determined by chloroform SEC calibrated using PS standards. [d] Reaction was done at 60 ℃ in 1,2-dichloroethane as a solvent due to low reactivity. [e] Only the *trans* diene underwent Diels-Alder reaction while all the *cis* diene remained.

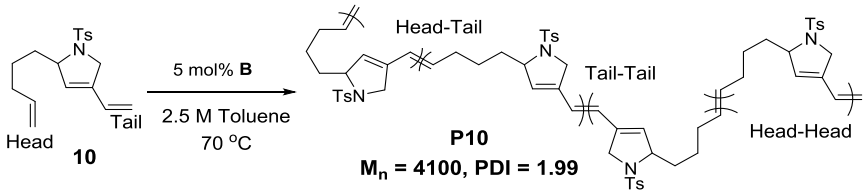
As a result of enyne metathesis reaction during polymerization, 1,3-diene moiety is generated in the polymer backbone. These backbones could be further functionalized by Diels-Alder reaction. Polymer **P1**, **P2** and **P3** containing pyrrolidine units have dienes with different stereoisomers (*E*/*Z* = 6/4), and when the polymer was reacted with tetracyanoethylene as a dienophile, only diene containing *trans*-alkene was fully converted by cycloaddition reaction, while diene containing *cis*-alkene did not react at all (Table 3, entries 1-3). Diels-Alder

reaction on **P3** required slightly higher temperature of 60 ℃ for complete conversion, possibly due to the congested structure of polymer backbone by the lack of methylene in polymer unit. Those dienes containing *cis*-alkene did not react with dienophiles, even at high temperature (up to 100 ℃). However, a more reactive dienophile, 4-methyl-1,2,4-triazole-3,5-dione underwent facile aza-Diels-Alder reaction with the remaining *cis*-isomers in **P1a** to form **P1b**, resulting in the quantitative conversion of all the dienes in **P1** (Entry 4). For **P6** containing six-membered ring structure, Diels-Alder post-modification with tetracyanoethylene underwent more rapidly, as both *E* or *Z* isomers were converted by cycloaddition reaction within just 8 hours (Entry 5). Although all the Diels-Alder post-modification caused total shift of polymer SEC trace while maintaining PDI, surprisingly, **P1a** showed decreased molecular weight after initial Diels-Alder reaction on **P1**, possibly due to the relationship between backbone tether length and hydrodynamic volume (See supporting informations for detail (Figure S1-S4)).



Scheme 3. Possible mechanisms of tandem metathesis polymerization

Since this relay-type tandem RO/RCM polymerization is unique and unprecedented, it would be worthwhile to investigate its mechanism in detail. There are three possible pathways: first, catalyst initiating from the alkyne selectively (Pathway **A**: Alkyne First); second, catalyst initiating from the cycloalkene selectively (Pathway **B**: Cycloalkene First); and last, random initiation of catalyst on either alkyne or cycloalkene non-selectively (Pathway **C**: Alkyne–Cycloalkene Mixed) (Scheme 3). If the catalyst selectively initiated and propagated on a single functional group such as in pathways **A** or **B**, the polymer unit structure would always have head-to-tail structure and as a result, the polymer would have a regular microstructure. On the other hand, non-selective pathway **C** would produce polymers comprising mixture junctions of head-to-tail, head-to-head, and tail-to-tail, and polymer structure would be completely random.



Scheme 4. ADMET polymerization of monomer **10**

To elucidate the mechanism of tandem metathesis polymerization, the synthesis of **P1** by ADMET polymerization was attempted as a comparison (Scheme 4). Monomer **10**, a product of the ring rearrangement reaction of **1** with ethylene ga s, was subjected to ADMET polymerization, yielding **P10** with low molecular w eight (M_n = 4100, PDI = 1.99) in 83% yield. In this process, new alkene signals that were not present in **P1** were observed by ^{1}H-NMR (Figure 4). These signals could be attributed to the *regio*-random cross coupling reaction occurring in this process. As the catalyst reacted with two different terminal alkenes with low selectivity, ADMET polymerizati

on gave all the possible mixtures of head-to-head, head-to-tail, and tail-to-tail junctions, whereas only *regio*-regular head-to-tail junction was observed for **P1**. In addition, only *trans*-alkenes were obtained by ADMET polymerization because this polymerization, which is essentially the repetition of the CM reaction, produced thermodynamically more stable *trans*-olefins, while the *regio*-regular polymer obtained by the kinetically controlled process contained olefins with an *E/Z* ratio of 6:4. These observations indicated that *regio*-regular **P1** resulting from tandem polymerization was formed by a single kinetically controlled reaction pathway, which rules out Pathway **C**.

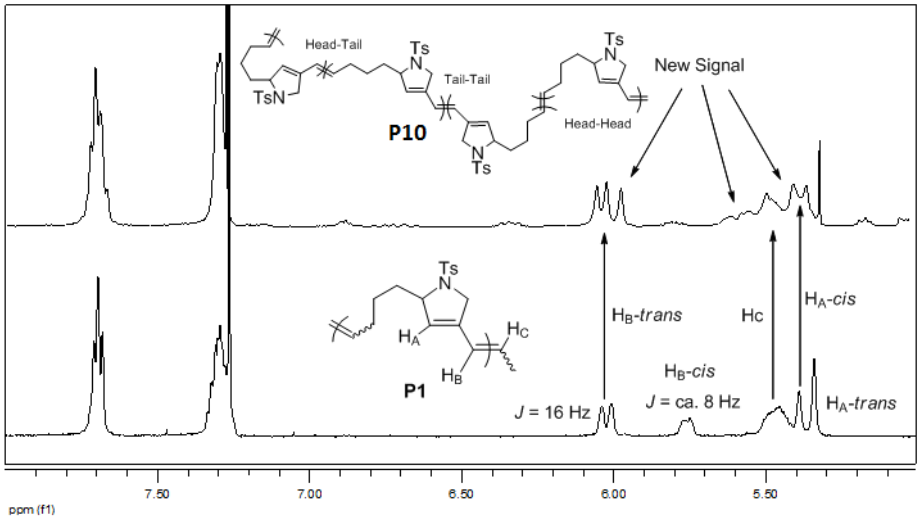
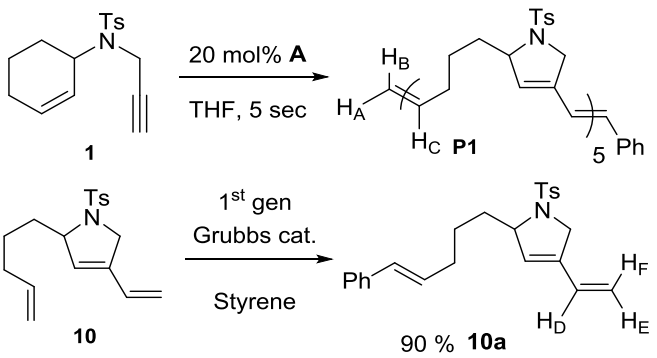


Figure 4. ^{1}H-NMR comparison between **P1** and **P10**



Scheme 5. Comparison between **P1** and CM product **10a**

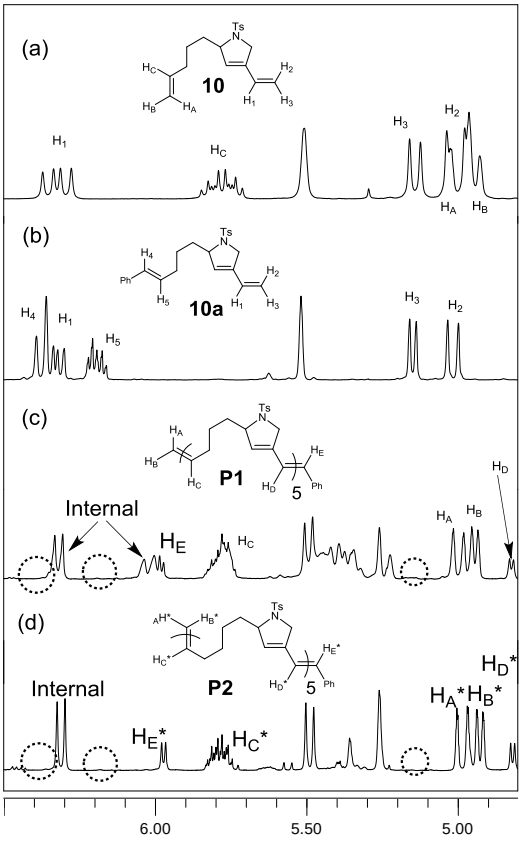
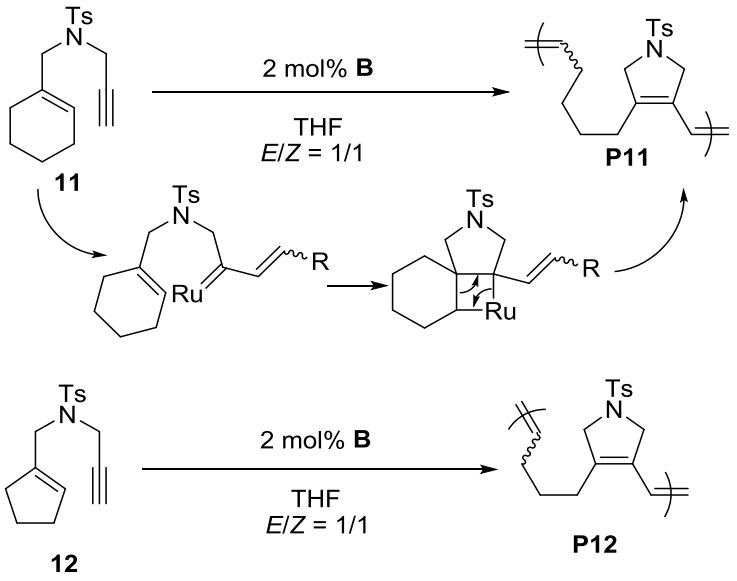


Figure 5. NMR spectra of (a) **10**, (b) **10a**, (c) oligo-**P1**, and (d) oligo-**P2**.

In order to confirm which mechanism was correct for the tandem polymerization, we performed mechanistic studies on monomers **1** and **2**. If the polymerization followed pathway **A**, the styryl group on the catalyst would be transferred onto the conjugated diene group and the chain-end group would be the terminal non-conjugated alkene obtained after quenching with ethyl vinyl ether. On the other hand, if the catalyst initiated on the cycloalkene first (pathway **B**), the styryl group would be transferred to the non-conjugated alkene and the chain-end group would be conjugated diene. Therefore, we could determine the actual mechanism for the tandem RO/RCM polymerization by conducting end-group analysis using ^{1}H-NMR analysis. Firstly, we prepared oligomeric **P1** by treating **1** with 20 mol% **A** and quenching the polymerization by adding ethyl vinyl ether so that its end-groups could be analyzed in detail. For a comparison study, **10a** was independently prepared by selective CM between styrene and the more reactive non-conjugated terminal alkene on **10** (Scheme 5). When the ^{1}H-NMR spectra of three substrates (**10**, **10a**, and oligo-**P1**) were compared, peaks for all the terminal olefins could be unambiguously assigned (Figure 5 (a-c)). From these data, we observed that oligo-**P1** vividly showed non-conjugated terminal alkene proton signals as H_A, H_B, and H_C, whereas chemical shifts corresponding to $H_{1\text{-}5}$ of **10a** were totally absent. This confirmed that tandem RO/RCM polymerization of **1** followed pathway **A** exclusively. We also conducted a similar mechanistic study on **2**, because the monomer containing cycloalkenes with higher ring strains might follow different pathway. A similar chemical shifts—H_A*, H_B*, and H_C* without $H_{1\text{-}5}$—were observed for the oligomeric **P2** as well, suggesting that the polymerization pathway was not altered by the ring strain of cycloalkenes (Figure 5d). All these observations proved that the mechanism of tandem RO/RCM polymerization follows pathway **A** exclusively (Scheme 4).

Table 4. Tandem metathesis polymerization of monomers with trisubstituted cycloalkenes

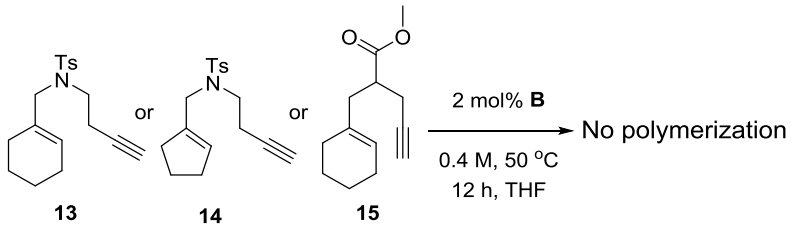


Entry	Mono.	Temp.	Conc.	Time	Conv.[a]	M_n[b]	PDI[b]
1	**11**	r. t.	0.4 M	3 h	0 %	-	-
2	**11**	50 ℃	0.4 M	6 h	37 %	4400	1.61
3	**11**	60 ℃	0.8 M	12 h	50 %	3900	1.25
4	**12**	50 ℃	0.4 M	12 h	65 %	8000	1.93
5	**12**	60 ℃	0.6 M	12 h	100 %	6000	1.57

[a] Conversion determined by crude ^{1}H-NMR. [b] Determined by THF SEC calibrated using PS standards.

Up to now, sterically hindered trisubstituted cycloalkenes with low ring strain, such as 1-methylcyclopentene or 1-methylcyclohexene, has not been polymerized by ROMP.[16] However, we envisioned that utilizing the relay sequence of this efficient RO/RCM process, monomers containing extremely challenging

trisubstituted cycloalkenes might undergo tandem polymerization just as 3-substituted cycloalkenes underwent efficient tadem RO/RCM polymerization. Initially, monomer **11** containing trisubstituted cyclohexene and propargyl group was subjected to 2 mol% of catalyst **B** at room temperature, but no polymer was obtained because of severe steric hindrance of trisubstituted olefin (Table 4, entry 1). In order to enhance the reactivity, reaction temperature was increased to 50 ℃ to yield **P11** containing tetrasubstituted cyclopentene moiety in 37 % conversion (Entry 2) and further to 60 ℃ to achieve 50 % conversion, with M_n of 3.9 k (Entry 3). To our delight, monomer **12** containing trisubstituted cyclopentene showed 65 % conversion at 50 ℃ and 100 % conversion at 60 ℃, implying that **12** was more reactive monomer than **11** at the same reaction condition (Entries 4 and 5). These results were contrast to the previous results which showed that the monomer containing propargyl group and cyclohexene (**1**) was more reactive than its cyclopentene derivative (**3**). In both cases, *E*/*Z* ratio on the newly generated olefin was 1/1, similar to the previous results.



Scheme 6. Unsuccessful tandem metathesis polymerization of monomers with trisubstituted cycloalkenes

On the other hand, monomers containing trisubstituted cycloalkenes and 1-butynyl moieties, **13** and **14**, were totally inactive for the tandem polymerization (Scheme 6). At least, polymerization result of **14** was rather disappointing because its 3-substituted cyclopentene derivative, **6**, showed good reactivity

toward the tandem polymerization to give the polymer having a six-membered ring repeat unit (Table 2, entries 8 and 9). Also, **15** with carbon linker failed to give any polymer (Scheme 6). This suggested that monomers with sterically hindered trisubstituted cycloalkenes were much more challenging to undergo the tandem polymerization compared to the disubstituted cycloalkene derivatives, and their reactivities were also sensitive to the monomer structures presumably.

Conclusion

In conclusion, we demonstrated ultrafast efficient tandem RO/RCM polymerization using monomers consisted with unreactive functional groups: cycloalkenes with low ring strain, and terminal alkyne. With the help of efficient tandem relay type metathesis reaction, those two unreactive monomers underwent metathesis reaction with high efficiency. By changing the structures of cycloalkene and alkyne functional groups, we could provide that broad scope of monomers could be used as a monomer for tandem polymerization. This polymerization method could be also used to block copolymerization thanks to its living polymerization characteristic, and polymer backbone could be modified with Diels-Alder cycloaddition reaction. Also, we studied reaction mechanism of tandem polymerization to reveal that the polymerization undergoes single pathway starting from the initiation on alkyne.

Part B. Strategies and deeper mechanistic study of monomers with low reactivity

Introduction

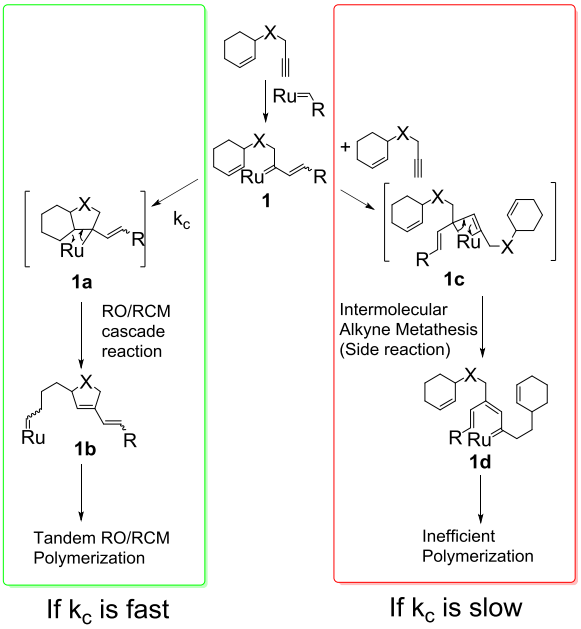
Development of tandem ring-opening/ring-closing metathesis (RO/RCM) polymerization allowed us to synthesize polymers from terminal alkyne and cycloalkene, which are known as a bad monomer, through selective cascade reaction.[17] Although various monomer scopes were studied for the polymerization, the monomer scope for tandem polymerization were not perfectly generalized, as monomers containing certain combinations of functional groups could undergo efficient polymerization, while other combinations did not, such as monomers containing homopropargyl group. Also, monomers containing more diverse functional groups should be studied, including monomers containing carbon or oxygen linker instead of optimized nitrogen linker, or internal alkyne instead of terminal alkynes. This chapter will describe about the strategies to greatly improve tandem RO/RCM polymerization and broaden the monomer scope to provide general polymerization method. In this regard, two strategies – modifying the monomers to enhance the Thorpe-Ingold effect and lowering the reaction concentration – successfully directed the reaction pathway toward effective polymerization. Also, detailed kinetic analysis was performed to observe reaction mechanism to explain the polymerization behavior and to validate our logic.

Results and Discussion

Previously, we successfully demonstrated tandem RO/RCM polymerization of monomers containing nitrogen linker groups, cycloalkenes, and propargyl groups. These optimized monomers exhibited extremely fast polymerization, with full

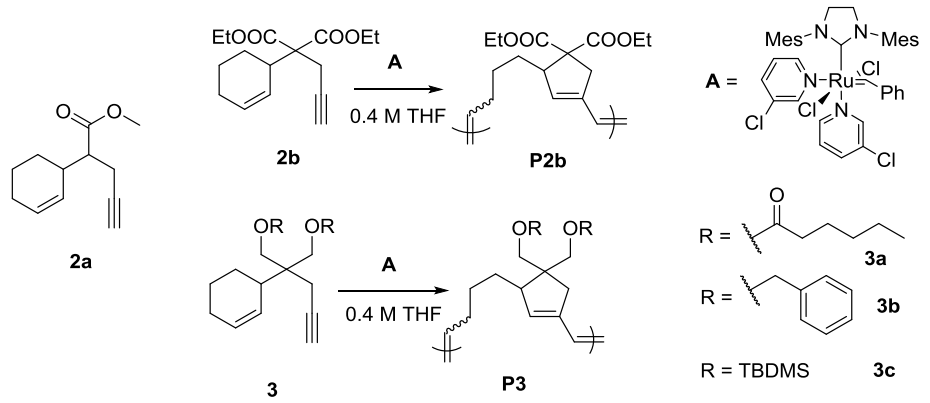
conversion within 1 minute at room temperature or 10 minutes at −30 ℃.[17] However, polymerization of certain monomers were very inefficient or totally inactive, such as monomer containing an analogous homopropargyl group. In order to explain this low reactivity, we proposed reaction mechanism. During tandem polymerization, the initiator reacted with an alkyne in α-addition manner to form a 1,1-disubstituted metal carbene intermediate (**1**); the resulting intermediate underwent intramolecular tandem RO/RCM reaction (**1a**) to form a propagating species (**1b**).[17] However, if this intramolecular cyclization rate (k_c) was relatively slow, metal carbene intermediate **1** would undergo side reactions such as intermolecular CM (**1c**), which would then afford inactive propagating species (**1d**). On the basis of this proposal, we devised with two strategies to favor cyclization selectivity, thereby enhancing the tandem polymerization reaction pathway.

Scheme 1. Possible competing reaction during the tandem RO/RCM process.



We first focused on designing new monomers to accelerate the intramolecular RO/RCM reaction by enhancing the Thorpe–Ingold effect. Thus, we focused on the monomers containing carbon linker group, as side chain modification is much easier than monomers with other kind of linker structure. Firstly, monoester substituted **2a** was subjected to the polymerization, but it did not undergo polymerization possibly due to the lack of Thorpe-Ingold effect by small monosubstitution. To improve polymerization, we added an additional ester substituent to the monomer to enhance the Thorpe–Ingold effect; as a result, disubstituted monomer **2b** underwent successful tandem polymerization in the presence of a third-generation Grubbs catalyst (**A**) to yield a high-molecular-weight polymer, with 80 % monomer conversion after 90 minutes at room temperature (Table 1, Entry 1).[18] Although this strategy appeared to be successful, polymerization of **2b** was still slow when compared to polymerization of the previously reported sulfonamide monomers that exhibited complete conversion within 1 minute under the same reaction conditions.[17] We reasoned that the relatively low reactivity of monomer **2b** was due to the small size of the ester substituent (A-value of -COOR: 1.27 kcal/mol)[19] and that changing the substituents to larger methoxy derivatives would increase the polymerization reactivity (A-value of -CH_2OH: 1.8 kcal/mol).[19]

Table 1. Polymerization of monomer with disubstituted carbon linker



Entry	Mono	M/I	Time	Temp.	Conv.[a]	M_n[b]	PDI[b]
1	**2a**	50	12 h	50 ℃	0 %	-	-
2	**2b**	50	90 min	r. t.	80 %	20000	1.49
3	**3a**	50	20 min	r. t.	100 %	33000	1.99
4	**3a**	50	15 min	-10 ℃	100 %	26000	1.17
5	**3a**	100	30 min	-10 ℃	87 %	48000	1.79
6	**3b**	50	1 min	r. t.	96 %	16000	1.18
7	**3b**	75	1.5 min	r. t.	100 %	26000	1.11
8	**3b**	100	2 min	r. t.	100 %	33000	1.32
9	**3b**	150	3 min	r. t.	80 %	37000	1.35
10	**3c**	50	30 sec	r. t.	100 %	27000	1.25
11	**3c**	100	30 sec	r. t.	95 %	50000	1.37
12	**3c**	75	8 min	0 ℃	100 %	34000	1.14
13	**3c**	100	10 min	0 ℃	100 %	50000	1.27
14	**3c**	150	20 min	0 ℃	100 %	84000	1.44

[a] Conversion determined by crude ^{1}H-NMR. [b] Determined by THF SEC, calibrated using polystyrene (PS) standards.

Tandem polymerization of monomer **3a** with hexanoyl groups underwent complete conversion within 20 minutes at room temperature to give a high-molecular-weight polymer; however, the polydispersity index (PDI) of this polymer was disappointingly broad because of the chain transfer reaction (Entry 2).[17] The chain transfer reaction was suppressed when the reaction temperature was reduced to −10 ℃ (Entry 3), but the PDI was still broad for polymerization at a higher monomer-to-initiator (M/I) ratio (Entry 4). To achieve living polymerization, monomers containing even larger substituents are necessary to enhance polymerization reactivity and suppress the chain transfer reaction. Thus, monomer **3b** containing bulkier benzyl ether substituents was synthesized, and the polymerization of **3b** yielded 96% monomer conversion within 1 minute; in addition, the PDI was narrower than 1.2 (Entry 5). The molecular weights of **P3b** were linearly controlled by increasing the M/I ratio such that the degree of polymerization (DP) was 120 and the PDIs remained relatively narrow (Entries 5–8, Figure 1). A monomer with bulkier *tert*-butyldimethylsilyl (TBDMS) substituents (**3c**) exhibited even higher reactivity, with complete monomer conversion within 30 seconds to give **P3c** with a narrow PDI (Entry 9). This monomer appeared to be more reactive than the previously reported amide analogues.[17] To ensure controlled polymerization, we decreased the reaction temperature to 0 ℃ to give **P3c** with a narrower PDI; the molecular weight was well controlled to a DP of 150 (Entries 10–13, Figure 1). These data suggested that the modification of monomer structures to enhance the Thorpe–Ingold effect was indeed a successful strategy to increase tandem polymerization reactivity and to achieve living polymerization.

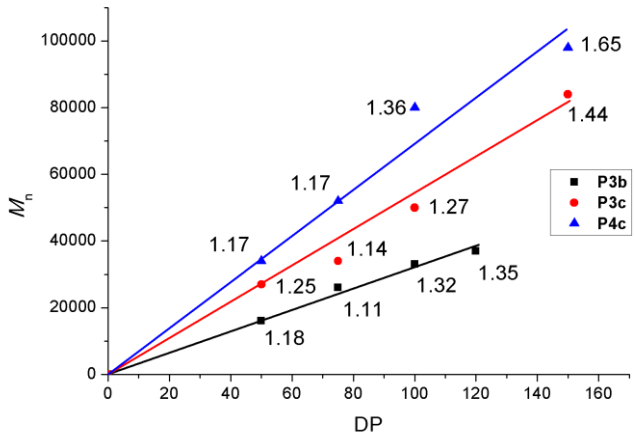
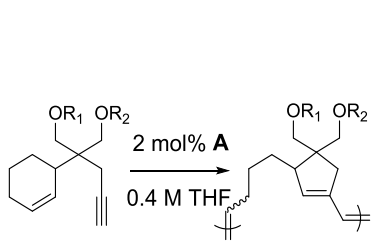
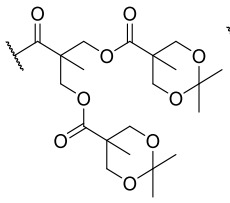
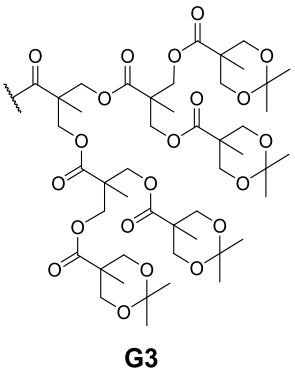


Figure 1. Plot of M_n versus DP for **P3b**, **P3c**, and **P4c**. The PDI values are shown as labels.

Table 2. Polymerization of monomer with dendronized substituent







4a - R_1, R_2 = **G2**
4b - R_1, R_2 = **G3**
4c - R_1 = TIPS, R_2 = **G3**

Entry	Mono	M/I	Time	Temp.	Conv.[a]	M_n[b]	PDI[b]
1	**4a**	50	2 h	r. t.	100 %	33000	1.39
2	**4b**	50	8 h	r. t.	0 %	-	-
3	**4c**	50	1 h	r. t.	100 %	34000	1.17
4	**4c**	75	1.75 h	r. t.	100 %	52000	1.17

5	**4c**	100	2.5 h	r. t.	100 %	80000	1.36
6	**4c**	150	3.5 h	r. t.	100 %	98000	1.65

[a] Conversion determined by crude ^{1}H-NMR. [b] Determined by THF SEC, calibrated using polystyrene (PS) standards.

To demonstrate the effectiveness of this strategy, we attempted tandem polymerization of even more challenging monomers to synthesize dendronized polymers *via* a macromonomer approach.[20] Although the macromonomer approach to dendronized polymers was extremely challenging because of the highly bulky dendron substituents, these dendrons could also induce a strong Thorpe–Ingold effect to increase polymerization reactivity. Initially, **4a** containing bis-substituted second-generation ester dendrons (**G2**)[21] was tested and resulted in complete conversion to polymer after 2 hour (M/I = 50) (Table 2, Entry 1). However, monomer **4b** containing two larger third-generation dendrons (**G3**) did not polymerize at all after long reaction times (Entry 2). The excessively bulky **G3** bis-substituents likely blocked the catalyst approach to the alkyne. To solve this problem, we substituted one of the **G3** dendron substituents to a smaller triisopropylsilyl (TIPS) substituent; as a result, monomer **4c** was completely converted into a 50-mer dendronized polymer with a narrow PDI within 1 hour (Entry 3). Furthermore, the controlled polymerization of **4c** was successful for M/I ratios up to 150 (Entries 3–6, Figure 1).

A substantial advantage of the dendronized polymer having bulky side chains was that it allowed us to clearly observe a single chain of the polymer by atomic force microscopy (AFM). Indeed, Figure 2 shows the relatively stretched chains of **P4c** for the 100-mer polymer whose length and height were approximately 75 nm and 0.3 nm, respectively. The rigidity of **P4c** was similar to that of polynorbornene-based dendronized polymers[20a] but was certainly less than that of polymers prepared by cyclopolymerization[18] or ROMP of *endo*-tricyclo[4.2.2.0]deca-3,9-

diene[20b] with the same dendron structure and dendron generation. This was due to the presence of flexible methylenes polymer backbone, which increased the conformational freedom of the polymer chain.

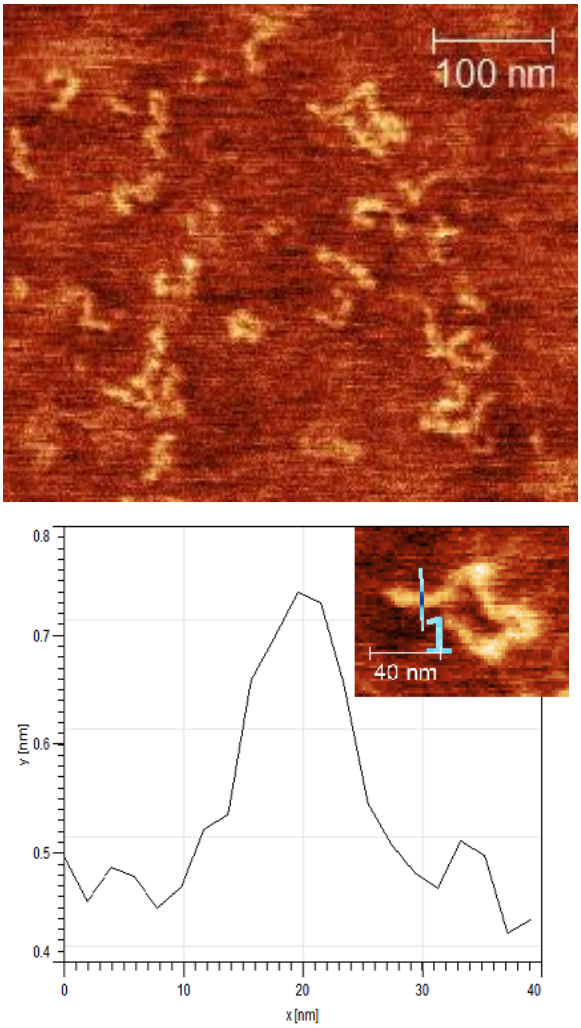
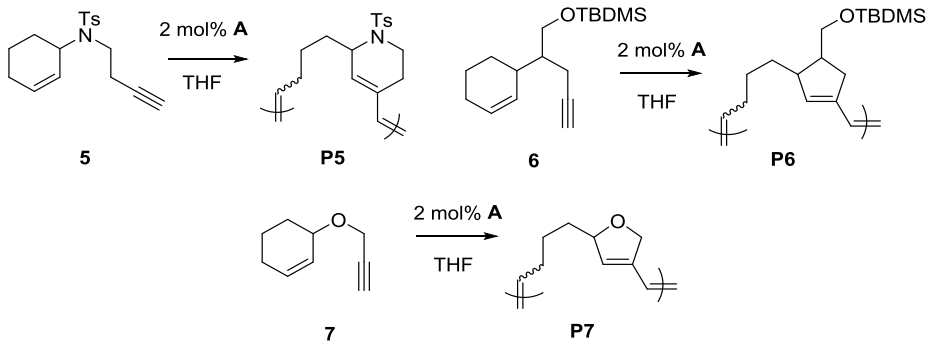


Figure 2. AFM image of **P4c** in phase mode and single-chain height profile in height mode. The polymer solution in DCM (1.25 mg/L) was spin-coated onto a mica surface.

Table 3. Polymerization of monomers with low reactivity



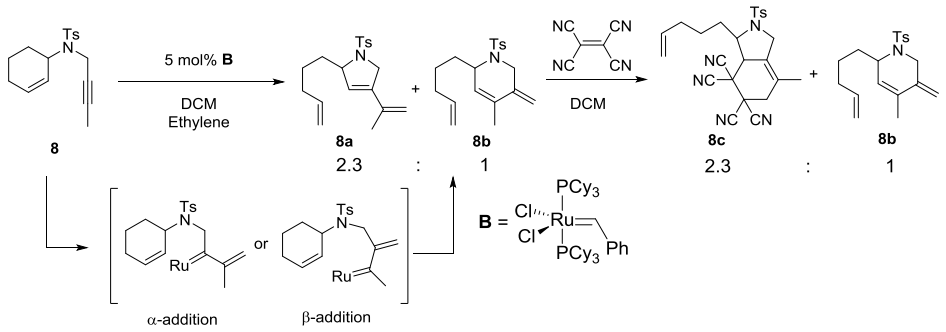
Entry	Mono	Conc.	Time	Temp.	Conv.[a]	M_n[b]	PDI[b]
1	**5**	0.4 M	12 h	r. t.	10 %	-	-
2	**6**	0.4 M	12 h	r. t.	16 %	-	-
3	**7**	0.4 M	12 h	r. t.	0 %	-	-
4	**5**	0.03 M	3 h	40 ℃	100 %	26000	1.50
5	**6**	0.03 M	3 h	r. t.	100 %	7700	2.88
6	**7**	0.03 M	30 min	r. t.	100 %	3600	1.51

[a] Conversion determined by crude ^{1}H-NMR. [b] Determined by THF SEC calibrated using polystyrene (PS) standards.

Although modifying monomer structures was an effective strategy to increase polymerization reactivity, an alternate strategy was required in cases where the monomer structures could not be modified. In such cases, we applied the second strategy of suppressing intermolecular side reactions by reducing the monomer concentration (Scheme 1). Previously, we reported that monomers containing a homopropargyl group (**5**), which could not undergo tandem polymerization (Table 3, Entry 1).[17] Similarly, monomers with monosubstituted carbon (**6**), or oxygen linker (**7**) did not yield polymers at 0.4 M concentration, which is the concentration typically used for this tandem polymerization (Table 3, Entries 2

and 3).[17] However, when the monomer concentration was decreased from 0.4 M to 0.03 M, all three monomers underwent complete conversion at room temperature or at slightly elevated temperature (40 °C for **5**) (Entries 4–6). These results indicate that the intramolecular RO/RCM reaction was indeed slow for these monomers (Scheme 1) and that consequently the competing side reaction stopped the tandem polymerization. Gratifyingly, simple dilution solved this problem. However, the polymerization reactions at low concentrations were inevitably much slower and the PDIs also broadened (Table 3).

Scheme 2. Ring rearrangement of a monomer containing internal alkyne **8** by ethylene.



With these successful strategies to promote efficient polymerization of various monomers, we focused on even broader monomer scope by using monomers with internal alkynes instead of terminal alkynes. Polymerization of the internal alkynes was even more challenging because of steric hindrance from the additional substituent. Moreover, unlike terminal alkynes, which exclusively undergo α-addition,[17] internal alkynes undergo both α-addition and β-addition non-selectively, thereby forming complex polymer microstructures.[22] As a control experiment, we tested the ring rearrangement reaction of **8** by performing ethenolysis with a first-generation Grubbs catalyst (**B**) and obtained a mixture of

two different products, **8a** and **8b**, which could be separated to **8c** and **8b** upon sequential Diels-Alder reaction, in a 2.3:1 ratio (Scheme 2, Figure 3). This result suggested that tandem polymerization of monomers containing internal alkynes would also form both five- and six-membered-ring repeating units as a result of non-selective α- and β-addition (Scheme 3).

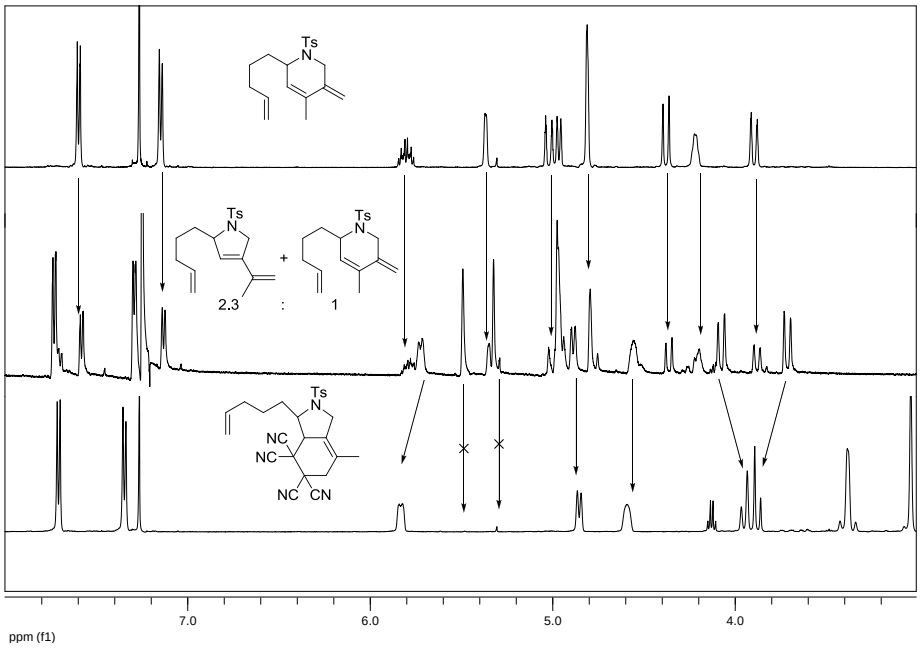


Figure 3. ^{1}H-NMR spectrum of ethenolysis products of **8**.

Scheme 3. Possible reaction mechanism of a monomer with internal alkyne

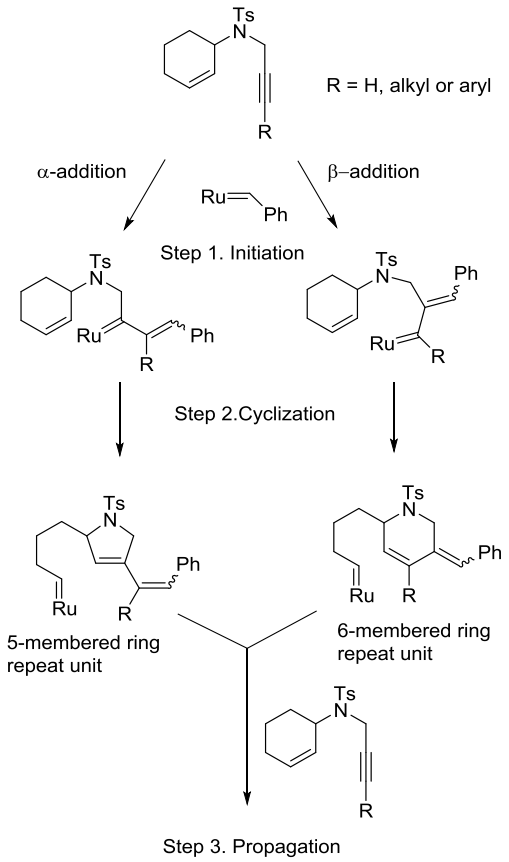
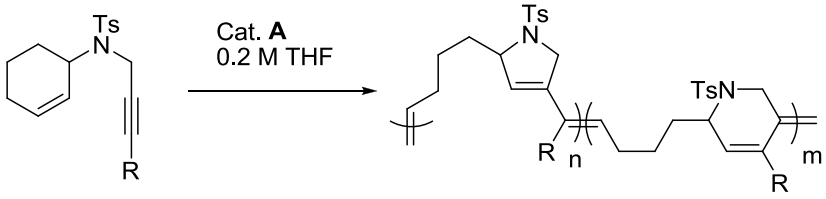


Table 4. Tandem polymerization of monomers containing an internal alkyne



8 - R = Me
9 - R = Et
10 - R = CF_3

P8 - R = Me
P9 - R = Et
P10 - R = CF_3

Entry	Mono	M/I	Time	Temp.	Conv.[a]	M_n[b]	PDI[b]	n : m[a]
1[c]	**8**	50	2 hr	r. t.	50 %	15000	1.50	2.3 : 1
2	**8**	50	5 min	r. t.	93 %	30000	1.20	2.3 : 1
3	**8**	50	10 min	15 ℃	93 %	20000	1.08	2.3 : 1
4	**8**	100	14 min	15 ℃	92 %	39000	1.24	2.3 : 1
5	**8**	150	15 min	15 ℃	95 %	65000	1.20	2.3 : 1
6	**8**	200	20 min	15 ℃	95 %	82000	1.31	2.3 : 1
7	**9**	25	5 min	10 ℃	85 %	10000	1.04	1.7 : 1
8	**9**	50	25 min	10 ℃	92 %	20000	1.07	1.7 : 1
9	**9**	100	30 min	10 ℃	92 %	36000	1.10	1.7 : 1
10	**9**	150	40 min	10 ℃	80 %	44000	1.36	1.7 : 1
11	**10**	50	10 min	r. t.	100 %	16000	1.06	1 : 0
12	**10**	100	1.5 h	15 ℃	89 %	42000	1.15	1 : 0
13	**10**	150	2.5 h	15 ℃	80 %	49000	1.44	1 : 0

[a] Determined by crude ^{1}H-NMR. [b] Determined by THF SEC calibrated using polystyrene (PS) standards. [c] Reaction concentration was 0.4 M.

Initially, we attempted the tandem polymerization of monomer **8** at a concentration of 0.4 M, but it only yielded 50% monomer conversion after 2 h, with a broad PDI (Table 4, Entry 1). We subsequently used the dilution strategy and observed that reducing the concentration to 0.2 M increased the conversion to 93% within just 5 min. Notably, this polymerization occurred rapidly and the resulting PDI was 1.2 (Entry 2). ^{1}H-NMR analysis of **P8** showed two different sets of signals corresponding to five- and six-membered-ring repeating units with an identical ratio of 2.3:1, favoring α-addition (Scheme 2). When the reaction temperature was lowered to 15 ℃, the chain-transfer reaction was further suppressed and the PDI became narrower than 1.1 (Entry 3). Again, we observed well-controlled polymerization behavior, where the molecular weight and DP exhibited a linear relationship up to a DP of 190 and the PDIs were narrow

(Entries 3–6, Figure 4). Similarly, controlled polymerization of monomer **9**, which contained an ethyl-substituted alkyne, was successful at 10 ℃ (Entries 7–10, Figure 4). A slight increase in steric bulkiness provided by an ethyl substituent (A-value: 1.75 kcal/mol)[19] in place of the methyl substituent (A-value: 1.70 kcal/mol)[19] decreased the selectivity between α-addition and β-addition to give a 1.7:1 ratio.

Lastly, we studied the polymerization of monomer **10**, which contained an electron-withdrawing trifluoromethyl (CF_3) substituent. For an M/I ratio of 50, monomer **10** was completely converted to a polymer with a PDI narrower than 1.1 (Entry 11). For high M/I ratios, a decrease in the reaction temperature to 15 ℃ appeared to result in greater polymerization efficiency (Entries 12 and 13). Interestingly, although the A-value of the CF_3 substituent is greater than that of a methyl or ethyl substituent (A-value: 2.1 kcal/mol)[19], only a five-membered-ring polymer unit was observed for **P10**, implying that α-addition occurred exclusively. These results suggested that the regioselectivity was not only dependent on the steric bulk but also the electronic effects of the alkyne substituent.

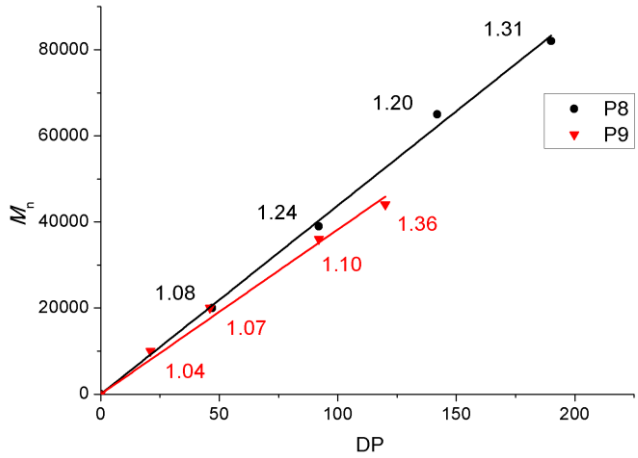


Figure 4. Plot of M_n versus DP for **P8** and **P9**. Numbers on the line indicate PDIs.

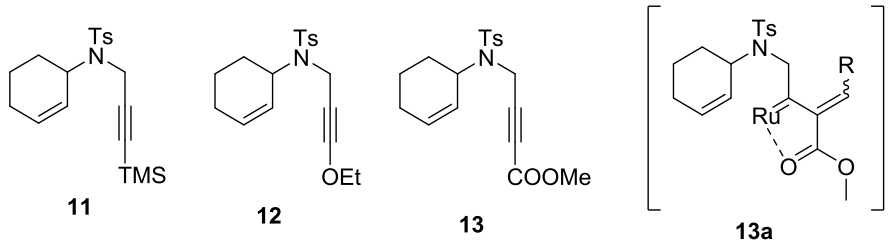
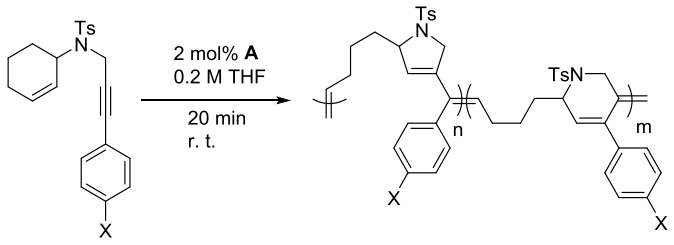


Figure 5. Unreactive monomers for tandem RO/RCM polymerization

However, monomers containing certain alkyne substituents were not suitable for tandem polymerization (Figure 5). For examples, bulky trimethylsilyl (TMS) group in monomer **11** blocked catalyst approach toward alkyne, and polymerization could not take place. Monomer **12** containing electron-rich ethoxy substituent also did not undergo polymerization. Surprisingly, monomer **13** containing electron-poor methyl ester substituent also did not undergo polymerization, unlike monomer **10** containing trifluoromethyl substituent. It seems that coordination effect from ester carboxyl group formed five-membered ring intermediate (**13a**), which suppressed catalyst activity. Thus, in order to perform polymerization, choice of alkyne substituent based on steric, electronic, and coordination effect is important for the polymerization.

Table 5. Polymerization of monomer with phenyl derivatives



11a - X = OMe
11b - X = Me
11c - X = H
11d - X = F
11e - X = CF_3

P11a - X = OMe
P11b - X = Me
P11c - X = H
P11d - X = F
P11e - X = CF_3

Entry	Mono	Conv.[a]	M_n[b]	PDI[b]	n : m[c]
1	**11a**	22 %	-	-	-
2[d]	**11b**	33 %	27000	1.31	-
3	**11c**	73 %	22000	1.25	2 : 1
4	**11d**	85 %	34000	1.31	2.7 : 1
5	**11e**	85 %	30000	1.48	1 : 1

[a] Conversion determined by crude ^{1}H-NMR. [b] Determined by THF SEC calibrated using polystyrene (PS) standards. [c] Ratio determined by ^{13}C-NMR. [d] SEC measurement was performed with crude polymerization sample because purification of polymer failed.

To investigate the electronic effects of the substituent toward the polymerization, we investigated the structure–reactivity relationship of monomers containing internal alkyne substituents with the same steric effect but different electronic effects. Therefore, we prepared several monomers containing 4-substituted phenyl substituents (**11a–e**) and tested for tandem polymerization with 2 mol% of catalyst **A** for 20 min. Monomer **11c**, which contained a neutral phenyl substituent, exhibited 73% conversion, whereas monomers with electron-donating groups (**11a**, **11b**) showed less than 40% conversion (Table 5, Entries 1–3) and monomers with electron-withdrawing groups (**11d**, **11e**) showed 85% conversion (Entries 4 and 5). Although the steric effects of phenyl substituents are quite high (A-value: 3.00 kcal/mol)[19], the ratio between five- and six-membered-ring units varied from 1:1 to 2.7:1 for **P11c–e**, as determined by ^{13}C-NMR experiments (see Supporting Information for details (Figure S5 and S6)). This complex α- and β-addition selectivity appears to originate by electronic effects of phenyl substituents.

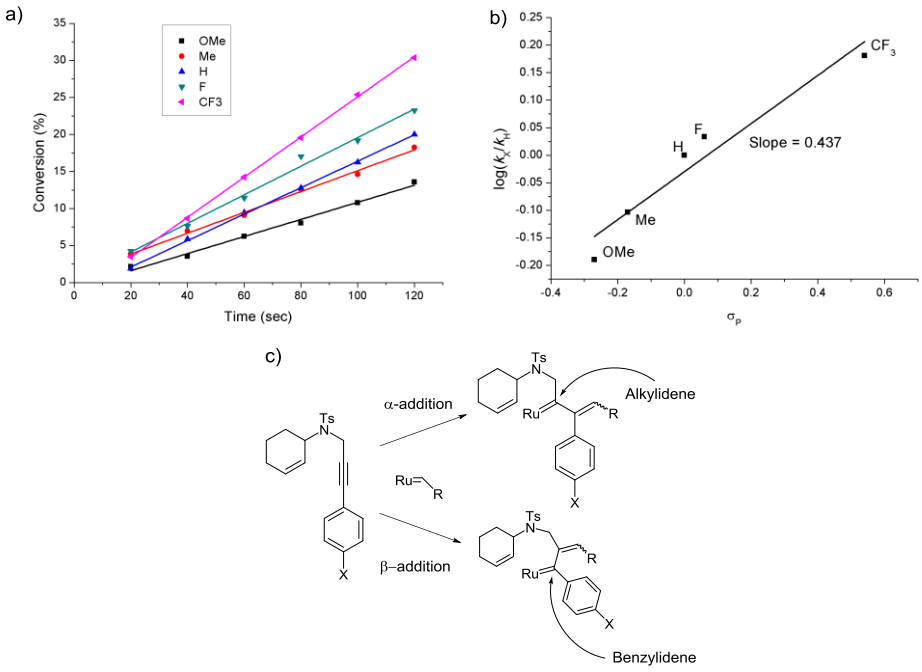


Figure 6. a) Plot of the polymerization rate of phenyl derivative monomers. b) Hammett plot of phenyl derivative monomers. c) Possible intermediates from the alkyne initiation step.

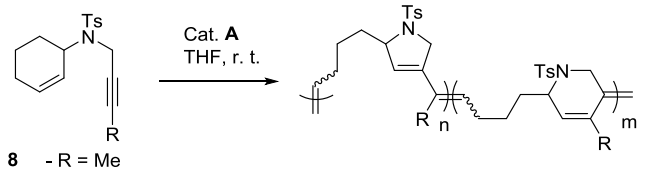
Table 6. Hammett plot data for reaction rate of monomer **11**.

Entry	X	[Mono]	[Cat]	*k*(obs)	log(k_D/k_H)	Sigma(σ_P)
1	OMe	0.02 M	0.4 mM	0.11541 M/sec	-0.18998	-0.27
2	Me	0.02 M	0.4 mM	0.14079 M/sec	-0.10365	-0.17
3	H	0.02 M	0.4 mM	0.17874 M/sec	0	0
4	F	0.02 M	0.4 mM	0.26933 M/sec	0.03363	0.06
5	CF3	0.02 M	0.4 mM	0.27113 M/sec	0.18096	0.54

To further elucidate the electronic effects of various phenyl substituents, we monitored the polymerization kinetics by ^{1}H-NMR and constructed Hammett plots (Figures 6a and 6b) from the propagation rate constants. The plots showed positive linear relationships between the Hammett constant and log(k_D/k_H) (ρ = 0.55), indicating that the polymerization rate was accelerated by electron-

withdrawing groups on the phenyl substituent. Similar ρ values were reported by Chen et al., who investigated the structure–reactivity relationship in olefin metathesis reactions involving benzylidenes with various electronic effects.[23] They explained that electron-deficient ruthenium benzylidenes reacted faster than electron-rich benzylidenes because electron-deficient benzylidenes were destabilized to a greater extent. For the tandem RO/RCM polymerization, β-addition of propagating carbene to alkynes formed a benzylidene intermediate (not an alkylidene intermediate formed after α-addition), whose reactivity was directly governed by the electronic effects of phenyl substituents, similar to the results reported by Chen et al. (Figure 6c).[23] On the basis of the kinetics data, we concluded that the rate-determining step involves intermediates that would show the electronic effect on phenyl substituents to affect the polymerization rate.(Similar relationship could be observed during initiation step. For detailed data, see Supporting Informations (Figure S7).)[24]

Table 6. Kinetics study of tandem RO/RCM monomers



8 - R = Me
10 - R = CF_3
11e - R = 4-CF_3-C_6H_4
12 - R = H

Entry	Monomer	[Monomer]	[**A**]	Rate[a] (M/sec)
1[b]	**12**	0.02 M	0.13 mM	$8.90X10^{-4}$
2[b]	**12**	0.01 M	0.13 mM	$4.85X10^{-4}$
3	**11e**	0.03 M	0.2 mM	$1.37X10^{-5}$
4	**11e**	0.02 M	0.2 mM	$1.57X10^{-5}$
5	**11e**	0.01 M	0.2 mM	$1.36X10^{-5}$
6	**10**	0.02 M	0.4 mM	$8.40X10^{-5}$

7	**10**	0.01 M	0.4 mM	$4.04X10^{-5}$
8	**8**	0.02 M	0.4 mM	$1.52X10^{-5}$
9	**8**	0.01 M	0.4 mM	$1.76X10^{-5}$

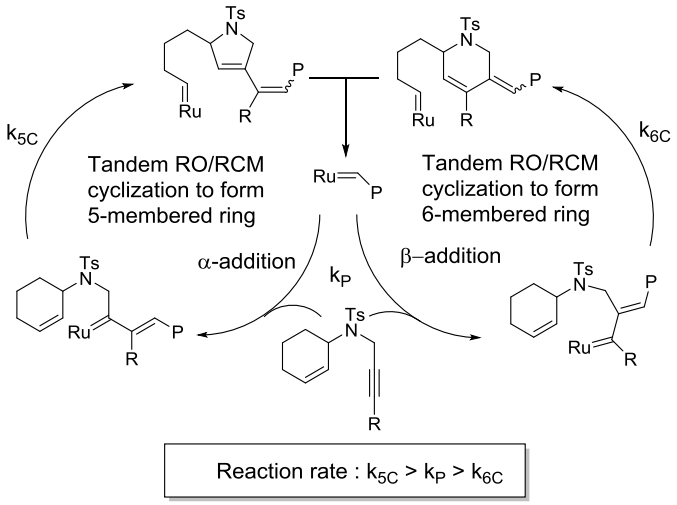
[a] Reaction rate is the linear slope of monomer disappearance versus time, as measured by ^{1}H-NMR. [b] The reaction temperature was −10 ℃.

Detailed understanding of the mechanism would require determination of the rate-determining step of tandem polymerization through a series of kinetics studies. Tandem RO/RCM polymerization fundamentally consists of two steps: the intermolecular propagation step between a growing active alkylidene and other monomers, followed by the intramolecular RO/RCM cyclization step forming the ring structure. Polymerization kinetics became more complex for monomers containing internal alkynes because depending on the selectivity of α- or β-addition, two different intermediates could form and undergo five- or six-membered-ring cyclization with different reaction rates (Schemes 1 and 3). With these polymerization pathways in mind, we performed kinetics studies for tandem RO/RCM polymerization at monomer concentrations ranging from 0.01 to 0.03 M to exclude any possible side reactions.

Initially, this kinetics study was performed with a highly reactive monomer **12** containing a terminal alkyne. Under a constant concentration of catalyst **A**, a twofold increase in the monomer concentration resulted in a doubling of the reaction rate, indicating that the reaction was first order in monomer **12** (Table 6, Entries 1 and 2). This result suggested that the rate-determining step was the intermolecular propagation step, as observed for typical living polymerization reactions, and that five-membered-ring cyclization was indeed fast. However, in the case of monomer **11e**, which contained an internal alkyne with a 4-CF_3-phenyl substituent, the kinetics study revealed that the reaction was zeroth order in monomer concentration (i.e., changing the monomer concentration did not

change the reaction rate) (Entries 3–5). This result suggested that the rate-determining step for the polymerization of **11e** was the intramolecular RO/RCM step. At this point, which cyclization step was the actual rate-determining step remained unclear because the two different cyclizations were possible for the internal alkyne.[18] We therefore performed a kinetics study on monomer **10**, which possesses an internal alkyne with a CF_3 substituent; and **10** only underwent five-membered-ring cyclization, and confirmed the first-order relationship in the monomer concentration, unlike **11e** with similar electron-withdrawing substituent (Entries 6 and 7). This result implies that the propagation step was the rate-determining step and that the five-membered-ring cyclization was still fast for monomer **10**. Unlike monomer **10**, kinetics study of monomer **8** containing methyl substituent with lower A-value confirmed the zero-order relationship in the monomer concentration (Entries 8 and 9). In conclusion, rate-determining step of tandem polymerization is affected by the presence of six-membered cyclization step from β-addition, not by the steric or electronic effects of alkyne substituents.

Scheme 4. Reaction kinetics of tandem RO/RCM polymerization



On the basis of the series of kinetics data, we drew several conclusions. The kinetics study suggested that the five-membered-ring cyclization (k_{5C}) after α-addition was the fastest step, which logically led us to believe that six-membered-ring cyclization (k_{6C}) from β-addition was, surprisingly, the slowest step, becoming the rate-determining step for monomers containing internal alkynes (Scheme 4). This conclusion also agreed with the interpretation of ρ values obtained from the Hammett plot, which suggested that the rate-determining step involved the olefin metathesis reactions from benzylidenes after β-addition (Figure 5). These results are unusual because the rate-determining step of conventional chain-growth polymerization reactions is typically the propagation step. Notably, with this understanding of the mechanism, where the cyclization step could be the rate-determining step, our previous failures, new proposals, and new strategies all became logically consistent. In short, controlling the intramolecular tandem RO/RCM cyclization is the key for the successful polymerization.

CONCLUSION

In this chapter, we studied the reaction mechanism of tandem RO/RCM polymerization to enhance polymerization efficiency for various challenging monomers. The previous unsuccessful polymerization was because of relatively slow intramolecular RO/RCM that led to the acceleration of competing side reactions such as intermolecular CM reactions. To this end, two strategies successfully solved this problem and greatly enhanced polymerization reactivity. First, we modified the monomer structures to accelerate the cyclization by enhancing the Thorpe–Ingold effect; this strategy also allowed living polymerization. Furthermore, the synthesis of dendronized polymers containing as large as third-generation dendrons was possible, and the resulting single polymer chain was visualized *via* AFM. The second strategy was to reduce the

reaction concentration to favor the intramolecular RO/RCM step over competing side reactions. The monomer scope was then further expanded to those containing internal alkynes, and polymerization of these monomers was more challenging because the selectivity issue between α- and β-addition resulted in the formation of more complex polymer microstructures comprising five- and six-membered-ring units. Nonetheless, polymerization of internal-alkyne-containing monomers was successful under dilute conditions, and their regioselectivity was governed by steric and electronic effects of the substituents. Lastly, the polymerization kinetics study and Hammett-plot analysis revealed the unique kinetics of tandem RO/RCM polymerization. As expected, the rate-determining step of the reactive monomers was the intermolecular propagation step. However, for challenging monomers containing internal alkynes, the intramolecular six-membered ring cyclization step was the rate-determining step. This observation agrees well with all the data we obtained and validates our strategies. In conclusion, studying the mechanism in detail not only provided deep insights into the polymerization pathway but also provided clues to greatly improve the polymerization efficiency and broaden the monomer scope.

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Chapter 4

Fast diyne cyclopolymerization of 1,7-octadiynes

Abstract

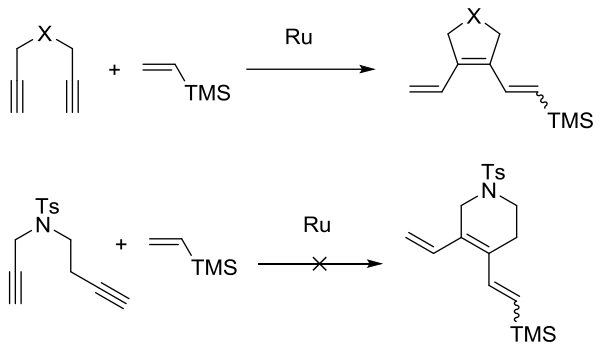
Fast cyclopolymerization of 1,7-octadiyne derivatives has been achieved. Cyclopolymerization of 1,7-octadiyne has been rarely studied due to the slow ring-closing metathesis reaction rate to form six-membered ring unit. Although 1,7-octadiyne could undergo cyclopolymerization by modifying monomer structure to contain sterically bulky substituent, which increase Thorpe-Ingold effect to accelerate cyclization rate, polymerization rate was too slow compared to that of 1,6-heptadiyne derivatives. In order to solve this problem, two monomer modification strategies were proposed. Firstly, dimethyl substituent was introduced to the α-position of side chain, which would be sterically bulky enough to induce Thorpe-Ingold effect to diyne tether in close proximity. Secondly, position of substituent groups were changed from 4,4-disubstitution to 4,5-disubstitution. Both strategies significantly increased cyclopolymerization rate and allowed controlled polymerization with narrow polydispersity index (PDI) and predictable molecular weight which has linear relationship with monomer-to-initiator (M/I) ratio. With this highly reactive controlled polymerization, block copolymerization and challenging dendronized polymer synthesis could be achieved. Resulting polymer was analyzed with various methods including UV-Vis spectroscopy to thoroughly study the structure of polymers.

Background

Acetylene polymerization is one of the most widely studied conjugated polymer synthesis method. Since the first polyene synthesis by Natta and co-workers,[1] various methodologies were developed to synthesize polyenes, such as Ziegler-Natta catalysis system, radical polymerization using radical initiator, and ionic polymerizations using anionic or cationic initiators.[2] Acetylene olefin metathesis reaction was one of the polyene synthesis methodology, which forms new carbon-

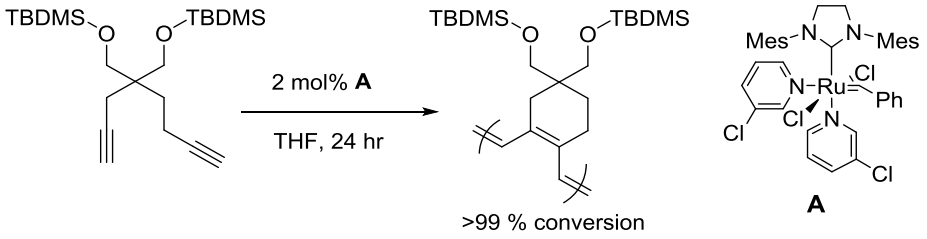
carbon double bonds between acetylene monomers through [2+2] reaction between metal carbene initiator and acetylene. Since the first polymerization of phenylacetylene by Masuda and co-workers,[3] various metals including tungsten[4], tantalum[5], molybdenum[6], and ruthenium[7] were used for metathesis polymerization. However, acetylene polymerization suffered from harsh reaction condition and low productivity, due to the formation of 1,1-disubstituted alkylidene intermediate with low reactivity from α-addition.

Instead of acetylene polymerization, chemists took notice on the cyclopolymerization of non-conjugated diynes.[8] Due to the fast ring-closing metathesis (RCM) reaction, 1,1-disubstituted alkylidene could rapidly undergo intramolecular cyclization to form monosubstituted alkylidene, which can undergo fast intermolecular propagation. However, initial cyclopolymerization suffered several problems, such as low molecular weighted polymer, insolubility of product, and low stability toward air oxidation. In 1990, chemists added substitution to diyne tether to solve these problems.[9] Starting from diphenyldipropargylmethane (DPDPM) and diethyldipropargylmalonate (DEDPM) monomers, various 4,4-disubstituted 1,6-heptadiyne monomers were polymerized with metathesis catalyst to yield polymers with high molecular weight and good solubility. This simple monomer modification allowed effective cyclopolymerization, and well controlled polymerization could be achieved with well-defined catalysts based on molybdenum[10] and ruthenium metal.[11]



Scheme 1. Diyne cycloisomerization-cross metathesis study

Theoretically, all non-conjugated α,ω-diyne substrates could act as a monomer for cyclopolymerization. However, only cyclopolymerization of 1,6-heptadiyne has been thoroughly studied, while other diyne substrates such as 1,7-octadiyne was rarely studied. This was due to the slow cyclization rate of 1,7-octadiyne to form six-membered ring unit compared to the fast cyclization rate of 1,6-heptadiyne to form five-membered ring unit. This tendency was studied by Blechert and co-workers at 1999.[12] When they reacted 1,7-octadiyne and allyltrimethylsilane with Grubbs catalyst to achieve enyne reaction and cycloisomerization, they could not observe any cyclization product, while the same reaction using 1,6-heptadiyne resulted efficient enyne reaction and cycloisomerization. (Scheme 1)



Scheme 2. Cyclopolymerization of 4,4-disubstituted 1,7-octadiyne with bulky substituents

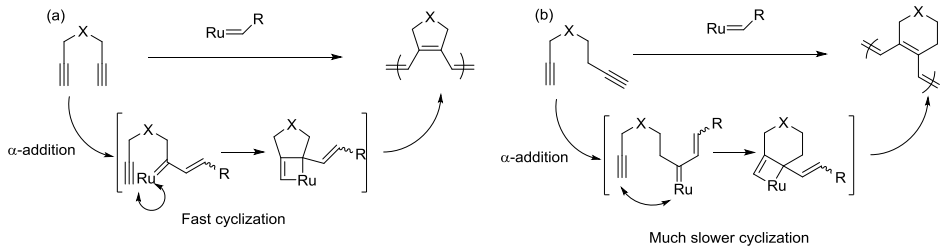
Recently, our group reported cyclopolymerization of 4,4-disubstituted 1,7-octadiyne by increasing the steric effect of substituents to enhance Thorpe-Ingold effect and increased cyclization rate (Scheme 2).[13] By changing the substituent group from less sterically bulky malonate group to sterically bulky *tert*-butyldimethylsilyl (TBDMS) group, well-controlled polymerization with narrow polydispersity index (PDI) and predictable molecular weight could be achieved. However, the polymerization rate was still too slow compared to the polymerization of 1,6-heptadiyne monomers, as polymerization of 50-mer 1,7-octadiyne required 24 hours, while 1,6-heptadiynes required less than 1 hour.

From the polymerization of DPDPM to 1,7-octadiynes, modification of monomer structures broadened monomer scope for cyclopolymerization. In this chapter, I suggest further modification of 1,7-octadiyne derivatives to achieve efficient cyclopolymerization comparable to the cyclopolymerization of 1,6-heptadiyne derivatives. In the first chapter, 1,1-dimethyl substitution was introduced to the substituent side chain, in order to induce Thorpe-Ingold effect more closely to diyne tether. In the second chapter, 4,5-disubstituted 1,7-octadiyne was polymerized instead of conventional 4,4-disubstituted 1,7-octadiyne to achieve even more efficient cyclopolymerization.

Part A. Cyclopolymerization of 1,7-octadiynes containing dimethyl substituents in α-position of side chain

Introduction

Diyne cyclopolymerization is a powerful method for the synthesis of conjugated polyenes via ring-closing metathesis (RCM) reactions using non-conjugated α,ω-diyne monomers. Since the development of polymerization, various catalyst systems using tungsten and molybdenum salt, or Schrock catalysts have been used for cyclopolymerization.[8-10] With the development of ruthenium based Grubbs catalyst,[14] monomer scope for cyclopolymerization was expanded due to the higher stability and functional group tolerances. Also, Grubbs catalyst underwent selective α-addition on terminal alkynes to form regioselective polymers containing five-membered ring unit exclusively.[11] Recent development of third-generation Grubbs catalyst[15] allowed the preparation of polymers with well-controlled molecular weight and narrow polydispersity index (PDI) value, due to the fast initiation rate of catalyst.

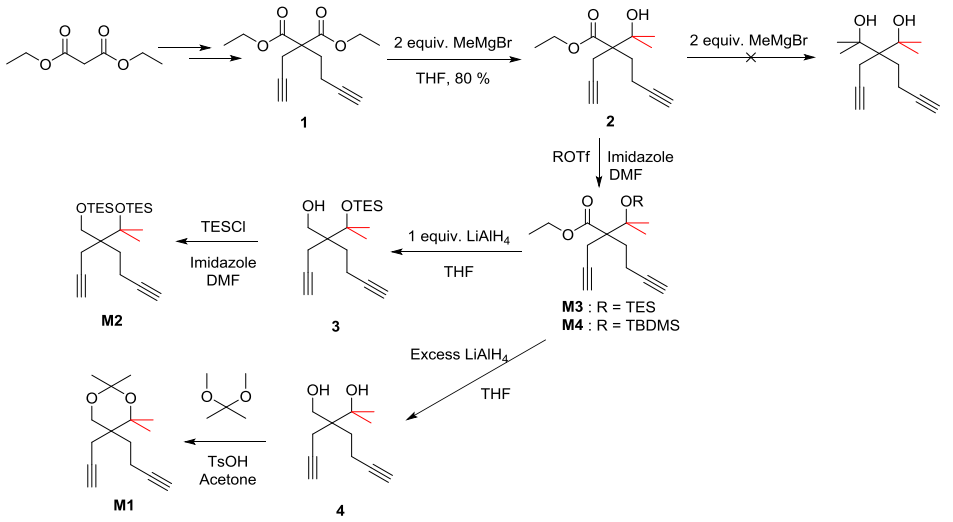


Scheme 1. Cyclopolymerization schemes for (a) 1,6-heptadiyne and (b) 1,7-octadiyne

Although cyclopolymerization has been studied thoroughly, polymerization of 1,6-heptadiyne was well studied, while polymerization of 1,7-octadiyne was

rarely studied.[13,16] It is because polymerization rate, or the cyclization rates of 1,7-octadiyne derivatives to produce cyclohexene moieties are significantly slower thant that of 1,6-heptadiyne derivatives, making them unsuitable for cyclopolymerization (Scheme 1). Our group previously reported cyclopolymerization of 4,4-disubstituted 1,7-octadiyne monomers using third-generation Grubbs catalyst. Among the various monomers, monomer with the bulky tert-butyldimethylsilyl (TBDMS) group showed high conversion toward polymer, with living polymerization characteristics.[13] This successful polymerization was due to the enhanced cyclization rate by Thorpe-Ingold effect.[17] However, even with this bulky substituent, polymerization rate was still low, as TBDMS group containing monomer required 24 hours for preparation of a polymer with degree of polymerization (DP) of 50. Simple solution to further accerelate cyclization rate is to further increase the substituent size. However, as TBDMS substituent is already sterically bulky, introducing even bulkier substituent could be challenging, and other methods should be tried. This chapter will discuss about the accelerated cyclopolymerization of 4,4-disubstituted 1,7-octadiyne monomers, as a result of an enhanced Thorpe-Ingold effect by introduction of dimethyl groups on the side chain α-position near the main chain. This introduction of additional bulky moieties in proximity to the octadiyne tether effectively enhanced Thorpe-Ingold effect and significantly increased polymerization rate.

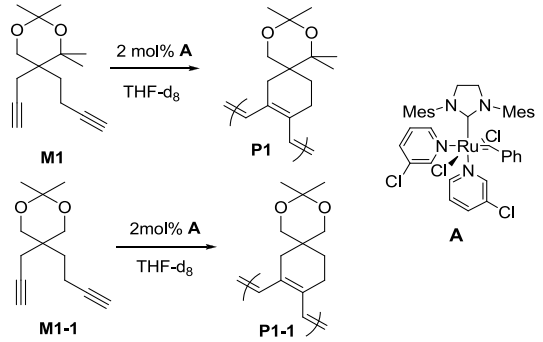
Results and discussions



Scheme 2. Introduction of dimethyl substitution to a 4,4-disubstituted 1,7-octadiyne monomer.

In order to accelerate polymerization rate of 1,7-octadiynes, monomers with faster cyclization rate should be designed with enhanced Thorpe-Ingold effect. Thus, new monomers with dimethyl substitution on α-position of the side chain at the 4-position of the main chain was designed, so that it can influence greater steric effect toward diyne tethers to accelerate cyclization rate. Also, this new group would be small enough not to block the catalyst approach toward alkynes, while effectively large enough to accelerate cyclization rate. In order to introduce dimethyl substitution onto the α-position of the side chain, 1,7-octadiyne substrate was prepared from diethyl malonate (Scheme 2). Then, **1** was treated with 2 equivalent of methyl magnesium bromide to yield tertiary alcohol **2**. From this alcohol, various monomers containing dimethyl substitution were prepared by simple organic chemistry reactions. Unfortunately, tetramethyl substituted

monomer was not prepared with this methodology, as excess amount of Grignard reagent caused retro-Aldol reaction to remove tertiary alcohol group to produce monosubstituted substrate. Also, similar reactions using other kinds of Grignard reagents (ex – ethyl magnisum bromide) or malonates (ex – dimethyl malonate) gave desired dimethyl substituted product with low yield, thus only ethyl malonate-methyl magnesium bromide combination was tried for monomer synthesis.



Scheme 3. Cyclopolymerization of acetal-protected monomers with and without dimethyl substitution

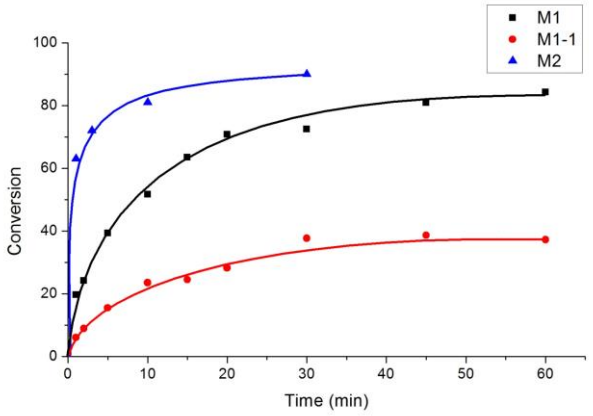
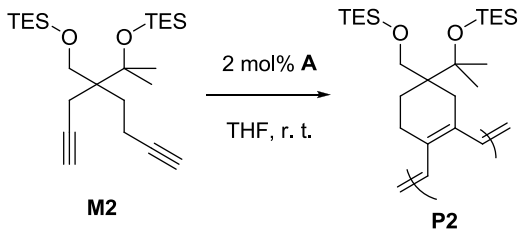


Figure 1. Kinetic study for polymerization of **M1**, **M1-1**, and **M2**

In the previous report by our group, 1,7-octadiyne monomer containing bulky silyl ether groups was reactive toward polymerization, while monomers containing smaller ester groups did not. Although the previous report reasoned that Thorpe-Ingold effect affected to the successful polymerization, but possible coordination effect from ester groups to ruthenium catalyst might slowed down the polymerization. Thus, previous studies could not separate steric effect from coordination effect to explain the faster cyclopolymerization of bulky, non-coordinating silylated monomers compared to smaller, coordinating ester-containing monomers. In order to confirm that Thorpe-Ingold effect was crucial for the cyclopolymerization rate, monomers with non-coordinating cyclic acetal-protected monomers were designed. Those acetal protected monomers **M1** (containing dimethyl substitution) and **M1-1** (without dimethyl substitution) were subjected to the polymerization kinetics study using ^{1}H-NMR experiment (Scheme 3, Figure 1). When the monomers were reacted with third-generation Grubbs catalyst **A**, initial propagation rate of **M1** containing dimethyl substitution was much faster than that of **M1-1** without dimethyl substitution. Also, conversion of **M1** was 80 % after 1 hour, while **M1-1** reached only 35 % conversion. This result support our proposal that introducing dimethyl substitution to side chains indeed accelerated the cyclopolymerization through enhanced Thorpe-Ingold effect.



Scheme 4. Cyclopolymerization of TES-1,7-octadiyne monomer

With the conclusion that the dimethyl substitution indeed accelerated the cyclopolymerization of 1,7-octadiynes, we investigated polymerization of monomer **M2** containing two bulky triethylsilyl (TES) ether groups (Scheme 4). The monomer structure was similar to the previously optimized monomer structure with the exception of additional dimethyl substitution.[13] ^{1}H-NMR kinetics experiment of **M2** polymerization with 2 mol% of catalyst **A** suggested that **M2** containing bulky side chain showed even faster propagation than **M1**, giving 90 % conversion within 30 minutes (Figure 1). This also matches our proposal that monomer with bulkier side chain undergoes faster cyclopolymerization due to the enhanced Thorpe-Ingold effect.

Table 1. Cyclopolymerization of **M2**

Entry	M/I	Time	Temp	Conv.[a]	M_n[b]	PDI[b]
1	50	1 hr	r. t.	>95 %	24000	1.36
2	15	3 hr	5 ℃	>99 %	7200	1.18
3	30	4.25 hr	5 ℃	>99 %	13300	1.22
4	50	6 hr	5 ℃	>99 %	22000	1.18
5[c]	100	3.75 hr	5 ℃	80 %	38000	1.28

[a] Conversion determined by crude ^{1}H-NMR. [b] Determined by THF SEC calibrated using polystyrene (PS) standards. [c] Monomer concentration was 0.8 M.

Polymerization of **M2** conducted at room temperature produced **P2** with an excellent convertion and a relatively narrow PDI of 1.36 within 1 hour. This result is much faster than the optimized result of previous report, which did not contain dimethyl substitution (Table 1, entry 1). In order to obtain polymers with narrower PDI, the reaction temperature was lowered to suppress chain transfer reaction. Although the reaction time was increased from 1 hour to 6 hours by reducing the reaction temperature from 25 ℃ to 5 ℃, **M2** showed high reactivity toward

cyclopolymerization due to the dimethyl substitution, and its polymerization could proceeded at a reasonable rate. Lowering the temperature successfully suppressed chain transfer reaction to reduce PDI narrower than 1.3 and molecular weight showed linear relationship with the monomer-to-initiator ratio (M/I) between 15 to 80 (Entries 2-5 and Figure 2).

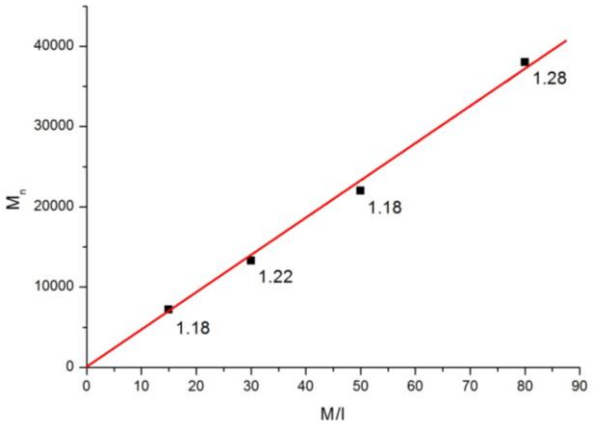
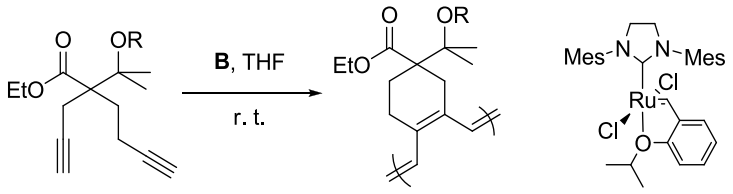


Figure 2. Plot of M_n versus M/I for **M2**. Numbers on the line indicate PDI values.

Table 2. Cyclopolymerization of monomers containing an ester group



M3 : R = TES
M4 : R = TBDMS

P3 : R = TES
P4 : R = TBDMS

B

Entry	Monomer	Catalyst	Time	Conv.[a]	M_n[b]	PDI[b]
1[c]	**M3**	2 mol%	1 hr	100 %	17000	1.43
2[c, d]	**M3**	2 mol%	8 hr	69 %	22000	1.39

3	**M3**	1 mol%	4 hr	93 %	31000	2.38
4[c]	**M4**	2 mol%	50 min	100 %	20000	1.48
5[c, d]	**M4**	2 mol%	5 hr	82 %	15000	1.38
6	**M4**	1 mol%	1 hr	96 %	32000	2.34
7	**M4**	0.5 mol%	3 hr	99 %	39000	1.87
8	**M4**	0.33 mol%	4.5 hr	80 %	40000	2.34

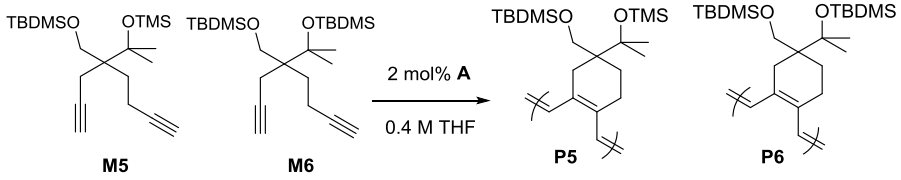
[a] Conversion determined by crude ^{1}H-NMR. [b] Determined by THF SEC calibrated using PS standards. [c] Catalyst **A** was used instead of **B**. [d] Reaction was performed at -10 ℃ instead of room temperature.

In the previous report, cyclopolymerization of 1,7-octadiyne monomers containing bis-ester substitution showed less than 60 % conversion, presumably due to the lack of Thorpe-Ingold effect. As newly introduced dimethyl substitution promoted efficient cyclopolymerization, it was expected that monomer containing ester groups with dimethyl substitution might also undergo efficient cyclopolymerization. Thus, monomer **M3** containing TES ether and ethyl ester substituents was prepared and subjected to the polymerization. Cyclopolymerization at room temperature resulted full conversion of **M3** within 1 hour, but a broad PDI of 1.43 was observed (Table 2, entry 1). In order to obtain **P3** with narrow PDI, reaction temperature was further decreased to -10 ℃. However, PDI was not narrowed enough and conversion was less than 70 %. (Entry 2). This phenomena was presumably due to the low steric effect of ester group in **M3**, which cannot provide enough shielding effect to protect olefins on the polymer backbone to suppress chain transfer reaction. Thus, instead of achieving controlled polymerization, we attempted to maximize the polymerization turn-over number (TON) to obtain high molecular weighted polymers. By using the more stable second-generation Hoveyda-Grubbs catalyst **B**, polymerization of **M3** showed TON up to 93 (Entry 3). PDI inevitably

increased over 2.0, because of the intrinsically slow initiation of catalyst **B**, as well as higher chance of chain transfer reaction at room temperature.

Monomer **M4** containing TBDMS substituent showed greater polymerization efficiency, resulting in full conversion within 50 minutes with 2 mol% of catalyst **A** at room temperature, although PDI was still over 1.4 (Entry 4). Again, **M4** was subjected to polymerization at -10 ℃ temperature in order to obtain polymer with narrow PDI, but PDI was still broader than 1.3 (Entry 5). However, as **M4** generally showed higher reactivity than **M3**, providing higher monomer conversions with shorter reaction times. Thus, higher molecular weighted **P4** could be synthesized with lower catalyst loading of **B**, with a maximum TON up to 240 and molecular weight up to 40 k obtained (Entries 6-8). This result implied that dimethyl substitution induced high Thorpe-Ingold effect for the efficient cyclization of 4,4-disubstituted 1,7-octadiyne monomers, as maximum TON of monomers without dimethyl substitution was only 75.[13]

Table 3. Cyclopolymerization of less reactive monomers



Entry	Mono	Time	Temp	Conv.[a]	M_n[b]	PDI[b]
1	**M5**	3.5 hr	r. t.	50 %	10000	1.53
2	**M6**	30 min	r. t.	>99 %	18000	1.46
3	**M6**	4 hr	5 ℃	60 %	14000	1.27

[a] Conversion determined by crude ^{1}H-NMR. [b] Determined by THF SEC calibrated using PS standards.

When **M5** with trimethylsilyl (TMS) and TBDMS group was reacted with catalyst **A**, only 50 % of monomer was converted to polymer, even at room temperature condition (Entry 1). We expect that less sterically hindered TMS group could not provide enough Thorpe-Ingold effect to accelerate cyclopolymerization, so that the polymerization efficiency was significantly decrease compared to **M2** study. **M6** with two TBDMS group, which have the same structure with the previously reported optimized monomer except of dimethyl group, showed excellent polymerization efficiency, with full monomer conversion within only 30 minutes, although PDI was broad. In order to suppress the chain transfer reaction and obtain **P6** with narrow PDI, **M6** was reacted under 5 ℃ condition. Surprisingly, reactivity of **M6** was significantly decreased, giving only 60 % conversion, while PDI of polymer was nearly 1.3.

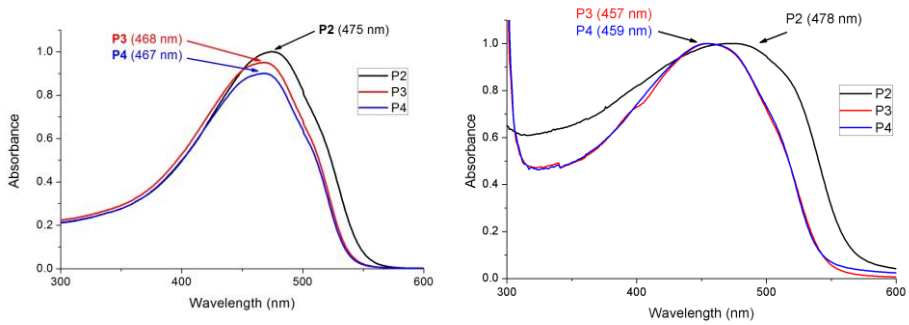
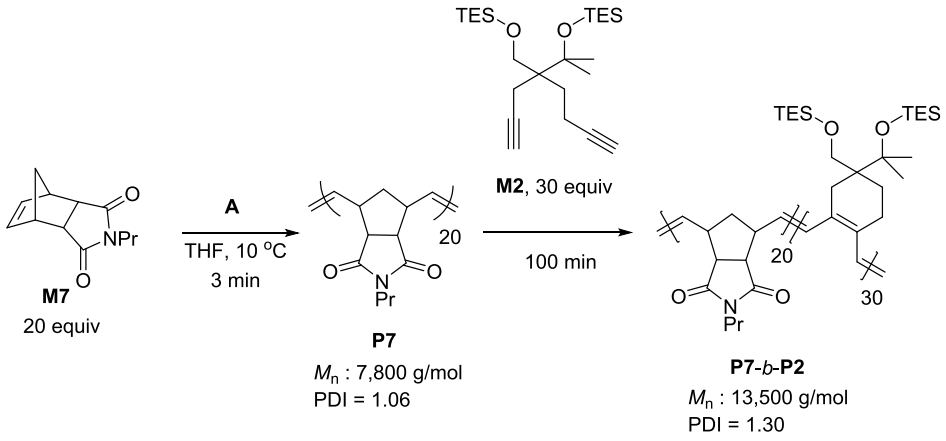


Figure 3. Solution (left) and film (right) state UV-Vis spectra of **P2**, **P3**, and **P4**: λ_{max} of each polymer is indicated.

Conjugated polymers containing a six-membered ring repeat unit were analyzed by UV-Vis spectroscopy. In both solution state and film state, all conjugated polymers (**P2**, **P3**, and **P4**) showed a bathochromic shift as the molecular weight of polymers increased, as a result of an increase in conjugation length (See supporting information for details (Figure S8-S10)). Bis-TES substituted polymer

P2 showed λ_{max} of 475 nm and 478 nm in THF solution and thin film state respectively (Figure 3, see SI for film state UV-Vis spectrum). Polymers **P3** and **P4** with ester side chains showed λ_{max} of 468 nm and 467 nm respectively in THF solution, and λ_{max} of 457 nm and 459 nm for film state, which are lower than those of **P2**. Notably, all these values were lower than λ_{max} of 1,7-octadiyne cyclopolymer without dimethyl substitution (λ_{max} of 486 nm and 482 nm for solution and film state).[13] Moreover, bandgaps of polymers with dimethyl substitution were slightly higher than that of 1,7-octadiyne cyclopolymer without dimethyl substitution (2.20 eV), showing 2.25 eV for **P2** and 2.28 eV for both **P3** and **P4**. These results implied that the polymers containing dimethyl substitution adjacent to the polymer backbone of the cyclohexene ring showed a slight twist in the polymer backbone, resulting in a slight decrease in polymer coplanarity and conjugation length.[18]



Scheme 5. Block copolymerization of **M2** with norbornene monomer **M7**

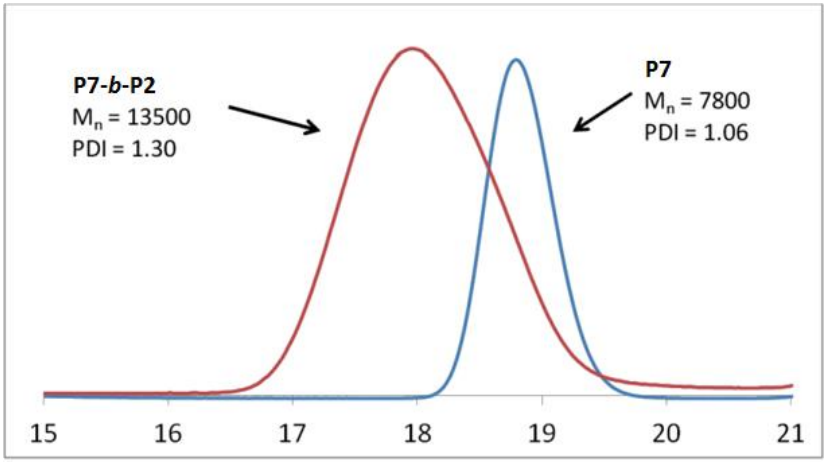


Figure 4. THF SEC trace of **P7** and block copolymer **P7**-*b*-**P2**.

As the dimethyl substitution increased the rate of cyclopolymerization for 1,7-octadiyne derivatives, it was thought that synthesis of diblock copolymers could also be made more efficiently by this method compared to the lengthy polymerization times of previous monomers without dimethyl substitution (24 hours).[5] Block copolymerization was carried with **M7** as a first block and **M2** as a second block with M/I = 20:30 (Scheme 5). Initially, **M7** was reacted with catalyst **A** at 10 ℃ for 3 minutes to produce **P7** with a very narrow PDI with 1.06. Then, **M2** was added to the reaction flask and after 100 min, the final diblock copolymer **P7**-*b*-**P2**, with PDI of 1.30, was isolated in 90% yield. The block microstructure was confirmed by the total shift of the SEC trace to left demonstrating the increase in molecular weight from 7,800 g/mol (**P7**) to 13,500 g/mol (**P7**-*b*-**P2**) (Figure 4). In short, a diblock polymer could be prepared in less than 2 hours rather than 24 hours, as previously reported.

Conclusion

In this chapter, we have introduced additional dimethyl substitution as an

activating group to a 4,4-disubstituted 1,7-octadiyne monomer skeleton. Using ^{1}H-NMR kinetic studies, we could unambiguously confirm that the presence of dimethyl substitution accelerated cyclopolymerization by maximizing the Thorpe-Ingold effect, such that full conversion of the monomer was achieved with 2 mol% catalytic loading in one hour at room temperature. With the newly designed monomer containing bulky silyl ether groups and dimethyl substitution, even controlled polymerization could be achieved, yielding polymers with narrow PDIs. Use of the bulky bis-TES group was also advantageous as it served to block chain transfer reactions. In addition, monomers containing ester groups on one side chain and dimethyl substitution on the other side chain showed high activities toward cyclopolymerization, giving TON values up to 240. Lastly, using the more reactive 1,7-octadiyne monomer **M2**, synthesis of the diblock copolymer was successfully carried out in a much shorter reaction time. This work demonstrates that optimal monomer design is crucial to achieve efficient polymerization of a seemingly challenging polymerization process.

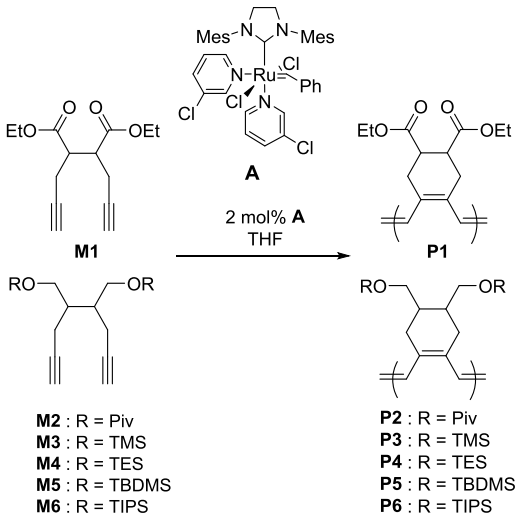
Part B. Cyclopolymerization of 4,5-disubstituted 1,7-octadiyne

Introduction

Introduction of 1,1-dimethyl substituent on the α-position of side chain on 4-position significantly increased cyclopolymerization of 1,7-octadiyne deriatives.[19] This simple modification decreased reaction time from 24 hours to 1 hour at room temperature to synthesize polymer with a degree of polymerization (DP) of 50. However, to achieve a well-controlled polymerization by suppressing the chain transfer reaction, reaction temperature was lowered to 5 ℃, and this increased the reaction time up to 6 hours. While we designing new monomer structures, Buchmeiser and co-workers reported cyclopolymerization of 4,5-disubstituted 1,7-octadiyne monomers using modified Hoveyda-Grubbs catalyst and Schrock catalysts.[16] Although the polymerization with the modified Hoveyda-Grubbs catalyst was unsuccessful,[16a] controlled polymerization with Schrock catalysts was successful.[16b] This 4,5-disubstitution might induce higher reactivity toward cyclopolymerization than conventional 4,4-disubstitution because of the effectively larger Thorpe-Ingold effect toward diyne tether.[17] Also, as molybdenum catalysts are less tolerant to air or functional groups, cyclopolymerization with much stable Grubbs catalyst would expand the scope of the monomers. This chapter will describe about the controlled polymerization of 4,5-disubstituted 1,7-octadiyne monomers using third-generation Grubbs catalyst. With high reactivity, various conjugated polyenes such as a diblock copolymer and challenging dendronized polymer containing exclusively six-membered ring polymer units were successfully prepared.

Result and Discussions

Table 1. Cyclopolymerization of 4,5-disubstituted 1,7-octadiyne monomers



Entry	Mono	Temp.	Time	Conv.[a]	M_n[b]	PDI[b]
1	**M1**	r. t.	50 min	>99 %	22000	1.82
2	**M2**	r. t.	30 min	>99 %	15000	1.86
3	**M3**	r. t.	45 min	>99 %	20000	1.49
4	**M4**	r. t.	50 min	>99 %	17000	1.36
5	**M5**	r. t.	50 min	>99 %	18000	1.28
6	**M6**	r. t.	40 min	>99 %	21000	1.25
7	**M1**	-20 ℃	5 h	90 %	13000	1.23
8	**M2**	-10 ℃	2 h	83 %	21000	1.17
9	**M3**	5 ℃	70 min	90 %	18000	1.28
10	**M4**	5 ℃	2 h	>99 %	14000	1.28

[a] Conversion determined by crude ^{1}H-NMR. [b] Determined by THF SEC calibrated using polystyrene (PS) standards.

Initially, 4,5-bis(ethyl ester) monomer **M1** was prepared and subjected to polymerization with 2 mol% of third-generation Grubbs catalyst (**A**)[15] in THF at room temperature. Within 50 minutes, the monomer was completely consumed (Table 1, Entry 1). As ruthenium-based catalysts react with terminal alkynes *via* regioselective α-addition[11,13], Grubbs catalysts tend to selectively give polymers with either five-membered or six-membered rings as repeat units from 1,6-heptadiynes or 1,7-octadiynes, respectively. In order to confirm whether the same trend would hold for **M1**, the ^{13}C NMR spectrum of **P1** was analyzed. Signals for two ester carbonyls (174.2, 172.8 ppm), two backbone olefins (131.8, 125.2 ppm), two methines in a six-membered ring (41.4, 39.8 ppm), and two methylenes in a six-membered ring (29.2, 27.4 ppm) were observed (Figure 1). These data match with those reported by Buchmeiser, who produced the same polyenes containing six-membered rings from the same monomer using a molybdenum catalyst,[16b] and this suggests that the polymerization of 4,5-disubstiuted 1,7-octadiyne derivatives with a Grubbs catalyst indeed promotes regioselective α-addition to give polymers with six-membered ring repeat units.

One would notice that the monomer **M1** is a mixture of two diastereomers, a *meso* and a *racemic* (1 : 1 mixture of (*R*, *R*) and (*S*, *S*) enantiomers) compound. From ^{1}H-NMR study of the monomer **M1**, the ratio of *meso* to *racemic* compounds were measured to 4 : 6. As the reactivity of each diastereomer towards cyclopolymerization may differ, we monitored the kinetics by ^{1}H-NMR on each diastereomer by treating them with 10 mol% of the catalyst **A** in deuterated DCM. When we compared the reaction rate of two diastereomers in 1st order kinetics, reaction rate of the *meso* compound was 0.50 min^{-1}, while reaction rate of the *racemic* compound was 0.31 min^{-1} (Figure 2). Overall, both diastereomers showed a comparable reactivity with slightly higher reactivity for the *meso* monomer, similar to the previous report by Buchmeiser.[16b]

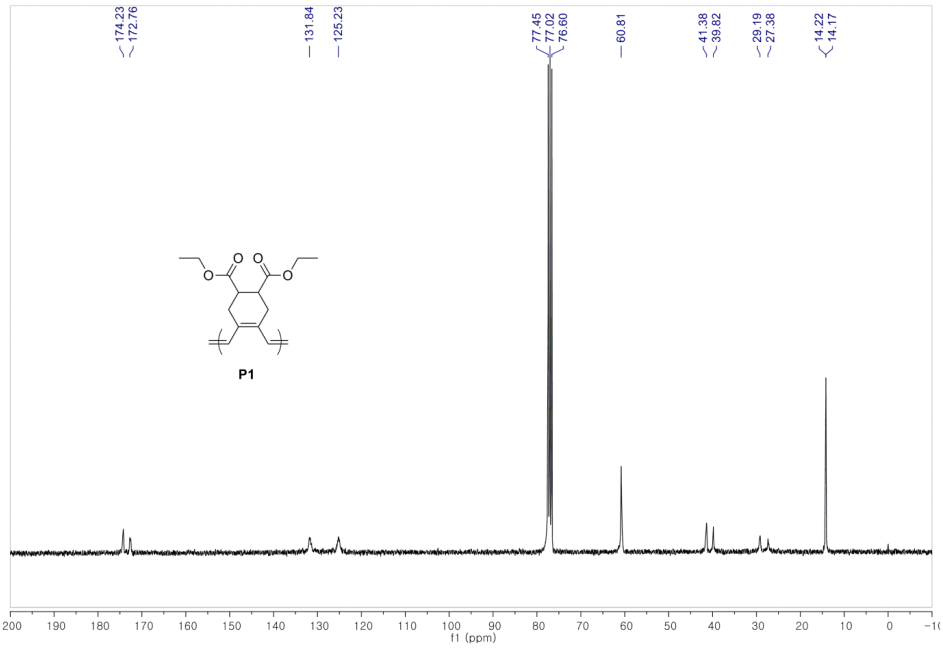


Figure 1. ^{13}C-NMR spectrum of **P1**

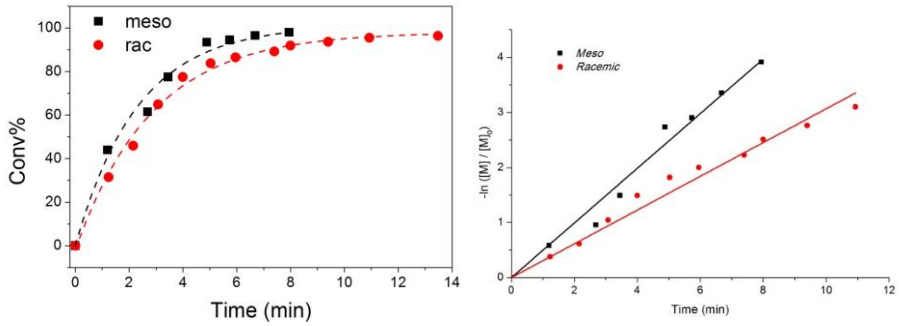
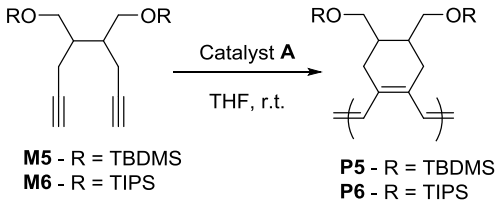


Figure 2. Plot of conversion vs. time (left) and -*ln* ([M]/[M]$_0$) vs. time (right) for *meso* and *racemic* diastereomer of monomer **M1** with M/I = 10 at room temperature.

Despite using the ultrafast initiating catalyst **A**, a broad PDI of 1.82 was observed for **P1**, presumably due to the facile chain transfer reaction at room temperature.

Thus, monomers with bulkier substituents were prepared to increase the shielding effect to protect the prepared polyenes and suppress the chain transfer reaction. Monomer **M2** with pivalate group was fully converted to **P2** within 30 min, but the PDI was still broad (1.86, Entry 2). To our delight, we observed that narrower PDIs were obtained for monomers having bulkier silyl protecting groups (1.49 for **P3** containing trimethylsilyl (TMS) and 1.36 for **P4** containing triethylsilyl (TES), Entries 3 and 4). Monomers with even bulkier groups such as TBDMS and triisopropylsilyl (TIPS) produced **P5** and **P6** with PDIs narrower than 1.3 even at room temperature (Entries 5 and 6). This implied that the shielding effect from the bulky substituents hindered the chain transfer reaction. For the monomers with smaller substituents (**M1**–**4**), the chain transfer reaction was suppressed at lower temperature (-20 to 5 ℃), and polymers with narrower PDIs (<1.3) were produced despite the longer reaction times (Entries 7–10).

Table 2. Cyclopolymerization of **M5** and **M6**



Entry	Mono	M/I	Time	Conv.[a]	M_n[b]	PDI[b]
1	**M5**	15	15 min	>99 %	6500	1.17
2	**M5**	30	28 min	>99 %	11000	1.23
3	**M5**	50	50 min	>99 %	18000	1.28
4 [c]	**M5**	100	120 min	90 %	25000	1.43
5	**M6**	20	8 min	92 %	7700	1.20
6	**M6**	30	23 min	>99 %	10000	1.29

7	**M6**	50	40 min	>99 %	21000	1.25
8	**M6**	75	60 min	99 %	33000	1.31
9	**M6**	100	70 min	>99 %	40000	1.57

[a] Conversion determined by crude ^{1}H-NMR. [b] Determined by THF SEC calibrated using PS standards. [c] The polymerization was conducted at 5 ℃.

Although the cyclopolymerization of many 4,5-disubstituted 1,7-octadiyne monomers produced polymers with narrow PDIs, we focused our study on the controlled polymerization of **M5** and **M6**, because **P5** and **P6** with narrow PDIs were prepared at room temperature. First, **M5** was polymerized with various monomer to initiator (M/I) ratios ranging from 15 to 100. At M/I ratios between 15 and 50, **P5** with a narrower PDI (<1.3) was produced at room temperature (Table 2, Entries 1–3), and a linear relationship between the M/I ratio and the molecular weight was observed (Figure 3a). At an M/I ratio of 100, the polymerization was conducted at 5 ℃ to obtain optimal results (Table 2, Entry 4). Cyclopolymerization of **M6**, containing the even bulkier TIPS group, showed a similar result as **M5**. By changing the M/I ratio from 20 to 100, the molecular weight of **P6** increased proportionally, and the PDI remained narrow in most cases, except when the M/I ratio was 100 (Entries 5–9, Figure 3b).

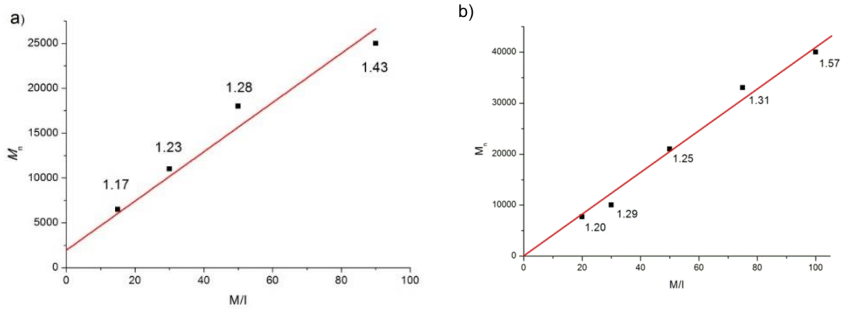
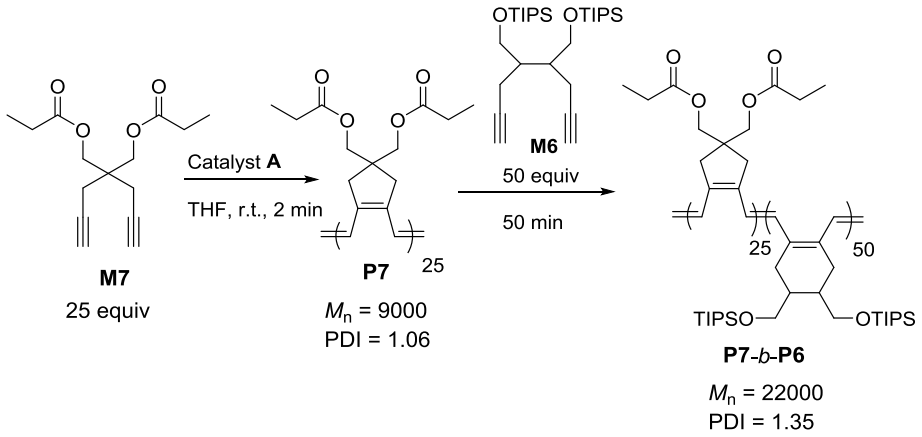


Figure 3. Plot of M_n versus M/I for a) **P5** and b) **P6**. The PDI values are shown as labels.



Scheme 1. Block copolymerization of **M6** with 1,6-heptadiyne monomer **M7**.

With the successful controlled polymerization of 4,5-disubstituted 1,7-octadiyne monomers in hand, we carried out the synthesis of a fully conjugated diblock copolymer from **M6** and 1,6-heptadiyne monomer **M7** (Scheme 1). Initially, 25 equiv of **M7** was added to the solution of catalyst **A**, and after 2 min, 50 equiv of **M6** was added. After 50 min at room temperature, monomers **M6** and **M7** were fully converted to diblock copolymer **P7**-*b*-**P6**. From size exclusion chromatography (SEC) analysis, the trace of the block copolymer was shifted to a higher molecular weight region (22000) from the 1st block of **P7** (9000), and the PDI of the block copolymer remained low (1.35) (Figure 4). Compared to our previous block copolymerization of a 1,6-heptadiyne monomer and a 4,4-disubstituted 1,7-octadiyne monomer that required 24 hours of reaction time, this new copolymerization using the 4,5-disubstituted monomer showed a significant improvement with a much shorter reaction time.[13] Buchmeiser and co-workers also reported a similar block copolymerization using a molybdenum catalyst, but their cyclopolymerization of a 1,6-heptadiyne monomer produced a small portion of six-membered rings as a defect, because the regioselectivity of the molybdenum catalyst was not exclusive and resulted in some β-addition.[16b]

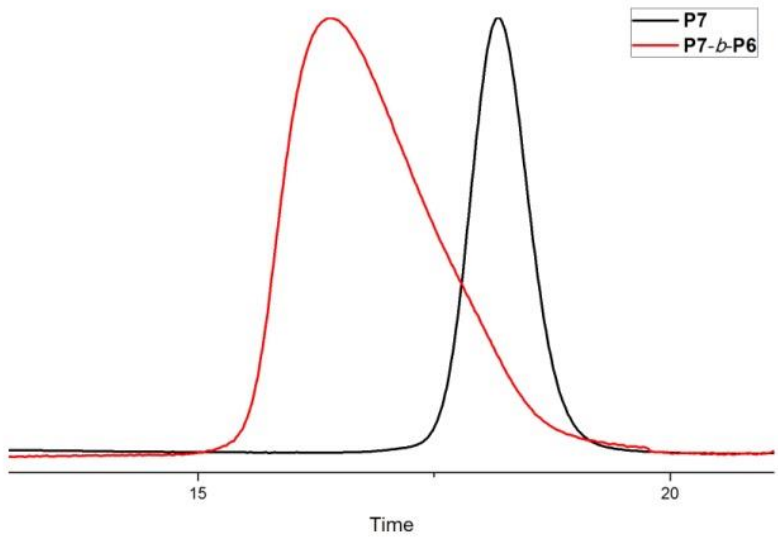


Figure 4. THF SEC traces for **P7** and **P7**-*b*-**P6**.

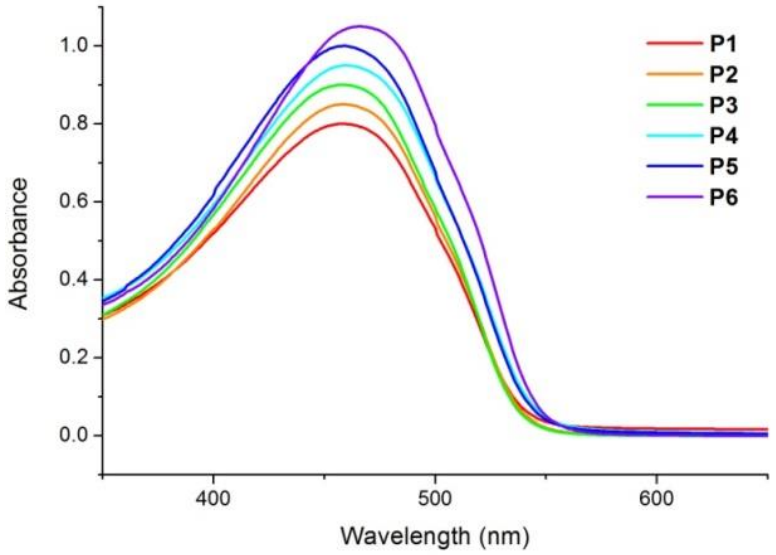


Figure 5. UV-Vis spectra of **P1**–**P6** in THF (0.25 mg/ml).

The newly synthesized conjugated polymers were characterized by UV-Vis

spectroscopy. In THF, λ_{max} of **P1** to **P6** was at 460–466 nm (Figure 5). As expected, when the molecular weights of polymers increased, λ_{max} of the polymers also increased because of the increased conjugation length (See supporting informations for details (Figure S11)). For the UV-Vis spectra of the thin films, λ_{max} of **P1** with the small ester substituent increased to 468 nm, while λ_{max} of **P2**–**P6** with bulkier substituents decreased to 452–458 nm (See supporting informations for details (Figure S12 and S13). This tendency is presumably due to the bulky substituents distorting the backbone planarity of the polymers in the film state, effectively decreasing the conjugation length of the polymers.[18]

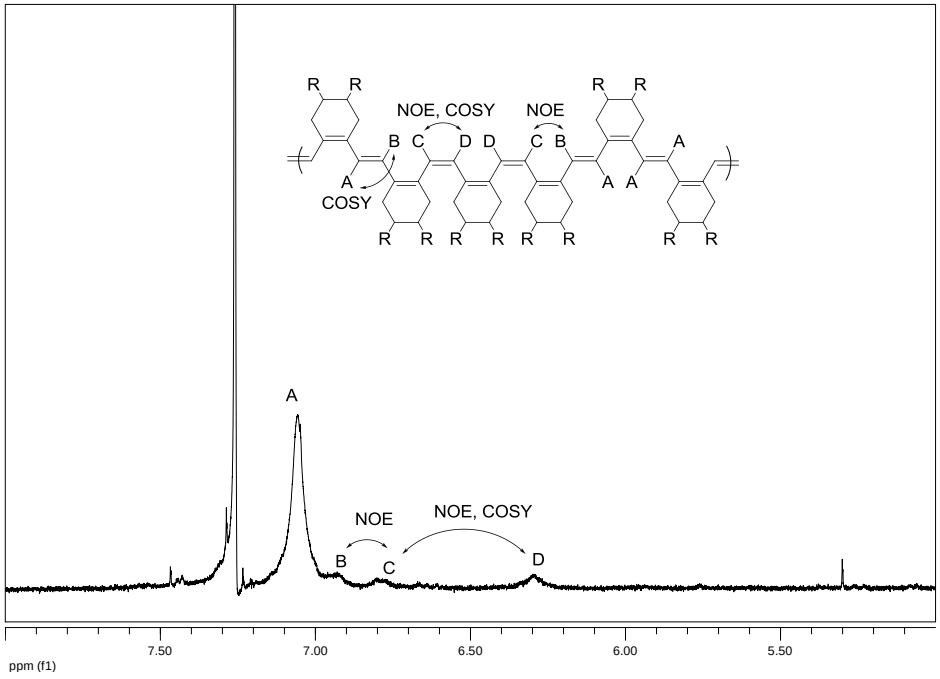


Figure 6. ^{1}H-NMR (500 MHz) spectrum of **P5** prepared from 4,5-disubstituted 1,7-octadiyne. Arrows indicate corresponding COSY correlation or NOE effect.

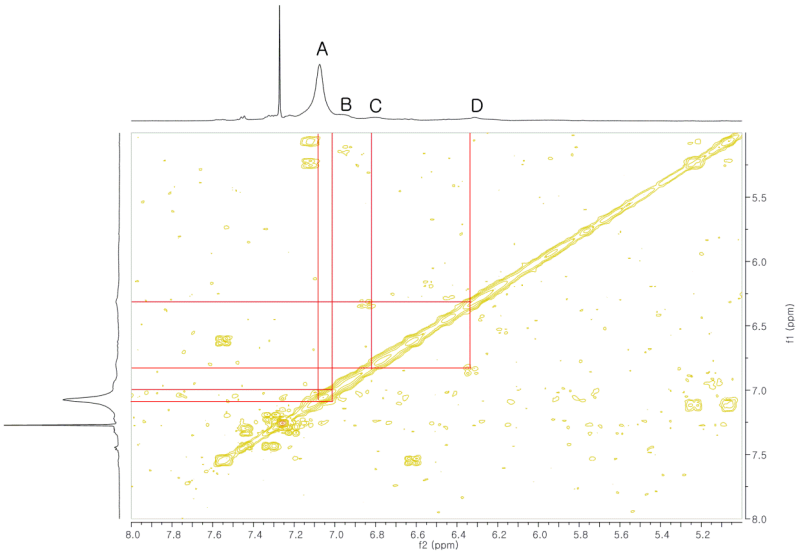


Figure 7. 2D ^{1}H-COSY correlation spectrum of **P5**. Red lines indicate COSY correlation.

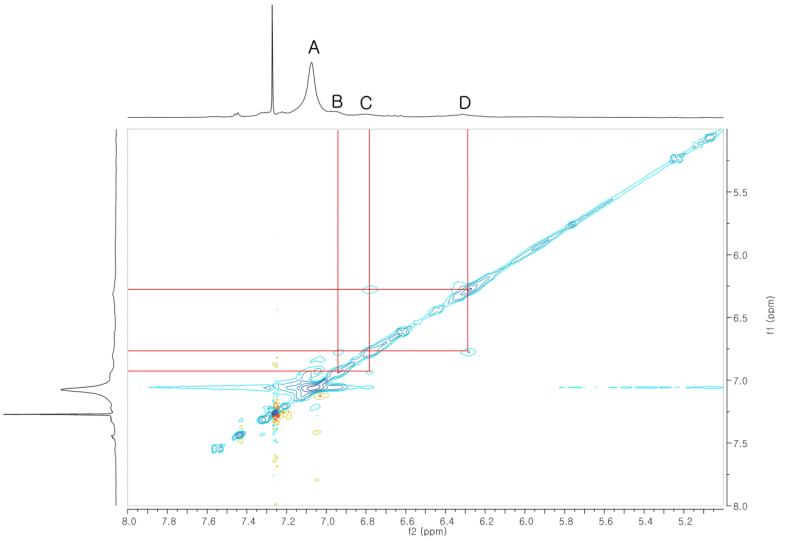


Figure 8. 2D ^{1}H-NOESY spectrum of **P5**. Red lines indicate NOE effect

Compared to the previously reported polymers from 4,4-disubstituted 1,7-octadiynes, the polymers from 4,5-disubstituted 1,7-octadiynes showed lower λ_{max} values. For example, λ_{max} of the polymer from 4,4-TBDMS disubstituted 1,7-octadiyne in solution and as a thin film were 486 and 482 nm, respectively, while λ_{max} of **P5** containing 4,5-TBDMS substituents in solution and as a thin film were 459 nm and 453 nm.[11] In order to explain the difference, the polymer structure was analyzed in detail by various ^{1}H-NMR techniques. As shown in Figure 6, the ^{1}H-NMR spectrum for **P5** showed one major signal, A, and three minor signals, B, C, and D. From 2D correlation spectroscopy (COSY) (Figure 7) and 2D nuclear Overhauser effect spectroscopy (NOESY) NMR experiments (Figure 8), A and B showed a COSY correlation, and B and C showed NOE effects, while C and D showed both NOE effects and a COSY correlation (See SI for details). Based on these observations, signals A and B corresponded to protons of a *trans* olefin, while signals C and D corresponded to protons of a *cis* olefin. From the NOESY correlation, signals B and C corresponded to protons where *trans* and *cis* olefins were adjacent to each other (Figure 6). A very similar assignment was achieved for the polymers from 1,6-heptadiyne monomers.[20] Based on the NMR analysis, one could conclude that the stereochemistry of the polymer backbone from 4,4-disubstituted 1,7-octadiyne was almost exclusively *trans*, while **P5** contained 74 % *trans* olefin. **P1**–**P6** showed similar ratios of 70–78 % *trans* olefin. This suggested that the lower λ_{max} of **P1** to **P6** was due to the presence of *cis* olefin, which decreased the conjugation length or the backbone planarity.

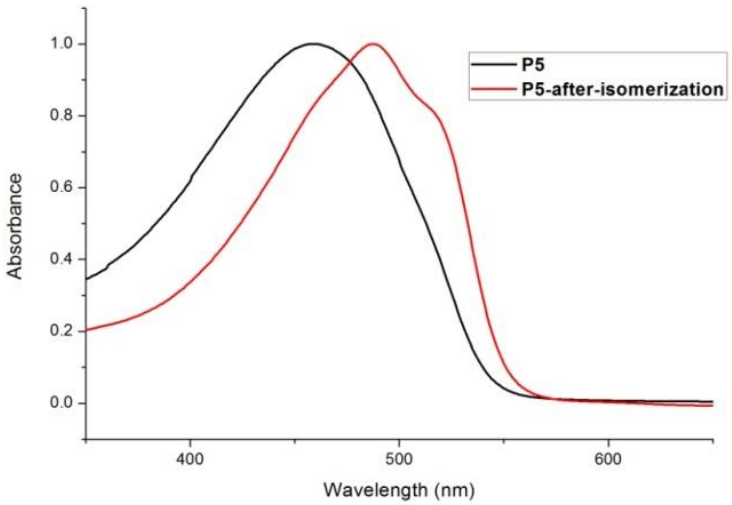
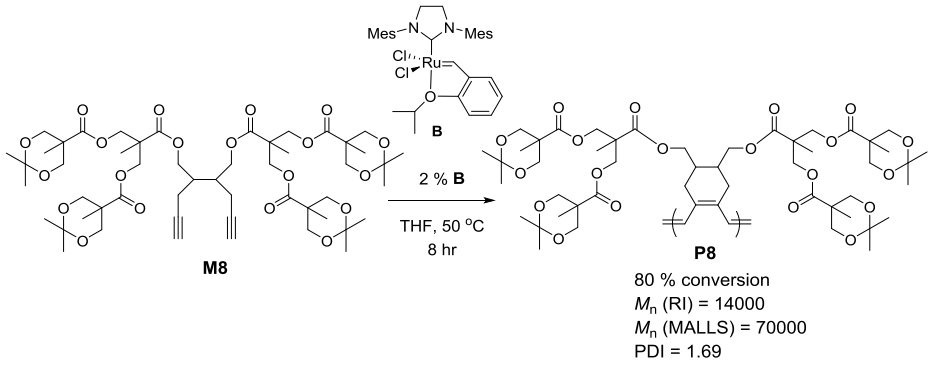


Figure 9. UV-Vis spectra of **P5** before isomerization (black) and after isomerization (red) in THF (0.25 mg/ml) (left) and NMR.

If λ_{max} of the UV-Vis spectrum depends on the ratio of *trans* olefin in the backbone, isomerization of *cis* olefin to *trans* will increase λ_{max} of the polymer. Therefore, **P5** in dichloromethane (1 mg/mL) was exposed to 480 nm blue LED irradiation for 1 hour,[20] and this completely isomerized the remaining *cis* olefin to *trans*, as confirmed by ^{1}H-NMR spectroscopy (See supporting informations for details (Figure S14)). Also, IR spectroscopy verified that the *cis* olefin stretching at 740 cm^{-1} disappeared after isomerization, while the *trans* stretching at 950 cm^{-1} remained (See supporting informations for details (Figure S15 and S16).[16b] As a result, λ_{max} of fully isomerized **P5** increased from 459 nm to 487 nm, which is similar to that of the polymer containing 4,4-disubstitution (Figure 9).[13] This suggests that the stereochemistry of the polyene backbone affects the conjugation length.[20]



Scheme 2. Synthesis of dendronized polymer **P8** from macromonomer **M8**.

To show that this enhanced cyclopolymerization could be applicable to prepare more complex molecules, we turned our attention to the synthesis of dendronized polymers. The study of dendronized polymers is interesting because they show an extended rod-like conformation because of the steric repulsion between the dendrons. However, their synthesis is quite challenging, especially via a macromonomer approach, because the propagation of bulky macromonomers becomes extremely slow. As monomers with bulky substituents such as TBDMS or TIPS group were successfully polymerized, we attempted a challenging cyclopolymerization of a macromonomer containing two dendrons at the 4 and 5 positions. Macromonomer **M8** containing two 2nd generation ester dendrons (equivalent to a 3rd generation dendron)[21] was synthesized and tested for polymerization.[22] Initially, **M8** was treated with 2 mol% of catalyst **A** at room temperature, but the reactivity of the monomer was too low with only 40 % conversion. Because the reactivity of **M8** was much lower than that of other monomers, the reaction temperature was raised to 50 ℃. However, catalyst **A** could not survive the long reaction time at 50 ℃. Therefore, 2 mol% of thermally stable 2nd generation Hoveyda-Grubbs catalyst (**B**) was used. After 8 hours, **P8** with an absolute molecular weight of 70k, as determined by multi-angle laser

light scattering (MALLS) analysis, was prepared in 80% yield (Scheme 2). Its PDI was inevitably broad (1.69) because of the slow initiating catalyst and reaction condition that enabled chain transfer reactions. This demonstrated that the reactivity of 4,5-substituted 1,7-octadiynes was high enough to produce dendronized polymers via a macromonomer approach.

P8 was imaged using atomic force microscopy (AFM). Although **P8** contained low-generation ester dendrons, and the molecular weight was not very high, clear images of a single polymer chain were obtained. As shown in Figures 7 and 8, **P8** showed an extended rod-like conformation approximately 50 nm in length and 0.4 nm in height. This single polymer chain can find potential application as an insulated molecular wire because the conjugated polymer backbone is covered by an insulating dendron.[23]

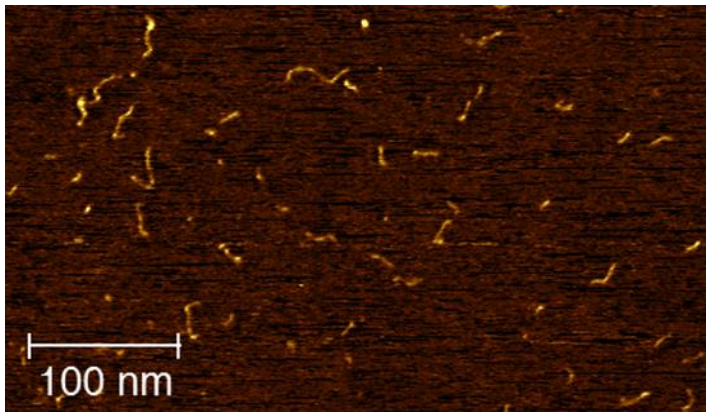


Figure 7. AFM image of **P8** in phase mode. The polymer solution in DCM (0.25 mg/L) was spin-coated onto mica.

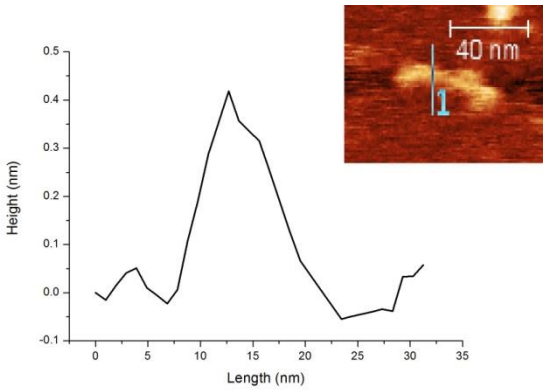


Figure 8. Single chain AFM image of **P8** in height mode with height profile. The average height of polymer chain was 0.4 nm.

Conclusions

In summary, we performed cyclopolymerization of various 4,5-disubstituted 1,7-octadiynes using a 3rd generation Grubbs catalyst to produce polyenes containing six-membered rings. These monomers showed higher reactivity than 4,4-disubstituted 1,7-octadiynes, and the corresponding polymers had narrow PDIs. Among the monomers tested, those with bulky substituents such as TBDMS and TIPS underwent controlled polymerization at room temperature within 1 h. With this high reactivity, a block copolymer was prepared more efficiently from **M6** and a 1,6-heptadiyne monomer. Finally, we applied this improved polymerization to the synthesis of a dendronized polymer from a macromonomer containing two 2nd generation ester dendrons, and AFM imaging revealed a rod-like conformation.

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Supporting Information

SEC trace of Diels-Alder modified polymers (Chapter 3A)

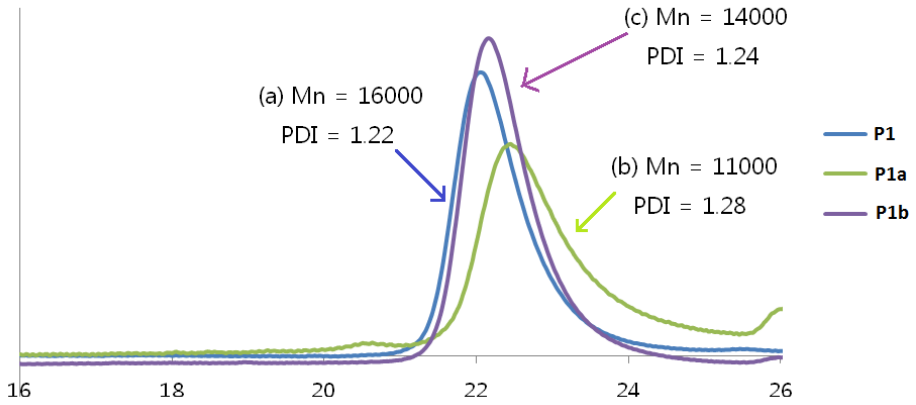

Figure S1. THF SEC trace of (a) **P1**, (b) **P1a**, and (c) **P1b**

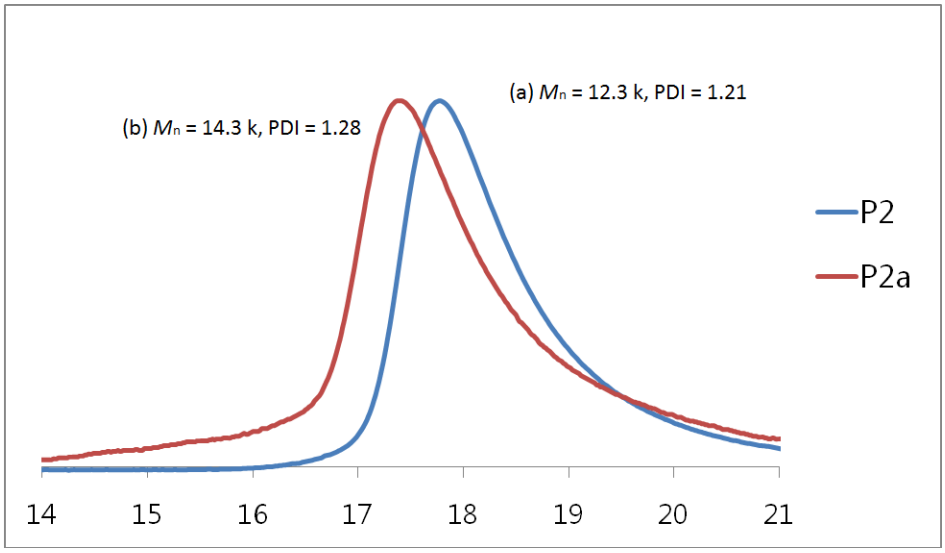

Figure S2. THF SEC trace of (a) **P2**, (b) **P2a**

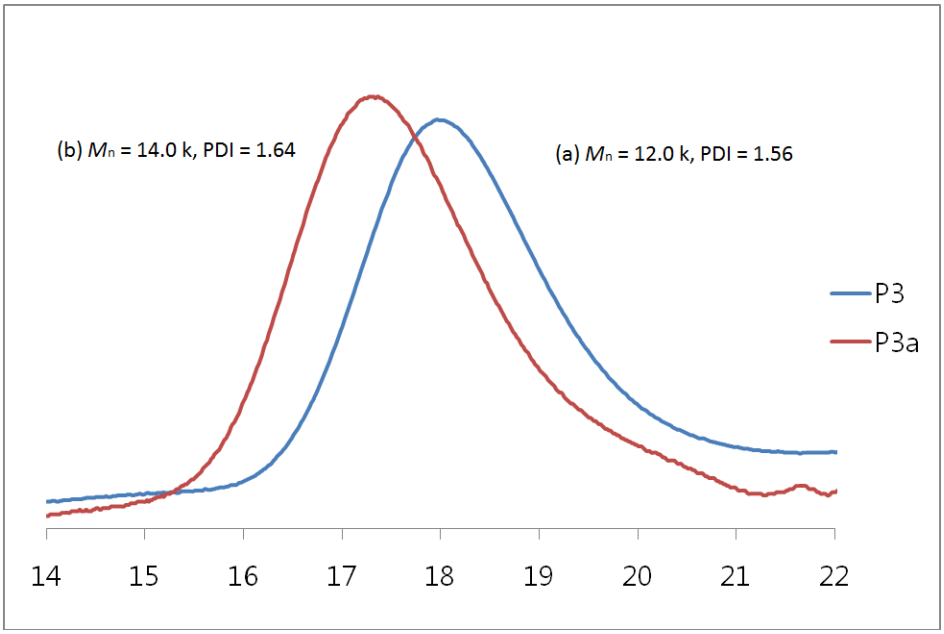

Figure S3. THF SEC trace of (a) **P3**, (b) **P3a**

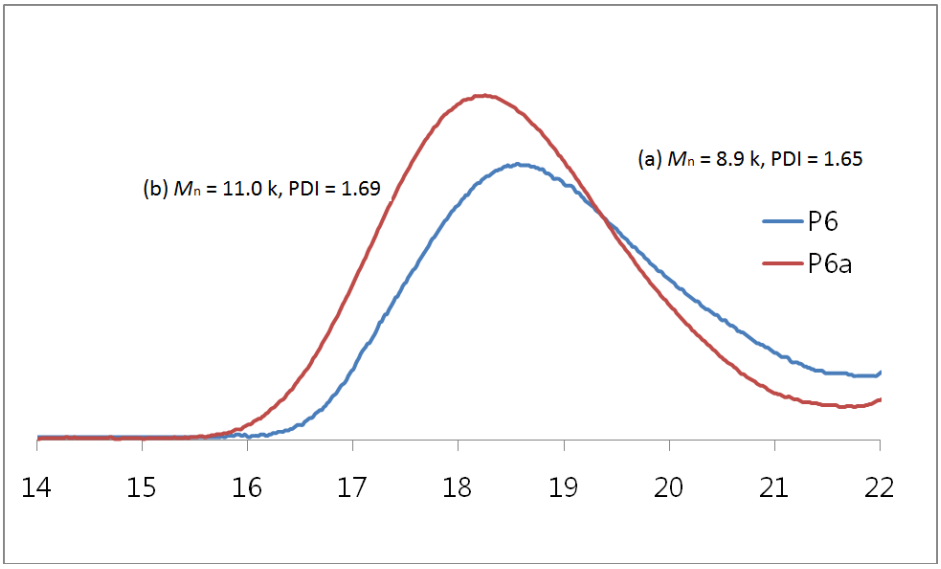

Figure S4. THF SEC trace of (a) **P4**, (b) **P4a**

Polymer unit ratio determination of Phenyl substituted polymers (Chapter 3B)

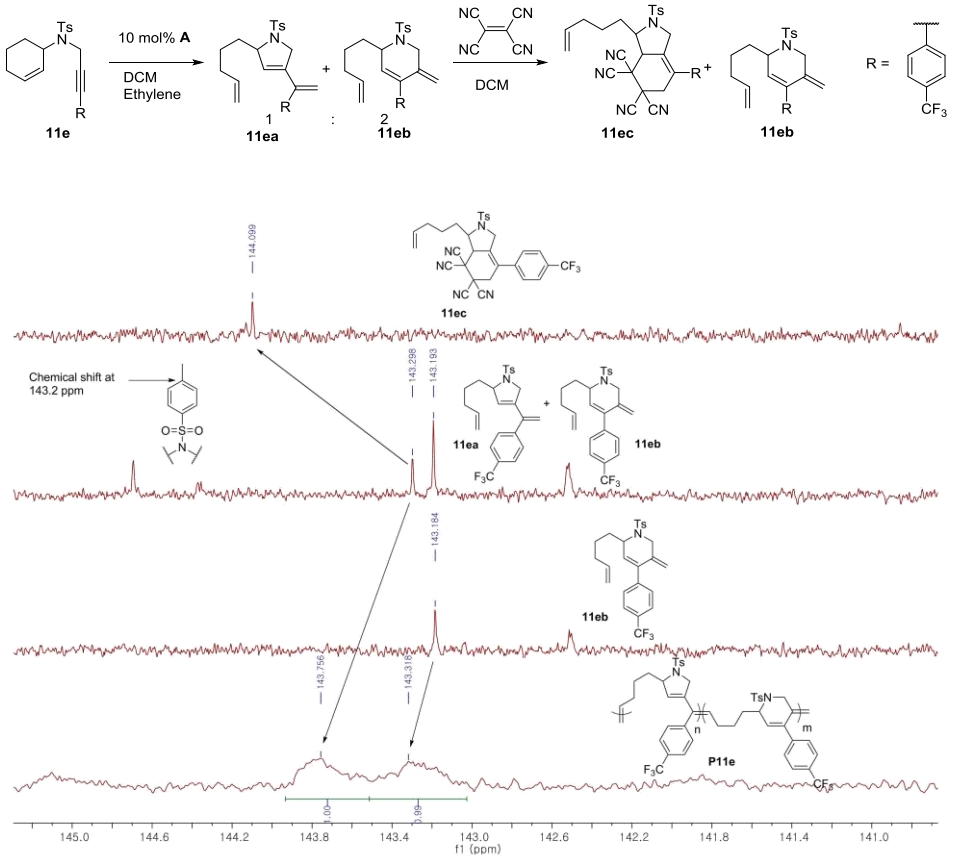

Figure S5. ^{13}C-NMR spectrum of ethenolysis products of **11e** and **P11e**.

Ethenolysis of monomer **11e** with 10 mol% of second-generation Grubbs catalyst **A** resulted the mixture of two molecules. Those inseparable mixture was reacted with 2 equivalent of tetracyanoethylene in 0.3 M DCM solvent. After 1 hour, DCM was evaporated and column chromatography (ethyl acetate : hexane = 1 : 5) resulted 2 products, **11eb** (R_f = 0.4) and **11ec** (R_f = 0.1) with 2 : 1 ratio. Presence of **11ec** suggests the formation of five-membered ring molecule **11ea** during initial ethenolysis, which was converted to **11ec** after Diels-Alder reaction.

By comparing the ^{13}C-NMR chemical shift of substrates and polymers, we observed that toluene chemical shift is different for each structures. **11ea** showed one peaks at 143.30 ppm, and **11eb** showed one peak at 143.19 ppm. **11ec** showed one peak at 144.10 ppm. Based on the observation, chemical shift at 143.30 ppm indicates five-membered ring structure, and chemical shift at 143.19 ppm indicates six-membered ring structure. With this observation, we analyzed the ^{13}C-NMR of **P11e** and observed two peaks at 143.76 ppm, and 143.32 ppm, which are slightly different from small molecules. This is possibly due to the chemical shift change during polymerization, similar to the ^{13}C-NMR chemical shift of **P8** (143.52, 143.38 ppm) and small molecule counterparts (142.99 ppm for **P8b**, and 144.25 ppm for **P8c**) cases. The integration ratio between two peaks of **P11e** showed almost 1 : 1 ratio, suggesting the polymeric unit ratio between five- and six-membered ring is 1 : 1.

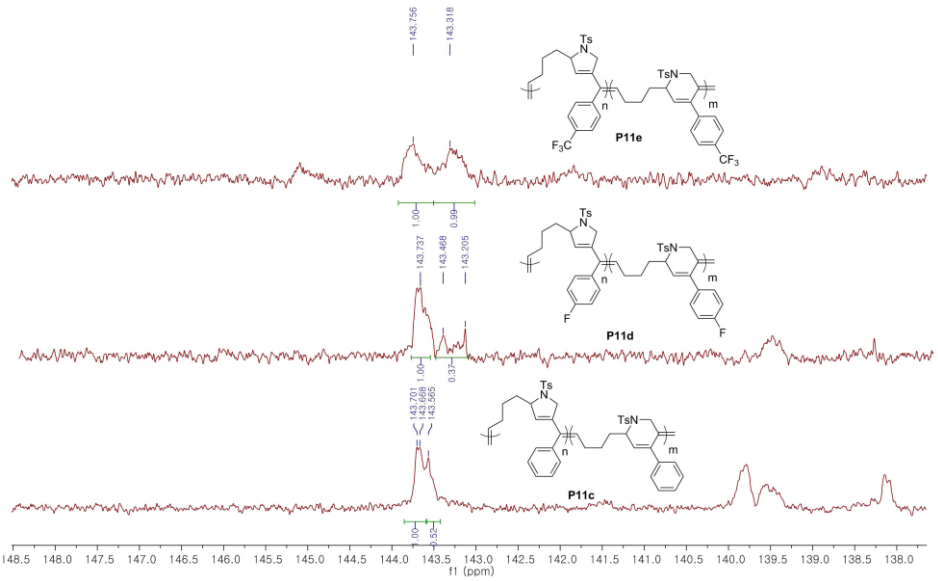

Figure S6. ^{13}C-NMR spectrum of **P11c-e**.

With this observation, tandem polymers with phenyl substituents were also observed to calculate the ratio between five- and six-membered ring units. **P11d** with 4-fluorophenyl substituent showed one large peak at 143.74 ppm and two small peaks at 143.47 and 143.21 ppm, possibly due to the cis/trans splitting. Ratio between those peaks are 2.7 : 1, suggesting the ratio between five- and six-membered ring units are 2.7 : 1. **P11c** with phenyl substituent showed two peaks at 143.70 ppm and 143.57 ppm, which showed 2 : 1 ratio upon integration, suggesting that the ratio between five- and six-membered ring units are 2 : 1.

Initiation rate kinetics study of monomer 11 with phenyl substituents (Chapter 3B)

To a 5 ml vial, catalyst **A** (27.85 mg, 0.000725 mmol) was added and purged with Ar gas. The catalyst was dissolved by 0.125 ml of THF-d^8 and 0.5 drop of hexamethyldisilane (HMDS) was added as a standard. 0.025 ml of mixture was injected to an Ar-purged NMR tube and diluted with 0.475 ml of THF-d^8 to calculate initial ratio between initiator carbene and standard. To another NMR tube, monomer **11** (0.06 mmol) and 0.5 ml THF-d^8 were added. After monomer was fully dissolved to NMR solvent, NMR tube was inserted into 400 MHz NMR. After obtaining initial NMR spectrum of monomer, 0.1 ml solution of catalyst **A** in THF-d^8 (0.01 mM) was quickly injected. After solution is fully mixed with quick shakes, NMR tube was inserted and both monomer conversion and carbene signal was monitored. Initiation rate was obtained by ratio between proton chemical shifts of initiator carbene (19.1 ppm) and internal standard (0.21 ppm). NMR data was collected up to 20 minutes, which were plotted as a function of time. After plotting the reaction rate, initial monomer/initiator ratio was extrapolated to remove errors from catalyst decomposition before injection. Reaction rates data showed zero order relation to monomer concentration. Obtained rate data was used to derive the Hammett plot.

Entry	X	[Mono] (M)	[I] (mM)	Corrected [I] (mM)	*k*(obs) (M/sec)	$\log(k_X/k_H)$	Sigma (ρ)
1	OMe	0.06	0.6	0.4332	0.01683	-0.13263	-0.27
2	Me	0.06	0.6	0.5148	0.01759	-0.11242	-0.17
3	H	0.06	0.6	0.4302	0.02278	0	0
4	F	0.06	0.6	0.387	0.02863	0.09843	0.06
5	CF3	0.06	0.6	0.3822	0.03761	0.21725	0.54

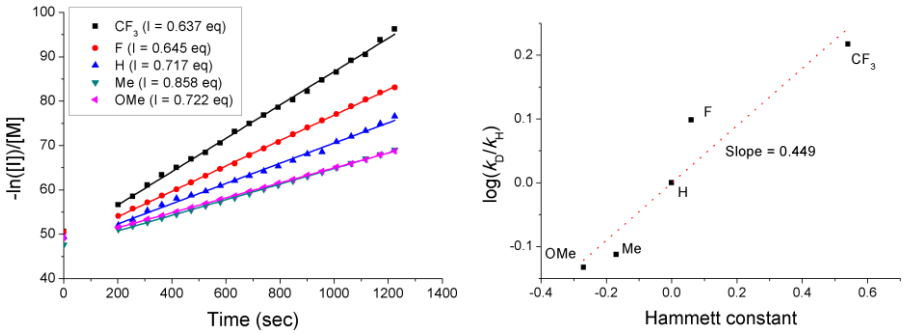

Figure S7. Initiation rate study result (left) and Hammett plot (right) of monomer **11a-11e** with phenyl substituents.

UV-Vis spectra of conjugated polymers (Chapter 4A)

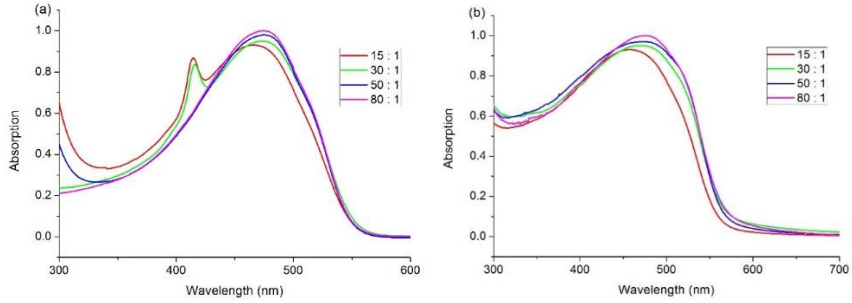

Figure S8. UV-Vis spectra of **P2** (a) in THF solution and (b) in thin film with different DPs (n = 15-80)

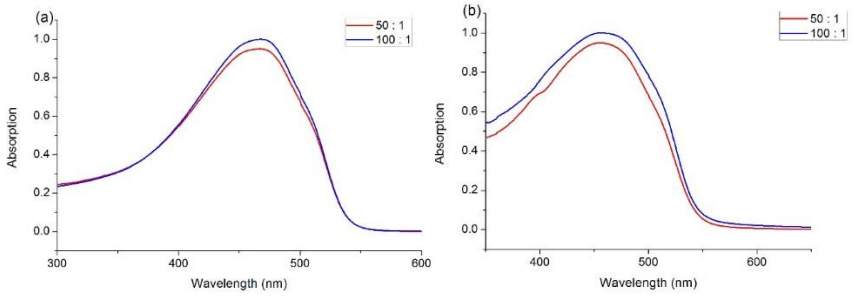

Figure S9. UV-Vis spectra of **P3** (a) in THF solution and (b) in thin film with different DPs (n = 50 and 100)

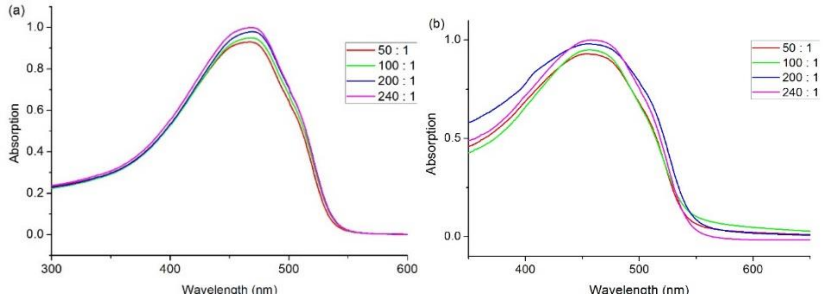

Figure S10. UV-Vis spectra of **P4** (a) in THF solution and (b) in thin film with different DPs (n = 50-240)

UV-Vis spectra of conjugated polymers (Chapter 4B)

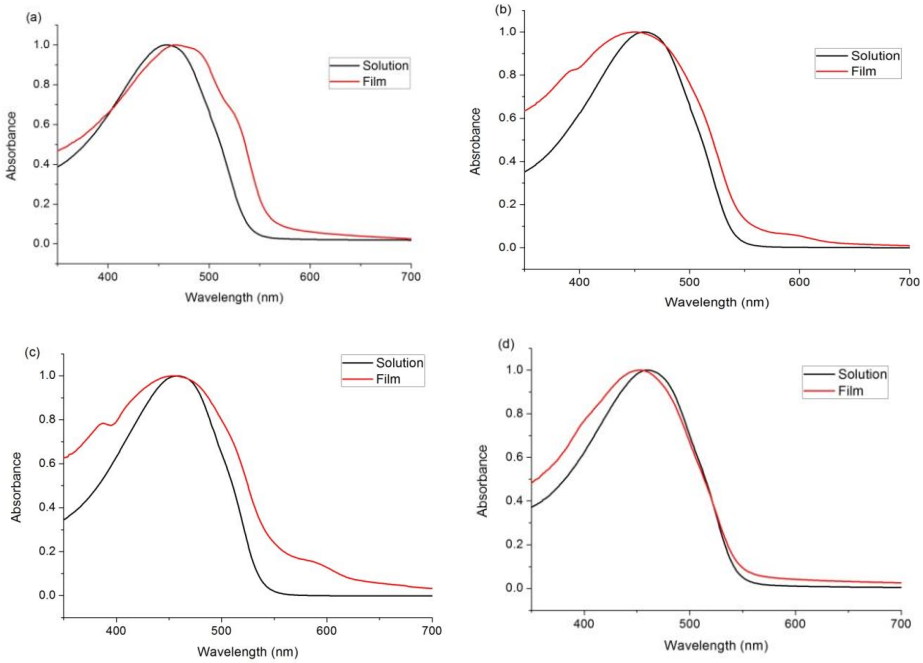

Figure S11. UV-Vis spectra of a) **P1**, b) **P2**, c) **P3**, and d) **P4** in THF solution and in thin film.

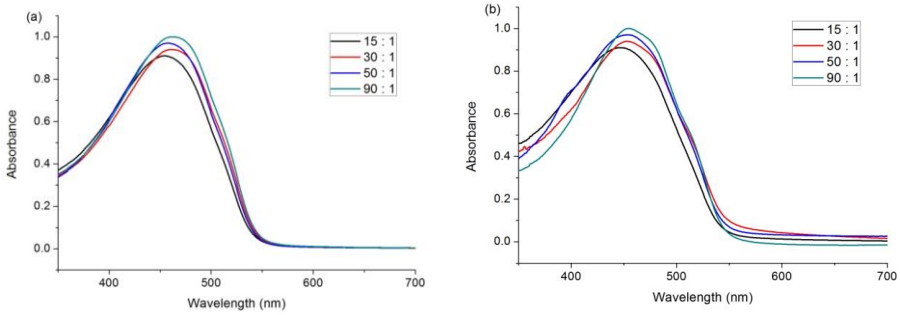

Figure S12. UV-Vis spectra of **P5** a) in THF solution and b) in thin film with different DPs (n = 15-90).

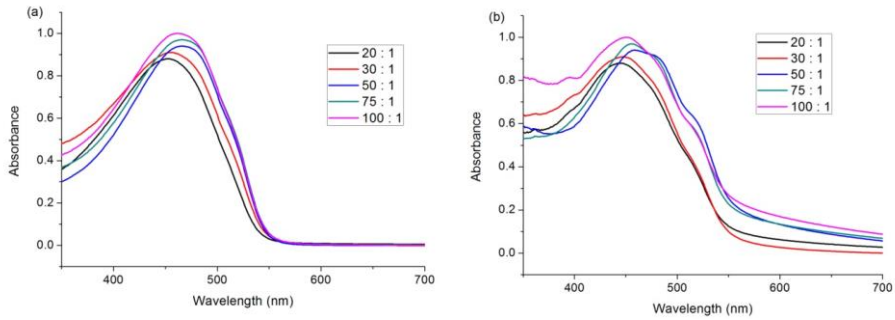

Figure S13. UV-Vis spectra of **P6** a) in THF solution and b) in thin film with different DPs (n = 20-100).

Isomerization data of P5

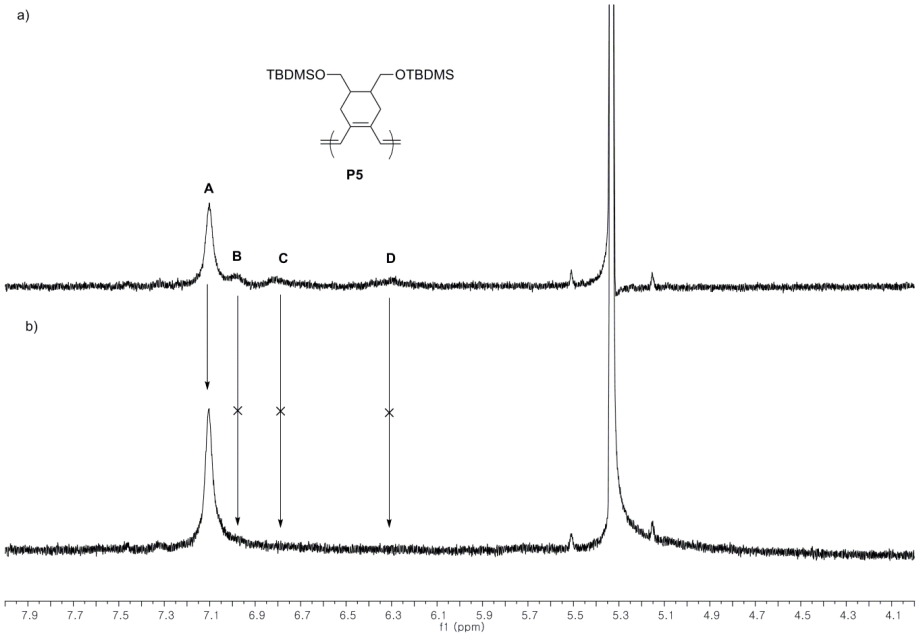

Figure S14. ^{1}H NMR spectrum of **P5** a) before isomerization and b) after isomerization in CD_2Cl_2. **P5** (0.4 mg) was put into NMR tube and dissolved in deuterated DCM (0.4 ml). The solution was irradiated by 480 nm blue LED light for 60 minutes.

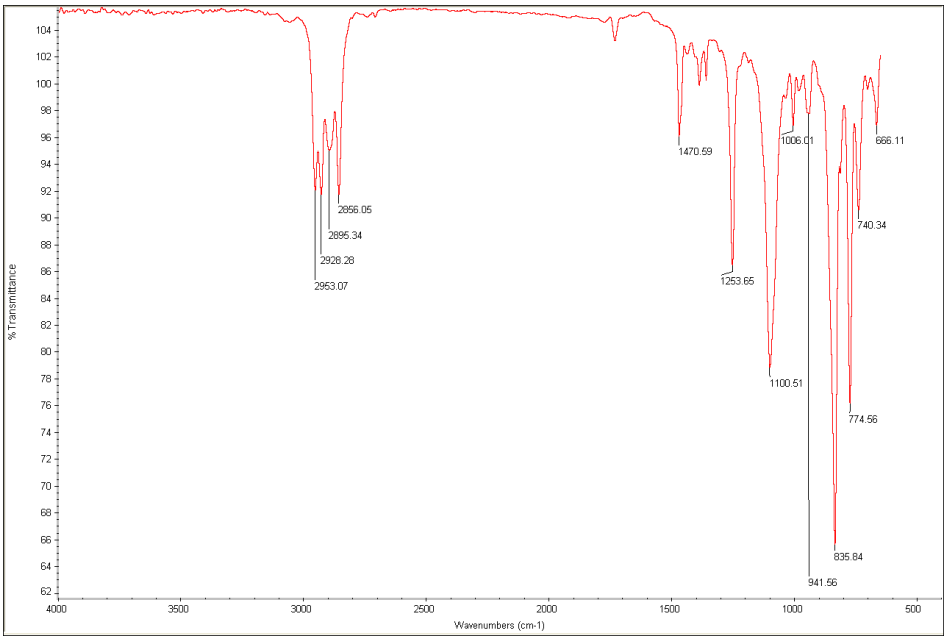

Figure S15. IR spectrum of **P5** before isomerization.

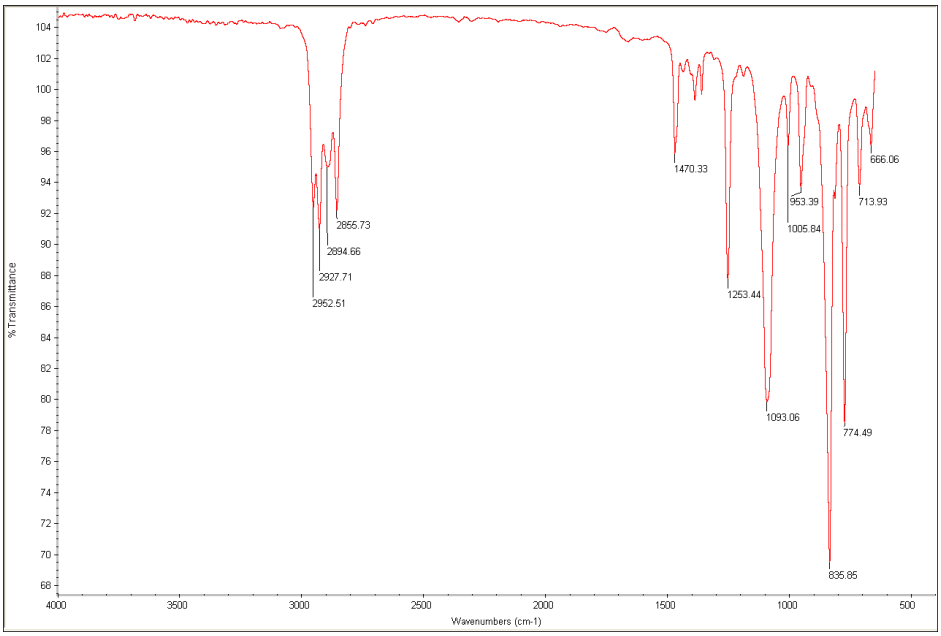

Figure S16. IR spectrum of **P5** after isomerization.

국문 초록

올레핀 메타테시스 반응은 탄소간 이중결합 위치를 변화시키는 반응으로, 이를 이용해서 다양한 종류의 유기 물질을 합성할 수 있다. 반응성이 높고 작용기에 대해 안정성이 높은 올레핀 메타테시스 촉매들이 개발 되면서 이 반응은 현대 유기화학에서 가장 중요한 반응 중 하나로 존재하게 되었다. 올레핀 메타테시스 반응에 사용되는 작용기 중에서도 알카인 물질의 경우, 촉매와 반응할 경우 1,3-다이인 형태의 작용기를 형성하게 되며, 이 작용기는 탠덤 반응을 통한 새로운 물질의 합성이나 전도성 고분자의 합성에 사용할 수 있다. 이 논문에서는 알카인을 이용한 올레핀 메타테시스 반응을 통해서 기존의 방법으로는 합성할 수 없었던 다양한 종류의 유기 화합물과 전도성 고분자를 합성하는 과정에 대해서 서술하였다.

제 2 장에서 다이인아인 물질에 대한 탠덤 고리 닫음 메타테시스 반응과 디엘스-알더 반응을 이용해서 다중고리 화합물을 합성하는 과정에 대해서 서술하였다. 일반적으로 탠덤 고리 닫음 메타테시스 반응을 통해서 이중고리 화합물을 합성하는 경우에는 촉매의 올레핀에 대한 반응 선택성이 없다는 단점 때문에 2 가지의 다른 종류의 물질이 형성되는 것이 일반적이다. 하지만 생성되는 고리의 크기 차이를 크게 해줄 경우, 고리화 반응의 속도 차이가 매우 커지기 때문에 하나의 물질만을 선택적으로 형성하는 것이 가능하다. 또한 이렇게 해서 형성된 1,3-다이인 작용기의 경우, 디엘스-알더 반응을 통해서 다중고리 화합물의 합성이 가능하게 되었다.

제 3 장에서 탠덤 고리 염/고리 닫음 메타테시스 반응을 이용해서 알카인과 사이클로알킨 물질을 가진 단분자의 고분자 중합을 진행한 것에 대한 연구를 서술하였다. 일반적으로 알카인과 사이클로알킨 작용기는 메타테시스 반응을 통한 고분자 중합이 매우 힘든 물질로 알려져 있다. 하지만 이 두 작용기를 하나의 단분자로 합칠 경우, 빠르고 비가역적인

탠덤 반응을 일으키면서 매우 빠른 속도로 분자량이 조절된 고분자를 합성하는 것이 가능하다. 이러한 새로운 반응을 개발하면서, 그에 따른 반응 메커니즘, 단분자 구조의 변경으로 인한 반응성의 변화, 그리고 반응 역학적인 연구를 같이 진행하였다.

제 4 장에서 1,7-옥타다이아인 물질에 대한 빠른 속도의 고리화 고분자 중합을 통한 전도성 고분자의 합성 과정을 서술하였다. 기존에 1,7-옥타다이아인 물질은 고리화 반응의 속도가 느린 편에 속해서 일반적으로 전도성 고분자를 합성하는데 적합하지 않았다. 이 문제를 해결하기 위해 단분자에 크기가 큰 작용기들을 도입하거나 작용기들의 위치를 바꿔 주는 것으로 짧은 시간 안에 원하는 고분자를 합성하는 것이 가능하게 되었다.

주요어 : 메타테시스, 고분자중합, 알카인

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