Olefin Metathesis:

A Versatile Tool for the Synthesis of

Small to Large Molecules

Thesis by

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Acknowledgments

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Abstract

In olefin metathesis, the designing of better catalysts has been the key to the success of its utility. Throughout the history of olefin metathesis research, the development of new and improved catalysts has brought new applications and new structures that are accessible by olefin metathesis routes. With the development of highly active catalyst containing an N-heterocyclic carbene, the field of olefin metathesis is currently in a period of renaissance opening up the versatile synthesis of both small organic molecules to macromolecules. Following four chapters describe recent applications toward the synthesis of molecules with various sizes.

Chapter 2 describes selective CM of various of α,β-unsaturated carbonyl compounds such as acrylic acid, acrylic amides, and vinyl phosphonate with terminal olefins and stryenes. For CM of acrylic amides, an interesting chelation effect which reduced the olefin metathesis activity of the catalyst containing an N-heterocyclic carbene was observed for electron rich amides. Also direct generation of enoic carbenes by catalyst was possible from acrylates, acrylic acid and vinyl ketones. Enoic carbenes were shown to catalytically ring-open cyclohexene for the first time. Chapter 2 also provides examples of challenging CM between Type II and Type III olefins.

Chapter 3 demonstrates facile tandem RCM strategies to rapidly synthesize complex small molecules by the catalyst containing an N-heterocyclic carbene. Tandem ring-opening/ring-closing metathesis and tandem enyne RCM provided bicyclic compounds with good yields. An example of bicyclic macrocycle is presented. Lastly tandem ring-opening/cross/ring-closing metathesis, also known as ring expansion metathesis (REM), provided a convenient route to various macrocycles from the smaller cycloalkenes.

Chapter 4 introduces a new concept of metathesis polymerization, multiple olefin metathesis polymerizations (MOMP). MOMP uses more than one olefin metathesis process to synthesize polymers with uniform polymer microstructures. Ring-opening insertion metathesis

polymerization (ROIMP) combines ROMP and CM process to yield highly A,B-alternating copolymers. Also ring-opening/ring-closing polymerization and ring-opening/closing addition polymerization were demonstrated.

Final chapter explores living ROMP of norbornene and its derivatives with a new ultra-fast-initiating catalyst. The modified catalyst produced the polymers with very narrow PDI and the monomers which used to be problematic with the previous catalysts also underwent living ROMP. Also amphiphilic block copolymers were prepared and shown to undergo spontaneous self-assembly in the reaction solution to produce stable nanoparticles even without cross-linking. Nanoparticles of 10 to 50 nm in radius were characterized by GPC, DLS and SEM.

In summary, this thesis describes the versatility of ruthenium catalysts being able to produce small molecules, macrocyles, polymers, and even supramolecules. Molecules that are described in the thesis have molecular weights ranging from 100 to 2 million g/mol, and the reactions to prepare those molecules with various sizes are fundamentally and mechanistically one transformation, the exchange of C=C bonds. This is a success story of how interdisciplinary efforts from organic, organometallic, and polymer communities have brought the new concept to chemical synthesis.

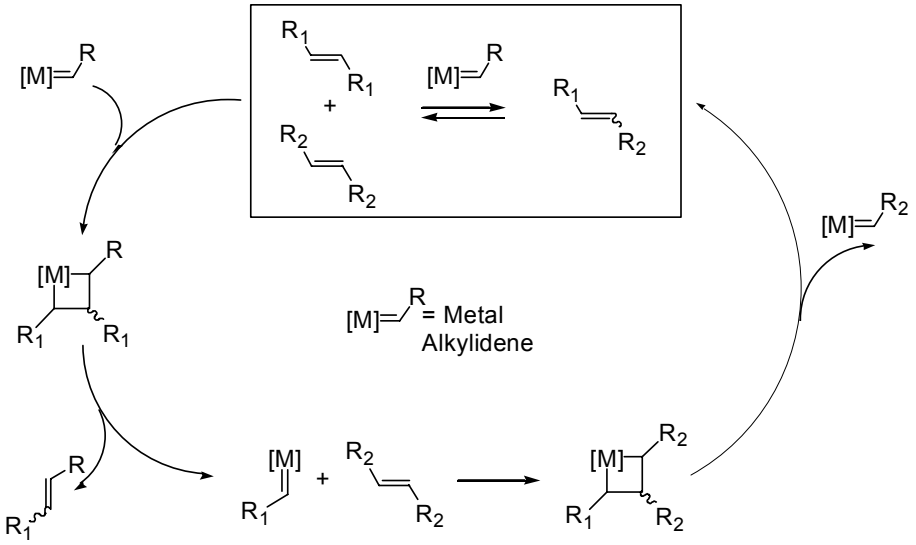
Table of Contents

Chapter 1:

Introduction to Olefin Metathesis

Brief History of Olefin Metathesis

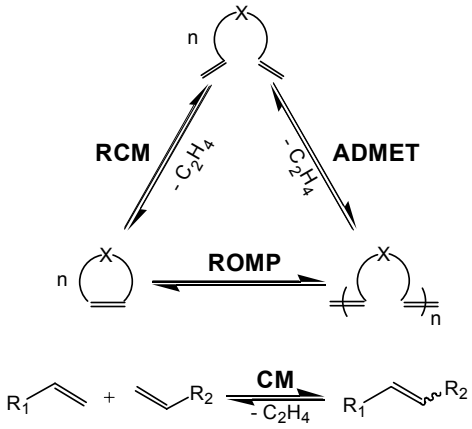
Olefin metathesis is a unique process undergoing C=C bond rearrangement as shown in Scheme 1.[1] The reaction is catalyzed by transition metal carebenes which form metallocyclobutane intermediates by a formal [2+2] cycloaddition. This mechanism, first proposed by Chauvin in 1971,[2] is now the accepted model for olefin metathesis reaction. The reaction is often reversible and the equilibrium is governed by thermodynamic control.



Scheme 1. Accepted mechanism of olefin metathesis

Although olefin metathesis is a fundamentally simple reaction, the reaction can be applied in vastly different ways to synthesize both small and large molecules (Scheme 2). This versatile process produces valuable molecules by three main reactions, ring-opening metatheis polymerization (ROMP),[3] ring-closing metathesis (RCM)[4] and cross metathesis (CM).[5] Also notable reaction is acyclic diene metathesis polymerization (ADMET) which is an extension of CM to the polymer synthesis (Scheme 2).[6] These three metathesis processes can be controlled to favor only one of three possible reactions by manipulating the reaction conditions and the substrates. Although the versatility of olefin metathesis should have immediately attracted tremendous attention from chemists since the first discovery in 1960's,[7] it was only the past fifteen years that the reaction was starting to be recognized and well appreciated among the

synthetic community. For a long time, the main problem had been the unavailability of the catalysts to promote all these useful reactions.



Scheme 2. Various processes of olefin metathesis

In the beginning, olefin metathesis was carried out with ill-defined multicomponent systems containing mixtures of transition metal salts (e.g., WCl_6, $MoCl_5$, $ReCl_5$) and main group organometallic cocatalysts (eg. $RAlCl_2$, SnR_4).[1, 8] Although these systems were highly active in performing metathesis reactions, they suffered greatly from the poor functional group tolerance. Therefore the use of olefin metathesis was limited to unfunctionalized hydrocarbon/fuel chemistry only. Furthermore the activities and the initiations of the classical ill-defined catalysts could not be controlled further diminishing its utility.

The first breakthrough came in mid 1980's when Grubbs reported the first single-component and well-defined metathesis catalyst **1** derived from Tebbe reagent (Figure 1).[9] The titanocyclobutane complex **1** promoted the first living polymerization (ROMP) of norbornene and showed excellent control of the initiation to produce polymers with narrow polydispersity index (PDI). However, the catalyst **1** did not solve the problem toward functional groups intolerance.

Shortly after the initial development of catalyst **1**, Schrock reported another family of well-defined catalysts based on molybdenum and tungsten $(NAr)(OR)_2M{=}CHR'$.[10] These catalysts were highly active and showed some improvement on the functional group tolerance. As a result, they were used to prepare polymers with well-defined microstructures by living ROMP,[11]

and also used to synthesize small molecules by RCM[12] and CM.[13] Nevertheless, oxophilic nature of molybdenum and tungsten still prevented the wide use of olefin metathesis as a general reaction as they exhibited low thermal stability and high sensitivity to air, moisture and some functional groups such as alcohols and aldehydes. In addition, dry-box technique, as well as rigorous purification of solvents and starting materials, was still required.

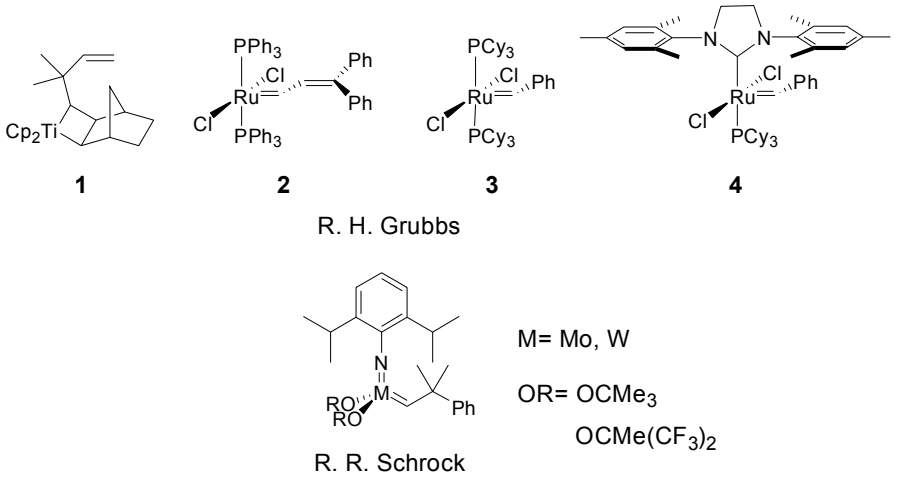


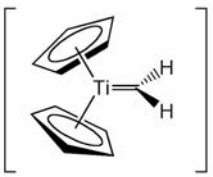
Figure 1. Representative examples of well-defined olefin metathesis catalysts

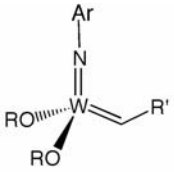
The second groundbreaking achievement that revolutionized olefin metathesis was made with the appearance of a new class of ruthenium-based catalysts.[14] Grubbs and Novak noted that ruthenium salts were able to promote ROMP of highly strained cycloolefins even in polar media.[15] This promising observation led to the development of the first well-defined ruthenium catalyst **2** by Nguyen and Grubbs in 1992.[16] The new catalyst was found to be tolerant to a wide range of functional groups including aldehydes, alcohol, acid, air and moisture. Unfortunately the catalyst was only active for ROMP of highly strained monomers. With the continuous efforts from Grubbs lab, the more active ruthenium catalyst **3** was developed by substituting triphenyl phosphine with tricyclohexyl phosphine.[17] The more bulky and electron-donating tricyclohexyl phosphine seemed to produce the more stabilized 14-electron-ruthenium intermediate which was believed to be the real active catalytic specie.[18] The increased activity of catalyst **3** allowed not only the ROMP of monomers with low strain, but also RCM and CM of various substrates with

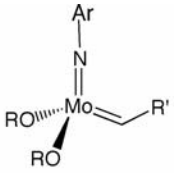
high yields. Therefore catalyst **3** was successfully applied in numerous areas such as total synthesis of many natural products,[19] drug discovery, fine chemical synthesis, biomaterials[20] and biopolymers,[21] conducting[22] and luminescence materials[23] and many other. However, catalyst **3** was still less active than early transition metal based catalysts.

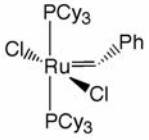
Table 1 shows a general trend of the inverse relationship between the functional group tolerance and the activity for different catalysts (the more active catalysts, the more sensitive to functional group). From the trend in Table 1, the activity of ruthenium-based catalysts seemed to be limited by nature, thus unable to rival with the previous early transition metal systems, but Grubbs group never gave up.

Table 1. Summary of properties for various catalysts









	Titanium	Tungsten	Molybdenum	Ruthenium
Increasing order of reactivity ↑	Acids	Acids	Acids	**Olefins**
	Alcohols, Water	Alcohols, Water	Alcohols, Water	Acids
	Aldehydes	Aldehydes	Aldehydes	Alcohols, Water
	Ketones	Ketones	**Olefins**	Aldehydes
	Esters, Amides	**Olefins**	Ketones	Ketones
	Olefins	Esters, Amides	Esters, Amides	Esters, Amides

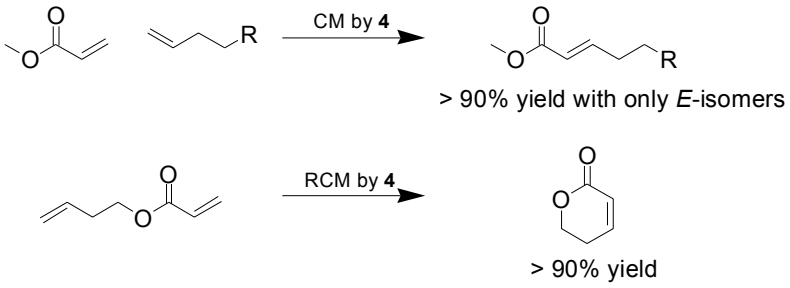
functional group tolerance →

← Activity

Three years after the discovery of catalyst **3**, the third major advance in the catalyst design came about with the development of highly active catalyst **4** whose activity was comparable to molybdenum catalyst if not better.[24] Major modification was made by incorporating N-heterocyclic carbene ligand ($IMesH_2$) in place of one of the tricyclohexyl phosphines. N-Heterocyclic carbenes stabilized by both resonance effect and inductive effect from two nitrogens is an even stronger σ-donor than any phosphines.[25] Thus more electron rich

metal center can further stabilize the real active 14-electron-specie. A detailed mechanistic study was performed to understand the origin of the increased activity and revealed that although the ligand dissociation of catalyst **4** to enter the catalytic cycles was 100 times slower than that of catalyst **3**, catalyst **4** can stay in the catalytic cycles 1000 times longer than catalyst **3**.[26] Therefore more catalyst turnover is observed.

Both increase in activity and stability allowed catalyst **4** to perform olefin metathesis reactions with a variety of substrates that had not been possible with the previous catalysts. A good example of such reaction is RCM and CM of acrylates containing substrates (Scheme 3).[27] Catalyst **3** did not react with acrylates in CM and Schrock's molybdenum and tungsten catalysts formed catalytically inactive metallocyclobutene intermediates by chelation from the carbonyl oxygen.[28] However catalyst **4** exhibited an excellent reactivity towards acrylates which will be also demonstrated in coming chapters. With catalyst **4**, expansion of substrates scope and development of new reactions is expected.



Scheme 3. Successful CM and RCM with catalyst **4**

Thesis Research

As seen from the history of olefin metathesis, development of new and improved catalysts brings new applications and new structures that are accessible by metathesis routes. With the development of highly active catalyst **4** containing N-heterocyclic carbene, the field of olefin metathesis is currently in a period of renaissance opening up the versatile synthesis of both

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Reference:

1. Ivin, K. J.; Mol, J. C. *Olefin Metathesis and Metathesis Polymerization*, Academic Press, San Diego, CA, **1997.**
2. Herrison, J. L.; Chauvin,Y. *Makromol. Chem*. **1971**, *141*,161.
3. For recent reviews, see: a) Novak, B. M.; Risse, W.; Grubbs, R. H. *Adv. Polym. Sci.* **1992**, *102*, 47; b) Grubbs, R. H.; Khosravi, E. *Material Science and Technology*, **1999**, *20*, 65; c) Buchmeiser, M. R. *Chem. Rev.* **2000**, *100*, 1565.
4. For recent reviews, see: a) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res*. **1995**, *28*, 446; b) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413; c) Armstrong, S. K. *J. Chem. Soc. Perkin Trans. 1* **1998**, 371.
5. For recent reviews, see: a) Schuster, M.; Blechert, S. *Angew. Chem*. **1997**, *109*, 2124; *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2067; b) Blechert, S. *Pure Appl. Chem.* **1999**, *71*, 1393; c) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **2003**, *41*, 3171.
6. a) Konzelman, J.; Wagner, K. B. Wagener, K. B. *Macromolecules* **1996**, *29*, 7657; b) Wolfe, P. S.; Gomez, F. J.; Wagener, K. B. *Macromolecules* **1997**, *30*, 714; c)Lehman, S. E.; Wagener, K. B. *Macromolecules* **2002**, *35*, 48.
7. Calderon, N. *Chem. Eng. News* **1967**, *45*, 51.
8. a) Grubbs, R. H.; *J. Macromol. Sci. Chem.* **1994**, *A31*, 1829; b) Schrock, R. R. *Pure Appl. Chem.* **1994**, *66*, 1447.
9. a) Tebbe, F. N.; Parshall, G. W.; Reddy, G. *J. Am. Chem. Soc.* **1978**, *100*, 3611; b) Lee, J. B.; Ott, K. C. Grubbs, R. H. *J. Am. Chem. Soc.* **1982**, *104*, 7491; c) Gilliom, L. R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1986**, *108*, 733.
10. a) Schrock, R. R.; Murdzek, J. S.; Bazan, G, C.; Robibins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875, b) Bazan, G. C. ; Oskam, J. H.; Cho, H.-N.; Park, L. Y.;

Schrock, R. R. *J. Am. Chem. Soc.* **1991**, *113*, 6899, c) Feldman, J.; Schrock, R. R. *Prog. Inorg, Chem.* **1991**, *39*, 1.

11. a) Schrock, R. R. *Acc. Chem. Res.* **1990**, *23*, 158; b) Bazan, G. C.; Schrock, R. R.; Cho, H. N.; Gibson, V. C. *Macromolecules* **1991**, *24*, 4495.
12. a) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 5426; b) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 7324.
13. a) Crowe, W. E.; Zhang, Z. *J. Am. Chem. Soc.* **1993**, *115*, 10998; b) Crowe, W. E.; Goldberg, D. R. *J. Am. Chem. Soc.* **1995**, *117*, 5162.
14. Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18.
15. Novak, B. M.; Grubbs, R. H. *J. Am. Chem. Soc.* **1988** *110*, 960.
16. a) Nguyen, S. T.; Johnson, L. K.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 3974; b) Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 3974.
17. Schwab, P.; Grubbs, R. H.; Ziller J. W., *J. Am. Chem. Soc.* **1996**, *118*, 100.
18. Dias, E. L.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1997**, *119*, 3887.
19. Furstner, A. *Angew. Chem. Int. Ed*. **2000**, *39*, 3013.
20. Huwe, C. M.; Woltering, T. J.; Jiricek,J; Weitz-Schmidt, G.; Wong, C. H. *Bioorg. Med. Chem.* **1999**, *7*, 773
21. a) Fraser, C.; Grubbs, R. H. *Macromolecules* **1995**, *28*, 7248; b) Mortell, K. H.; Weatherman, R. V.; Kiessling, L. L. *J. Am. Chem. Soc.* **1996**, *118*, 2297; c) Maynard, H. D.; Okada, S.;Grubbs, R. H. *J. Am. Chem. Soc.* in press.
22. a) Gorman, C. B.; Ginsburg, E. J.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 1397; b) Royappa, A. T.; Saunders, R. S.; Rubner, M. F.; Cohen, R. E. *Langmuir* **1998**, *14*, 6207.
23. a) Wagaman, M. W.; Grubbs, R. H. *Syn. Met.* **1997**, *84*, 327; b) Pu, L.; Wagaman, M. W.; Grubbs, R. H. *Macromolecules* **1996**, *119*, 1138.
24. Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.

25. a) Arduengo, A. J.; Georlich, J.; Marshall, W. *J. Am. Chem. Soc.* **1991**, *113*, 361, b) Bourissou, D.; Guerret, O.; Gabbai, F. P.; Bertrand, G. *Chem. Rev.* **2000**, *100*, 39.
26. Sanford, M. S.; Ulman, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 749.
27. Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783.
28. Feldman, J.; Murdzek, J. S .; Davis, W. M.; Schrock, R. R. *Organometallics* **1989**, *8*, 2260.

Chapter 2:

Cross Metathesis of Functionalized Olefins by an N-Heterocyclic Carbene Containing Ruthenium Catalyst

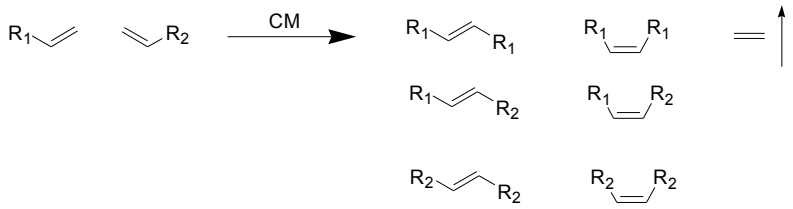
Abstract

Cross metathesis (CM) has been an under-investigated area due to the lack of catalysts' activity and selectivity compared to other olefin metathesis process. Over the past few years, controlling product selectivity has been the key issue on CM. With the development of a highly active and functional group tolerant catalyst **1** bearing an N-heterocyclic carbene, substrate scope has been greatly expanded, opening a mild route to many valuable reagents by CM. Also, the product selectivity has been greatly improved, often yielding one product exclusively. In this chapter, new substrate scopes, mainly α,β-unsaturated carbonyl compounds and efforts to control the product selectivity by catalyst **1** are described.

Background

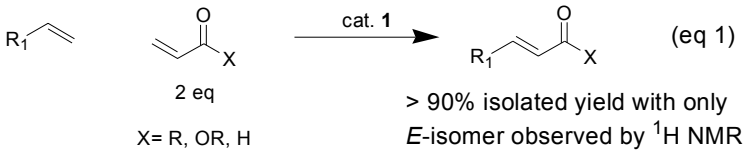
Cross metathesis (CM) is an the intermolecular coupling of two olefins forming a new internal olefin.[1] CM has advantages over other metal-catalyzed coupling reactions such as high catalyst stability and ready availability or accessibility (easy synthesis) of the reagents, olefins. Also, many times the reactions are run at room temperature or slightly elevated temperature (40 ^{o}C) with relatively short reaction time (less than 12 hours). Since the development of well-defined catalysts, $Cl_2(PCy_3)_2Ru$=CHPh (**2**)[2] and $((CF_3)_2MeCO)_2$(ArN)-Mo=CH(*t*-Bu) (**3**),[3] the use of CM has begun to increase along with the increase in the catalysts' functional group tolerance, especially with catalyst **2** which showed high functional group tolerance even with moisture and air, but decreased activity compared to **3**.

However, CM reactions have a limitation that other transition metals do not suffer from. For example, Suzuki reaction catalyzed by Pd(0) promotes exclusive coupling between aryl halides with its organoboronic acids or esters.[4] Also the olefin-forming Suzuki reaction between vinyl halides and organoboronic acids or esters exclusively produces only one new internal olefin with the same olefin geometry of the vinyl halides. However, due to the similar reactivity of two olefins and the thermodynamic control of olefin metathesis process, typical CM produces six different products, a statistical mixture of cross-coupled product, and two homo-coupled products with each having two stereoisomers, *cis* and *trans* isomers (Scheme 1). Out of these six possible CM products, only one of them is typically desired. For example, use of a 1: 1 ratio of two reagents produces only 50% of the desired CM product with mixture of *cis* and *trans* isomers. To achieve higher than 90% yield of the desired product, an impractical ratio at least 10 : 1 of two reagents are required. Even so, the yield is again eroded by the mixture of stereoisomers although many times, the reversible thermodynamic control of olefin metathesis gives moderate to high *E* / *Z* ratios.



Scheme 1. Possible mixture of prodcuts obtained by CM

A breakthrough in CM came with the development of highly active and functional group tolerant catalyst **1** from our group.[5] The new catalyst made CM more useful by improving the E / Z ratio to 10: 1 from 4 : 1, and expanding the substrate scope to include olefins which were unreactive with the previous catalysts, **2** and **3**. Most importantly, catalyst **1** was able to react with different rates depending on the electronics and sterics of the two olefins. Therefore, CM between two olefins with different reactivities allowed the selective CM. The first examples of the selective CM reactions between terminal olefins and acrylein, acrylates and vinyl ketones were demonstrated by Dr. Chatterjee in our lab (eq 1).[6]



(eq 1)

This chapter further expands the substrates scope accessible by catalyst **1**.[7] Also, some new strategies to increase the product selectivity and new reactions are demonstrated here. From the results of CM reactions from the literature reports and our group, as well as data presented in this chapter, we devised a general model based on the categorization of olefin reactivity which can be used to predict both selective and non-selective cross metathesis reactions.[8]

Although the various possible alkylidene intermediates and the numerous primary and secondary metathesis pathways involved in a cross metathesis reaction complicate the attempts to fully understand and predict the CM outcome, we can empirically categorize or rank olefins with different reactivity based on their ability to homodimerize. However, instead of simply looking at the absolute rates of homodimerization, we looked at the relative homodimerization rates to other olefins and describe olefins on a gradient scale of their propensity to undergo homodimerization, and more importantly, the

subsequent reactivity of their homodimers. This analysis leads to a general model that comprises four distinct olefin Types which can be used to predict both selective and non-selective CM reactions (Figure 1).

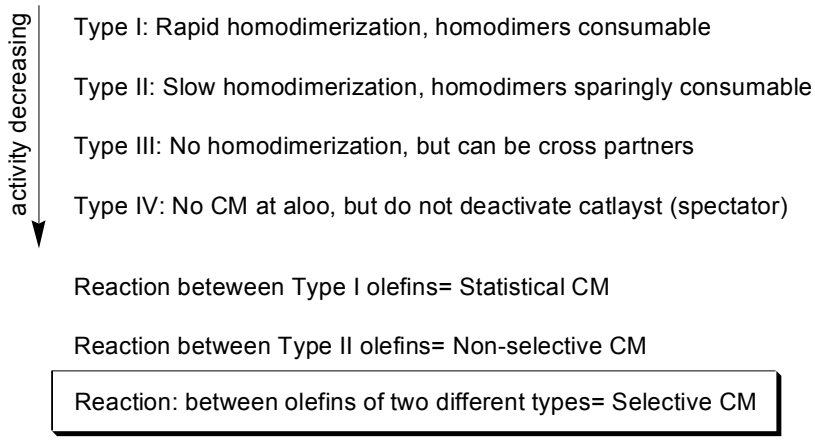


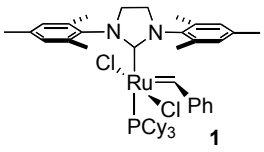
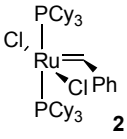
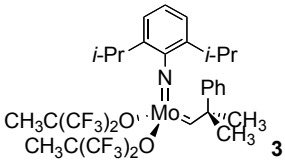
Figure 1. Categorization of olefins and rules for selective CM

Type I olefins are categorized as those able to undergo a rapid homodimerization, and whose homodimers can participate in further CM. Type II olefins homodimerize slowly, and unlike Type I olefins, their homodimers can only be sparingly consumed in subsequent metathesis reactions. Type III olefins are essentially unable to be homodimerized by the catalyst, but are still able to undergo CM with Type I and Type II olefins. Type IV olefins are not able to participate in CM with a particular catalyst, but do not inhibit catalyst activity toward other olefins. Outside these categories are olefins that deactivate the catalyst. In general, a reactivity gradient exists from most active Type (Type I olefin) to least active Type (Type IV), with sterically unhindered, electron-rich olefins categorized as Type I and increasingly sterically hindered and/or electron-deficient olefins falling into Types II through IV.

To achieve selective CM reaction, two olefins with different types should be coupled. For example, CM between terminal olefins (Type I) and methyl acrylate (Type II) by catalyst **1** gives the desired CM product with 95% isolated yield.[6] On the other hand, reactions between the same type of olefins result in either statistical CM (for Type I olefins) or non-selective CM (for Type II olefins). The main difference between statistical and non-selective CM is that the CM products of Type I olefins can be

re-equilibrated to give statistical mixtures, but the CM products of Type II olefins can hardly undergo further metathesis reactions. In addition, the conversion of more challenging Type II olefins tends to be lower than Type I. Table 1 shows categorization of various olefins reported in the literature for three most used catalysts.

Table 1. Olefin Categories for Selective Cross Metathesis

Olefin type	 1	 2	 3
Type I (fast homodimerization)	terminal olefins, 1° allylic alcohols, esters, allyl boronate esters, allyl halides, styrenes (no large ortho substit.), allyl phosphonates, allyl silanes, phosphine oxides, sulfides, protected amines	terminal olefins, allyl silanes, 1° allylic alcohols, ethers, esters, allyl boronate esters, allyl halides	terminal olefins, allyl silanes
Type II (slow homodimerization)	styrenes (large ortho substit.), acrylate, acrylamides, acrylic acids, acrolein, vinyl ketones, unprotected 3° allylic alcohols, vinyl epoxides, 2° allylic alcohols, perfluorinated alkane olefins	styrene, 2° allylic alcohols, vinyl dioxolanes, vinyl boronates	styrene, allyl stannanes
Type III (no homodimerization)	1,1-disubstituted olefins, non-bulky trisub. olefins, vinyl phosphonates, phenyl vinyl sulfone, 4° allylic carbons (all alkyl substituents), 3° allylic alcohols (protected)	vinyl siloxanes	tertiary allyl amines, acrylonitrile
Type IV (spectators to CM)	vinyl nitro olefins, trisubstituted allylic alcohols (protected)	1,1-disubstituted olefins, disub. α,β-unsaturated carbonyls, 4° allylic carbon containing olefins, perfluorinated alkane olefins, 3° allylamines (protected)	1,1-disubstituted olefins

Part I. Cross Metathesis of Functionalized Olefins

Introduction

Over the past few years, olefin metathesis has become a useful reaction in organic,[9] polymer[10] and bioorganic chemistry.[11] Among olefin metathesis reactions, ring-closing metathesis (RCM) and ring-opening metathesis polymerization (ROMP) have received the most attention. However, cross metathesis (CM) is also of increasing utility in new C=C bond formation under mild conditions.[12] The synthesis of trisubstituted[14] and functionalized alkenes[6] by cross-metathesis has become possible due to the development of the more active and the more stable catalyst **1**, containing the 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene ligand,[5] Catalyst **1** not only has activity comparable to early transition metal catalysts, but also retains functional group tolerance comparable to catalyst **2**.[2]

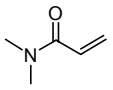
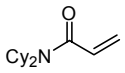
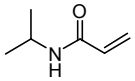
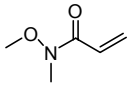
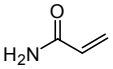
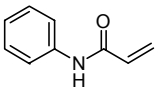
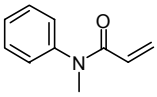
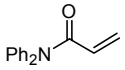
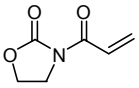
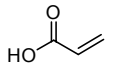
The efficient preparation of α,β-unsaturated amides remains as one of underdeveloped areas of organic synthesis. Current approaches to acrylic amides include Wittig and aldol chemistry which requires strong bases. Therefore milder methodology by CM would be valuable. This section describes a versatile cross-coupling reaction of various α,β-unsaturated amides with terminal olefins and styrene, and shows that CM efficiency is affected by the substituents on the amide nitrogen.

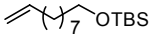
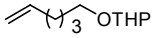
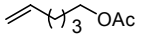
Results and Discussion

Several acrylic amides (Type II olefin) were screened for CM with terminal olefins (Type I olefin) (Table 2). Initially, dimethyl acrylamide with 1.25 equivalents of terminal olefin **I** (entry 1a) was tried and a disappointingly low yield of 39% of CM product was obtained. However, with higher catalyst loading, (9 mol % of catalyst **1**) and 1.5 equivalents of terminal olefin, the yield was improved to 83% (entry 1b). Other substrates showed good to excellent yields ranging from 77% to 100% with excellent diastereoselectivity (*E*: *Z* > 25: 1). Particularly valuable is the compatibility with Weinreb amides[14] (entry 4) and oxazolidinone imides (entry 9).[15] These functional groups are used widely in organic synthesis and CM now provides synthons for further manipulations. In particular, oxazolidinone imides are widely used

in asymmetric reactions[16] such as Michael additions,[17] aldol,[18] and Diels-Alder reactions.[19] Surprisingly, acrylic acid shown to be an excellent cross partner with terminal olefins (entry 10) even though acids are known to accelerate the catalyst decomposition.[20] Another valuable cross partner, styrene (Type I olefin), was examined for CM with acrylic amides. The yields with styrene are lower but show a similar trend in yields (ranging from 25% to 87%) to CM with terminal olefins (Table 2).

Table 2. CM of acrylamides with terminal olefins[a] and stryene[b]

entry	acrylamide	terminal olefin	isolated yield of CM with terminal olefin(*E*/*Z*) [%]	isolated yield of CM with styrene [%][c]
1a		I	**4:** 39 (25:1)	**5:** 25
1b[d]		I	**4:** 83 (25:1)	
2		I	**6:** 77	**7:** 57
3		II	**8:** 80	**9:** 62
4		II	**10:** 89 (60:1)	**11:** 66
5		III	**12:** 89	**13:** 69
6		II	**14:** 90	**15:** 69
7		II	**16** 97 (28:1)	**17:** 83
8		II	**18:** 100 (40:1)	**19:** 87
9		I	**20:** 87 (60:1)	**21:** 40[e]
10		II	**22:** 100	**23:** 63

I:  **II**:  **III**: 

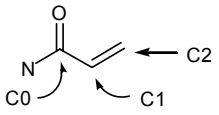
[a] Reactions with 5 mol% catalyst **1** and 1.25 eq terminal olefin in 0.2 M CH_2Cl_2 at 40 °C for 12 hours. [b] Reaction with 5 mol% catalyst **1** and 1.9 eq styrene in 0.2 M CH_2Cl_2 at 40 °C for 12 hours. [c] Only E-isomers observed by ^{1}H NMR. [d] Reaction with 9 mol% catalyst **3** and 1.5 eq terminal olefin. [e] Yield determined by ^{1}H NMR.

A certain trend on the nature of nitrogen substituents seemed to govern the yield of CM. Electron-donating substituents, such as alkyl groups, on the amide nitrogen resulted in lower yields of cross products, whereas electron-withdrawing substituents resulted in higher yields. These observations led us to suggest that the amide carbonyl group might be chelated to the metal center, (Scheme 2, **A** or **B**) thus decreasing catalyst turnover. The degree of chelation would depend on the electron density on the amide oxygen. Ab initio calculations (HF 6-31G**) of several amides showed a distinct inverse relationship between the calculated electron density on the carbonyl oxygen of the amides and the observed CM yields. (Table 3)

Table 3. Electron Density Calculation[a]

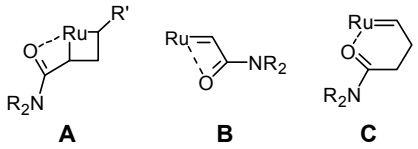
atom(NPA)	Me_2N	iPrNH	NH_2	HNPh	MeNPh	Ph_2N
N	-.572	-.754	-.929	-.748	-.579	-.582
C0	.829	.830	.815	.831	.831	.835
C1	-.370	-.375	-.370	-.376	-.365	-.368
C2	-.305	-.304	-.309	-.306	-.314	-.311
O	-.741	-.735	-.725	-.725	-.730	-.707
Yield[b]:	25%	62%	69%	69%	83%	87%

[a] Calculation was done by Spartan using Hartree-Fock 6.31G ** method.
[b] Yields of CM with 1.9 eq styrene.



Chelation effects in olefin metathesis have been seen occasionally. Schrock isolated a metallocyclobutane moiety possessing a 4-membered chelate from the reactions between Mo and W based catalysts and acrylates and acrylic amides.[21] The new species were catalytically inactive suggesting strong chelation. Although ruthenium-based catalysts are much less oxophilic than the early transition metal catalysts, and the more electron rich catalyst **1** is even less prone to chelation than **2**,[22] chelation to form stable 5- and 6-membered rings with both catalysts **1** and **2** has been previously observed or proposed.[23] Although no direct evidence for catalyst deactivation by chelation of carbonyl oxygen to the Ru metal center was known, more electron rich carbonyl containing acrylic amides might have a higher propensity for chelation. In addition, dicyclohexyl acrylamide (Table 2, entry 2) gave higher a yield in

CM than dimethyl acrylamide (entry 1), despite the similar electronic properties. Perhaps unfavorable steric interactions between bulky dicyclohexyl group and bulky imidazolylidene ligand decreased carbonyl chelation, and increased catalyst turnover.



A **B** **C**

Scheme 2. Proposed chelation

Kinetic studies were performed in order to obtain detailed information about the CM reactions with terminal olefins. As expected, the more electron rich amides reacted more slowly than the electron poor amides. Most notably, when dimethyl acrylamide was the CM partner, only 33% of the terminal olefin participated in either CM or dimerization after 1 hour. In contrast, when diphenyl acrylamide was used, 93% of the terminal olefin participated in metathesis reactions in the same period of time. This strongly supports our speculation that chelation effect of electron-rich amides slows down the metathesis activity by lowering catalytic turnover.

Further kinetic study of the homodimerization of four terminal olefins provides support for the proposed catalyst inhibition by chelation (Figure 2). Of the four olefins, the non-functionalized terminal olefin **I** dimerized fastest followed by substrates **IV**, **V**, and **VI**, respectively. The fact that the rate of dimerization decreases as the electron density on the carbonyls increases (**IV** < **V** < **VI**), supports the six-membered chelate intermediate (Scheme 2 **C**). In all cases, the metathesis reaction was slow enough for a new alkylidene to be observed by ^{1}H NMR (18.5 ppm in CD_2Cl_2) at the beginning of the reaction. A second new alkylidene peak at 18.6 ppm, assigned as the chelated alkylidene, was detected in significant amounts during the dimerization of olefin **VI**. This observation strongly supports the deactivation of the catalyst by chelation of the electron-rich carbonyl group.

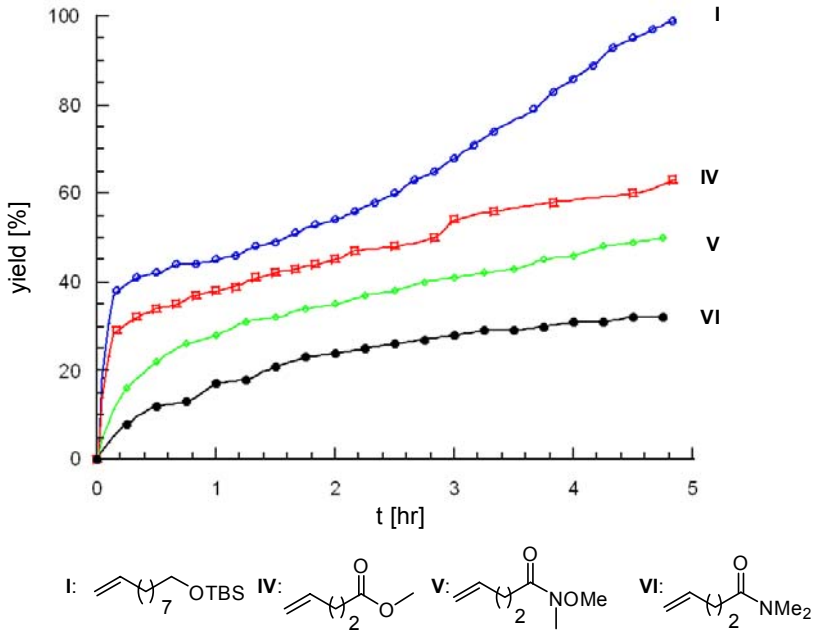
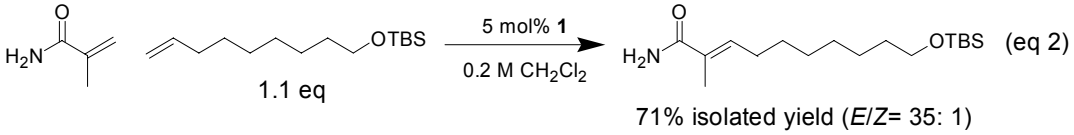


Figure 2. Kinetic studies of various terminal olefins by ^{1}H NMR

Synthesis of trisubstituted acrylamides further extended the application of CM reactions. Methacrylic amide underwent successful CM of terminal olefin **I** with a good yield and an excellent stereoselectivity to produce a trisubstituted acrylic amide (eq 2). This is a typical example of CM between Type I and III olefin (methacrylamide).

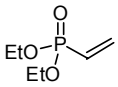
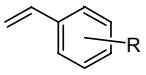
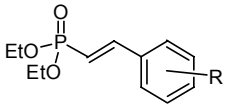
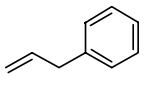
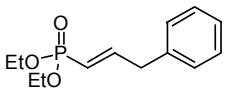
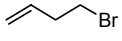
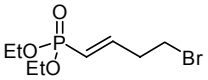


Vinylphosphonates are important synthetic intermediates[24] and have been investigated as biologically active compounds.[25] Vinylphosphonates[26] have been used as intermediates in stereoselective synthesis of trisubstituted olefins[27] and in heterocycle synthesis.[28] The synthesis of vinylphosphonates has also been widely examined and a variety of non-catalytic approaches have been described in the literature.[29] Recent metal-catalyzed methods include palladium catalyzed cross-coupling[30] and Heck coupling of aryldiazonium salts with vinyl phosphonates,[31] but are limited by the requirement of highly reactive functional groups in the substrates. Therefore, a more mild, general and stereoselective method

for the synthesis of vinyl phosphonates using commercially available starting materials would be valuable, and may provide an additional degree of orthogonality to the previously reported syntheses.

Firstly, the participation of a variety of styrenes in the CM reaction with another Type II olefin, vinyl phosphonate was investigated. These results indicate a variety of styrenes were converted to (*E*)-cinnamyl phosphonates in excellent yield (Table 4). Notably, 4-bromostryene crossed product (**26**) was obtained in an excellent yield which can be further functionalized by conventional Pd(0) couplings. Sterically challenging substrates like 2,4-dimethly styrene also gave good yield (compound **27**). However, substrate with bulky and electron withdrawing group at *ortho* position gave a poor result (compound **30**). In general, the CM method tolerates electronic and some steric constraints in the styrene partner and allows for CM between two electron-deficient olefins. Also, 4-bromobutene and allyl benzene were shown to be good substrates of CM with diethyl vinyl phosphonate (compound **31** and **32**).

Table 4. Cross metathesis of diethyl vinyl phosphonate

substrate	cross partner(1.5 eq)	product[b]	isolated yield [%]
			**24:** 97 R = H **25:** 97 R = 4-OMe **26:** 93 R = 4-Br **27:** 77 R = 2,4-$(CH_3)_2$ **28:** 73 R= 4- OAc **29:** 68 R= 4- NO_2 **30:** 34 R= 2-Cl
			**31:** 90
			**32:** 82

[a] 5 mol% catalyst **1** at 40 °C in 0.2 M CH_2Cl_2 for 12 hours [b] Only *E* isomer observed by ^1H NMR

Conclusion

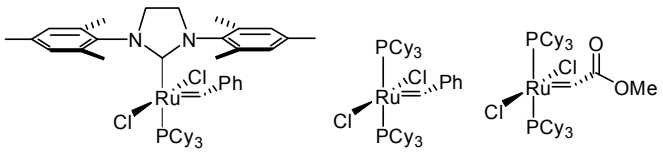
In summary, α,β-unsaturated amides are excellent cross metathesis partners with terminal olefins and styrene. This method allows for an efficient one-step formation of functionalized α,β-unsaturated

amides under mild conditions. More electron rich amides give lower yields due to lower metathesis activity resulting from carbonyl chelation to the Ru center. However, higher catalyst loading compensates for the chelation effect. Also, vinyl phosphonate was a good CM partner with Type I olefins.

Part II. Cross Metathesis of Enoic Carbenes

Introduction

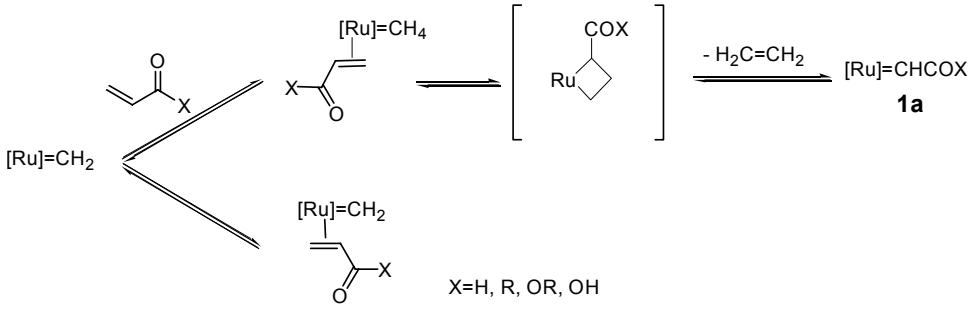
Olefin metathesis has become a valuable reaction in organic synthesis, as has been demonstrated by its frequent use as the key bond constructions for total syntheses of many natural products.[10] With the recent discovery of highly active catalyst **1**,[6] trisubstituted alkenes and functionalized alkenes have been synthesized efficiently by cross metathesis (CM), further expanding the substrate scope for this reaction.[7, 14] With these successes in hand, unprecedented metathesis reactions were explored. There have been no previous reports of the dimerization of α,β-unsaturated carbonyl compounds by a metathesis mechanism. Molybdenum and tungsten-based catalysts form metallocyclobutane with acrylates, but the newly formed intermediates are inactive due to carbonyl oxygen chelation.[21] Our group reported the synthesis of enoic carbene **2a** by a non-metathesis route and showed that **2a** was extremely reactive to be the first carbene to ring-open cyclohexene although the reaction was stoichiometric in **2a**.[32] Due to non-trivial synthesis, lack of stability, and the absence of catalytic turnover, enoic carbene **2a** has not been investigated further.



1 **2** **2a**

Previous reports on the mechanism of cross metathesis reactions between terminal olefins and α,β-unsaturated carbonyl compounds state that catalyst **1** reacts preferentially with terminal olefins to form an alkylidene which crosses onto α,β-unsaturated carbonyl compounds to form methylidene and CM product.[7, 33] At that time, the formation of the unstable enoic carbene **1a** was believed to be less likely. However it was recently discovered that the electron rich catalyst **1** was, in fact, able to react with

α,β-unsaturated carbonyl compounds directly to form enoic carbene **1a** effectively under certain conditions. Herein, we report the first efficient generation of enoic carbenes **1a** in situ with catalyst **1** (Scheme 3), and successful catalytic CM and ring-opening reactions of previously inactive metathesis substrates.



Scheme 3. Direct generation of enoic carbene

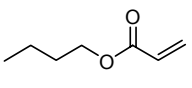
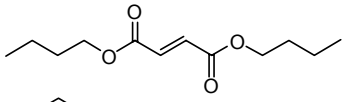
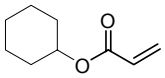
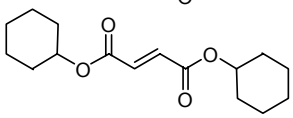
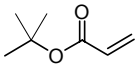
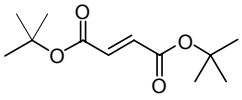
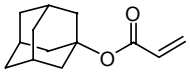
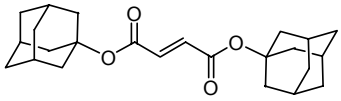
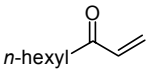
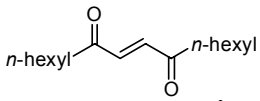
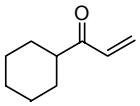
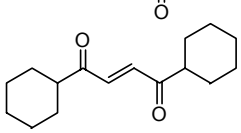
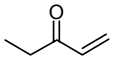
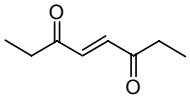
Results and Discussion

The formation of enoic carbene **1a** was initially discovered in the dimerization of acrylates to form fumarates. Initial attempts to dimerize *n*-butyl acrylate at 0.2 M in refluxing CH_2Cl_2 only gave 44% of the desired product of *E*-isomer, and the balance as starting material. GC analysis showed the reaction was completed in less than two hours and no carbene peak including the parent benzylidene or methylidene was observed by ^1H NMR after two hours. This suggests enoic carbene **5** is still unstable, with a much shorter lifetime than other alkylidene or benzylidene. To our delight, an attempt to increase the rate by doubling the concentration to 0.4 M resulted in 87% yield of dimer (Table 5, entry 1). Other solvents like $CHCl_3$, CCl_4, C_6H_6, and THF were tried, but they all produced much poorer results than CH_2Cl_2. Normally, olefin metathesis catalysts are not extremely sensitive to solvents conditions except for coordinating solvents like THF or protic solvent, so the dramatic observed solvent effect is unprecedented. It is speculated that enoic carbene **5** is the most stable in CH_2Cl_2 among other solvents. Various acrylates with different sizes, even the tertiary acrylates were effectively dimerized by this

procedure (Table 5, entry 1-4). However, the dimerization of phenyl acrylate was unsuccessful, implying the enoic carbenes might have a subtle electronic effect.

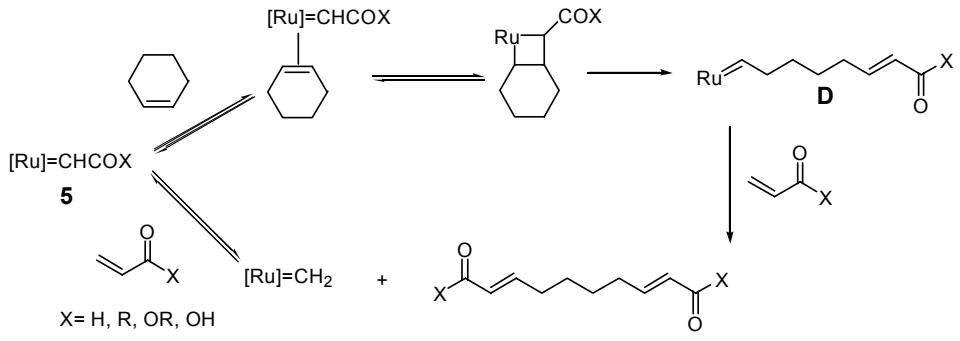
Interestingly, vinyl ketones behaved quite differently from acrylates. Dimerization of hexyl vinyl ketone at 0.4 M gave only 29% of the desired product, and increasing concentration further decreased the yield (less than 5% at 0.6 M by ^{1}H NMR). However, decreasing the concentration increased the yield and an optimized yield was obtained at 0.05 M (Table 5, entry 5-7). Following the reactions by ^{1}H NMR revealed that at 0.05 M, the rate of formation of enoic carbene from vinyl ketones was at least five times faster than that of acrylates. Therefore, a high concentration is required for acrylates to speed up the reactions whereas at that condition, much higher concentration of unstable enoic carbene leads to bimolecular decomposition.[32] Again, similar to the phenyl acrylate case, phenyl vinyl ketone dimerized with low conversion. It is still unknown why the phenyl functionality suppress the dimerization of α,β-unsaturated carbonyl compounds.

Table 5. Dimerization of α,β-unsaturated carbonyl compounds[a]

entry	substrate	product [b]	isolated yield [%]
1			87
2			75
3			94
4			80
5			77
6			95
7			94[c]

[a] 5 mol% catalyst **1** at 0.4 M for acrylates and 0.05 M for vinyl ketones in refluxing CH_2Cl_2 for 3 hrs.
[b] Only the *E* isomer was obtained. [c] Yield was determined by ^1H NMR.

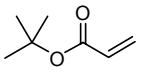
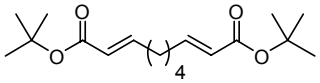
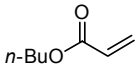
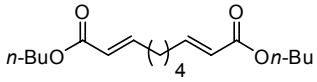
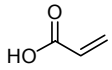
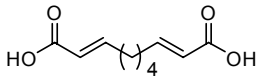
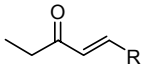
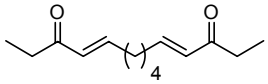
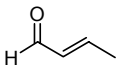
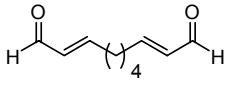
GC analysis showed dimethyl maleate (*Z* isomer) isomerized to dimethyl fumarate (*E* isomer) very slowly when compared to normal internal *cis* olefins.[13] This observation again reflects the unfavorable formation of enoic carbenes compared to alkylidenes. Also, only the *E* isomer was obtained even at early conversion in dimerization reactions, suggesting that the *E* isomer is the kinetic as well as thermodynamic product in these CM reactions.



Scheme 4. Ring-opening of cyclohexene with enoic carbene

Applications of the enoic carbenes to various metathesis reactions beyond simple dimerization are shown in Table 6. Cyclohexene is unique compared to other cycloalkenes because it is not polymerized by ROMP due to the equilibrium exclusively favoring ring-closure. An interesting observation was made when catalyst **2a** unlike catalysts **1**-**3**, could ring-open thermodynamically stable cyclohexene.[32] However, this reaction was stoichiometric in catalyst **2a** because the product of one turnover is an alkylidene which was unreactive towards cyclohexene or acrylates. However, now that enoic carbene **1a** could be generated in situ by catalyst **1**, ring opening of cyclohexene could be achieved in a catalytic fashion (Scheme 4) yielding linear C-10 chains doubly capped with α,β-unsaturated carbonyl compounds (Table 6, entries 1-6). We believe that the reversed ring-closure for intermediate alkylidene **D** is greatly slowed down because it would produce the unstable enoic carbene from more stable alkylidene. Therefore the CM with another molecule of acrylate becomes relatively favored. An excess of cyclohexene (3 equiv.) was used to minimize the dimerization of α,β-unsaturated carbonyl compounds since ring-opening reaction competes with dimerization whose products hardly undergo secondary metathesis reactions. For ethyl vinyl ketone, a relatively fast dimerization became a problem resulting in a lower yield of the ring-opening product. To slow down the undesired dimerization, 2-hexen-4-one was used instead and gave a higher yield for the desired product and less dimer (Table 6, entry 4).

Table 6. Ring-opening cross metathesis reactions of cyclohexene[a]

entry	carbene precusor	cross-partner	product[b]	isolated yield [%]	
1				88	
2				56	
3				94	
4				57 72	R= H R= Me
6				43	

[a] 5 mol% catalyst **1** with 3 eq. of cyclohexene at 0.1 - 0.3 M in refluxing CH_2Cl_2 for 3 hrs. [b] Only the *E* isomer was observed by ^1H NMR.

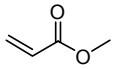
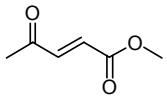
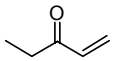
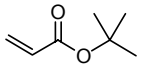
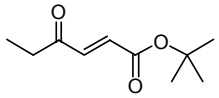
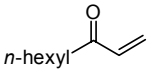
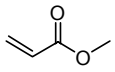
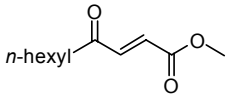
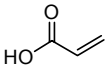
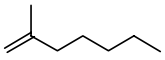
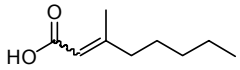
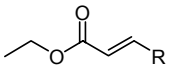
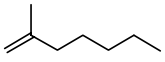
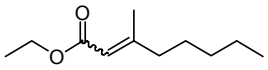
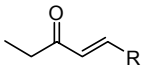
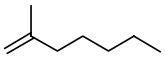
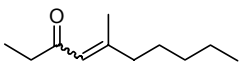
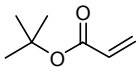
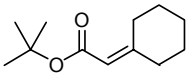
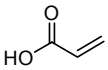
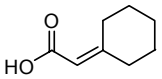
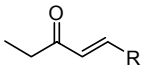
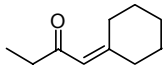
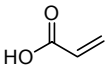
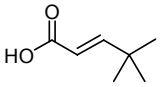
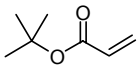
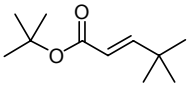
Utilizing enoic carbenes to general CM seems challenging as Type II olefins react slowly with catalyst **1** and their dimers do not undergo further CM reaction. CM between acrylates and vinyl ketones were attempted and only up to 41% of the cross-coupled products were obtained (Table 7, entry 1- 3). Therefore attempts to couple two Type II olefins only result in non-selective CM. Excess of acrylates (2 equiv.) was added to slow down the otherwise faster dimerization of vinyl ketones.

Cross metathesis reactions between α,β-unsaturated carbonyl compounds (Type II) and α-methyl disubstituted olefin (Type III) are more promising because of their different reactivity. Since catalyst **1** reacted preferentially with more reactive Type II olefins to form enoic carbene **1a**, excess of α-methyl disubstituted olefin can be used without resulting in dimerization. Although the formation of **1a** is thermodynamically less favorable, it seems kinetically preferred over reacting with bulky disubstituted alkenes.[14] However, increasing the stoichiometry of the disubstituted olefins produced CM products with good yields. For example, with 2 equiv of α-methyl disubstituted olefin, a 5: 4 mixture of acrylate dimer and the cross product yield was obtained, whereas up to 83% yield of the cross product was achieved by using 4 equiv of α-methyl disubstituted olefin with an *E* to *Z* ratio of 2: 1 (Table 7, entries 4- 6). The rest

was a trace amount of acrylate dimer and the remaining unreacted starting material which can be recovered. Not surprisingly, less sterically hindered methylenecyclohexane proved to be a better cross partner producing up to 99% of the CM products with 2 equiv. of the *gem*-disubstituted olefin.

Compared to terminal α,β-unsaturated carbonyl compounds, β-methyl-disubstituted α,β-unsaturated carbonyl compounds improved the CM yields by 2-40% because the rate of dimerization was suppressed by the methyl group, thereby increasing the relative rate for CM reaction. (Entries 5, 6 and 9). This strategy is particularly useful in the reactions where dimer was substantial side-product. Another example of Type III olefin is 3,3-dimethyl-1-butene which was also a good cross partner (Entries 10 and 11). Since the reagent is relatively cheap and low boiling, it was used as a solvent.

Table 7. Cross metathesis of enoic carbenes[a]

entry	carbene precusor	cross-partner	product	isolated yield [%]	
1				41[b, c]	
2				41[b, c]	
3				33[b, c]	
4				83[e, f]	
5				55[d, e] 83[d, e]	R= H R= Me
6				26[d, e] 68[d, e]	R= H R= Me
7				75[f]	
8				83[f]	
9				57[f] 99[f]	R= H R= Me
10				73[b, g]	
11				73[b, g]	

[a] 5 mol% catalyst at 0.1 - 0.3 M in refluxing CH_2Cl_2 for 3 hrs. [b] Only the *E* isomer was observed by ^1H NMR. [c] 2 eq of acrylates used. [d] 4 eq 2-methyl 1-heptene used. [e] *E* / *Z* = 2.0 determined by 1H NOE NMR. [f] 2 eq of methylenecyclohexene used. [g] 3,3-dimethyl-1-butene was used as a solvent.

Conclusion

We have demonstrated that the highly active catalyst **1** reacts with α,β-unsaturated carbonyl compounds directly to form enoic carbene **1a**, whose activity is dependent on solvent and concentration. It illustrates that the electron rich catalyst **1** sufficiently stabilizes the electron deficient enoic carbene **1a**.

With the in situ generation of enoic carbenes, dimerization, CM with Type III olefins, and catalytic ring-opening of cyclohexene are now attainable.

Acknowledgement: I would like to thank the NIH for generous support of this research, and Dr. C. W. Lee, Dr. A. K. Chatterjee, Dr. M. Scholl, Dr. J. P. Morgan, Daniel P. Sanders, Prof. F. D. Toste, Christie Morrill and Dr. S. D. Goldberg for helpful discussions.

Experimental Section

General Experimental Section. NMR spectra were recorded on Varian-300 NMR. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) with reference to internal solvent. Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), and multiplet (m). The reported ^{1}H NMR data refer to the major olefin isomer unless stated otherwise. The reported ^{13}C NMR data include all peaks observed and no peak assignments were made. High-resolution mass spectra (EI) were provided by the UCLA Mass Spectrometry Facility (University of California, Los Angeles).

Analytical thin-layer chromatography (TLC) was performed using silica gel 60 F254 precoated plates (0.25 mm thickness) with a fluorescent indicator. Flash column chromatography was performed using silica gel 60 (230-400 mesh) from EM Science. All other chemicals were purchased from the Aldrich, Strem, or Nova Biochem Chemical Companies, and used as delivered unless noted otherwise. CH_2Cl_2 was purified by passage through a solvent column prior to use.

General procedure for Part I:

To a flask charged with α,β-unsaturated olefin (1.0 eq) in CH_2Cl_2, catalyst **1** (0.05 eq) in CH_2Cl_2 was added by cannulation followed by addition of either terminal olefin (1.25 eq) or styrene (1.5 to 1.9 eq) via syringe. The flask was fitted with a reflux condenser and was refluxed under argon for 12 hours. The

reaction was monitored by TLC. After the solvent was evaporated, the product was purified directly by a silica gel chromatography.

Compound 4. See **General Procedure**. The product was purified directly on a silica gel column (1x15 cm), eluting with 1: 2= ethyl acetate: hexane. A viscous oil (R_f= 0.45 in 1: 1= EA: Hx) was obtained (26 mg, 39% yield 1.0 mg of *cis* compound separated) ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.85 (1H, dt, *J*= 7.0, 17.0 Hz), 6.20 (1H, d, *J*= 17.0 Hz), 3.58 (2H, t, *J*= 6.7 Hz), 3.00 (6H, s), 2.18 (2H, dt, *J*= 6.7, 6.7 Hz), 1.42 (4H, m), 1.30 (8H, m) 0.82 (9H, s), 0.0 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 167.0, 146.5, 120.4, 63.5, 33.1, 33.8, 30.0, 29.6, 29.4, 29.0, 26.5, 26.1, 18.7, -4.99. HRMS (EI) calcd.for $C_{19}H_{39}NO_2Si$: 341.2750. Found: 341.2747.

Compound 5. See **General Procedure**. The product was purified directly on a silica gel column (1x15 cm), eluting with 2: 1= EA: Hx. A solid was obtained (R_f= 0.30 in 2: 1= EA/Hx, 8.3 mg, 25% yield). Characterization by: Gill, G. etc. *J. Chem. Soc. Perkin Trans.1* **1994**, 369-378.

Compound 6. See **General Procedure**. The product was purified directly on a silica gel column (1x15 cm), eluting with 1: 10=EA: Hx. A viscous oil was obtained (R_f= 0.30 in 1: 10= EA: Hx, 75.6 mg, 77% yield) ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.70 (1H, dt, *J*= 7.0, 17.0 Hz), 6.16 (1H, d, *J*= 17.0 Hz), 3.58 (2H, t, *J*= 6.7 Hz), 3.00 (6H, s), 2.18 (2H, dt, *J*= 6.7, 6.7 Hz), 1.42 (4H, m), 1.30 (8H, m) 0.82 (9H, s), 0.0 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 116.7, 144.5, 123.4, 63.6, 33.2, 33.8, 32.1, 30.7, 29.8, 29.7, 29.5, 28.8, 26.8, 26.5, 26.3, 26.1, 25.8, 18.7, -4.9. HRMS (EI) calcd. for $C_{29}H_{55}NO_2Si$: 477.4002. Found: 477.4018.

Compound 7. See **General Procedure**. The product was purified directly on a silica gel column (1x15 cm), eluting with 1:10= EA: Hx. Solid was obtained (R_f= 0.30 in 1: 10= EA: Hx, 20 mg, 57% yield). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.76 (1H, d, *J*= 17.0 Hz), 7.50 (2H, m), 7.35 (3H, m), 6.84 (1H, d, *J*= 17.0 Hz), 3.56 (2H, broad), 2.15 (2H, broad), 1.80 (6H, broad), 1.65 (6H, broad), 1.20 (6H, broad). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 166.4, 140.9, 136.0, 128.9, 127.8, 121.2, 56.1, 30.7, 26.9, 25.8. HRMS (EI) calcd. for $C_{21}H_{29}NO$: 311.2249. Found: 311.2254.

Compound 8. See **General Procedure**. The product was purified directly on a silica gel column (1x15 cm), eluting with 1: 1= EA: Hx. Viscous oil was obtained (R_f= 0.30 in 1: 1= EA: Hx, 41.9 mg, 80% yield). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.80 (1H, dt, *J*= 7.0, 17 Hz), 5.70 (1H, d, *J*= 17.0 Hz), 5.2 (1H, broad), 4.56 (1H, t, *J*= 4.0 Hz), 4.10 (1H, m), 3.82 (1H, m), 3.72 (1H, m), 3.46 (1H, m), 3.38 (1H, m), 2.20 (2H, dt, *J*= 6.7, 6.7 Hz), 1.45-1.80 (10H, m), 1.18 (6H, d, *J*= 7.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 165.3, 144.1, 124.3, 99.1, 67.5, 62.6, 41.5, 32.1, 31.1, 29.6, 25.8, 25.3, 23.1, 20.0. HRMS (EI) calcd for $C_{15}H_{27}NO_3$: 269.1991. Found: 269.1997.

Compound 9. See **General Procedure**. The product was purified directly on a silica gel column (1x15 cm), eluting with 1: 1= EA: Hx. Solid was obtained (R_f= 0.40 in 1: 1= EA: Hx, 24.0 mg, 62% yield). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.60 (1H, d, *J*= 17.0 Hz), 7.48 (2H, m), 7.38 (3H, m), 6.26 (1H, d, *J*= 17.0 Hz), 5.40 (1H, broad), 1.19 (6H, d, *J*= 7.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 165.2, 140.7, 135.1, 129.2, 127.7, 121.3, 41.8, 23.5, 22.9. HRMS (EI) calcd. for $C_{12}H_{15}NO$: 189.1154. Found: 189.1152.

Compound 10. See **General Procedure**. The product was purified directly on a silica gel column (1x15 cm), eluting with 1: 2= EA: Hx. Viscous oil was obtained (R_f= 0.30 in 1: 2= EA: Hx, 64.1 mg, 89% yield). ^{1}H NMR (300MHz, $CDCl_3$, ppm): δ 6.90 (1H, dt, *J*= 7.0, 17 Hz), 6.30 (1H, d, *J*= 17.0 Hz), 4.50 (1H, t, *J*= 4.0 Hz), 3.82 (1H, m), 3.72(1H, m), 3.61 (3H, s) 3.46 (1H, m), 3.38 (1H, m), 3.17 (1H, s), 2.20 (2H, dt, *J*= 6.7, 6.7 Hz), 1.45-1.80 (10H, m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 167.0, 147.6, 119.0, 99.0, 67.4, 62.5, 61.9, 32.6, 31.0, 29.6, 25.8, 25.4, 20.0. HRMS (EI) calcd. for $C_{14}H_{25}NO_4$: 271.1784. Found: 271.1791.

Compound 11. See **General Procedure**. The product was purified directly on a silica gel column (1x15 cm), eluting with 1: 2= EA: Hx. Viscous oil was obtained (R_f= 0.35 in 1: 2= EA: Hx, 25.2 mg, 66% yield). Characterization by: Solladie. G. etc.*J. Org. Chem.* **1999**, *64*, 2309-2314.

Compound 12. See **General Procedure**. The product was purified directly on a silica gel column (1x15 cm), eluting with 2: 1= EA: Hx. Solid was obtained (R_f= 0.30 in 3: 1= EA: Hx, 72 mg, 89% yield). ^{1}H

NMR (300 MHz, $CDCl_3$, ppm): δ 6.78 (1H, dt, *J*= 7.3, 17.0 Hz), 6.22 (2H, broad) 5.83 (1H, d, *J*= 17.0 Hz), 4.01 (2H, t, *J*= 7.0 Hz), 2.20 (2H, m), 2.00 (3H, s), 1.60 (2H, m), 1.50 (2H, m), ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 171.4, 168.4, 145.5, 123.6, 64.4, 31.8, 28.4, 24.9, 21.4. HRMS (EI) calcd. for $C_9H_{15}NO_3$: 185.1052. Found: 185.1061.

Compound 13. See **General Procedure**. The product was purified directly on a silica gel column (1x15 cm), eluting with 4: 1= EA: Hx. Solid was obtained (R_f= 0.35 in 4: 1= EA: Hx, 20.3 mg, 69% yield). Characterization by: Moriarty, R.M. etc. *J. Org. Chem.* **1993**, *58*, 2478-2482.

Compound 14. See **General Procedure**. The product was purified directly on a silica gel column (1x15 cm), eluting with 1: 3= EA: Hx. Solid was obtained (R_f= 0.35 in 1: 3= EA: Hx, 55.4 mg, 90% yield). ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 7.58 (2H, d, *J*= 11 Hz), 7.25 (2H, m), 7.10 (1H, t, *J*= 11 Hz) 6.95 (1H, dt, *J*= 7.3, 17 Hz), 5.93 (1H, d, *J*= 17.0 Hz), 4.58 (1H, t, *J*= 4.0 Hz), 3.82 (1H, m), 3.72(1H, m), 3.61 (3H, s) 3.46 (1H, m), 3.38 (1H,m), 3.17 (1H, s), 2.22 (2H, dt, *J*= 6.7, 6.7 Hz), 1.45-1.80 (10H, m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 166.3, 147.9, 140.6, 130.9, 126.3, 126.1, 122.0, 101.2, 69.4, 64.6, 34.1, 33.1, 31.6, 27.8, 27.2, 22.1. HRMS (EI) calcd.for $C_{18}H_{25}NO_3$: 303.1834. Found: 303.1840.

Compound 15. See **General Procedure**. The product was purified directly on a silica gel column (1x15 cm), eluting with 1: 3= EA: Hx. Solid was obtained (R_f= 0.35 in 1: 3= EA: Hx, 30.5 mg, 69% yield). Characterization by: Wang, T. etc. *Synthesis* **1997**, 87-90.

Compound 16. See **General Procedure**. The product was purified directly on a silica gel column (1x15 cm), eluting with 1: 2= EA: Hx. Viscous oil was obtained (R_f= 0.30 in 1: 2= EA: Hx, 62.0 mg, 97% yield). ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 7.40 (3H, m), 7.16 (2H, d, *J*= 11.0 Hz) 6.83 (1H, dt, *J*= 7.3, 17 Hz), 5.70 (1H, d, *J*= 17.0 Hz), 4.52 (1H, t, *J*= 4.0 Hz), 3.80 (1H, m), 3.62 (1H, m), 3.44 (1H, m), 3.38 (1H,m), 3.35 (3H, s), 2.06 (2H, dt, *J*= 6.7, 6.7 Hz), 1.45-1.80 (10H, m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 166.3, 145.8, 143.9, 129.7, 127.6, 127.5, 121.7, 98.9, 67.4, 62.5, 37.7, 32.3, 31.0, 29.5, 25.8, 25.4, 19.9 HRMS (EI) calcd. for $C_{19}H_{27}NO_3$: 317.1991. Found: 317.1996.

Compound 17. See **General Procedure**. The product was purified directly on a silica gel column (1x15 cm), eluting with 1: 3= EA: Hx. Solid was obtained (R_f= 0.30 in 1: 3= EA: Hx, 43.2 mg, 83% yield). Characterization by: Froeyen, P. etc. *Synth. Commun.* **1995**, *25*, 959-968.

Compound 18. See **General Procedure**. The product was purified directly on a silica gel column (1x15 cm), eluting with 1: 5= EA: Hx. Viscous was obtained (R_f= 0.35 in 1: 3= EA: Hx, 76.7 mg, 100% yield). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.35 (6H, m), 7.23 (8H, m), 7.00 (1H, dt, *J*= 7.3, 17 Hz), 5.82 (1H, d, *J*= 17.0 Hz), 4.56 (1H, t, *J*= 4.0 Hz), 3.80 (1H, m), 3.62 (1H, m), 3.44 (1H, m), 3.38 (1H,m), 2.18 (2H, dt, *J*= 6.7, 6.7 Hz), 1.45-1.80 (10H, m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 166.3, 147.1, 143.0, 129.4, 127.6, 126.8, 122.9, 99.0, 67.4, 62.5, 32.5, 31.1, 29.6, 25.8, 25.4, 20.0 HRMS (EI) calcd. for $C_{24}H_{29}NO_3$: 379.2147. Found: 379.2144.

Compound 19. See **General Procedure**. The product was purified directly on a silica gel column (1x15 cm), eluting with 1: 1= toluene: methylene chloride. Solid was obtained (R_f= 0.30 in 1: 1= toluene: methylene chloride, 52.3 mg, 87% yield). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.81 (2H, 2, *J*= 16 Hz), 7.23-7.42 (10H, m), 6.50 (1H, d, *J*= 16 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 166.3, 142.9, 135.3, 123.0, 129.5, 129.0, 128.2, 127.1, 120.0. HRMS (EI) calcd. for $C_{21}H_{17}NO$: 299.1310. Found: 299.1301.

Compound 20. See **General Procedure.** The product was purified directly on a silica gel column (1x15 cm), eluting with 1: 3= EA: Hx. Viscous oil was obtained (R_f= 0.40 in 1: 5= EA: Hx, 66.4 mg, 87% yield). ^{1}H NMR (300MHz, $CDCl_3$, ppm): δ 7.24(1H, d, *J*= 17 Hz), 7.17 (1H, dt, *J*= 6.7, 17 Hz), 4.41 (2H, t, *J*= 12 Hz), 4.08 (2H, t, *J*= 12 Hz), 3.57 (2H, t, *J*= 11 Hz), 2.25 (2H, m), 1.50 (4H, m), 1.25 (8H, m), 0.84 (9H, s), 0.00 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 165.6, 154.8, 152.1, 120.2, 63.6, 62.4, 43.1, 33.2, 33.1, 29.8, 29.7, 29.5, 28.4, 26.4, 26.1, 18.8, -4.85. HRMS (EI) calcd. for $C_{20}H_{37}NO_4Si$: 383.2492. Found: 383.2496.

Compound 22. See **General Procedure**. The product was purified directly on a silica gel column (1x15 cm), eluting with 1: 2= EA: Hx. Viscous oil was obtained (R_f= 0.25 in 1: 2= EA: Hx, 46 mg, 100% yield). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 11.2 (1H, broad), 7.07 (1H, dt, *J*= 7.7, 17.3 Hz), 5.82 (1H, d, *J*=

17.3 Hz), 4.58 (1H, t, *J*= 4.0 Hz), 3.82 (1H, m), 3.72 (1H, m), 3.46 (1H, m), 3.38 (1H, m), 3.17 (1H, s), 2.24 (2H, dt *J*= 6.7, 6.7 Hz), 1.45-1.80 (10H, m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 171.9, 151.9, 121.1, 99.0, 67.4, 62.6, 32.4, 31.0, 29.5, 25.8, 25.0, 19.9. HRMS (EI) calcd. for $C_{12}H_{20}O_4$: 228.1362. Found: 228.1369.

Compound 23. To a stirred solution of catalyst **1** in CH_2Cl_2,, (1.0 mL), styrene (42 *u*l, 0.39 mmol) and arylic acid (14 *u*l, 0.20 mmol) was added by syringe. The flask was fitted with a condenser and refluxed under argon for 18 hours. The reaction was quenched by evaporating the solvent and purified directly on a silica gel column (1x15 cm), eluting with 1: 2= EA: Hx. Viscous oil was obtained (R_f= 0.30 in 1: 2= EA: Hx, 19.0 mg, 63% yield). Characterization by: Kim, T. etc. *J. Chem. Soc. Perkin Trans.1* **1995**, 2257.

Compound in eq 2. To a flask charged with methacrylamide (17.2 mg, 0.20 mmol), TBS protected 9-decen-1-ol (65 mg, 0.24 mmol) and 1 (8.5mg, 0.01 mmol, 5 mol%), solvent of 1 ml CH_2Cl_2 was added via syringe. The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 2: 1= hexane: ethyl acetate. Clear oil was obtained (46.6 mg, 71% yield, >20: 1 = *E*: *Z*). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.39 (1H, t, *J*= 7.5 Hz), 5.87 (2H, br), 3.55 (2H, *J*= 6.6 Hz), 2.10 (2H, m), 1.80 (3H, s), 1.2- 1.48 (12H, m), 0.86 (9H, s), 0.00 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 171.7, 138.2, 129.9, 63.6, 33.2, 29.8, 29.7, 29.7, 29.1, 28.8, 26.3, 26.1, 18.7, 13.1, -4.8. R_f = 0.35 (1: 1=hexane: ethyl acetate); HRMS (EI) calcd for $C_{18}H_{37}NO_2Si$ 327.2594, found 327.2594.

Compound 24. See **General Procedure.** The product was purified directly on a silica gel column, eluting with 2: 1= ethyl acetate: hexane and yielded 45.3 mg of the product in 97% (R_f= 0.3 in EA: Hx= 2: 1, clear oil). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.2-7.4 (6H, m), 6.10 (1H, t, *J*=17.4 Hz), 4.00 (4H, dq, *J*= 0.9, 8.1Hz), 1.22 (6H, t, *J*= 4.2 Hz)

Compound 25. See **General Procedure.** The product was purified directly on a silica gel column, eluting with 1: 4=hexane: ethyl acetate and yielded 51.2 mg of the product in 97% (R_f= 0.5 in EA, clear oil). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.50 (1H, dd, *J*= 17.4, 22.8 Hz), 7.44 (2H, d, *J*= 8.7 Hz), 6.89

(2H, d, *J*=8.7 Hz), 6.06 (1H, t, *J*= 17.7 Hz), 4.12(4H, dq, *J*= 0.9, 8.1 Hz), 3.81 (3H, s), 1.32(6H, t, *J*= 7.2 Hz).

Compound 26. See **General Procedure.** The product was purified directly on a silica gel column, eluting with ethyl acetate and yielded 40.5 mg of the product in 77% (R_f = 0.4 in EA, clear oil). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.39 (2H, d, *J*= 6.6 Hz), 7.37 (1H, dd, *J*= 18.6, 22.8 Hz), 7.20 (2H, d, *J*= 6.6Hz), 6.12 (1H, t, *J*= 17.4 Hz), 4.00 (4H, dq, *J*= 1.2, 8.1Hz), 1.22 (6H, t, *J*=4.2 Hz).

Compound 27. See **General Procedure.** The product was purified directly on a silica gel column, eluting with ethyl acetate and yielded 42.4 mg of the product in 73% (R_f = 0.3 in EA, clear oil). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.73 (1H, dd, *J*= 17.4, 22.8 Hz), 7.43 (1H, d, *J*= 8.7 Hz), 7.00 (2H, m), 6.11 (1H, t, *J*= 17.4 Hz), 4.10 (6H, dq, *J*= 0.6, 7.2 Hz), 2.37 (3H, s), 2.30 (3H, s), 1.22 (6H, t, *J*= 4.2 Hz).

Compound 28. See **General Procedure.** The product was purified directly on a silica gel column, eluting with ethyl acetate and yielded 37.8 mg of the product in 68% (R_f = 0.4 in EA, clear oil). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.5 (3H, m), 7.10 (2H, d, *J*= 6.0 Hz), 6.18 (1H, t, *J*= 17.4 Hz), 4.10 (4H, dq, *J*= 1.5, 7.2 Hz), 2.27 (3H, s), 1.32 (6H, t, *J*= 6.9 Hz).

Compound 29. See **General Procedure.** The product was purified directly on a silica gel column, eluting with ethyl acetate and yielded 18.0 mg of the product in 34% (R_f = 0.4 in EA, clear oil). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 8.22 (2H, d, *J*= 6.0 Hz), 7.4-7.6 (4H, m), 6.40 (1H, t, *J*= 17.4 Hz), 4.10 (4H, dq, *J*= 1.5, 7.2 Hz), 1.32 (6H, t, *J*= 6.9 Hz).

Compound 31. See **General Procedure.** The product was purified directly on a silica gel column, eluting with ethyl acetate and yielded 44.4 mg of the product in 90% (R_f = 0.3 in EA, clear oil). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.30 (5H, m), 6.90 (1H, m), 6.60 (1H, t, *J*= 18.6 Hz), 4.05 (4H, dq, *J*= 1.5, 6.9 Hz), 3.55(2H, d, *J*=5.7 Hz), 1.30 (6H, t, *J*= 6.9 Hz).

Compound 32. See **General Procedure.** The product was purified directly on a silica gel column, eluting with ethyl acetate and yielded 14.0 mg of the product in 82% (R_f = 0.3 in EA, clear oil). ^{1}H NMR

(300 MHz, $CDCl_3$, ppm): δ 6.70 (1H, m), 5.75 (1H, t, *J*= 17.4 Hz), 4.10 (4H, dq, *J*= 1.5, 6.9 Hz), 3.43(2H, t, *J*= 6.9 Hz), 2.78 (2H, m), 1.33 (6H, m).

General Procedure for Part II: To a flask charged with catalyst **1** (0.05 equiv in 0.05 to 0.4 M CH_2Cl_2), α,β-unsaturated carbonyl compounds, or disubstituted olefins were added via syringe. The flask was fitted with a condenser and refluxed under argon for 3 to 5 hours. The reaction was monitored by TLC. After the solvent was evaporated, the product was purified directly on a silica gel column.

Compound in Table 5, entry 1. See **General Procedure**. The product was purified directly on a silica gel column, eluting with 1: 10 = ethyl acetate: hexane. 40 *u*l of *n*-butyl acrylate gave 22.7 mg of the dimer in 87% yield (R_f = 0.3 in 1: 10 = EA: Hx, white solid). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 6.83 (2H, s), 4.19 (4H, t, *J* = 6.6 Hz), 1.65 (4H, m), 1.38 (4H, m), 0.93 (6H, q, *J* = 7.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 165.2, 133.8, 65.5, 30.9, 19.5, 14.0. HRMS (EI) calcd for $C_{12}H_{20}O_4$ 228.1362, found 228.1373.

Compound in Table 5, entry 2. See **General Procedure**. The product was purified directly on a silica gel column, eluting with 1: 15 = ethyl acetate: hexane. 50.6 mg of cyclohexyl acrylate gave 34.7 mg of the dimer (R_f = 0.5 in 1: 10 = EA: Hx, white solid). Characterization by: Kansui, H.; Hiraoka, S.; Kunieda, T.; *J. Am.Chem. Soc.* **1996,** *118*, 5346.

Compound in Table 5, entry 3 see **General Procedure**. The product was purified directly on a silica gel column, eluting with 1: 20 = ethyl acetate: hexane. 30 *u*l of *t*-butyl acrylate gave 21.9 mg of the dimer (R_f = 0.5 in 1: 10 = EA: Hx, clear oil). Characterization by: Charlton, J. L.; Maddaford, S. *Can. J. Chem*. **1993**, *71*, 827.

Compound in Table 5, entry 4. see **General Procedure**. The product was purified directly on a silica gel column, eluting with 1: 20 = ethyl acetate: hexane. 40.0 mg of admantyl acrylate gave 37.3 mg of the dimer (R_f = 0.4 in 1: 10 = EA: Hx, white solid). Characterization by: Matsumoto, A.; Otsu, T. *Chem. Lett.* **1991**, *8*, 1361.

Compound in Table 5, entry 5. see **General Procedure**. The product was purified directly on a silica gel column, eluting with 1: 20 = ethyl acetate: hexane. 14.0 mg of hexyl vinyl ketone gave 9.7 mg of the dimer (R_f = 0.4 in 1: 10 = EA: Hx, white solid). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.65 (2H, s) 2.62 (4H, t, *J* = 8.0 Hz), 1.59 (4H, m), 1.27(12H, m), 0.863(6H, t, *J* = 7.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 200.9, 136.4, 42.0, 31.9, 29.1, 24.1, 22.8, 14.4. HRMS (EI) calcd for $C_{16}H_{28}O_2$ 252.2089, found 252.2090.

Compound in Table 5, entry 6. see **General Procedure**. The product was purified directly on a silica gel column, eluting with 1: 20 = ethyl acetate: hexane. 13.8 mg of cyclohexyl vinyl ketone gave 11.8 mg of the dimer (R_f = 0.4 in 1: 10 = EA: Hx, white solid). Characterization by: House, H.O. et al. *J. Org .Chem*. **1971**, *36*, 3429.

Compound in Table 5, entry 7. To a flask charged with catalyst **1** (0.05 equiv in 0.05 CD_2Cl_2), 20 *u*l of ethyl vinyl ketone was added via syringe. After 3 hours, the crude solution was put into a NMR tube. The conversion was determined by integration ratio between 6.8 ppm and 6.4 ppm. Characterization by Bach, J.; Berenguer, R.; Garcia, J.; Lopez, M.; Manzanal, J.; Vilarrasa, J. *Tetrahedron* **1998**. *54*, 14947.

Compound in Table 6, entry 1. see **General Procedure**. The product was purified directly on a silica gel column, eluting with 1: 15 = ethyl acetate: hexane. 28.0 mg of the product was obtained (R_f = 0.4 in 1: 10 = EA: Hx, clear oil). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.80 (2H, dt, *J* = 15.6, 6.9 Hz), 5.70 (2H, d, *J* = 15.9 Hz), 2.14 (4H, m), 1.44 (22H, m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): 166.2, 147.6, 123.4, 80.3, 32.1, 28.5, 27.9. HRMS (EI) calcd for $C_{18}H_{30}O_4$ 310.2144, found 310.2151.

Compound in Table 6, entry 2. see **General Procedure**. The product was purified directly on a silica gel column, eluting with 1: 10 = ethyl acetate: hexane. 18.3 mg of the product was obtained (R_f = 0.3 in 1: 10 = EA: Hx, clear oil). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 6.89 (2H, dt, *J*= 7.0, 16.8 Hz), 5.82 (2H, d, *J*= 16.8 Hz), 4.13 (4H, t, *J*= 6.6 Hz), 2.20 (4H, m), 1.62 (4H, m), 1.48 (4H, m),1.37 (4H, m), 0.94 (6H, q, *J*= 7.4 Hz).

Compound in Table 6, entry 3. see **General Procedure**. The product was purified directly by filtering and washed with dichloromethane. 29.1 mg of the product was obtained (white solid). ^{1}H NMR (300 MHz, THF-d_8, ppm): δ 10.64 (2H, s), 6.80 (2H, dt, *J* = 15.6, 6.3 Hz), 5.75 (2H, d, *J* = 15.6 Hz), 2.20 (4H, m), 1.50 (4H, m). ^{13}C NMR (75 MHz,THF-d_8, ppm): δ 168.3, 149.9, 123.9, 33.8, 29.8. HRMS (EI) calcd for $C_{10}H_{14}O_4$ 198.0893, found 198.0896.

Compound in Table 6, entry 4. see **General Procedure**. The product was purified directly on a silica gel column, eluting with 1: 4 = ethyl acetate: hexane. 15.4 mg of the product was obtained (R_f = 0.3 in 1: 3 = EA: Hx, clear oil). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.80 (2H, dt, *J* = 15.6, 6.9 Hz), 6.05 (2H, d, *J* = 15.6 Hz), 2.52 (4H, q, *J* = 7.5 Hz), 2.19 (4H, m), 1.47 (4H, m), 1.06 (6H, t, *J* = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 201.1, 146.4, 130.5, 39.7, 32.5, 28.0, 8.5. HRMS (EI) calcd for $C_{14}H_{22}O_2$ 222.1620, found 222.1622.

Compound in Table 6, entry 5. see **General Procedure**. The product was purified directly on a silica gel column, eluting with 1: 2 = ethyl acetate: hexane. 7.4 mg of the product was obtained in 41% yield. (R_f = 0.3 in 1: 2 = EA: Hx, clear oil).^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 9.49 (2H, d, *J* = 7.8 Hz), 6.81 (2H, dt, *J* = 15.6, 6.9 Hz), 6.10 (2H, ddt, *J* = 15.6, 7.8, 1.5 Hz), 2.35 (4H, m), 1.47 (4H, m).

Compound Table 7, entry 1. see **General Procedure**. The product was purified directly on a silica gel column, eluting with 1: 3 = ethyl acetate: hexane. 25.0 mg of the product was obtained (R_f = 0.3 in 1: 3 = EA: Hx, white solid). Characterization by: Verhe,R. et al. *J. Org. Chem.* **1977**, *42*, 1256.

Compound Table 7, entry 2. see **General Procedure**. The product was purified directly on a silica gel column, eluting with 1: 15 = ethyl acetate: hexane. 15.0 mg of the product was obtained (R_f = 0.4 in 1: 10 = EA: Hx, clear oil). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.94 (1H, d, *J* = 16.2 Hz), 6.57 (1H, d, *J* = 15.9 Hz), 2.63 (2H, q, *J* = 7.2 Hz), 1.49 (9H, s), 1.10 (3H, t, *J* = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 200.5, 164.9, 138.6, 132.8, 82.2, 34.9, 28.3, 8.0 HRMS (EI) calcd for $C_{10}H_{16}O_3$ 184.1099, found 184.1103.

Compound Table 7, entry 3. see **General Procedure**. The product was purified directly on a silica gel column, eluting with 1: 10 = ethyl acetate: hexane. 6.5 mg of the product was obtained (R_f = 0.3 in 1: 10 = EA: Hx, clear oil). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.05 (1H, d, *J* = 15.9 Hz), 6.55 (1H, d, *J* = 16.2 Hz), 3.80 (3H, s), 2.61 (2H, t, *J* = 7.2 Hz), 1.27 (8H, br), 0.86 (3H, t, *J* = 6.3 Hz).

Compound Table 7, entry 4. see **General Procedure**. The product was purified directly on a silica gel column, eluting with 1: 15 = ethyl acetate: hexane. 29.7 mg of the product was obtained (R_f = 0.4 in 1: 10 = EA: Hx, clear oil). *E* / *Z* ratio was confirmed by ^{1}H NOE. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 5.62 (1H, s), 4.12 (2H, m), [2.58 (2H, t, *J* = 7.5 Hz), 1.84 (3H, s) for *cis*], [2.11 (3H, s), 2.00 (2H, *J* = 7.5 Hz), for *trans*] 1.50 (2H, m), 1.30 (6H, m), 0.86 (3H, *J* = 6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ [167.0, 160.5, 115.6, 59.7, 41.2, 31.7, 27.4, 22.8, 19.1, 14.7, 14.4. for *trans*], [166.5, 160.9, 116.1, 59.7, 33.7, 32.3, 28.2, 25.5, 22.9, 14.7, 14.3. for *cis*]. HRMS (EI) calcd for $C_{11}H_{20}O_2$ 184.1463, found 184.1460.

Compound Table 7, entry 5. see **General Procedure**. The product was purified directly on a silica gel column, eluting with 1: 5 = ethyl acetate: hexane. 26.5 mg of the product was obtained (R_f = 0.3 in 1: 5 = EA: Hx, white solid). *E* / *Z* ratio was confirmed by ^{1}H NOE. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 5.67 (1H, s), [2.60 (2H, t, *J* = 7.5 Hz), 1.90 (3H, s) for *cis*], [2.14 (3H, s), 2.10 (2H, *J* = 7.0 Hz), for *trans*] 1.50 (2H, m), 1.30 (6H, m), 0.87 (3H, *J* = 6.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ [172.6, 163.8, 115.2, 41.5, 31.7, 27.4, 22.8, 19.4, 14.4. for *trans*], [172.6, 163.8, 115.7, 33.8, 32.2, 28.2, 25.9, 19.4, 14.4. for *cis*]. HRMS (EI) calcd for $C_9H_{16}O_2$ 156.1150, found 156.1145.

Compound Table 7, entry 6. see **General Procedure**. The product was purified directly on a silica gel column, eluting with 1: 15=ethyl acetate: hexane. 22.0 mg of the product was obtained (R_f = 0.4 in 1: 10 = EA: Hx, white solid). *E* / *Z* ratio was confirmed by ^{1}H NOE. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.02 (1H, s), [2.54 (2H, t, *J* = 7.5 Hz), 1.83 (3H, s) for *cis*], [2.10 (3H, s), 2.08 (2H, *J* = 7.0 Hz), for *trans*], 2.40 (2H, *J* = 5.4 Hz), 1.50 (2H, m), 1.30 (6H, m), 1.00 (3H, *J* = 6.6 Hz), 0.87 (3H, *J* = 6.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ [201.8, 158.7, 123.0, 41.5, 37.7, 31.8, 27.5, 22.8, 19.6, 14.4, 8.5. for

trans], [201.2, 159.4, 123.5, 37.7, 34.1, 32.3, 28.3, 25.8, 22.9, 14.4, 8.5. for *cis*]. HRMS (EI) calcd for $C_{10}H_{20}O$ 168.1514, found168.1513.

Compound Table 7, entry 7. see **General Procedure**. The product was purified directly on a silica gel column, eluting with 1: 30 = ethyl acetate: hexane. 30.6 mg of the product was obtained (R_f = 0.35 in 1: 30 = EA: Hx, clear oil). Characterization by: Inoue, S.; Sato, Y. *J. Org. Chem.* **1991**, *56*, 347.

Compound Table 7, entry 8. see **General Procedure**. The product was purified directly on a silica gel column, eluting with 1: 3 = ethyl acetate: hexane. 23.8 mg of the product was obtained (R_f = 0.35 in 1: 3 = EA: Hx, white solid). Characterization by: Brittelli, D. R. *J. Org.Chem.* **1981**, *46*, 2514.

Compound Table 7, entry 9. see **General Procedure**. The product was purified directly on a silica gel column, eluting with 1: 15 = ethyl acetate: hexane. 29.3 mg of the product was obtained (R_f = 0.40 in 1: 10 = EA: Hx, clear oil). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 5.94 (1H, s), 2.77 (2H, s), 2.39 (2H, t, *J* = 7.2 Hz), 2.13 (2H, t, *J* = 5.1 Hz), 1.56 (6H, m) 1.03 (3H, t, *J* = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 202.4, 161.7, 120.9, 38.4, 37.8, 30.3, 29.2, 28.3, 26.6, 8.5. HRMS (EI) calcd for $C_{10}H_{16}O$ 152.1201, found 152.1203.

Compound in Table 7, Entry 10. To flask charged with **1** (12.4 mg, 0.015 mmol, 5.0 mol%), acrylic acid (20 *u*l, 0.29 mmol) and 2,2-dimethyl 3-butene (1 ml, 7.75 mmol) were added via syringe. The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The product was purified directly on a silica gel column, eluting with 1: 2 = ethyl acetate: hexane. 20.2 mg of the product was obtained (73%, R_f = 0.30 in 1: 2 = EA: Hx, white solid). Spectra match those of a previously characterized product, see: Freeman, F.; Kappso, J. C. *J. Org. Chem.* **1986**, *51*, 1654.

Compound in Table 7, Entry 11. To flask charged with **1** (8.5 mg, 0.01 mmol, 5.0 mol%), *t*-butyl acrylate (30 *u*l, 0.21 mmol) and 2,2-dimethyl 3-butene (1 ml, 7.75 mmol) were added via syringe. The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The product was purified directly on a silica gel column, eluting with 1: 30 = ethyl acetate: hexane. 27.5 mg of the product was

obtained (73%, R_f = 0.40 in 1: 20 = EA: Hx, white solid). Spectra match those of a previously characterized product, see: Inoue, S.; Sato, Y. *J. Org. Chem.* **1991**, *56*, 347.

Reference:

1. For recent reviews, see: a) Schuster, M.; Blechert, S. *Angew. Chem*. **1997**, *109*, 2124; *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2067; b) Blechert, S. *Pure Appl. Chem.* **1999**, *71*, 1393; c) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **2003**, *41*, 3171.
2. Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100.
3. a) Schrock, R. R.; Murdzek, J. S.; Bazan, G, C.; Robibins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875, b) Bazan, G. C. ; Oskam, J. H.; Cho, H.-N.; Park, L. Y.; Schrock, R. R. *J. Am. Chem. Soc.* **1991**, *113*, 6899, c) Feldman, J.; Schrock, R. R. *Prog. Inorg, Chem.* **1991**, *39*, 1.
4. Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.
5. Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.
6. Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783.
7. This portion of work is published, see: a) Choi, T.-L.; Chatterjee, A. K. Grubbs R. H. *Angew. Chem.* **2001***, 113*, 1317; *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 1277. b) Chatterjee, A. K.; Choi, T.-L.; Grubbs R. H. *Synlett* **2001**, 1034; c) Choi, T.-L.; Lee. C. W.; Chatterjee, A. K.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 10417.
8. Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.
9. For recent reviews on organic applications, see: a) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446; b) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413; c) Armstrong, S. K. *J. Chem. Soc. Perkin Trans. 1* **1998**, 371; d) Furstner, A. *Angew. Chem., Int. Ed. Engl* **2000**, *39*, 3013.
10. For recent reviews on ROMP, see: a) Novak, B. M.; Risse, W.; Grubbs, R. H. *Adv. Polym. Sci.*

1992, *102*, 47; b) Ivin, K. J.; Mol, J. C. *Olefin Metathesis and Metathesis Polymerization*, Academic Press, San Diego, CA, **1997**; c) Grubbs, R. H.; Khosravi, E. *Material Science and Technology*, **1999**, *20*, 65; d) Buchmeiser, M. R. *Chem. Rev.* **2000**, *100*, 1565.

11. a) Fraser, C.; Grubbs, R. H. *Macromolecules* **1995**, *28*, 7248; b) Mortell, K. H.; Weatherman, R. V.; Kiessling, L. L. *J. Am. Chem. Soc.* **1996**, *118*, 2297; c) Huwe, C. M.; Woltering, T. J.; Jiricek,J; Weitz-Schmidt, G.; Wong, C. H. *Bioorg. Med. Chem.* **1999**, *7*, 773; d) Maynard, H. D.; Okada, S.;Grubbs, R. H. *J. Am. Chem. Soc.* in press.
12. Blackwell, H. E.; O'Leary, D. J.; Chatterjee, A. K.; Washenfelder, R. A.; Bussmann, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 58.
13. Chatterjee, A. K.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 1751.
14. Nahm, S; Weinreb, S. M *Tetrahedron Lett.* **1981**, *22*, 3815.
15. Gage, J. R.; Evans, D. A. *Org. Synth.* **1990**, *68*, 83.
16. For a recent review, see: Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325.
17. Evans, D. A.; Willis, M. C.; Johnston, J. N. *Org. Lett.* **1999**, *1*, 865.
18. a) Evans, D. A.; Bartroli,J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127; b) Evans, D. A; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.
19. Evans, D. A.; Miller, S. J.; Lectka, T.; von Matt P., *J. Am. Chem. Soc.* **1999**, *121*, 7559.
20. For detailed study, see: Morgan, J. P. *Ph. D. Thesis, Caltech*, **2003**.
21. Feldman, J.; Murdzek, J. S.; Davis, W. M.; Schrock, R. R. *Organometallics* **1989**, *8*, 2260.
22. Smulik, J. A.; Diver, S. T. *Org. Lett.* **2000**, *2*, 2271.
23. a) Furstner, A.; Langemann, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130; b) Ghosh, A. K.; Cappiello, J.; Shin,.D. *Tetrahedron Lett.* **1998**, *39*, 4651; c) Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791; d) Coalter, J. N.; Bollinger, J. C.;. Huffman, J. C.; Werner-Zwanziger, U.; Caulton, K. G.; E. Davidson, R.; Gerard, H.; Clot, E.;

Eisenstein, O. *New J. Chem.* **2000**, *24*, 9; e) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.;Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168.

24. For a review see: Minami, T.; Motoyoshiya, J. *Synthesis* **1992**, 333.
25. a) Stowasser, B.; Budt, K.-H.; Jian-Qi, L.; Peyman, A.; Ruppert, D. *Tetrahedron Lett.* **1992**, *33*, 6625. b) Hirschmann, R.; Smith, A. B.; Taylor, C. M.; Benkovic, P. A.; Taylor, S. D.; Yager, K. M.; Sprengeler, P. A.; Benkovic, S. J. *Science* **1994**, *265*, 234. c) Wester, R. T.; Chambers, R. J.; Green, M. D.; Murphy, W. R. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2005.
26. A wide variety of reactions have been performed on vinylphosphonate alkenes: Conjugate additions: a) Afarinkia, K.; Binch, H. M.; De Pascale, E. D. *Synlett* **2000**, *12*, 1769. b) Afarinkia, K.; Binch, H. M.; Forristal, I. *Synlett* **2000**, *12*, 1771. c) Cuprate additions: Li, N.-S.; Yu, S.; Kabalka, G. W. *Organometallics* **1999**, *18*, 1811. d) Aminohydroxylation: Thomas, A. A.; Sharpless, K. B. *J. Org. Chem.* **1999**, *64*, 8379. e) Cycloadditions: Ruder, S. M.; Ding, M. *J. Chem. Soc., Perkin Trans. 1*, **2000**, 1771. f) McClure, C. K.; Hansen, K. B.; Herzog, K. J.; Link, J. S.; Arnold, F. P. *Phosphorus Sulfur* **1996**, *109-110*, 333. g) Hydroboration: Pergament, I.; Srebnik, M. *Org. Lett.* **2001**, *3*, 217. h) Asymmetric hydrogenation: Burk, M. J.; Stammers, T. A.; Straub, J. A. *Org. Lett.* **1999**, *1*, 387. i) Ozonolysis: Gil, J. M.; Hah, J. H.; Park, K. Y.; Oh, D. Y. *Synth. Commun.* **2000**, *30*, 789. j) Oxime ether synthesis: Shen, Y.; Jiang, G.-F. *Synthesis* **2000**, 502.
27. a) Shen, Y.; Jiang, G.-F. *Synthesis* **2000**, 99. b) Tago, K.; Kogen, H. *Org. Lett.* **2000**, *2*, 1975.
28. a) Kouno, R.; Okauchi, T.; Nakamura, M.; Ichikawa, J.; Minami, T. *J. Org. Chem.* **1998**, *63*, 6239. b) Kouno, R.; Tsubota, T.; Okauchi, T.; Minami, T. *J. Org. Chem.* **2000**, *65*, 4326.
29. a) Probst, M. F.; Modro, A. M.; Modro, T. A. *Can. J. Chem.* **1997**, *75*, 1131.b) Gil, J. M.; Oh, D. Y. *J. Org. Chem.* **1999**, *64*, 2950. c) Zhong, P.; Huang, X.; Xiong, Z. X. *Synlett* **1999**, 721. d) Otaka, A.; Mitsuyama, E.; Watanabe, H.; Tamamura, H.; Fujii, N. *J. Chem. Soc., Chem. Commun.* **2000**, 1081. e) Braga, A. L.; Alves, E. F.; Silveira, C. C.; de Andrade, L. L.

Tetrahedron Lett. **2000**, *41*, 161. f) Jang, W. B.; Oh, D. Y.; Lee, C.-W. *Tetrahedron Lett.* **2000**, *41*, 5103.

30. a) Holt, D. A.; Erb, J. M. *Tetrahedron Lett.* **1989**, *30*, 5393. b) Han, L.-B.; Tanaka, M. *J. Am. Chem. Soc.* **1996**, *118*, 1571. c) Kazankova, M. A.; Trostyanskaya, I. G.; Lutsenko, S. V.; Beletskaya, I. P. *Tetrahedron Lett.* **1999**, *40*, 569. d) Okauchi, T.; Yano, T.; Fukamachi, T.; Ichikawa, J.; Minami, T. *Tetrahedron Lett.* **1999**, *40*, 5337. e) Zhong, P.; Xiong, Z. X.; Huang, X. *Synth. Commun.* **2000**, *30*, 273. f) Han, L.-B.; Mirzaei, F.; Zhao, C.-Q.; Tanaka, M. *J. Am. Chem. Soc.* **2000**, *122*, 5407.
31. Brunner, H.; de Courcy, N. L.; Genet, J.-P. *Synlett* **2000**, 201.
32. Ulman, M.; Belderrain, T. R.; Grubbs, R. H. *Tetrahedron Lett.* **2000**, *41*, 4689.
33. Choi, T.-L.; Grubbs, R. H. *Chem. Comm.* **2001**, 2648.

Chapter 3:

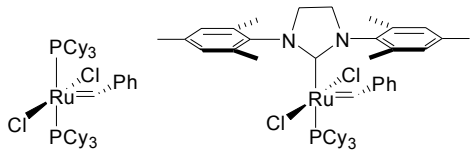
Tandem Ring-Closing Metathesis Reactions with Ruthenium Catalyst Containing N-Heterocyclic Carbene Ligand

Abstract

Catalyst **1**, $Cl_2(PCy_3)_2Ru=CHPh$ has popularized ring-closing metathesis (RCM) over the past seven years. However, the activity of **1** was limited to simple alkenes for RCM. With the development of more active catalyst **2**, $Cl_2(PCy_3)(IMesH_2)Ru=CHPh$, more challenging functionalized olefins were successfully ring-closed in high yields. In this chapter, catalyst **2** was used to synthesize complex molecules with functionalized olefins by tandem cyclization reactions. In the first part of the chapter, tandem ring-opening/ring-closing and tandem enyne ring-closing metathesis strategies are applied in the synthesis of bicyclic compounds. In the second half, synthesis of macrocycles are demonstrated by tandem ring-opening/cross/ring-closing metathesis also known as ring expansion metathesis (REM).

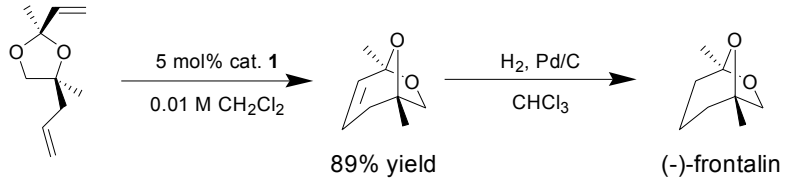
Background

Ring-closing metathesis (RCM) is the most frequently used reaction among the olefin metathesis processes in organic synthesis.[1] Typically 5- or 6-membered rings are produced by the facile intramolecular ring-closure of 1,7- or 1,8-dienes.[2] The equilibrium of RCM is heavily favored to the ring-closed product since thermodynamically stable five- or six-membered rings are formed with entropic gain by loss of ethylene gas. This reaction was further popularized with the development of the functional group tolerant ruthenium-based catalysts.[3] Even though Ru catalysts were less active than early transition metal based catalysts, mainly Mo catalysts, their high tolerance to many functional groups allowed chemists to perform RCM on the highly functionalized substrates. The versatility of RCM was demonstrated by $Cl_2(PCy_3)_2Ru{=}CHPh$ (**1**)



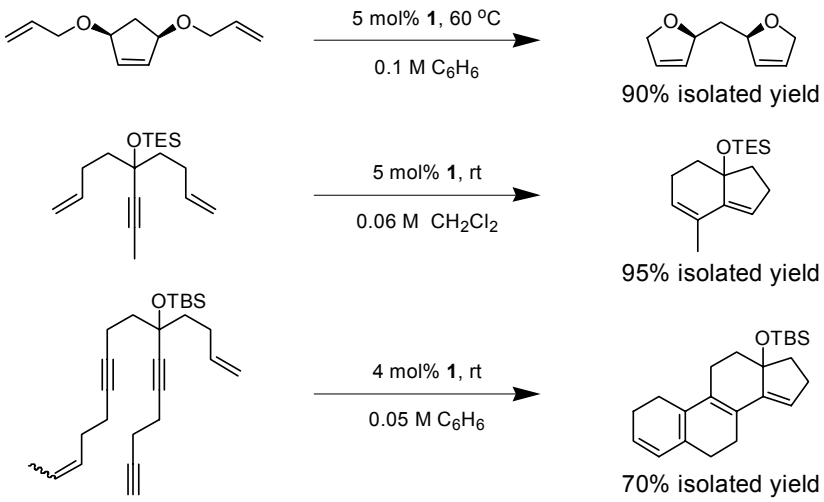
1 **2**

in the total synthesis of many natural products and drugs, in which the RCM was involved in the late stages as a key step for the completion of the syntheses.[4] As an example, our group reported an efficient RCM to provide a concise total synthesis of (-)-frontalin (Scheme 1).[5]



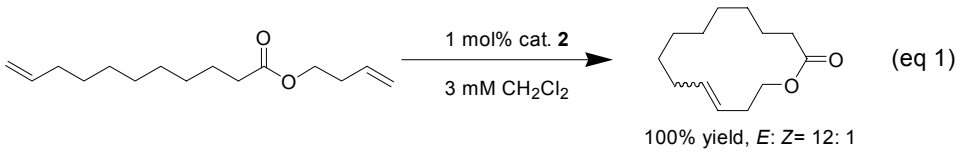
Scheme 1. Synthesis of (-)-frontalin by RCM

A recent advance in RCM includes tandem RCM to prepare complex molecules such as fused bicycles and polycycles (Scheme 2).[6] In these tandem events, cycloalkenes and alkynes were used to promote domino metathesis relay. The power of tandem RCM was demonstrated when the steroid-like skeleton was successfully synthesized in one tandem event (Scheme 1, the last example).[6c]



Scheme 2. Tandem RCM by catalyst **1**

With the development of a highly active and functional group tolerant catalyst **2** bearing N-heterocyclic carbene,[7] more challenging substrates such as acrylates and *gem*-disubstituted olefins were successfully incorporated into the ring system.[8] Also catalyst **2** allows efficient macrocyclization with high stereoselectivity on the newly formed olefins (eq 1).[9] Therefore highly active catalyst **2** opens up the possibility of preparing various ring systems with new functionalities. This chapter demonstrates the efforts to prepare complex bicyclic compounds and macrocycles by tandem RCM strategies.[10]



(eq 1)

Part I. Tandem RCM to Synthesize Bicyclic Compounds

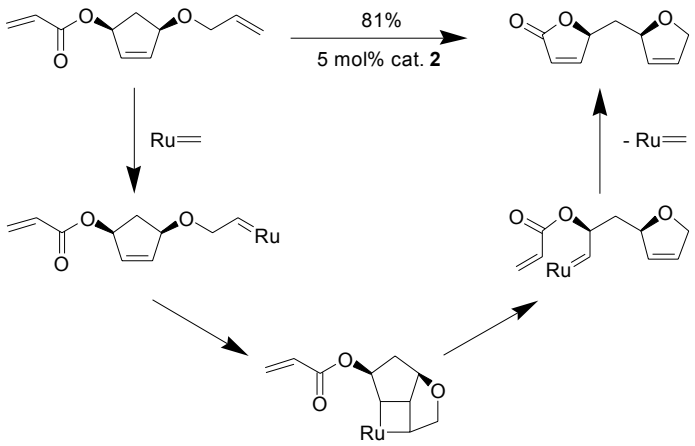
Introduction

Tandem cyclization reactions build up molecular complexity rapidly from relatively simple starting substrates.[11] Complicated molecules have been synthesized in a single step by carbanion,[12] carbocation,[13] free radical,[14] cycloaddtion[15] and Pd coupling reactions[16] whose novelty and efficiency were demonstrated by total syntheses of many natural products.[17] Olefin

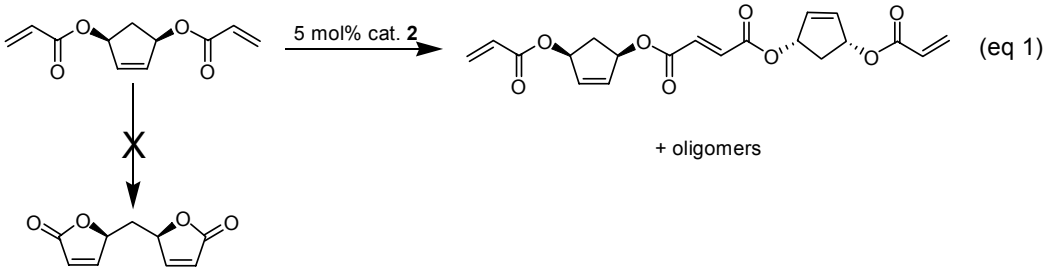
metathesis has become a useful reaction in organic synthesis,[1] and our group has recently demonstrated the viability of tandem ring closing metathesis reactions using catalyst **1**.[6] Unfortunately, catalyst **1** could not incorporate more synthetically valuable functionalized olefins such as α,β-unsaturated carbonyl compounds. However, with the development of the more active catalyst **2**,[7] containing an N-heterocyclic ligand, functionalized olefins could participate in RCM and cross metathesis reactions.[8] Herein, we report tandem RCM reactions, using catalyst **2,** to make synthetically useful α,β-unsaturated lactones and enones.

Results and Discussion

Various substrates containing different olefin arrays were examined for the tandem cyclization, and Table 1 demonstrates the viability of tandem ring-opening/ring-closing metathesis. In entry 1, catalyst **2** reacts with the more reactive terminal olefin, and the resulting alkylidene opens the 5-membered ring (Scheme 3). The sequence of the tandem events is completed by ring-closing onto the α, β-unsaturated carbonyl. It is likely that ring-opening of the substituted cyclopentene ring is not the initial metathesis event because the substrate shown in Scheme 4 did not yield any desired bicyclic compound, instead the products were dimer and other oligomers, which were formed by the enoic carbine intermediate (Chapter 2).[18] In addition 1,4-bisacetoxycyclopentene is not able to undergo ring-opening metathesis polymerization (ROMP).[19] It is believed that bis-allylic substituents on cyclopentene rings greatly suppress the ring-opening reaction. The substrate in entry 2 of Table 1 undergoes a similar domino cyclization as shown to the one Scheme 3 because the acyclic 2, 3-disubstituted olefin in this case is more reactive than the acrylates and the cyclopentene ring. Fused 5,5,7- and 7,5,7-tricyclic compounds were synthesized from highly strained norbornene moiety, but the yields were lower due to competing norbornene polymerization by ROMP (Entries 3 and 4).



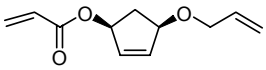
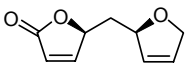
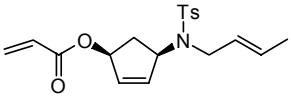
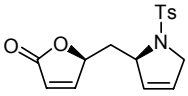
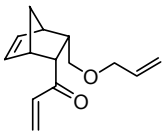
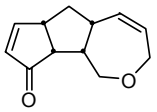
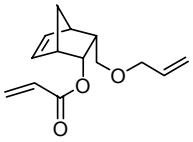
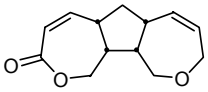
Scheme 3. Ring-opening / ring-closing tandem RCM



(eq 1)

Scheme 4. Undesired dimerization of diacrylate

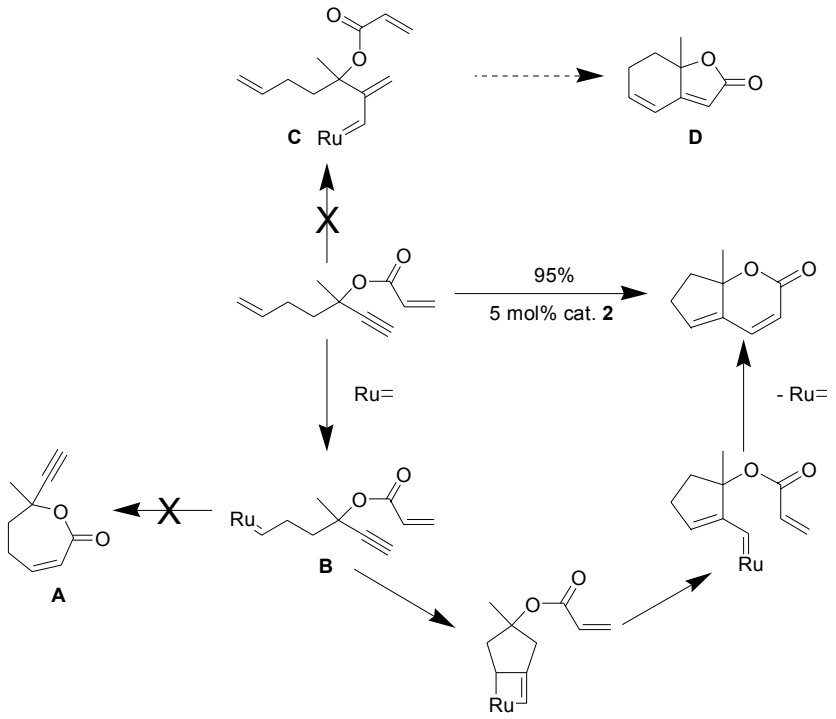
Table 1. Tandem ring-opening/closing metathesis to install functionalized olefins[a]

entry	substrate	concentration [M]	product	yield [%]
1		0.05		81
2		0.05		89
3		0.005		45
4		0.005		47

[a] 5 mol% catalyst **2** at 40 °C in CH_2Cl_2 for 6-12 hrs.

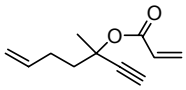
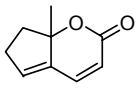
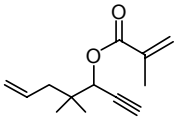
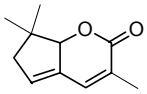
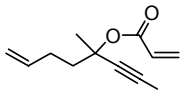
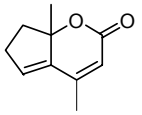
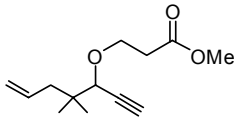
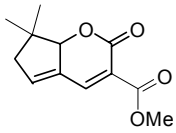
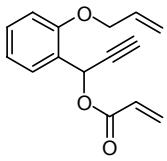
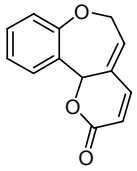
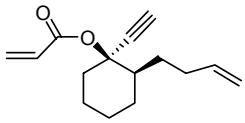
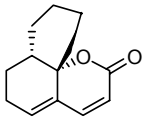
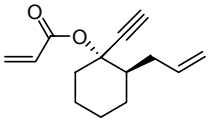
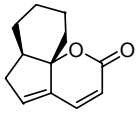
Another type of tandem RCM reaction is demonstrated by tandem enyne ring closing metathesis to form fused bicyclic ring systems (Table 2). Like the previous examples, catalyst **2**

reacts with the terminal olefins preferentially, and undergoes rapid intermolecular enyne metathesis to form the first ring, then reacts with the α,β-unsaturated carbonyl olefin to form the final ring (Scheme 5). The fact that 7-membered lactone **A** is never observed implies that prior to the first RCM event, the newly formed alkylidene **B** exclusively reacts with alkynes over acrylates. Blechert and co-workers have suggested a different mechanism where alkynes reacted first with the catalyst.[20] If such a mechanism is operative in this case, then the resultant intermediate **C** should lead to the product **D**. We do not believe that this mechanism is operative in our cases because compound **D** was not observed. More challenging trisubstituted α,β-unsaturated carbonyl olefins were also successfully cyclized using this methodology (Table 2, entries 2-4) and 7,6-fused bicyclic compound were synthesized in moderate yield (Entry 5). Lastly, tandem RCM to make 6,5,6- and 6,6,6-fused tricyclic compounds are shown in entries 6 and 7, which demonstrate, that this methodology has potential applications in the synthesis of complex natural products.



Scheme 5. Enyne Tandem RCM

Table 2. Tandem enyne ring-closing metathesis to install functionalized olefins[a]

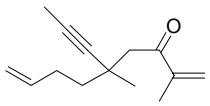
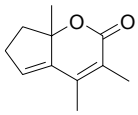
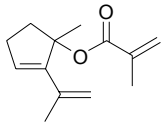
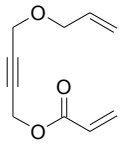
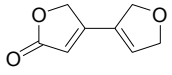
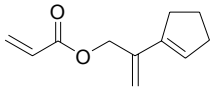
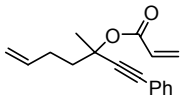
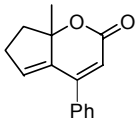
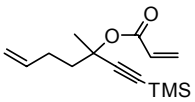
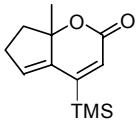
entry	substrate	concentration [M]	product	yield [%]
1		0.03		95
2		0.03		86
3		0.03		72
4		0.03		95
5		0.03		58
6		0.03		100
7		0.06		74

[a] 5-7 mol% catalyst **2** at 40 ^{o} C in CH_2Cl_2 for 6-12 hrs.

Tandem RCM reactions have some limitations, which are illustrated in Table 3. An attempt to make tetrasubstituted α,β-unsaturated carbonyl compound was less than satisfactory, yielding only 10% of desired product and the major product being the half-closed product (Table 3, entry 1). The second ring-closure to make the tetrasubstituted olefin seems to be very slow, so the resulting disubstituted alkylidene of the initial RCM event reacts faster with the terminal olefin of another molecule, yielding the half-closed product as a major product. Entry 2 shows a failed tandem RCM reaction because disubstituted alkylidene from the first ring-closure and the

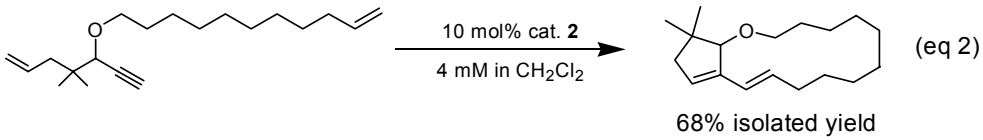
acrylate were likely in conformation unfavored for the final RCM. Bulky substituents on alkynes, such as TMS or phenyl, do not promote even the first enyne RCM (entries 3 and 4).

Table 3. Unsuccessful tandem enyne RCM reactions[a]

entry	substrate	desired product	yield [%]	major product[b]
1			10	
2			0	
3			0	starting material
4			0	starting material

[a] 5 mol% catalyst **2** at 40 °C for 12 hrs. [b] The major products were obtained in greater than 50% yield.

This methodology was further applied to tandem enyne macrocyclization where a small 5-membered ring and a 14-membered macrocyle were formed in one pot (eq 2). Higher catalyst loading (10 mol%) and high dilution (4 mM) were required to produce the bicyclic macrocycle in a moderate yield. Only *E*-isomer product was observed by ^{1}H NMR.



(eq 2)

Conclusion

The highly active catalyst **2** was used in tandem RCM reactions to make molecules possessing various ring systems. The ability to incorporate α,β-unsaturated carbonyl olefins into

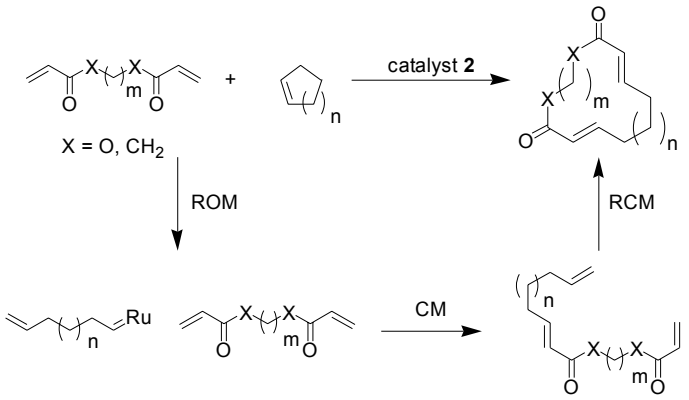
these products makes tandem RCM reactions synthetically more valuable since further manipulation is possible.

Part II. Ring Expansion Metathesis (REM)

Introduction

Olefin metathesis is an efficient reaction for the formation of C=C bonds.[1] Catalyst **1**, $Cl_2(PCy_3)_2Ru=CHPh$, greatly helped to open metathesis to the organic community due to its functional group tolerance and stability to air and moisture.[3] The recent development of the highly active and highly stable catalyst **2**[7] has broadened the utility of olefin metathesis for organic synthesis, as shown by the successful ring-closing and cross metathesis reactions of the functionalized olefins such as α,β-unsaturated carbonyl compounds.[8, 21]

Ring-closing metathesis has provided a new approach to the challenging problem of macrocyclization.[10, 22, 23] The efficiency of this process has been improved by the higher activity of catalyst **2**; not only in improved yields but also by reducing the catalyst loading and in improved stereoselectivity of the newly formed olefins.[10a, 23] Thus metathesis provides an efficient and mild route for the synthesis of macrocycles, especially carbocycles whose formation is considered harder than macrolactonization or lactamization. Herein, we report a novel method of macrocycle formation by a ring expansion metathesis (REM) reaction in which all three types of olefin metathesis (ring-opening, cross, and ring-closing) reactions occur sequentially to yield macrocycles (Scheme 6).



Scheme 6. Proposed route of ring expansion metathesis

Results and Discussion

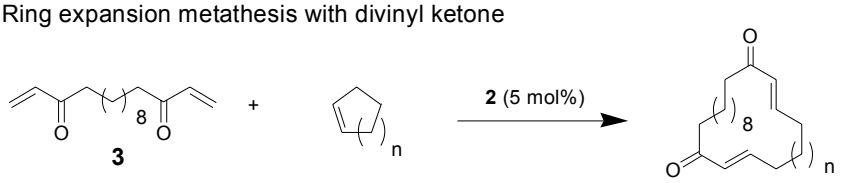
As shown in Scheme 6, the ring expansion is envisioned to occur between cycloalkenes and acyclic dienes. For a successful ring expansion, several conditions must be satisfied. First, cycloalkenes must be able to undergo the ring-opening reaction. Once opened, they must react selectively with the acyclic diene for both CM and RCM to minimize side-products. Finally, acyclic diene should not undergo metathesis reactions with itself, such as cyclization or dimerization and oligomerization by cross metathesis.

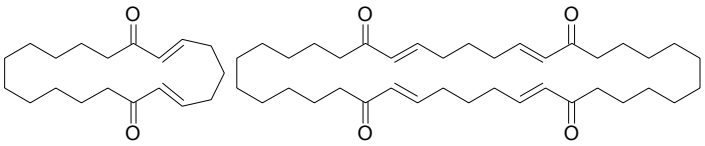
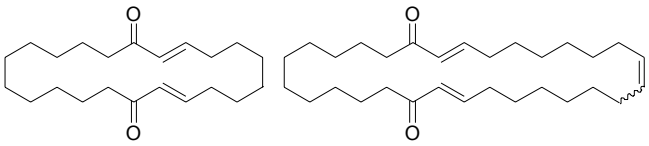
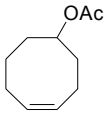
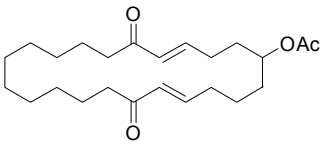
To test this idea, we chose diacrylates and divinyl ketones as acyclic dienes (or linkers) because they are known to react selectively with terminal olefins in excellent yields and less favorably with themselves.[8b] Catalyst **2** (5 mol%) was added to a solution of divinyl ketone (compound **3**, Table 4) and cyclopentene (5 equiv.) in CH_2Cl_2 (5 mM in **3**). After refluxing for 12 hours, several products were obtained with the complete consumption of **3**. The major products were the desired (1 + 1) fashion (**3** and cyclopentene) ring expanded product **4** with *E*-isomer in 43% isolated yield and the (2+ 2) double ring expanded product **5** in ratio of 1.3/1 (entry 1, Table 4). As anticipated, increasing the concentration to 25 mM decreased the product ratio of **4**/**5** to 1/2.3 (entry 2), because at higher concentration, competing oligomerization became more favorable.

Next, more readily ring-opening cyclooctene was tested for REM. Due to its higher ring strain favoring ROMP process, the relationship of concentration between cyclooctene and the product distribution was initially explored (Table 1, entries 3 to 5).[24] With 5 equiv. of cyclooctene (effectively 25 mM in cyclooctene), a low yield of 1:1 ratio of the desired (1+ 1) product **6** (23% yield) and (1+ 2) cyclooctene double inserted product **7** was obtained. The rest were higher oligomers of larger macrocycles. Decreasing the equivalents of cyclooctene to 2 (effectively 10 mM in cyclooctene) increased the yield to 34% with **6**/**7** ratio of 1.2/1, and finally the optimal yield of 53% for the desired product **6** was isolated with 1.1 equivalents of cyclooctene (entry 5). Functionalized cyclooctenes are also viable substrates for ring expansion (entry 6). We believe that the rate of ROMP of cyclooctene is greatly reduced at such low concentration (5 mM) yielding satisfactory amounts of desired ring expanded products.

With good conditions for REM in hand, we investigated other acyclic dienes and found diacrylates were also successful in ring expansion reactions (Table 5). 1,4-Butanediol diacrylate and 1,6-hexanediol diacrylate underwent ring expansion metathesis with cyclooctene to give 18 and 22-membered macrocycles with moderate yields (entries 1 and 2). The best yields for ring expansion with cyclooctene were obtained when diacrylate **9** was used (entry 3). Even though 1,6-hexanediol diacrylate and **9** have the same number of atomic linker units, the presence of less conformationally constraining oxygen atoms in **9** favors the formation of the desired REM products.[23c, e, 25] With the best diene identified, various cycloalkenes were screened to create a family of macrocycles (entries 3 – 9). For cyclopentene and cycloheptene, 5 equiv. of cycloalkenes could be used to give reasonable yields since their rates of ROMP were slow, unlike cyclooctene, which can easily polymerize under the same conditions. A medium ring cyclododecene also underwent REM to give a 26-membered macrocycle with 53% yield.

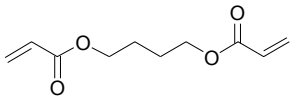
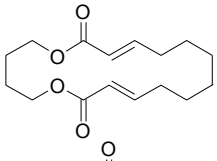
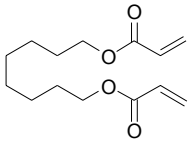
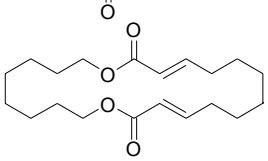
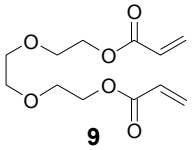
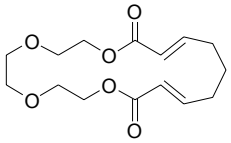
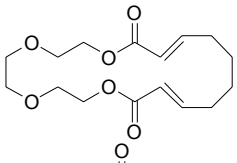
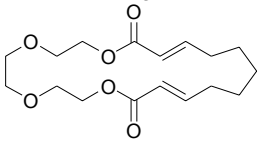
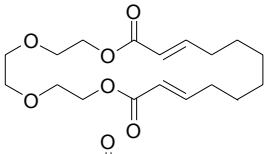
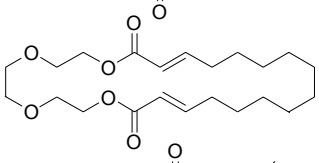
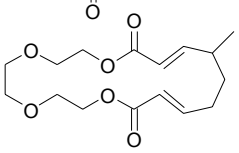
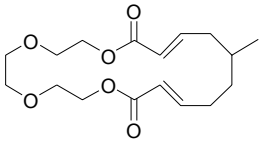
Table 4. Ring expansion metathesis with divinyl ketone



entry	ring sizeb (eq)	conc. [mM]	products[c] [%]
1	5 (5.0)	5	 **4** (43) **5** (34)
2	5 (5.0)	25	**4** (15); **5** (30)
3	8 (5.0)	5	 **6** (23) **7** (23)
4	8 (2.0)	5	**6** (34); **7** (28)
5	8 (1.1)	5	**6** (53)
6	 (1.1)	5	 **8** (43)

[a] Reactions were performed in refluxing CH_2Cl_2 under an atmosphere of argon. [b] Ring size : 5: cyclopentene; 8: cyclooctene. [c] Only (*E*)-isomers were observed by ^1H NMR.

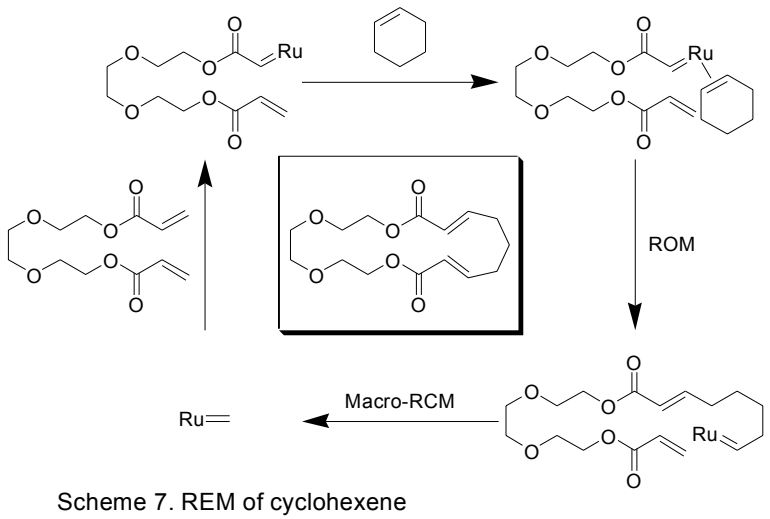
Table 5. Extended Scope of REM

entry	acyclic diene	ring size (eq)	product	yield [%]
1		8 (1.1)		45
2		8 (1.1)		47
3	 **9**	5 (5.0)		52
4		6 (5.0)		39
5		7 (5.0)		63
6		8 (1.1)		59
7		12 (1.1)		53
8	 (5.0)			50
9	 (5.0)			37

[a] Reactions were performed using catalyst **2** (5 mol%) in refluxing CH_2Cl_2 (5 mM) under an atmosphere of argon.
[b] Ring size of cycloalkenes: 5: cyclopentene; 6: cyclohexene; 7: cycloheptene; 8: cyclooctene; 12: cyclododecene.
[c] Only (*E*)-isomers were observed by ^1H NMR.

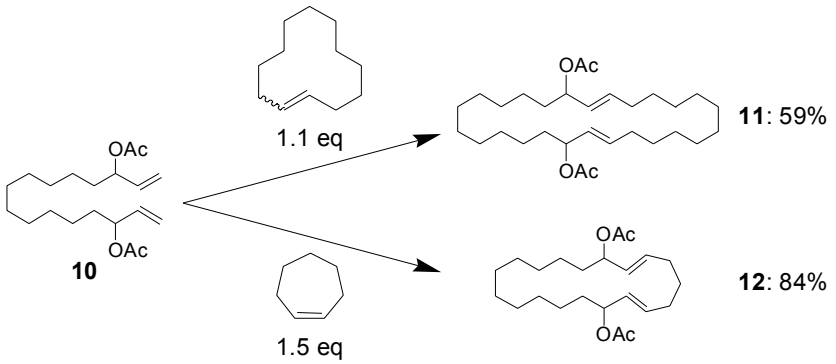
The REM reaction with cyclohexene gave the poorest yield (Table 5, entry 4) even though one might have expected a yield comparable to that for cyclopentene if not better. However, cyclohexene is a unique cycloalkene that does not produce ROMP polymers,[26] so a different mode of ring expansion is required. Since cyclohexene will not undergo olefin

metathesis reactions with catalyst **2**, the initial step is the formation of the enoic carbene, [Ru=CO_2R] in situ, which then can ring-open cyclohexene successfully (Chapter 2) and macrocyclize to give a 20-membered ring (Scheme 7).[18, 27] Since the enoic carbene is less stable than catalyst **2** and its other catalytic intermediates, fewer catalytic turnovers thus lower yields are expected (entry 4). The remaining unreacted **9** can be recovered as a starting material for the next reaction. Methyl substituted cycloalkenes reacted in a similar way to produce methyl substituted macrocycles (entries 8 and 9).



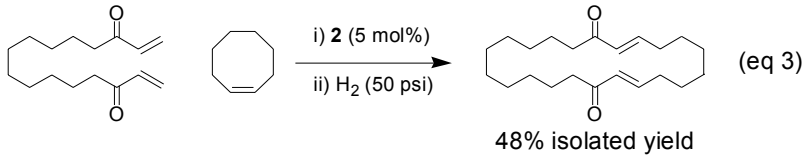
Scheme 7. REM of cyclohexene

Other acyclic dienes that undergo selective cross metathesis should also undergo REM reaction (Scheme 7). One such substrate, bis-allylic acetate compound **10,** yielded 59% of the macrocyle under conditions similar to the acrylate reactions. However, a higher catalyst loading of **2** (7 mol%) was required to completely consume **10,** which seemed to be less reactive than acrylates and vinyl ketones. Protected secondary allylic alcohols are also Type II olefins like acrylates and vinyl ketones (Chapter 2),[29] so the dimerization or cyclization of **10** by itself should be slower than cross metathesis with ring-opened cycloalkenes and subsequent macrocyclization. Especially, REM with cycloheptene gave an excellent yield to produce 19-membered ring (compound **12**).



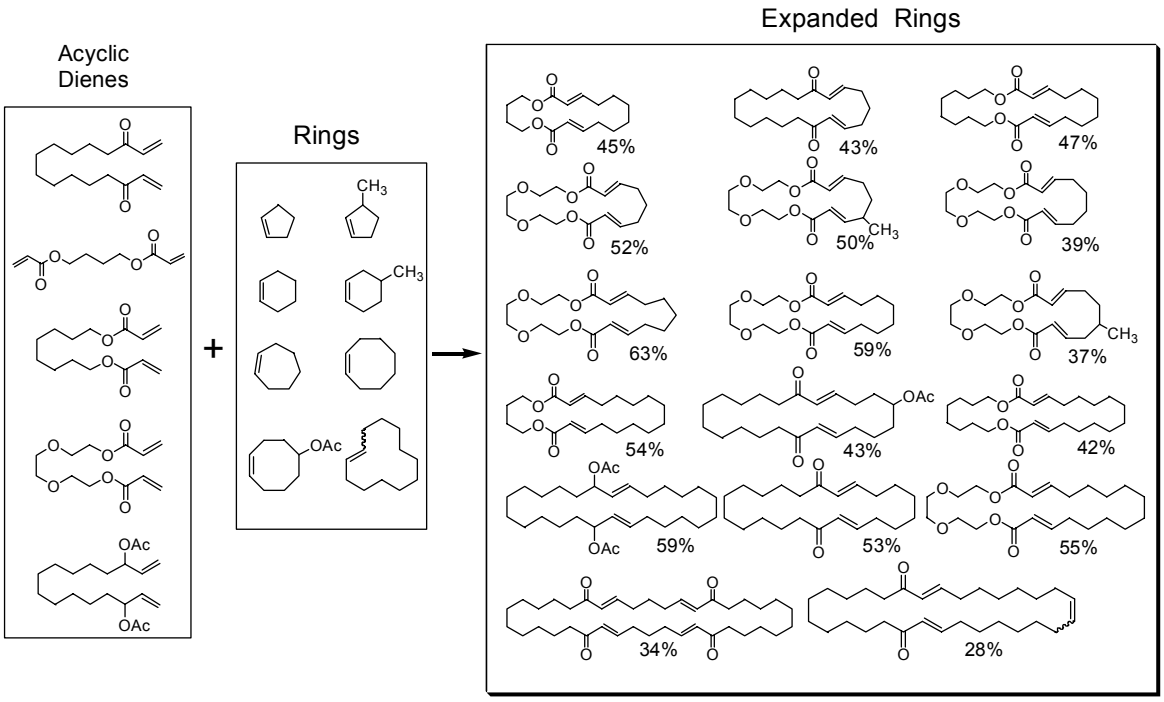
Scheme 7. REM with bis-allylic acetate

This methodology can be extended to the synthesis of macrocyclic ketones in a one-pot process. Using the tandem catalysis recently developed in our group, 22-membered cyclic dione was obtained in 48% isolated yield over two reactions in one pot (eq 3).[28]



Conclusion

In summary, we have demonstrated the synthesis of various macrocycles by ring expansion metathesis using catalyst **2**, where varying the concentration and the stoichiometry of cycloalkenes controlled the product distribution (Scheme 8). Although the yields of the ring expansion products are moderate, this methodology provides an easy access to a variety of macrocycles whose ring sizes can be simply adjusted by using readily available cyclic olefins. REM demonstrates the unique mechanism of olefin metathesis, reversible and thermodynamically controlled process.



Scheme 8. Library of macrocycles synthesized by REM

Acknowledgement: I would like to thank the NIH for generous support of this research, and Dr. C. W. Lee, Dr. H. M. Kim, Dr. A. K. Chatterjee, Dr. M. Scholl, J. P. Morgan, and Dr. S. D. Goldberg for helpful discussions.

Experimental Section

General Experimental Section. NMR spectra were recorded on Varian Mercury-300 NMR (300 MHz for ^{1}H and 74.5 MHz for ^{13}C). Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) with reference to internal solvent. Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), and multiplet (m). The reported ^{1}H NMR data refer to the major olefin isomer unless stated otherwise. The reported ^{13}C NMR data include all peaks observed and no peak assignments were made. High-

resolution mass spectra (EI and FAB) were provided by the UCLA Mass Spectrometry Facility (University of California, Los Angeles).

Analytical thin-layer chromatography (TLC) was performed using silica gel 60 F254 precoated plates (0.25 mm thickness) with a fluorescent indicator. Flash column chromatography was performed using silica gel 60 (230-400 mesh) from EM Science. All other chemicals were purchased from the Aldrich, Strem, or Nova Biochem Chemical Companies, and used as delivered unless noted otherwise. CH_2Cl_2 was purified by passage through a solvent column prior to use.

General procedure for RCM:

To a flask charged with substrate olefin (1.0 eq) in CH_2Cl_2, catalyst **2** (0.05 eq) in CH_2Cl_2 was added by cannulation. The flask was fitted with a condenser and refluxed under argon for 6 to 12 hours. The reaction was monitored by TLC. After the solvent was evaporated, the product was purified directly by a silica gel chromatography

Compound in Table 1, entry 1. See **General Procedure.** The product was purified directly on a silica gel column, eluting with 1: 1 = ethyl acetate: hexane. 28.7 mg of the product in 81% yield was obtained (R_f= 0.3 in 1: 1 = EA: Hx, white solid). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.53 (1H, d, *J*= 6.0 Hz), 6.10 (1H, dd, *J*= 2.0, 6.0 Hz), 5.95 (1H, m), 5.82 (1H, m), 5.14 (1H, m), 4.94 (1H, m), 4.64 (2H, m), 2.02 (2H, m).

Compound in Table 1, entry 2. See **General Procedure.** The product was purified directly on a silica gel column, eluting with 1: 1 = ethyl acetate: hexane. 39.3 mg of the product in 89% yield was obtained (R_f= 0.2 in 1: 1 = EA: Hx, white solid). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.69 (2H, d, *J*= 9.6 Hz), 7.60 (1H, d, *J*= 6.0 Hz), 7.32 (2H, d, *J*= 9.6 Hz), 6.13 (1H, dd, *J*= 2.4, 5.0 Hz), 5.64 (2H, m), 5.26 (1H, m), 4.04- 4.19 (2H, m), 2.41 (3H, s), 2.08-2.33 (2H, m).

Compound in Table 1, entry 3. See **General Procedure.** The product was purified directly on a silica gel column, eluting with 1: 3 = ethyl acetate: hexane. 21 mg of the product in 45% yield

was obtained (R_f= 0.4 in 1: 2 = EA: Hx, white solid). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.58 (1H, dd, *J*= 4.0, 4.0Hz), 5.96 (1H, dd, *J*= 4.0, 8.0Hz), 5.20- 5.40 (2H, m), 4.00- 4.30 (3H, m), 3.62 (1H, dd, *J*= 12.8, 16.0 Hz), 3.40 (1H, m), 3.15 (1H, m), 2.80 (2H, m), 2.0-2.1 (1H, m), 1.5-1.6 (1H, m).

Compound in Table 1, entry 4. See **General Procedure.** The product was purified directly on a silica gel column, eluting with 1: 1 = ethyl acetate: hexane. 20.3 mg of the product in 47 % yield was obtained (R_f= 0.2 in 1: 3 = EA: Hx, solid). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 6.35 (1H, dd, *J*= 2.4, 12 Hz), 5.89 (1H, dd, *J*= 2.0, 14.0Hz), 5.60 (1H, m), 5.42 (1H, m), 4.20- 4.35 (2H, m), 4.18 (2H, m), 3.82 (1H, dd, *J*= 4.0, 8.8 Hz), 3.70 (1H, dd, *J*= 6.0, 12.8 Hz), 2.80- 3.00 (2H, m), 2.66 (1H, m), 2.31 (1H, m.), 1.56 (1H, m).

Compound in Table 2, entry 1. See **General Procedure.** The product was purified directly on a silica gel column, eluting with 1: 3 = ethyl acetate: hexane. 25.5 mg of the product in 95 % yield was obtained (R_f= 0.1 in 1: 10 = EA: Hx, white solid). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.08 (1H, d, *J*= 9.6 Hz), 6.02 (1H, t, *J*= 2.7 Hz), 5.90 (1H, d, *J*= 9.6 Hz), 2.4- 2.6 (2H, m), 2.2 (2H, m), 1.40 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 164.5, 138.5, 136.3, 133.1, 119.8, 90.2, 39.5, 30.6, 24.4.

Compound in Table 2, entry 2. See **General Procedure.** The product was purified directly on a silica gel column, eluting with 1: 10 = ethyl acetate: hexane. 30.0 mg of the product in 86% yield was obtained (R_f= 0.3 in 1: 5 = EA: Hx, white solid). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.89 (1H, s), 5.83 (1H, d, *J*= 2.7 Hz), 4.99 (1H, d, *J*= 2.4 Hz), 2,28 (2H, m), 1.94 (3H, s), 1.26 (3H, s), 1.00 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 166.0, 133.8, 133.6, 129.4, 127.5, 90.2, 46.9, 45.0, 26.3, 22.6, 18.2.

Compound in Table 2, entry 3. See **General Procedure.** The product was purified directly on a silica gel column, eluting with 1: 3 = ethyl acetate: hexane. 24.4 mg of the product in 72 % yield was obtained (R_f= 0.3 in 1: 3 = EA: Hx, white solid). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.05

(1H, t, *J*= 2.7 Hz), 5.73 (1H. s), 2.3- 2.6 (2H, m), 2.15 (2H, m), 2.02 (3H, s), 1.36 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 164.9, 146.7, 141.2, 130.6, 116.6, 89.9, 39.5, 30.0, 24.6, 18.5.

Compound in Table 2, entry 4. See **General Procedure.** The product was purified directly on a silica gel column, eluting with 1: 10 = ethyl acetate: hexane. 39.8 mg of the product in 96 % yield was obtained (R_f= 0.5 in 1: 5 = EA: Hx, white solid). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.30 (1H, d, *J*= 1.5 Hz), 5.86 (1H. s), 4.63 (1H, d, *J*= 17.1 Hz), 4.33 (1H, m), 4.04 (1H, s), 3.72 (3H, s), 2.20 (2H, m), 1.22 (3H, s), 0.91 (3H, s), ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 166.1, 136.5, 131.1, 130.5, 129.3, 87.3, 66.0, 52.0, 47.3, 43.2, 27.1, 22.2. HRMS (EI) calcd. for $C_{12}H_{16}O_3$, 208.1099, found, 208.1089.

Compound in Table 2, entry 5. See **General Procedure.** The product was purified directly on a silica gel column, eluting with 1: 2 = ethyl acetate: hexane. 26.4 mg of the product in 58 % yield was obtained (R_f= 0.3 in 1: 2 = EA: Hx, white solid). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.52 (1H, d, *J*= 7.8 Hz), 7.24 (2H, m), 7.11 (1H, d, *J*= 7.8 Hz), 7.00 (1H, m), 6.83 (1H, d, *J*= 9.9 Hz), 5.89 (1H,d, *J*= 9.6 Hz), 5.70 (1H, m), 4.99 (1H, m), 4.50 (1H, m), ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 162.1, 154.9, 143.9, 136.6, 132.6, 130.6, 129.5, 125.3, 124.3, 121.5, 116.0, 77.3, 76.9, 75.7, 71.4. HRMS (EI) calcd. for $C_{13}H_{10}O_3$, 214.0630, found, 214.0631.

Compound in Table 2, entry 6. See **General Procedure.** The product was purified directly on a silica gel column, eluting with 1: 5 = ethyl acetate: hexane. 36 mg of the product in 100 % yield was obtained (R_f= 0.3 in 1: 10 = EA: Hx, white solid). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.00 (1H, d, *J*= 9.3 Hz), 6.15 (1H, m), 5.80 (1H, dd, *J*= 0.6, 9.3 Hz), 2.37 (2H, d, *J*= 12.9 Hz), 1.1-2.2 (11H, m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 165.2, 142.8, 135.6, 135.1, 118.9, 80.0, 45.1, 35.5, 27.5, 26.5, 26.3, 25.6, 22.0.

Compound in Table 2, entry 7. See **General Procedure. 7** mol**%** catalyst **2** was used for the reaction. The product was purified directly on a silica gel column, eluting with 1: 4 = ethyl acetate: hexane. 14 mg of the product in 74% yield was obtained (R_f= 0.3 in 1: 3 = EA: Hx, white

solid). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.05 (1H, d, *J*= 9.6 Hz), 5.98 (1H, t, *J*= 2.4 Hz), 5.89 (1H, dt, *J*= 0.6, 9.6 Hz), 1.2- 2.6 (11H, m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 164.8, 140.7, 136.3, 131.4, 119.6, 88.1, 46.2, 34.67, 34.5, 23.7, 21.7, 19.9**.**

Compound in Eq 2. See **General Procedure.** 10 mol% catalyst **2** in 4 mM CH_2Cl_2 was used to complete the reaction. The product was purified directly on a silica gel column, eluting with 1: 35 = ethyl acetate: hexane. 21 mg of the product in 68 % yield was obtained (R_f= 0.5 in 1: 20 = EA: Hx, clear oil). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.10 (1H, d, *J*= 15.3 Hz), 5.75 (1H, m), 5.65 (1H, m), 3.98 (1H, s), 3.70 (1H, m), 3.30 (1H, dt, *J*= 3.0, 9.0 Hz), 2.35 (1H, s), 2.29 (1H, s), 2.00 (2H, m), 1.35 (14H, m), 1.12 (3H, s), 1.03 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 140.6, 132.0, 130.3, 126.8, 91.2, 68.6, 47.0, 42.4, 32.3, 30.4, 29.7, 26.9, 26.0, 25.9, 25.8, 24.8, 24.3, 23.2. HRMS (EI) calcd. for $C_{18}H_{30}O$, 262.2297, found, 262.2288.

General Procedure for REM:

To a flask charged with catalyst **2** (0.05 equiv in 0.005 to 0.006 M CH_2Cl_2), α,β-unsaturated carbonyl compounds, and cycloalkenes were added via syringe. The flask was fitted with a condenser and refluxed under argon for 12 hours. The reaction was monitored by TLC. After the solvent was evaporated, the product was purified directly on a silica gel column.

Compound 4 and 5. See **General Procedure**. The product was purified directly on a silica gel column, eluting with 1: 4 = ethyl acetate: hexane. 10.0 mg of the product **4** in 43 % yield was obtained (R_f= 0.4 in 1: 2 = EA: Hx, colorless liquid). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.80 (2H, dt, *J*= 6.9, 15.9 Hz), 6.15 (2H, dt, *J*= 1.5, 15.9 Hz), 2.49 (4H, t, *J*= 6.9 Hz), 2.29 (4H, dq, *J*= 1.2, 6.9 Hz), 1.70 (6H, m), 1.29 (12H, m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 202.2, 146.8, 131.2, 40.0, 31.4, 28.6, 28.5, 28.3, 26.7, 25.7. HRMS (EI) calcd. for $C_{19}H_{30}O_2$, 290.2246, found, 290.2241.

8.0 mg of the product **5** in 34 % yield was obtained (R_f= 0.3 in 1: 2 = EA: Hx, white solid).). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.79 (4H, dt, *J*= 6.9, 15.9 Hz), 6.10 (4H, dt, *J*= 1.5, 15.9 Hz), 2.52 (8H, t, *J*= 7.2 Hz), 2.24 (8H, q, *J*= 6.6 Hz), 1.67 (12H, m), 1.27 (24H, m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 201.0, 145.2, 131.1, 40.4, 31.9, 29.6, 29.4, 29.3, 26.8, 24.5. HRMS (EI) calcd. for $C_{38}H_{60}O_4$, 580.4492, found, 580.4486.

Compound 6 and 7. See **General Procedure**. The product was purified directly on a silica gel column, eluting with 1: 9 = ethyl acetate: hexane. 10.0 mg of the product **7** in 23 % yield was obtained (R_f= 0.6 in 1: 2 = EA: Hx, colorless liquid). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.80 (2H, m), 6.07 (2H, d, *J*= 15.6 Hz), 5.37 (2H, m), 2.51 (4H, t, *J*= 6.9 Hz), 2.20 (4H, m), 2.00 (4H, m), 1.6- 1.27 (24H, m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 201.5, 147.8, 130.8, 130.7, 130.5, 40.0, 32.7, 32.6, 28.1-29.8 (m), 24.7. HRMS (EI) calcd for $C_{22}H_{36}O_2$: 332.2715, found, 332.2712. 9.0 mg of the product **6** in 23 % yield was obtained (R_f= 0.5 in 1: 2 = EA: Hx, colorless liquid). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.78 (2H, dt, *J*= 7.2, 15.9 Hz), 6.09 (2H, dt, *J*= 1.5, 15.9 Hz), 2.49 (4H, t, *J*= 6.9 Hz), 2.22(4H, dq, *J*= 1.5, 6.9 Hz), 1.63(4H, m), 1.47 (4H, m), 1.24 (16H, m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 202.2, 148.0, 131.1, 39.8, 32.3, 29.2, 29.0, 28.8, 28.5, 28.1, 25.8. HRMS (EI) calcd. for $C_{30}H_{50}O_2$:442.3811, found, 442.3806.

Compound 8. See **General Procedure**. The product was purified directly on a silica gel column, eluting with 1: 3 = ethyl acetate: hexane. 13.0 mg of the product in 43 % yield was obtained (R_f= 0.4 in 1: 2 = EA: Hx, colorless liquid). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.78 (2H, m), 6.12 (2H, d, *J*= 16.2 Hz), 4.87 (1H, m), 2.50 (4H, m), 2.22 (4H, m), 2.06 (3H, s), 1.6- 1.25 (14H, m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 201.6, 170.8, 146.8, 146.1, 131.2, 131.1, 72.7, 40.2, 40.1, 33.5, 32.9, 32.0, 29.1, 28.9, 28.8, 28.5, 25.7, 25.6, 24.1, 21.6. HRMS (EI) calcd. for $C_{24}H_{38}O_4$: 390.2770, found, 390.2770.

Compound in Table 5, entry 1. See **General Procedure**. The product was purified directly on a silica gel column, eluting with 1: 10 = ethyl acetate: hexane. 13.3 mg of the product in 45 % yield

was obtained (R_f = 0.3 in 1: 5 = EA: Hx, colorless liquid). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.86 (2H, dt, *J*= 6.9, 15.6 Hz), 5.73 (2H, dt, *J*= 1.5, 15.6 Hz), 4.21 (4H, m), 2.20 (4H, m), 1.81 (4H, m), 1.50 (4H, m), 1.23 (4H, m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 166.7, 149.8, 121.9, 64.0, 31.1, 27.7, 27.1, 26.3. HRMS (EI) calcd. for $C_{16}H_{24}O_4$: 280.1675, found 280.1680.

Compound in Tabel 5, entry 2. See **General Procedure**. The product was purified directly on a silica gel column, eluting with 1: 15 = ethyl acetate: hexane. 25.7 mg of the product was obtained in 47% yield (R_f = 0.4 in 1: 10 = EA: Hx, colorless liquid). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.93 (2H, dt, *J*= 6.9, 15.6 Hz), 5.82 (2H, dt, *J*= 1.8, 15.6 Hz), 4.14 (4H, t, *J*= 5.7 Hz), 2.20 (4H, m),1.63 (4H, m), 1.5- 1.3 (16H, m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 166.9, 149.2, 121.7, 64.9, 31.4, 29.5, 29.0, 27.5, 27.1, 26.6. HRMS (EI) calcd. for $C_{20}H_{32}O_4$: 336.2301, found 336.2298.

Compound in Tabel 5, entry 3. See **General Procedure**. The product was purified directly on a silica gel column, eluting with 1: 1 = ethyl acetate: hexane. 9.0 mg of the product was obtained in 52 % yield (R_f= 0.3 in 1: 1 = EA: Hx, white solid). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.85 (2H, dt, *J*= 7.2, 15.6 Hz), 5.84 (2H, dt, *J*= 1.5, 15.6 Hz), 4.26 (4H, m), 3.72 (4H, m), 3.67 (4H, s), 2.29 (4H, m), 1.77 (2H, m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 166.4, 148.1, 123.2, 70.7, 69.3, 63.9, 31.7, 24.6. HRMS (EI) calcd. for $C_{15}H_{22}O_6$: 298.1416, found 298.1416.

Compound in Tabel 5, entry 4. See **General Procedure**. The product was purified directly on a silica gel column, eluting with 1: 1 = ethyl acetate: hexane. 7.0 mg of the product was obtained in 39 % yield (R_f= 0.35 in 1: 1 = EA: Hx, white solid). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.85 (2H, dt, *J*= 7.2, 15.6 Hz), 5.84 (2H, dt, *J*= 1.5, 15.6 Hz), 4.26 (4H, m), 3.75 (4H, m), 3.67 (4H, s), 2.23 (4H, m), 1.45 (4H, m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 166.5, 149.2, 122.1, 71.0, 69.4, 64.0, 31.2, 26.3. HRMS (EI) calcd. for $C_{16}H_{24}O_6$: 312.1573, found 312.1584.

Compound in Tabel 5, entry 5. See **General Procedure**. The product was purified directly on a silica gel column, eluting with 1: 1 = ethyl acetate: hexane. 12.0 mg of the product was obtained

in 63 % yield (R_f= 0.35 in 1: 1 = EA: Hx, white solid). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.92 (2H, dt, *J*= 7.2, 15.6 Hz), 5.83 (2H, dt, *J*= 1.5, 15.6 Hz), 4.28 (4H, m), 3.73 (4H, m), 3.66 (4H, s), 2.24 (4H, m), 1.48 (4H, m), 1.24 (2H, m).^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 166.7, 149.4, 121.9, 71.2, 69.5, 64.1, 32.2, 27.8, 27.7. HRMS (EI) calcd. for $C_{17}H_{26}O_6$: 326.1729, found 326.1732.

Compound in Tabel 5, entry 6. See **General Procedure**. The product was purified directly on a silica gel column, eluting with 1: 1 = ethyl acetate: hexane. 29.4 mg of the product was obtained in 59 % yield (R_f= 0.40 in 1: 1 = EA: Hx, colorless liquid). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.98 (2H, dt, *J*= 6.9, 15.6 Hz), 5.84 (2H, dt, *J*= 1.5, 15.6 Hz), 4.29 (4H, m), 3.74 (4H, m), 3.68 (4H, s), 2.21 (4H, dq, *J*= 1.5, 6.6 Hz), 1.50 (4H, m), 1.29 (4H, m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 166.7, 149.8, 121.5, 71.2, 69.6, 64.0, 31.2, 27.3, 26.9. HRMS (EI) calcd. for $C_{18}H_{28}O_6$: 340.1886, found 340.1893.

Compound in Tabel 5, entry 7. See **General Procedure**. The product was purified directly on a silica gel column, eluting with 1: 2 = ethyl acetate: hexane. 31.3 mg of the product was isolated in 55 % yield. (R_f= 0.55 in 1: 1 = EA: Hx, colorless liquid). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.95 (2H, dt, *J*= 7.2, 15.6 Hz), 5.81 (2H, dt, *J*= 1.5, 15.6 Hz), 4.26 (4H, m), 3.70 (4H, m), 3.65 (4H, s), 2.20 (4H, m), 1.44 (4H, m), 1.23 (12H, m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 166.8, 150.2, 121.4, 71.1, 69.8, 64.0, 32.2, 29.1, 28.9, 28.4, 27.7. HRMS (EI) calcd. for $C_{22}H_{36}O_6$: 396.2512, found 396.2507.

Compound in Tabel 5, entry 8. see **General Procedure**. The product was purified directly on a silica gel column, eluting with 1: 1 = ethyl acetate: hexane. 9.0 mg of the product was isolated in 50 % yield. (R_f= 0.35 in 1: 1 = EA: Hx, colorless liquid). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.83 (1H, dt, *J*= 6.9, 15.6 Hz), 6.71 (1H, dd, *J*= 9.6, 15.6 Hz), 5.81 (2H, dt, *J*= 1.5, 15.6 Hz), 4.36 (2H, m), 4.13 (2H, m), 3.73 (4H, m), 3.67 (4H, s), 2.35 (1H, m), 2.25 (2H, m), 1.79 (1H, m), 1.50 (1H, m), 1.04 (3H, d, *J*= 6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 166.7, 166.5, 153.0,

148.4, 123.0, 121.6, 70.7, 70.5, 69.2, 69.2, 63.8, 63.8, 37.2, 33.1, 30.7, 21.1. HRMS (EI) calcd for $C_{16}H_{24}O_6$: 312.1573, found 312.1581.

Compound in Tabel 5, entry 9. See **General Procedure**. The product was purified directly on a silica gel column, eluting with 1: 1 = ethyl acetate: hexane. 7.0 mg of the product was isolated in 37 % yield. (R_f= 0.35 in 1: 1 = EA: Hx, colorless liquid). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.91 (2H, m), 5.81 (2H, d, *J*= 15.6 Hz), 4.20 (4H, m), 3.72 (4H, m), 3.67 (4H, s), 2.20 (4H, m), 1.5- 1.3 (3H, m), 0.95 (3H, d, *J*= 6.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 166.5, 149.3, 148.3, 122.8, 121.9, 71.1, 70.1, 69.4, 69.3, 64.1, 39.2, 33.5, 31.3, 29.1, 20.6. HRMS (EI) calcd. for $C_{17}H_{26}O_6$ 326.1729, found 326.1728.

Compound 11. See **General Procedure**. This time 8 mol% of catalyst **2** was used. The product was purified directly on a silica gel column, eluting with 1: 10 = ethyl acetate: hexane. 25.4 mg of the product was isolated in 59 % yield. (R_f= 0.5 in 1: 5 = EA: Hx, colorless liquid). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 5.60 (2H, m), 5.33 (2H, dd, *J*= 8.1, 15.9 Hz), 5.13 (2H, m) 2.10 (2H, m), 2.00 (6H, s), 1.60 (2H, m), 1.50 (2H, m), 1.40 (2H, m), 1.2 (24H, m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 170.5, 134.8, 128.9, 75.5, 34.4, 32.1, 29.8, 29.6, 29.2, 29.1, 28.6, 28.2, 24.9, 21.8. HRMS (EI) calcd. for $C_{26}H_{44}O_4$: 420.3240, found 420.3247.

Compound 12. See **General Procedure**. This time 7 mol% of catalyst **2** was used. The product was purified directly on a silica gel column, eluting with 1: 10 = ethyl acetate: hexane. 28 mg of the product was isolated in 84 % yield. (R_f= 0.5 in 1: 5 = EA: Hx, colorless liquid). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 5.62 (2H, m), 5.32 (2H, dd, *J*= 15.3, 7.5 Hz), 5.13 (2H, m), 2.20 (2H, m), 2.00 (6H, s), 1.60 (4H, m), 1.20- 1.40 (14H, m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 170.3, 135.7, 135.3, 128.7, 128.6, 75.8, 75.6, 34.1, 34.0, 32.6, 32.4, 29.5, 29.4, 29.0, 28.8, 28.7, 28.0, 27.8, 23.9, 21.9. HRMS (EI) calcd. for $C_{21}H_{34}O_4$: 350.2457, found 350.2453.

Compound in Eq 3. See **General Procedure**. After metathesis reaction was done, the pot was pressured up with 50 psi hydrogen gas, and ran for overnight. The product was purified directly

on a silica gel column, eluting with 1: 10 = ethyl acetate: hexane. 13.0 mg of the product was isolated in 48 % yield. (R_f= 0.45 in 1: 4 = EA: Hx, white solid). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 2.39 (8H, t, *J*= 6.9 Hz), 1.58 (8H, m), 1.23 (24H, m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 212.5, 41.6, 29.1, 29.0, 28.8, 24.1. HRMS (EI) calcd. for $C_{22}H_{40}O_2$: 336.3028, found 336.3024.

Reference:

1. For recent reviews on organic applications of olefin metathesis, see: (a) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res*. **1995**, *28*, 446. (b) Schuster, M.; Blechert, S. *Angew. Chem*. **1997**, *109*, 2124; *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2067. (c) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (d) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371. (e) Blechert, S. *Pure Appl. Chem.* **1999**, *71*, 1393.
2. a) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 5426; b) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 7324; c) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9856.
3. Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100.
4. Furstner, A. *Angew. Chem. Int. Ed*. **2000**, *39*, 3013.
5. Scholl, M. ; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 1425.
6. a) Kim, S. H.; Bowden, N. B.; Grubbs, R. H. *J. Am. Chem. Soc.* **1994**, *116*, 10801; b) Kim, S. H.;. Zuercher, W. J; Bowden, N. B.; Grubbs R. H. *J. Org. Chem.* **1996**, *61*, 1073; c) Zuercher, W. J.; Hashimoto, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 6634; d) Zuercher, W. J.; Scholl, M.; Grubbs, R. H. *J. Org. Chem.* **1998**, *63*, 4291.
7. Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.
8. Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783.
9. Lee, C. W.; Grubbs, R. H. *Org. Lett*. **2000**, *2*, 2145.

10. This portion of works was published. See; a) Choi, T.-L.; Grubbs, R. H. *Chem. Comm.* **2001**, 2648; b) Lee, C. W.; Choi, T.-L.; Grubbs, R. H. *J. Am. Chem. Soc.* **2002**, *124*, 3224.
11. a) Teitze, L. F. *Chem. Rev.* **1996**, *96*, 115; b) Hudlickly, T. *Chem. Rev.* **1996**, *96*, 3; c) Ho, T.-L. *Tandem Reactions in Organic Synthesis*; Weley-Interscience: New York, 1992.
12. Ihara, M; Makita, K; Tokunaga, Y.; Fukumoto, F. *J. Org. Chem.* **1994**, *59*, 6008.
13. Johnson, W. S.; Wiedhaup, K.; Brady, S. F; Olson. G. L. *J. Am. Chem. Soc.* **1974**, *96*, 3979.
14. Takahashi, T.; Katouda, W.; Sakamoto, Y.; Tomida, S.; Yamada, H. *Tetrahedron Lett.* **1995**, *36*, 2273.
15. a) Denmark, S. E.; Thorarensen, A. *Chem. Rev.* **1996**, *96*, 137; b) Winkler, J. D. *Chem. Rev.* **1996**, *96*, 167.
16. a) Zhang, Y.; Wu, G.; Angel, G.; Negishi, E. *J. Am. Chem. Soc.* **1990**, *112*, 8590; b) Trost, B. M.; Shi, Y. *J. Am. Chem. Soc*. **1993**, *115*, 9421.
17. Parsons, P. J.; Penkett, C. S.; Shell, A. J. *Chem. Rev.* **1996**, *96*, 195.
18. Choi, T.-L.; Lee. C. W.; Chatterjee, A. K.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 10417.
19. Scherman, O. S.; Grubbs, R. H. *Unpublished result*, **2001**.
20. a) Stragies, R.; Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2518; b) Schurer, S. C.; Blechert, S. *Chem. Commun.* **1999**, 1203; c) Schurer, S. C.; Blechert, S. *Tetrahedron Lett.* **1999**, *40*, 1877; d) Stragies, R.; Voigtmann, U.; Blechert, S. *Tetrahedron Lett.* **2000**, *41*, 5465.
21. a) Chatterjee, A. K.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 1751; b) Choi, T-L.; Chatterjee, A. K. Grubbs R. H. *Angew. Chem.* **2001***, 113*, 1317; *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 1277. c) Chatterjee, A. K.; Choi, T.-L.; Grubbs R. H. *Synlett* **2001**, 1034.
22. For a review on macrocycle synthesis, see: Roxburgh, C. J. *Tetrahedron* **1995**, *51*, 9767.

23. a) Furstner, A.; Thiel, O. R.; Kindler, N.; Bartkowska, B. *J. Org. Chem*. **2000**, *65*, 7990; b) Garbaccio, R. M.; Danishefsky, S. J. *Org. Lett*. **2000**, *2*, 3127; c) Furstner, A.; Thiel, O. R.; Ackermann, L. *Org. Lett*. **2001**, *3*, 449; d) Schultz, L. G.; Zhao, Y.; Zimmerman, S. C. *Angew. Chem, Int. Ed*. **2001**, *40*, 1962; e) Lee, C. W.; Grubbs, R. H. *J. Org. Chem*. **2001**, *66*, 7155.

24. Bielawski, C. W.; Grubbs, R. H. *Angew. Chem, Int. Ed*. **2000**, *39*, 2903.

25. Delgado, M.; Martin, J. D. *J. Org. Chem.* **1999**, *64*, 4798.

26. Ivin, K. J.; Mol, J. C. *Olefin Metathesis and Metathesis Polymerization*, Academic Press, San Diego, CA, **1997**.

27. a) Ulman, M.; Belderrain, T. R.; Grubbs, R. H. *Tetrahedron Lett.* **2000**, *41*, 4689; b) Randl, S.; Connon, S. J.; Blechert, S. *Chem. Commun.* **2001**, 1796.

28. Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.

29. a) Bielawski, C. W.; Louie, J.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 2872; b) Louie, J.; Bielawski, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 11312.

Chapter 4:

Multiple Olefin Metathesis Polymerizations (MOMP)

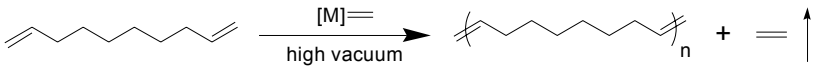
Abstract

Olefin metathesis polymerization, in particularly ring-opening metathesis polymerization (ROMP), has been a popular topic of modern research. Two other types are acyclic diene metathesis polymerization (ADMET) and cyclopolymerization of diynes. To date, there has been no report on a metathesis polymerization utilizing more than one metathesis process. Herein, the concept of multiple olefin metathesis polymerizations (MOMP) is introduced where two or three types of olefin metathesis reactions are used to generate well-defined polymer architectures. In the first half of this chapter, ROMP and ADMET processes are combined to produce highly A,B-alternating copolymers. In the second half, a polymerization where ROMP and cyclopolymerization are performed in a domino fashion is disclosed. Finally, a transformation involving all three types of olefin metathesis reaction, ring-opening, ring-closing, and cross metathesis cooperatively and orderly generate only one uniform polymer microstructure.

Background

Among the various olefin metathesis processes, ring-opening metathesis polymerization (ROMP) is the oldest reaction. ROMP has attracted the attention of polymer chemists for its many advantages over other polymerization methods.[1] With the right choice of catalyst and monomer, living polymerization to produce well-defined polymers with good molecular weight control and a narrow polydispersity index (PDI) is possible by ROMP.[2] With functional group tolerant catalysts, polymerization operates under mild conditions, such as room temperature, bench-top chemistry and short reaction times.[3] Furthermore, these catalysts allow the production of highly functionalized polymers and biologically relevant polymers.[4] Lastly, end-functionalized telechelic polymers are efficiently prepared by ROMP with the use of chain transfer agents.[5]

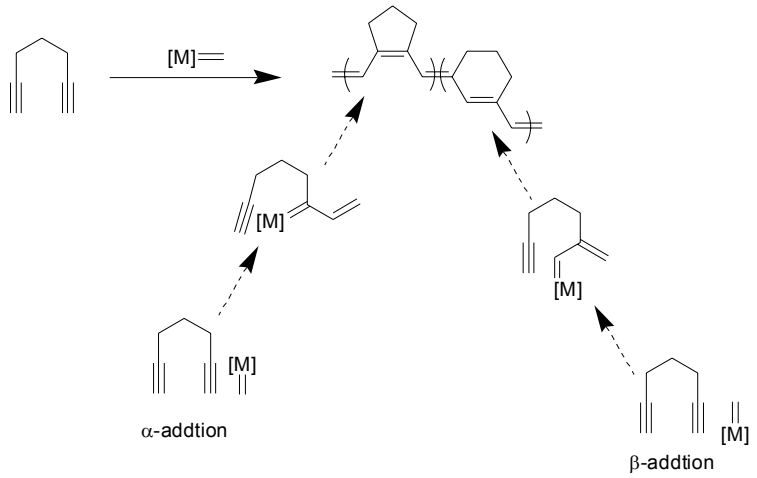
In addition to ROMP, there are two other metathesis polymerization methods, acyclic diene metathesis polymerization (ADMET) and cyclopolymerization. ADMET is a step-growth polymerization where dienes are polymerized by continuous cross metathesis (Scheme 1).[6] Therefore, by nature, ADMET produces polymers with broad PDIs and poor molecular weight control. It is hard to prepare high molecular weight polymers by ADMET since the thermodynamic control of olefin metathesis process does not facilitate conversions necessary to reach high molecular weight. The main shortcoming is that the enthalpically neutral bond formation in ADMET process does not provide a strong thermodynamic driving force for polymerization. In order to overcome the equilibrium issue, high vacuum system is used to entropically force the polymerization by removing ethylene gas.



Scheme 1. An example of ADMET

Cyclopolymerization occurs when diynes are treated with the right choice of catalyst (Scheme 2).[7] With the well-defined molybdenum catalyst, living polymerization is also possible to produce polymers with a narrow PDI and good molecular weight control.[8] The polymerization

goes to high conversion because the alkynes transform into conjugated dienes with a substantial gain in enthalpy. However, the generation of two possible polymer microstructures by α, and β-addition complicates the study of the resulting polymers.[7, 9] In addition, only early transition metal-based catalysts which are very sensitive to many functional groups, can promote the efficient polymerization. Unfortunately, attempts to promote cyclopolymerization by various functional group tolerant catalysts such as $Cl_2(PCy_3)_2Ru=CHPh$ (**1**)[3], $Cl_2(PCy_3)(IMesH_2)Ru=CHPh$ (**2**)[10], Hoveyda-Grubbs catalyst,[11] and Cl_2(3-BrPyr)$_2(IMesH_2)Ru=CHPh$ (**3**)[12] were unsuccessful, only yielding low molecular weight oligomers. This drawback has inhibited the general use of cyclopolymerization.



Scheme 2. An example of cyclopolymerization and two microstructures

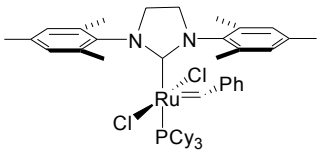
Although ADMET and cyclopolymerization have been far less investigated for the reasons stated before, these two polymerizations have their certain advantages over ROMP. ADMET sometimes provides an easier access to monomers when attaching a desired monomer precursor to a strained cycloalkene is problematic. Cyclopolymerization provides an efficient route to conjugated polymers which exhibit interesting physical properties such as conductivity and luminescence.[13] Therefore, developing new olefin metathesis polymerization and new monomers to produce new microstructures will further expand the utility of the metathesis reaction. For example, no general metathesis methods exist to produce A,B-alternating

copolymers or hyperbranched polymers. In this chapter a new concept of multiple olefin metathesis polymerizations (MOMP) is introduced.[14]

Part I. Synthesis of A,B-Alternating Copolymers by Ring-Opening Insertion Metathesis Polymerization (ROIMP)

Introduction

Alternating copolymers are normally formed by step-growth polymerization of AA and BB or AB type monomers[15] and in some special chain growth reactions, for example, copolymerization of ethylene and CO by Pd catalyst.[16] Although recent developments in ring opening metathesis polymerization (ROMP)[1] and acyclic diene metathesis polymerization (ADMET)[6] have extended the versatility of both chain-growth and step-growth reactions, these metathesis polymerizations have not provided a general solution to alternating copolymers. Examples of alternating copolymers by ROMP are rare due to the difficulty of finding systems in which there is an alternation in the affinity of the propagating metal carbene for the monomers.[17] Although ADMET is a step growth polymerization, examples of alternating copolymerization with two monomers by this mechanism have not been reported since most olefins studied have similar reactivity and would produce only random copolymers.[18] Therefore, a general metathesis route toward A,B-alternating copolymers would allow for the synthesis of new functional polymers.



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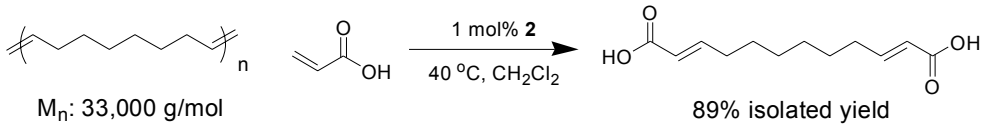
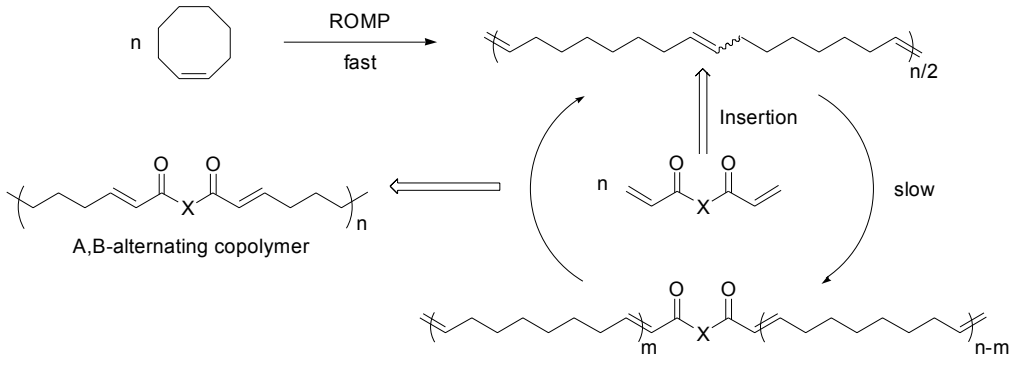
Although well-defined olefin metathesis catalysts such as $((CF_3)_2MeCO)_2(ArN)$-Mo=CH(*t*-Bu) and $Cl_2(PCy_3)_2Ru$=CHPh (**1**) have proven useful for polymer synthesis, the highly active molybdenum catalyst suffers from sensitivity to some polar functional groups[2] while the

functional group tolerant catalyst **1** shows decreased reactivity.[3] These disadvantages were recently addressed with the development of catalyst **2**, which exhibits high activity and remains tolerant of many functional groups.[10] Furthermore, catalyst **2** promotes ring-closing metathesis and selective cross metathesis (CM) of α,β-unsaturated carbonyl olefins with high conversions,[19] thereby expanding the scope of olefin metathesis in organic synthesis. In addition, a polyoctenomer synthesized by ROMP of cyclooctene was efficiently depolymerized using acrylic acid and catalyst **2** (Scheme 3).[20] This suggests that catalyst **2** should be able to produce polymers



Scheme 3. Depolymerization of polyoctenomer

from α,β-unsaturated carbonyl olefins. Also, if the coupling between internal olefins and α,β-unsaturated carbonyl olefins is selective, as is the case in cross metathesis, diacrylate monomers should be selectively inserted into ROMP polyolefins to yield alternating copolymers (Scheme 4). Herein, we report the development of a general method for synthesizing A,B-alternating copolymers by ring opening insertion metathesis polymerization (ROIMP).



Scheme 4. Proposed Mechanism for ROIMP

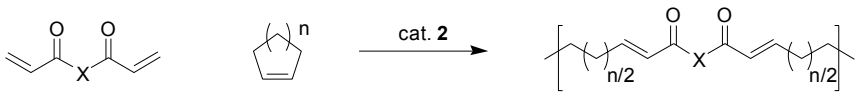
Results and Discussion

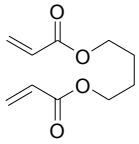
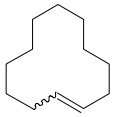
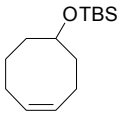
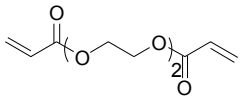
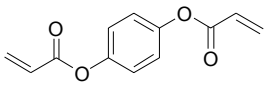
Treatment of a 1:1 mixture of monomers A (diacrylate) and B (cycloalkene) with catalyst **2**, indeed, yielded highly A,B-alternating copolymers in high yields. Examples of alternating

copolymers generated from a variety of diacrylates and cycloalkenes are shown in Table 1. For example, using a total monomer to catalyst ratio of just 290:1, a 1:1 mixture of 1,4-butanediol diacrylate and cyclooctene gave a copolymer with up to 99% A,B-alternation and a molecular weight of 90,100 g mol^{-1} with expected broad PDI (entry 1). It is important to match the stoichiometry of cyclooctene and diacrylates because any excess of cyclooctene results in oligocyclooctene blocks, lowering alternation, and a shortage limits the molecular weight of the polymer.

The extent of alternation could be easily determined by ^{1}H NMR, since olefinic protons for alternating units have a distinct chemical shift well resolved from the starting materials and homo-coupled units. *E*-Acrylate dimers produce a sharp singlet at 6.9 ppm (Figure 1a), while polycycloalkenes display a multiplet at 5.4 ppm (Figure 1c). On the other hand, A,B-alternating units produce a doublet of triplets at 7.0 ppm and a doublet at 5.8 ppm (Figure 1b). Therefore, the extent of A,B-alternation can be easily calculated by integrating these peaks. The sharp coupling patterns demonstrate a highly uniform polymer structure with *E* olefin isomer (J =15.9 Hz). ^{13}C NMR also shows high alternation, displaying only two olefinic carbon peaks for carbons α and β to the carbonyl group (Figure 1d). Such observation of the sharp peaks by ^{1}H, and ^{13}C NMR is very rare for polymers which tend to give broad signals.

Table 1 Examples of ROIMP products.



entry	acylic diene	cycloalkene[a]	[M] /[C][b]	conc.[c] [M]	yield[d] [%]	A,B-alt.[e] [%]	Mn / PDI[f] [10^{-3}g mol^{-1}]
1			290	0.2	84	99	90.0 / 1.73
2			125	0.4	75	96	20.3 / 1.58
3			125	0.4	93	97	14.0 / 1.80
4			200	0.5	91	94	26.1 / 1.71
5			250	0.4	69	94.5	21.4 / 1.43
6			200	0.2	99	98.5	26.5 / 1.80
7			100	0.1	98	97	25.2 / 2.06

[a] 1.0 eq of cycloalkene was used except cyclopentene (1.3 eq) [b] Ratio of total monomer to catalyst
[c] Concentration with respect to acyclic diene [d] Isolated yields after precipitation into hexane or methanol
[e] Determined by ^{1}H NMR [f] Determined by CH_2Cl_2 GPC relative to polystyrene standards

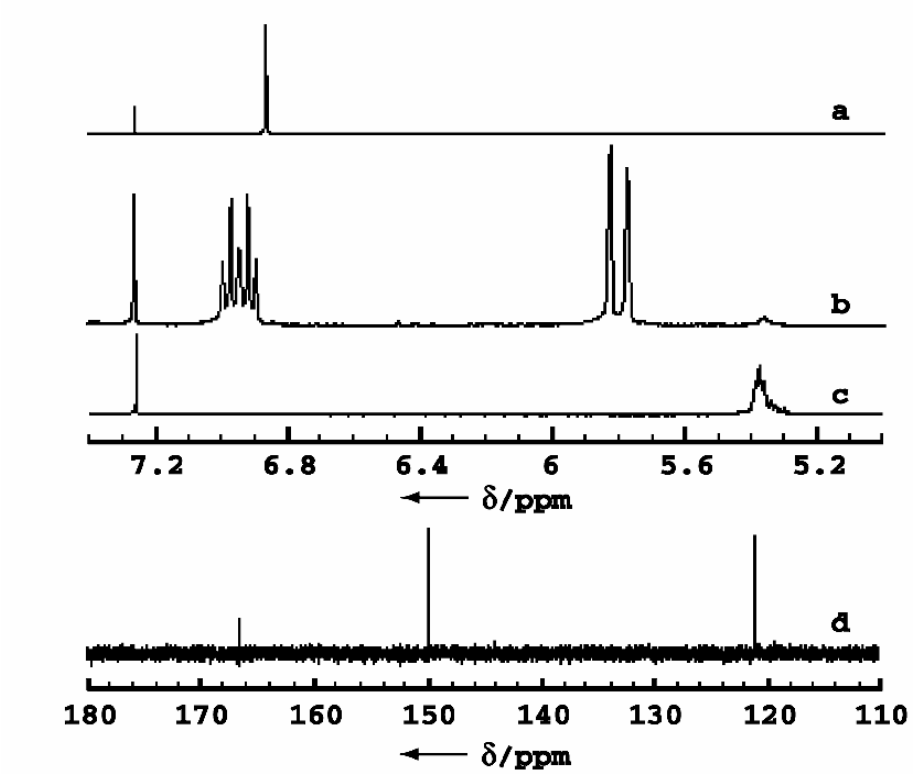


Figure 1. NMR spectra for a ROIMP product

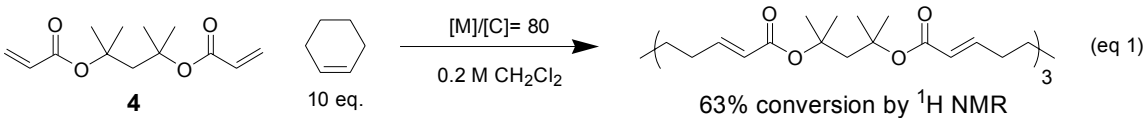
In support of the mechanism shown in Scheme 4, an independently prepared polyoctenamer was treated with 1,4-butanediol diacrylate and catalyst **2**, and the reaction also yielded an copolymer similar to the product of entry 1 in Table 1. In addition, monitoring a ROIMP reaction by ^{1}H NMR showed the rapid and complete ROMP of cyclooctene followed by gradual appearance of peaks corresponding to A,B-alternating units. Furthermore, when a ROIMP reaction was terminated after 20 minutes, a polymer enriched in homo-polycycloalkene olefin units was obtained. These results strongly suggest a mechanism whereby ROMP of the cycloalkene initially produces an unsaturated polymer scaffold to which subsequent insertion of the diacrylate forms the final A,B-alternating structure.

Other cycloalkenes were also viable ROIMP monomers and yielded highly alternating polymers (Table, entries 2 – 4). However, monomers with particularly low ring strains, such as cyclopentene and cycloheptene, required a lower monomer to catalyst ratio of 125:1 due to the slow rate of ROMP.[5a] In order to obtain a high A,B-alternation with volatile cyclopentene (bp 44

^{o}C), a slight excess of 1.3 equiv. of the cycloalkene relative to the diacrylate was used to produce a copolymer with 96% alternation. Even with 2.0 equiv. of cyclopentene, a polymer with higher than 85% A,B-alternation was obtained. Also, treating an isolated polymer of lower A, B-alternation with fresh catalyst **2** yielded a final polymer with higher A,B-alternation. These results suggest that the equilibrium for cyclopentene lies toward the cyclic form at 40 ^{o}C. Therefore, excess homo-polycyclopentene units depolymerize back to cyclopentene and leave the system by evaporation.[21]

Synthesis of A,B-alternating copolymers with cyclohexene was also attempted. Due to very low ring strain, it can not typically be polymerized by olefin metathesis process. Only one report is known for ring opening of cyclohexene where oligomers are formed in low yield by ill-defined classical metathesis catalyst WCl_6 with a turnover number less than 1 at -80 ^{o}C.[22] Recently, after the discovery of the ring-opening of cyclohexene by enoic carbene catalyst,[23] the first catalytic ring-opening of cyclohexene by catalyst **2** and acrylates was reported to produce bis-capped ring-opening-cross products (Chapter 2).[24] This methodology was applied to synthesize A,B-alternating copolymers from cyclohexene.

From the enoic carbene studies, it was known that bulky acrylates generated more stable enoic carbenes. Therefore substrate **4** and cyclohexene were used for ring-opening-cross metathesis polymerization (eq 1). Not surprisingly, low activity and poor stability of enoic carbenes only yield perfectly A,B-alternating oligomers (average of 3 alternating repeat units corresponding to M_n of 900 g/mol) with 63% conversion.



4 10 eq. 63% conversion by ^{1}H NMR (eq 1)

Notably, various functional groups can be incorporated into ROIMP copolymers. 5-*t*-Butyldimethylsilyloxycyclooctene proved to be a viable monomer, comparable to the parent cyclooctene (Table 1, entry 5). In this way, free alcohol groups could be installed into alternating

monomer units upon simple deprotection. 5-Acetoxycycloctene is also a viable monomer for ROIMP reaction, but requires higher catalyst loading presumably due to carbonyl group of the monomer slowing down the insertion by the chelation effect.[19c] Further variations such as ethylene glycol and phenyl groups can be substituted into diacrylate units as shown in entries 6 and 7. These results demonstrate that the regioselective incorporation of functional groups is possible by the appropriate choice of monomers A and B, thus opening up a new class of polymers that can be synthesized by ROIMP.

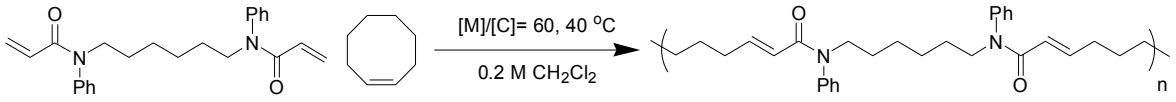
ROIMP exhibits remarkable conversion and selectivity. Compared to ADMET, where high vacuum and elevated temperature are required to drive the polymerization to high conversion by removal of ethylene gas,[6] ROIMP can give high conversion under gentle reflux conditions for two reasons. First, ROMP of cycloalkenes is efficient in making the initial polyalkenomers chains. Second, the formation of 1,2-disubstituted α,β-unsaturated carbonyl cross product is enthalpically favored by more than 3 kcal mol^{-1}.[25] These enthalpic factors, combined with the loss of ethylene, drive the reaction to high conversion. Additionally, the unfavorable oligomerization of diacrylates, where the intermediate is an unstable enoic carbene, leads to high A, B-alternation.[25] Therefore, ROIMP combines benefits of both chain-growth and step-growth polymerization, leading to high molecular weight and high selectivity.

To optimize conversion, other polymerization conditions were investigated. It was found that 0.1-0.5 M solutions in CH_2Cl_2 at 40 ^oC yield the best results. In contrast to ROMP, increasing the concentration beyond 0.5 M resulted in lower conversions. Switching to toluene or 1,2-dichloroethane as solvent also gave lower conversions, at either 40 ^oC or 60 ^oC. While there is precedence for CH_2Cl_2 being the best solvent for cross metathesis of functionalized olefins,[24] the concentration dependence for ROIMP is somewhat surprising, since concentrations of 0.1–0.5 M are considered dilute conditions for conventional step growth polymerization reactions.

Controlling the molecular weight of polymers is a very important issue since polymers with different molecular weights exhibit different properties. For alternating copolymers

produced by ROIMP, the molecular weight can be roughly controlled by changing the relative stoichiometry of the two monomers. For example, using 0.96 equiv. of cyclooctene to 1.0 equiv. of hydroquinone diacrylate gave 17,800 g mol^{-1} with 98% A,B-alternation (PDI = 1.64). In contrast, a copolymer of 45,200 g mol^{-1} and 95.5% alternation (PDI = 1.69) was obtained by increasing to 1.06 equiv. of cyclooctene. These results show that, compared with the 1:1 case (entry 7, Table 1), using a slight excess of hydroquinone diacrylate shortens the polymer chain, but a slight excess of cyclooctene gives higher molecular weight at the cost of alternation due to the oligomeric blocks of polycyclooctene.

This polymerization was further expanded to the synthesis of polyamides by incorporating diacrylic amides into the ROMP polymers. However, as seen in Chapter 2, CM efficiency of acrylic amides by catalyst **2** is heavily dependent on the substituents on the nitrogen.[19c] Similar trends appear to hold true for ROIMP. Insertion of *N*,*N*-dialkyl acrylic amides was very poor, yielding a copolymer with low A,B-alternation. Insertion of *N*-alkyl acrylic amides was more successful, but premature precipitation of polymers occurred since the resulting polyamides are highly insoluble due to their hydrogen bonding ability with other polymer chains. These polyamides were only soluble in strong acids, such as TFA, formic acid and sulfuric acids, similar to commercial Nylons. A ROIMP polymer was successfully prepared from *N*,*N*-diphenyl 1,6-hexyl diacrylic amide and cyclooctene, yielding polyamides with excellent yield and alternation and with moderate molecular weight (Scheme 5). Higher catalyst loading (M/C= 60) was required to improve the insertion of the diacrylic amide.



99% isolated yield, 95% alternation
Mn: 9,700 g/mol, PDI: 1.5

Scheme 5. Synthesis of polyamide by ROIMP

Conclusion

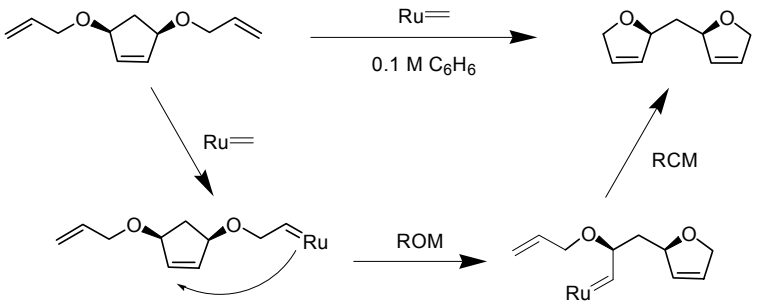
In this section, we have demonstrated a new, general method for synthesizing highly alternating copolymers by olefin metathesis. The high conversion and degree of alternation arise from the thermodynamically driven selective bond formation between diacrylates and cycloalkenes.

Part II. Ring-Opening-Closing-Addition Metathesis Polymerization

Introduction

There are three main transformations in olefin metathesis, ring-opening, ring-closing and cross metathesis reactions. These transformations are well applied to polymerization, ring-opening olefin metathesis polymerization (ROMP),[1] cyclopolymerization[16] and acyclic diene metathesis polymerization (ADMET),[17] respectively. All the polymerizations so far reported use only one of the three types of polymerizations because combining more than one polymerization produces ill-defined random polymers due to lack of control of polymer microstructures. Ring-opening insertion metathesis polymerization (ROIMP),[14] described in part I of this chapter, presents the first example of multiple olefin metathesis polymerization (MOMP) where ring-opening and cross metathesis reactions are combined in one pot to produces A,B-alternating copolymers.

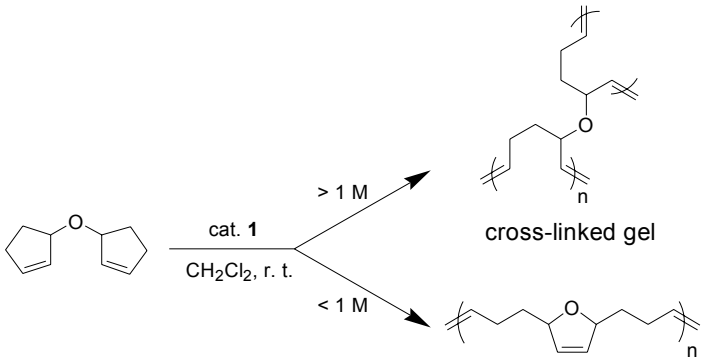
In search for a new olefin polymerization method, applying tandem ring-opening/ ring-closing metathesis presented in Chapter 3[26] to polymerization was envisioned (Scheme 6). In theory this polymerization will combine ROMP and RCM in one pot. Furthermore, incorporating CM into this process will provide a polymerization where three metathesis transformations are combined to produce one uniform polymer microstructure. This section describes efforts to achieve MOMP with 2-cyclopenten-1-yl ether and diacrylates.



Scheme 6. Tandem ring-opening/ring-closing metathesis reaction

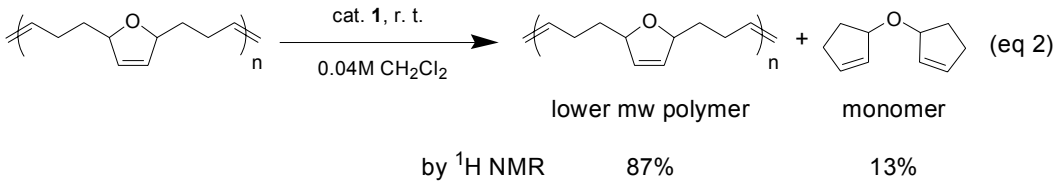
Results and Discussion

2-Cyclopenten-1-yl ether (**5**) has two cyclopentene moieties which can be polymerized by ROMP. Indeed, under typical conditions for the ROMP of cyclopentene (2 M, 23 ^{o}C), a solution of **5** became viscous upon the addition of catalyst **1** implying polymer formation. After 10 minutes, the solution turned into a gel. It is no surprise that **5** having two polymerizable functional groups, cyclopentene moiety, can cross-link to produce insoluble gel. However, in dilute conditions (< 1.0 M) totally different polymers were obtained (Scheme 7). At 0.1 M, ^{1}H NMR showed that **5** was polymerized into poly(2,5-disubstituted-2,5-dihydrofuran) with 87% conversion and E : Z = 3: 1 for acyclic olefins after 24 hours. Increasing the concentration also increased the conversion of the monomers, for example, at 0.5 M and M/C= 100 a conversion of 97% was observed by ^{1}H NMR. Precipitation into methanol gave a rubbery polymer in moderate yield with M_n of 59,000 g/mol. Broad PDI of 1.67 obtained by CH_2Cl_2 GPC relative to polystyrene standards is expected since the reaction appears to be reversible and extensive chain transfer occurs at the acyclic internal olefins.



Scheme 7. Concentration-dependent polymerization

The polymerization appears to be in thermodynamic equilibrium, thus reversible. The isolated polymers were re-dissolved to make 0.04 M CH_2Cl_2 solution and fresh catalyst was added. After 12 hours, 13 mol% of monomers was observed by ^{1}H NMR implying depolymerization in dilute conditions (eq 2). Furthermore, the cross-linked gel obtained at a 2.0 M concentration of **5** was diluted to 0.5 M and the gel disappeared completely after 6 hours yielding mainly a soluble polymer with microstructure of dihydrofuran moiety. It is believed that in dilute concentrations, the degree of cross-linking is reduced due to depolymerization or back-biting to produce cyclized poly(2,5-dihydrofuran).



Poor molecular weight control is observed for this polymerization. Increasing the monomer to catalyst ratio does not linearly increase the molecular weight of the polymers (Table 2). Other catalysts also promote this polymerization, but catalyst **1** outperforms other more reactive catalysts. Catalyst **2**[10] reaches the equilibrium much slowly due to its slower initiation,[27] and ultra-fast initiating catalyst **3** gives polymer with low conversion (25% by ^{1}H NMR) due to the instability of the resulting terminal alkylidene.[12] Unfortunately, monomer to catalyst ratio higher than 300 completely shut down the polymerization. At [M]/[C] = 500, only monomer remained with none of the peaks corresponding to polymer observed by ^{1}H NMR. The catalyst

appeared to be totally decomposed or at least became metathesis inactive catalyst because even the addition of reactive monomers such as norbornene into the solution did not yield polynorbornene. Other more reactive catalysts were used to polymerize with [M]/[C] = 500 and the conversions lower than 25% were observed by ^{1}H NMR. It is speculated that a small amount of 2-cyclopenten-1-yl ether isomerized to enol ethers which react with the catalysts to form catalytically inactive Fischer carbenes.

Table 2. Domino polymerization of **5**[a]

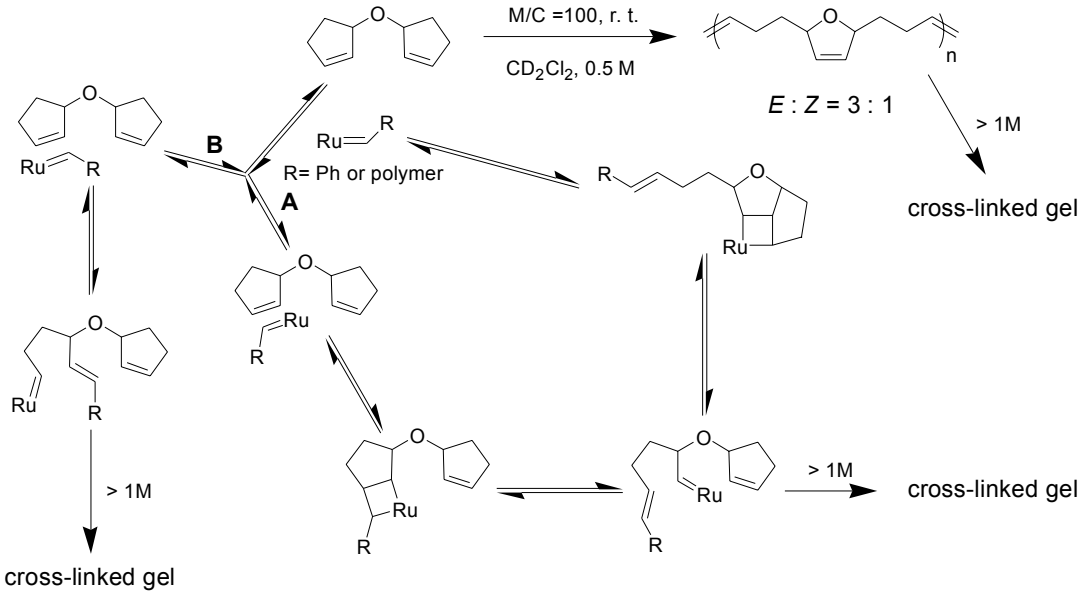
[M]/[C]	M_n[b] [x10^3 g/mol]	PDI[b]
50	52	1.7
100	59	1.7
200	72	2.9
250	128	2.5

[a] Cat. **1** in 0.06 M CH_2Cl_2 at 23 ^oC.[b] Determined by CH_2Cl_2 GPC relative to polystyrene standards

It is likely that the polymerization occurs by a systematic domino metathesis reaction of ring-opening/ring-closing polymerization (Scheme 8). To investigate the mechanism of the polymerization, the reaction was monitored ^{1}H and ^{13}C NMR. Firstly, monitoring the reaction at high concentration (2 M) revealed the peak corresponding to the desired cyclized polydihydrofuran as well as several other peaks corresponding to randomly cross-linked polymers. However, at 0.5 M, ^{1}H and ^{13}C NMR only shows the peak corresponding to the desired polymer throughout the polymerization. This implies that at 0.5 M, only domino metathesis reactions of ring-opening-closing polymerization is operative, and the reversible formation to the desired polymer microstructure from the cross-linked random polymerization is less likely to occur.

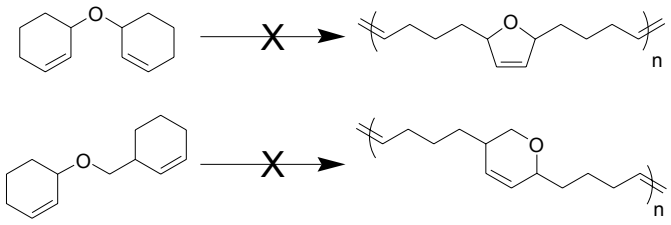
Although there are two possible binding modes for the catalyst, only the path **A** results in the desired domino ring-opening/ring-closing polymerization (Scheme 8). At low concentration, the path **B** do not intervene the polymerization since the ring-opened alkylidene should reversibly go back to the monomer by the non-productive intramolecular RCM. However, at high

concentration, intermediates of both path **A** and **B** as well as the final product can form the cross-linked gel. Notably, this polymerization is the first example to produce polymers by using both ring-opening and ring-closing metathesis reactions.



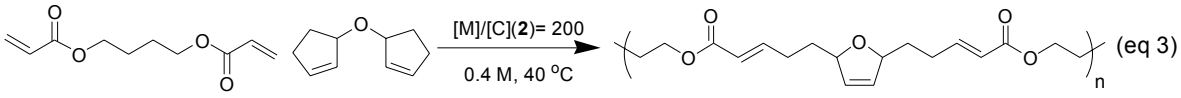
Scheme 8. Proposed mechanism of ring-opening/ring-closing metathesis polymerization

Interestingly, 2-cyclopenten-1-yl ether can be polymerized at even below 0.1 M despite possessing the low-strained olefin. In contrast, cyclopentene does not undergo ROMP at dilute concentration (< 1 M) because the concentration is below the critical concentration for cyclopentene meaning that ring-closing rate is much faster than the rate of ROMP rate at concentrations below 1 M. This difference can be explained by the fact that the facile domino ring-opening/ring-closing metathesis produces lower ring-strained 2,5-dihydrofuran. Also, due to the substitutions at the 2 and 5-positions of the dihydrofuran, the backward domino reaction to depolymerize the chains is slowed down relative to chain propagation. Encouraged by this result, attempts to polymerize challenging monomers containing a cyclohexene moiety were made (Scheme 9). Cyclohexene and its derivatives have been impossible to polymerize by olefin metathesis.[1] Unfortunately, monomers of similar structures to 2-cyclopenten-1-yl ether but with cyclohexenyl rings did not polymerize, and only the starting materials remained.



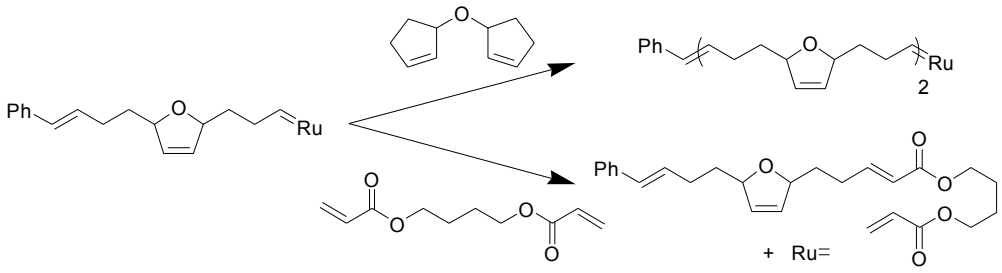
Scheme 9. Attempts to polymerize monomers with cyclohexene moieties

This multiple olefin metathesis polymerization (MOMP) can be further extended by combination with ROIMP.[14] Treating 2-cyclopenten-1-yl ether and 1,4-butanediol-diacrylate with catalyst **2** produced polymer with high A,B-alternation in high yield (eq 3). Here the concentration of the reaction is also crucial as a cross-linked gel is formed at high concentrations. This is the first polymerization where all three types of olefin metathesis transformation (ring-opening, ring-closing and cross metathesis reactions) are combined in orderly manners to produce a uniform polymer microstructure.



99% isolated yield, 97% A,B-alternation
Mn= 13,800 g/mol, Mw= 27,000 g/mol, PDI= 1.95

To understand the detailed mechanism of ring-opening-closing-addition metathesis polymerization, the reaction was monitored by ^{1}H NMR. Unlike the ROIMP case, the chain propagation of 2-cyclopenten-1-yl ether is not as fast as ROMP of cyclooctene. ^{1}H NMR spectra reveal that the chain propagation of 2-cyclopenten-1-yl ether to another monomer unit is about as fast as the cross coupling with the diacrylates (Scheme 10). Therefore, a mixture of the polymer chains with different microstructures grows at the beginning of the reaction, which gradually converge into one uniform microstructure at the end of the polymerization. It is notable that three different metathesis reactions are independently and simultaneously occurring in one-pot, but cooperatively produce the final polymer with one well-defined polymer microstructure.



Scheme 10. Similar rates for the both reactions

Conclusion

To summarize 2-cyclopenten-1-yl ether undergoes domino ring-opening/ring-closing metathesis polymerization at dilute concentration. When combined with ROIMP, a polymerization where all three types of olefin metathesis, ring-opening, ring-closing, and cross metathesis are utilized, is possible. This chapter demonstrates that mechanistically interesting multiple olefin metathesis polymerizations can produce well-defined polymer microstructures.

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Experimental Section

General Experimental Section. NMR spectra were recorded on Varian Mercury-300 NMR (300 MHz for ^{1}H and 74.5 MHz for ^{13}C). Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) with reference to internal solvent. Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), and multiplet (m). The reported ^{1}H NMR data refer to the major olefin isomer unless stated otherwise. The reported ^{13}C NMR data include all peaks observed and no peak assignments were made. Gel

permeation chromatography (GPC) analysis in CH_2Cl_2 was obtained on a HPLC system using a Shimadzu LC-10AP_{vp} pump, Shimadzu DGU-14A degasser, a Rheodyne model 7125 injector with a 100 *u*l injection loop through Polymer Standard 10 micron mixed bed columns, and a Knauer differential refractometer. Molecular weights and molecular weight distributions, M_w/M_n, are reported relative to narrow disperse polystyrene standards (Showa Denko).

Analytical thin-layer chromatography (TLC) was performed using silica gel 60 F254 precoated plates (0.25 mm thickness) with a fluorescent indicator. Flash column chromatography was performed using silica gel 60 (230-400 mesh) from EM Science. All other chemicals were purchased from the Aldrich, Strem, or Nova Biochem Chemical Companies, and used as delivered unless noted otherwise. CH_2Cl_2 was purified by passage through a solvent column prior to use.

Procedure for Scheme 3: To a flask charged with polyoctenomer (56.0 mg, 0.51 mmol) in 0.5 ml of CH_2Cl_2, catalyst **2** (4.3 mg) and acrylic acid (87 *u*l, 1.27 mmol) were added. Quick degassing by dynamic vacuum was conducted and the flask was fitted with a condenser and refluxed under argon for 6 hours. The product (102 mg, 89%) was precipitated from the solution. The solid was filtered and washed with CH_2Cl_2. ^{1}H NMR (300MHz, $CDCl_3$, ppm): δ 10.66 (2H, br), 6.87 (2H, dt, J= 15.6, 6.9 Hz), 5.78 (2H, dd, J= 15.6, 1.5 Hz), 2.20 (4H, m), 1.47 (4H, m), 1.35 (4H, m). HRMS (EI) calcd. for $C_{12}H_{18}O_4$: 227.1283, found 227.1292.

Procedure for Table 1, entry 1: To a flask charged with 1,4-butanediol diacrylate (90 mg, 0.45 mmol) in 2 ml of CH_2Cl_2, catalyst **2** (2.7 mg) and cyclooctene (65 *u*l, 0.45 mmol) were added. Quick degassing by dynamic vacuum was conducted and the flask was fitted with a condenser and refluxed under argon for 6 hours. The product (108 mg, 84%) was precipitated into methanol. ^{1}H NMR (300MHz, $CDCl_3$, ppm): δ 6.93 (1H, dt, *J*= 7.2, 15.9 Hz), 5.77 (1H, d, *J*= 15.9 Hz), 4.13 (2H, br), 2.12 (2H, m), 1.73 (2H, m), 1.43 (2H, m), 1.30 (2H, m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 166.8, 149.6, 121.3, 64.0, 32.5, 29.3, 28.2, 25.8.

Procedure for Table 1, entry 2: To a flask charged with 1,4-butanediol diacrylate (34 mg, 0.15 mmol) in 0.4 ml of CH_2Cl_2, catalyst **2** (2.3 mg) and cyclopentene (20 *u*l, 0.15 mmol) were added. Quick degassing by dynamic vacuum was conducted and the flask was fitted with a condenser and refluxed under argon for 6 hours. The product (37 mg, 75%) was precipitated into hexane. ^{1}H NMR (300MHz, $CDCl_3$, ppm): δ 6.85 (1H, dt, *J*= 7.2, 15.9 Hz), 5.82 (1H, d, *J*= 15.9 Hz), 4.10 (2H, br), 2.22 (2H, m), 1.60-1.75 (3H, m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 166.5, 148.4, 121.9, 64.0, 31.7, 30.7, 26.6, 25.6.

Procedure for Table 1, entry 3: To a flask charged with 1,4-butanediol diacrylate (60 mg, 0.30 mmol) in 0.8 ml of CH_2Cl_2, catalyst **2** (4.1 mg) and cycloheptene (35.5 *u*l, 0.30 mmol) were added. Quick degassing by dynamic vacuum was conducted and the flask was fitted with a condenser and refluxed under argon for 6 hours. The product (74 mg, 93%) was precipitated into hexane. ^{1}H NMR (300MHz, $CDCl_3$, ppm): δ 6.93 (1H, dt, *J*= 6.9, 15.3 Hz), 5.78 (1H, dt, *J*= 1.5, 17.0 Hz), 4.13 (2H, br), 2.17 (2H, m), 1.72 (2H, m), 1.30- 1.42 (3H, m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 166.8, 149.5, 121.4, 64.0, 32.4, 29.0, 28.1, 25.8.

Procedure for Table 1, entry 4: To a flask charged with 1,4-butanediol diacrylate (60 mg, 0.30 mmol) in 0.6 ml of CH_2Cl_2, catalyst **2** (2.6 mg) and cyclododecene (58 *u*l, 0.30 mmol) were added. Quick degassing by dynamic vacuum was conducted and the flask was fitted with a condenser and refluxed under argon for 6 hours. The product (92 mg, 91%) was precipitated into methanol. ^{1}H NMR (300MHz, $CDCl_3$, ppm): δ 6.94 (1H, dt, *J*= 7.2, 15.3 Hz), 5.80 (1H, dt, *J*= 1.5, 15.9 Hz), 4.13 (2H, t, *J*= 5.1 Hz), 2.16 (2H, dt, *J*= 6.9, 6.6 Hz), 1.73 (2H, t, *J*= 3.0 Hz), 1.42 (2H, m), 1.24 (7H, m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 166.9, 149.9, 121.2, 64.0, 32.6, 29.9, 29.8, 29.5, 28.4, 25.8.

Procedure for Table 1, entry 5: To a flask charged with 1,4-butanediol diacrylate (40 mg, 0.20 mmol) in 0.5 ml of CH_2Cl_2, catalyst **2** (1.4 mg) and cyclododecene (54 mg, 0.20 mmol) were added. Quick degassing by dynamic vacuum was conducted and the flask was fitted with a

condenser and refluxed under argon for 6 hours. The product (60 mg, 69%) was precipitated into methanol. ^{1}H NMR (300MHz, $CDCl_3$, ppm): δ 6.96 (1H, dt, *J*= 6.6, 16.2 Hz), 5.80 (1H, d, *J*= 15.9 Hz), 4.16 (2H, br), 3.69 (1H, m), 2.20 (2H, m), 1.75 (2H, br), 1.58 (1H, m) 1.46 (2H, m), 0.90 (9H, s), 0.03 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 166.7, 149.6, 149.3, 121.5, 121.2, 71.4, 64.0, 36.7, 35.5, 21.7, 28.3, 26.2, 25.8, 24.0, 18.4, -3.9, -4.0.

Procedure for Table 1, entry 6: To a flask charged with tri(ethylene glycol) diacrylate (53 mg, 0.21 mmol) in 1 ml of CH_2Cl_2, catalyst **2** (1.8 mg) and cyclooctene (28 *u*l, 0.21 mmol) were added. Quick degassing by dynamic vacuum was conducted and the flask was fitted with a condenser and refluxed under argon for 6 hours. The product (68 mg, 99%) was precipitated into hexane. ^{1}H NMR (300MHz, $CDCl_3$, ppm): δ 6.95 (1H, dt, *J*= 6.9, 15.9 Hz), 5.82 (1H, d, *J*= 15.9 Hz), 4.26 (2H, t, *J*= 4.8 Hz), 3.70 (2H, t, *J*= 5.1 Hz), 3.64 (2H, s), 2.16 (2H, dt, *J*= 6.6, 6.6 Hz), 1.42 (2H, m) 1.29 (2H, m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 166.7, 150.0, 121.2, 70.8, 69.6, 63.6, 32.5, 29.3, 28.2.

Procedure for Table 1, entry 7: To a flask charged with hydroquinone diacrylate (44 mg, 0.21 mmol) in 1 ml of CH_2Cl_2, catalyst **2** (3.5 mg) and cyclooctene (27.5 *u*l, 0.21 mmol) were added. Quick degassing by dynamic vacuum was conducted and the flask was fitted with a condenser and refluxed under argon for 6 hours. The product (60 mg, 98%) was precipitated by hexane. ^{1}H NMR (300MHz, $CDCl_3$, ppm): δ 7.11- 7.20 (3H, m), 6.00 (1H, d, *J*= 15.3 Hz), 2.27 (2H, dt, *J*= 6.9, 6.3 Hz), 1.52 (2H, broad), 1.37 (2H, broad). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 165.0, 152.0, 148.2, 122.6, 120.7, 32.7, 29.3, 28.2.

Procedure for Scheme 5: To a flask charged with diamides (58 mg, 0.16 mmol) in 1 ml of CH_2Cl_2, catalyst **2** (4.4 mg) and cyclooctene (21 *u*l, 0.16 mmol) were added. Quick degassing by dynamic vacuum was conducted and the flask was fitted with a condenser and refluxed under argon for 6 hours. The product (76 mg, 100%) was precipitated by hexane. ^{1}H NMR (300MHz,

$CDCl_3$, ppm): δ 7.2- 7.4 (6H, m), 7.1 (4H, d, *J*= 6.9 Hz), 6.81 (2H, dt, *J*= 15.6, 6.6 Hz), 5.57 (2H, d, *J*= 15.0 Hz), 3.69 (4H, t, *J*= 6.9 Hz), 1.94 (4H, m), 1.47 (4H, br), 1.25 (8H, br) 1.11 (4H, br).

Procedure for 5: To a vial charged with **5** (64 *u*l, 0.41 mmol) in 0.7 ml of CH_2Cl_2, catalyst **1** (1.2 mg) was added. Quick degassing by dynamic vacuum was conducted and stirred for 12 hours. The product (42 mg, 68%) was precipitated by methanol. ^{1}H NMR (300MHz, $CDCl_3$, ppm): δ 5.76 (2H, m), 5.43 (2H, m), 4.80 (2H, br), 2.06 (4H, br), 1.58 (4H, br). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 130.3, 130.2, 130.1, 130.0, 129.8, 85.5, 85.4, 37.1, 36.2, 23.7.

Procedure for eq 3: To a flask charged with 5 (50 *u*l, 0.32 mmol) and 1,4-butanediol diacrylate (62.5 mg, 0.32 mmol) in 1 ml of CH_2Cl_2, catalyst **2** (3.5 mg). Quick degassing by dynamic vacuum was conducted and the flask was fitted with a condenser and refluxed under argon for 6 hours. The product (60 mg, 98%) was precipitated by hexane. ^{1}H NMR (300MHz, $CDCl_3$, ppm): δ 7.11- 7.20 (3H, m), 6.00 (1H, d, *J*= 15.3 Hz), 2.27 (2H, dt, *J*=6.9, 6.3 Hz), 1.52 (2H, broad), 1.37 (2H, broad). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 166.7, 149.2, 149.0, 130.3, 130.1, 121.6, 121.4, 85.2, 85.1, 64.0, 35.2, 34.4, 28.6, 28.2, 25.7.

Reference:

1. For recent reviews on ROMP, see: a) Novak, B. M.; Risse, W.; Grubbs, R. H. *Adv. Polym. Sci.* **1992**, *102*, 47; b) Ivin, K. J.; Mol, J. C. *Olefin Metathesis and Metathesis Polymerization*, Academic Press, San Diego, CA, **1997**; c) Grubbs, R. H.; Khosravi, E. *Material Science and Technology*, **1999**, *20*, 65; d) Buchmeiser, M. R. *Chem. Rev.* **2000**, *100*, 1565.
2. a) Schrock, R. R. *Acc. Chem. Res.* **1990**, *23*, 158; b) Bazan, G. C.; Schrock, R. R.; Cho, H. N.; Gibson, V. C. *Macromolecules* **1991**, *24*, 4495.
3. a) Kanaoka, S.; Grubbs, R. H. *Macromolecules* **1995**, *28*, 4707; b) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100; c) Weck, M.; Schwab, P.; Grubbs, R.

H. *Macromolecules* **1996**, *29*, 1789.

4. a) Mortell, K. H.; Weatherman, R. V.; Kiessling, L. L. *J. Am. Chem. Soc.* **1996**, *118*, 2297; b) Huwe, C. M.; Woltering, T. J.; Jiricek,J; Weitz-Schmidt, G.; Wong, C. H. *Bioorg. Med. Chem.* **1999**, *7*, 773; c) Maynard, H. D.; Okada, S.;Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 1275.
5. a) Bielawski, C. W.; Grubbs, R. H. *Angew. Chem, Int. Ed.* **2000**, *39*, 2903; b) Bielawski, C. W.; Benitez, D.; Grubbs, R. H. *Macromolecules* **2001**, *34*, 8610; c) Scherman, O. A.; Kim, H. M.; Grubbs, R. H. *Macromolecules* **2002**, *35*, 5366.
6. Lehman, S. E.; Wagener, K. B. *Macromolecules* **2002**, *35*, 48.
7. Choi, S. K.; Gal, Y. S.; Jin, S. H.; Kim, H. K. *Chem. Rev.* **2000**, *100*, 1645.
8. a) Fox, H. H.; Wolf, M. O.; O'Dell. R, Lin, B. L.; Schrock, R. R., Wrighton, M. S. *J. Am. Chem. Soc.* **1994**, *116*, 2827; b) Schrock, R. R.; Luo, S.; Lee, J. C.; Zanetti, N. C.; Davis, W. M. *J. Am. Chem. Soc.* **1996**, *118*, 3883.
9. For the recent efforts of developing regiospecific catalysts, see: a) Schattenmann, F. J.; Schrock, R. R.; Davis, W. M. *J. Am. Chem. Soc.* **1996**, *118*, 3295; b) Kim, S. H.; Kim, Y. H.; Cho, H. N.; Kwon, S. K.; Kim, H. K.; Choi, S. K. *Macromolecules* **1996**, *29*, 5422; c) Buchmeiser, M. *Macromolecules* **1997**, *30*, 2274; d) Anders, U.; Nuyken, O.; Buchmeiser, M.; Wurst, K. *Angew. Chem, Int. Ed.* **2002**, *41*, 4044.
10. Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.
11. Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168.
12. Love, J. A.; Morgan, J. P.; Trnka, T. M.; Grubbs, R. H. *Angew. Chem, Int. Ed.* **2002**, *41*, 4035.
13. a) Gorman, C. B.; Ginsburg, E. J.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 1397; b) Royappa, A. T.; Saunders, R. S.; Rubner, M. F.; Cohen, R. E. *Langmuir* **1998**, *14*, 6207;

c) Wagaman, M. W.; Grubbs, R. H. *Syn. Met.* **1997**, *84*, 327; d) Pu, L.; Wagaman, M. W.; Grubbs, R. H. *Macromolecules* **1996**, *119*, 1138.

14. This portion of the work is published, see; Choi, T.-L.; Rutenberg, I. M.; Grubbs, R. H. *Angew. Chem, Int. Ed.* **2002**, *41*, 3839.
15. Odian, G. *Principles of Polymerizations*, Wiley, New York, **1991**.
16. Drent, E; Budzelaar, P. H. M. *Chem. Rev.* **1996**, *96*, 663.
17. a) Al Samak, B.; Carvill, A. G.; Hamilton, J. G.; Rooney, J. J.; Thompson, J. M. *Chem. Commun.* **1997**, 2057; b) Al Samak, B.; Amir-Ebrahimi, V.; Corry, D. G.; Hamilton, J. D.; Rigby, S.; Rooney, J. J.; Thompson, J. M. *J. Mol. Cat.* **2000**, *160*, 13; c) Ilker, M. F.; Coughlin E. B. *Macromolecues* **2002**, *35*, 54.
18. a) Konzelman, J.; Wagner, K. B. Wagener, K. B. *Macromolecules* **1996**, *29*, 7657; b) Wolfe, P. S.; Gomez, F. J.; Wagener, K. B. *Macromolecules* **1997**, *30*, 714; c)Lehman, S. E.; Wagener, K. B. *Macromolecules* **2002**, *35*, 48.
19. a) Chatterjee, A. K.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 1751; b) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783; c) Choi, T.-L.; Chatterjee, A. K.; Grubbs R. H. *Angew. Chem.* **2001***, 113*, 1317; *Angew. Chem, Int. Ed.* **2001**, *40*, 1277; d) Chatterjee, A. K.; Choi, T.-L.; Grubbs R. H. *Synlett*. **2001**, 1034. e) Lee. C. W.; Choi, T.-L.; Grubbs, R. H. *J. Am. Chem. Soc.* **2002**, *124*, 3224.
20. Choi, T.-L.; Grubbs, R. H. *unpublished result*, **2001**.
21. Schrock, R. R.; Yap, K. B.; Yang, D. C.; Sitzmann, H.; Sita, L. R.; Bazan, G. C. *Macromolecules* **1989**, *22*, 3191.
22. Patton, P. A.; Lillya, C. P.; McCarthy, T. J. *Macromolecules* **1986**, *19*, 1266.
23. Ulman, M.; Belderrain, T. R.; Grubbs, R. H. *Tetrahedron Lett.* **2000**, *41*, 4689.
24. Choi, T.-L.; Lee, C. W.; Chatterjee, A. K.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 10417.
25. The number was obtained by AM1 calculations using Spartan v 1.1, Wavefunction.

26. Choi, T.-L.; Grubbs, R. H. *Chem. Commun.* **2001**, 2648.

27. a) Sanford, M. S.; Ulman, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 749; b) Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543.

Chapter 5:

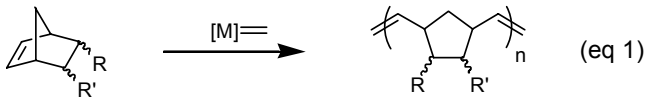
Ring-Opening Metathesis Polymerization with an Ultra-fast-initiating Ruthenium Catalyst

Abstract

Ring-opening metathesis polymerization (ROMP) is one of the most widely used polymerizations. With the development of well-defined catalysts, such as (*t*-BuO)$_2$(ArN)-Mo=CH(*t*-Bu) (**1**), $Cl_2(PCy_3)_2Ru$=CHPh (**2**), and $Cl_2(PCy_3)(IMesH_2)Ru$=CHPh (**3**), more controlled polymer structures have been obtained by either living polymerization or chain transfer induced polymerization. However, these catalysts suffer from a number of limitations. This chapter describes ROMP with the recently developed catalyst **4** which solves many problems of catalysts **1**-**3**. The first is described the living polymerization of norbornene and norbornene derivatives by catalyst **4** to produce polymers with very narrow polydispersity index (PDI) and good molecular weight control. It also promotes living ROMP of several monomers that previous catalysts had problems with. Lastly, syntheses of block copolymers are also described. In the second half of the chapter, ROMP of more challenging protic monomers are demonstrated. Amphiphilic block copolymers have been prepared by catalyst **4** which spontaneously undergo self-assembly into stable nanoparticles (10- 50 nm in radius) in non-hydrogen bonding solvents such as CH_2Cl_2 and $CHCl_3$. Polymeric nanoparticles are characterized by NMR, GPC, DLS and SEM.

Background

Ring-opening metathesis polymerization (ROMP) is one of the most used and studied chain growth polymerizations.[1] Unlike the step growth olefin polymerization, acyclic diene metathesis polymerization (ADMET),[2] ROMP is highly efficient for strained cycloalkenes because the metathesis equilibrium is shifted highly toward the ring opening process in order to release the ring stain. Over the last fifteen years, chemists have expanded the utility of ROMP by developing well-defined catalysts whose initiation and propagation can be controlled to produce well-define polymers.[3] With the discovery of living polymerization of norborenes to produce polymers with good molecular weight control and narrow PDI (eq 1),[4] ROMP was applied to many areas including electronic materials, electroluminescent material, packaging, solid support, and bioactive polymers.[1]



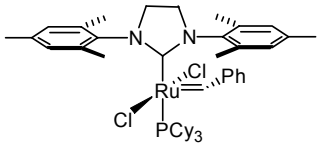
(eq 1)

Recent advances include the efficient preparation of telechelic polymers (containing functionality at both ends of the polymer chains) with the highly active ruthenium catalyst,[5] and tandem polymerization with a single component ruthenium catalyst performing three mechanistically different catalyses in one pot (ROMP, atom transfer radical polymerization and hydrogenation).[6] The newest attraction in the field of ROMP is a modified ruthenium catalyst (cyclic catalyst or endless catalyst) producing high molecular weight cyclic polymers.[7] This polymerization represents the first general method to produce cyclic polymers with high yields and very low linear polymers contamination. In this chapter, living ROMP by the ultra-fast-initiating catalyst[8] and its application to the preparation of stable nanoparticles are described.

Part I. Living Ring-Opening Metathesis Polymerization with an Ultrafast-initiating Ruthenium Catalyst

Introduction

Ring-opening metathesis polymerization (ROMP) has expanded the realm of polymer synthesis, providing access to many structurally unique polymers.[1] With the development of well-defined olefin metathesis catalysts such as (*t*-BuO)$_2$(ArN)-Mo=CH(*t*-Bu) (**1**)[3] and Cl$_2$(PCy$_3$)$_2$Ru=CHPh (**2**),[9] controlled living polymerizations became possible, making ROMP a novel method to synthesize polymers with various architectures. However, these catalysts suffer from either poor functional group tolerance (for **1**) or decreased activity and broader PDI (for **2**). The recently developed N-heterocyclic carbene ruthenium catalysts **3**[10] exhibits activity comparable to or higher than **1** while retaining the functional group tolerance of **2**. Catalyst **3** was found to be extremely useful in organic transformations, such as cross and ring-closing metathesis reactions.[11] However, **3** generally gives polymers with uncontrolled molecular weight and broad PDIs due to the high activity but slow initiation leading to incomplete initiation (small k_i/k_p)[12] and competing chain transfer reactions.[5]



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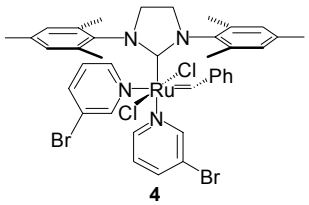
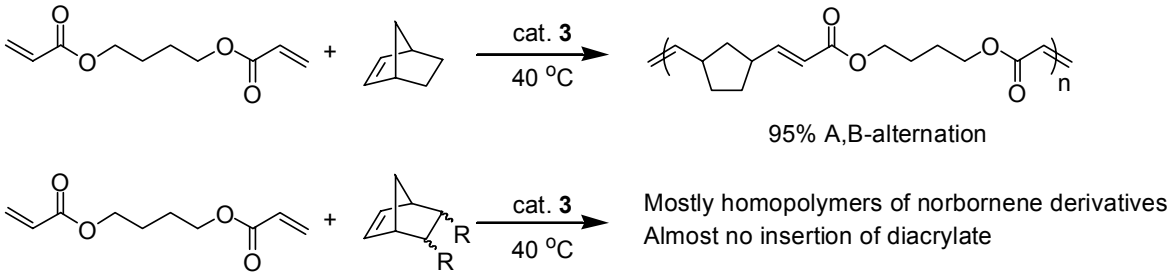


4

From the previous study on ring opening-insertion metathesis polymerization (ROIMP),[13] we found that norbornene was a good comonomer, allowing to efficient insertion or chain transfer with diacrylates to yield A,B-alternating copolymers (Scheme 1). However, 2,3-disubstituted norbornenes were not viable comonomers since the steric hinderance around the olefin in the polymers prevented the required insertion of catalyst **3**. This suggested that chain transfer or back-biting was minimal even with the active catalyst **3** at 40 ^{o}C.[14] Recently a new member of the family of catalysts, **4**, has been found to initiate extremely rapidly, at least a

million times faster than **3**.[15] Therefore, increased k_i/k_p should promote living polymerization if chain transfer and chain termination reactions are absent. Herein, we report living ROMP of norbornene and 7-oxonorbornene derivatives by highly active and ultra-fast initiating ruthenium catalyst **4** to make monodisperse homopolymers and block copolymers.



Scheme 1. ROIMP of norbornene and norbornene derivatives

Results and Discussion

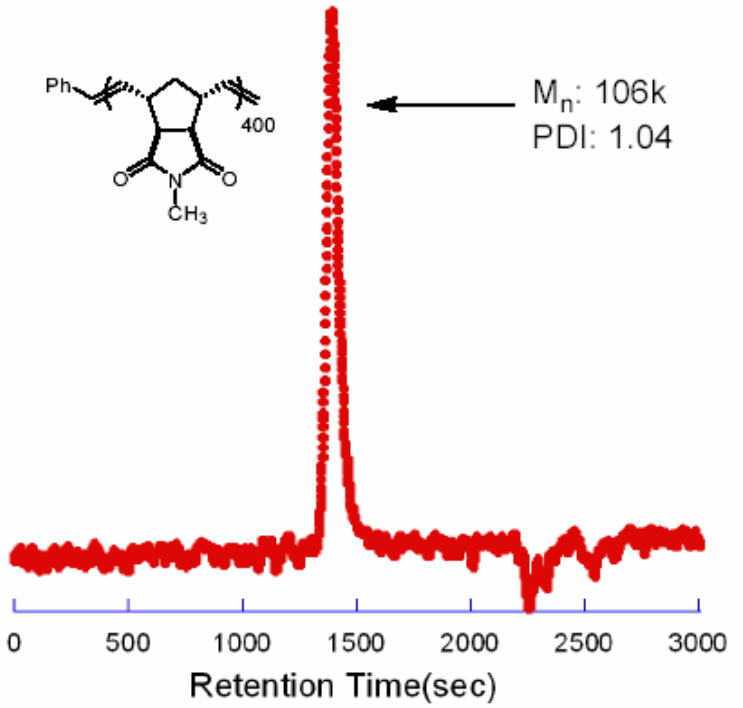
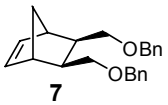
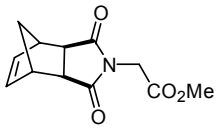
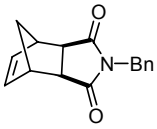
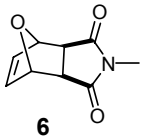
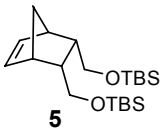
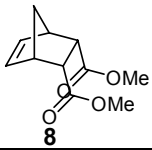
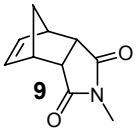
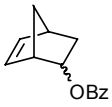


Figure 1. GPC trace of a narrow polydisperse polymer by catalyst **4**

Upon the addition of monomer solution to a solution of catalyst **4** in 0.2 – 0.4 M dichloromethane, the color instantaneously changes from green to yellow implying immediate

initiation of catalyst **4**. After 30 minutes, polymers were obtained by quenching the reactions with ethyl vinyl ether and precipitating them into methanol. As shown in Table 1, various polymers were obtained in high yields with PDIs as low as 1.04 (Figure 1 obtained by CH_2Cl_2 GPC), which is indicative of controlled polymerization. It is worth noting that all the PDIs are much lower than typical controlled living ROMP products obtained from catalyst **2** (PDI around 1.2). Also *endo*-monomers **8** and **9**, which polymerize slowly if at all with catalyst **2**, undergo ROMP readily with highly active catalyst **4**.[9] PDIs less than 1.10 for the ROMP polymers from *endo*-monomers are remarkably improved compared to PDI of 1.3 for the ROMP of *endo*-*N*-alkyl norbornene dicarboxyimides by catalyst **1.**[16]

Table 1. ROMP of various norbornene derivatives

monomer	M/C	obs. M_n[a] (x 10^3)	theo. M_n[b] (x 10^3)	PDI[a]
 **7**	100	30.4	33.5	1.05
	200	60.0	67.0	1.07
	400	131.5	133.9	1.06
	100	27.5	23.6	1.04
	200	68.3	47.1	1.04
	400	134.5	94.2	1.04
	100	53.1	18.0	1.04
	200	128.0	26.8	1.04
 **6**	100	29.1	18.0	1.05
	150	41.7	26.8	1.05
	200	53.1	35.9	1.06
	400	106.0	71.7	1.04
 **5**	100	24.5	38.3	1.06
	200	50.0	76.6	1.05
	400	114.0	153.1	1.04
 **8**	100	21.9	38.3	1.06
	200	63.7	76.6	1.06
 **9**	50	11.5	8.9	1.08
	100	22.9	17.8	1.08
	200	40.2	35.5	1.09
	100	28.7	19.9	1.10
	200	50.6	39.7	1.10
	400	91.1	79.4	1.09

[a] Determined by CH_2Cl_2 GPC relative to polystyrene standards.
[b] Assuming quantitative conversion.

Encouraged by the narrow PDIs obtained wuth catalyst **4**, we examined the relationship between the molecular weight and monomer to catalyst ratio ([M]/[C]). The representative graph of M_n versus [M]/[C] for monomers **6** and **7** is shown in Figure 2, which clearly shows a linear relationship between M_n and [M]/[C]. It is important to note that the linear relationship holds for

both low (as low as DP= 10) and high molecular weight polymers with narrow PDIs (< 1.1). Other monomers display similar linear relationships. The molecular weight control by [M]/[C] and the low PDIs suggest that for catalyst **4**, k_i/k_p is high enough that all the chains initiate and grow at a similar rate. The high k_i/k_p is attributed to the fact that although k_p of catalyst **4** is much larger than catalyst **2**, extremely high k_i (more than ten thousands times)[12, 15] overrides the increase in k_p relative to catalyst **2**, resulting in narrower PDI and good molecular weight control. Thus catalyst **4** promotes living ROMP with both higher activity and better control.

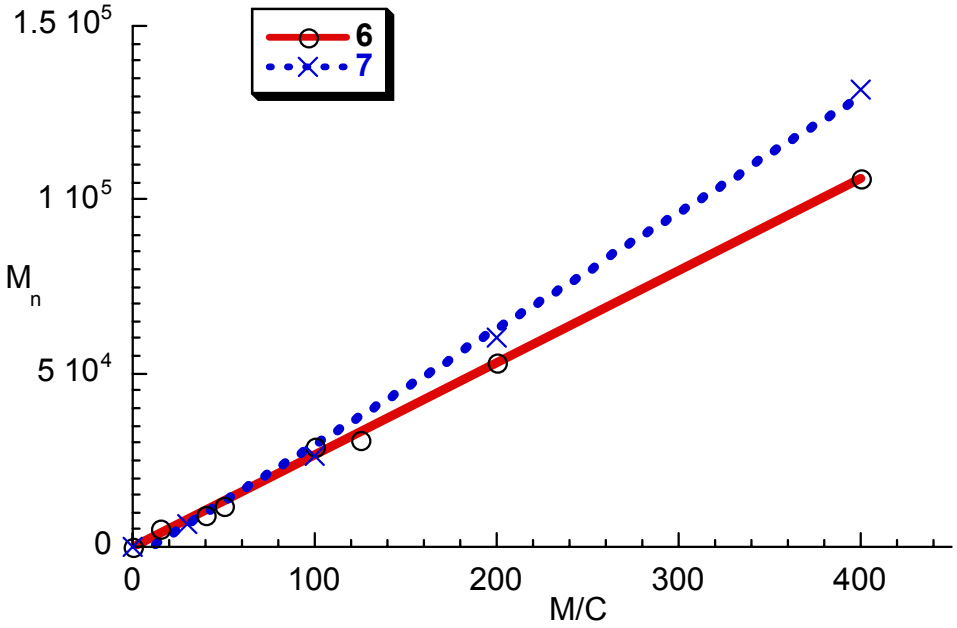


Figure 2. Relationship between M_n and [M]/[C] for momomers **6** and **7**

Table 2. Living ROMP of norbornene at -20 °C

M/C	obs. M_n[a] (x 10^3)	theo. M_n[b] (x 10^3)	PDI[a]
50	4.4	4.8	1.08
100	9.0	9.5	1.09
150	15.1	14.2	1.06
200	22.0	18.9	1.10

[a] Determined by CH_2Cl_2 GPC relative to polystyrene standards. A correction factor of 0.5 applied [b] Assuming quantitative conversion.

Norbornene is a unique monomer since only catalyst **1** and $Cl_2(PPh_3)_2Ru=CHPh$,[9b] promote living polymerization. Catalyst **2** and **3** give broad PDI (around two) for polynorbornene (PNB) due to chain transfer reactions.[5b, 9b] Not surprisingly, **4** also produced (PNB) with broad PDI of 1.65 at room temperature. However, PNB with narrower PDI (1.28) was obtained when the polymerization was run at 0 ^{o}C and finally PDI was further decrease to 1.08 when the polymerization was run at –20 ^{o}C. It is notable that **4** initiates rapidly even at -20 ^{o}C, and the low PDI indicates that chain transfer reactions on PNB are suppressed at low temperatures. Furthermore, good molecular weight control by varying [M]/[C]. Close matching of observed M_n and theoretical M_n showed that catalyst **4** could also promote living ROMP of norbornene at -20 ^{o}C (Table 2, and Figure 3).

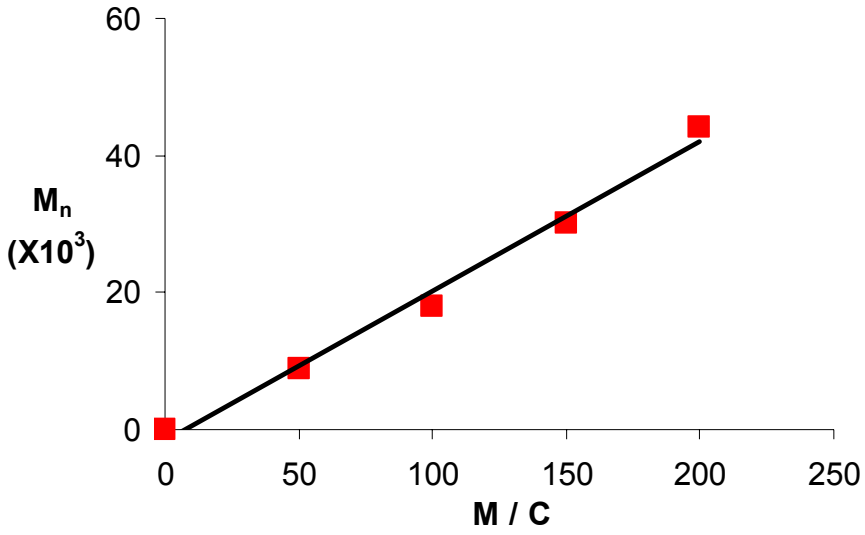


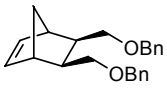
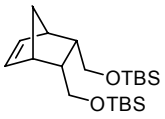
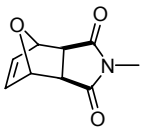
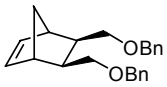
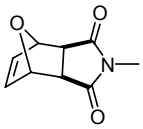
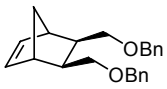
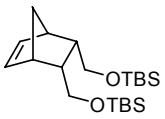
Figure 3. Relationship between M_n and [M]/[C] for norbornene

The effects of changing the polymerization conditions were studied using 100 equivalents of monomer **6** relative to catalyst **4**. Lowering the reaction concentration to 0.05 M in dichloromethane or lowering the temperature to 0 ^{o}C had no effects on the isolated yields, molecular weights, or PDI. Changing to different solvents had no marked effects, but raising the temperature from 23 ^{o}C to 55 ^{o}C in 1,2-dichloroethane gave a polymer with similar M_n but much

broader PDI of 1.25. This suggests that chain transfer or back-biting does occur at higher temperatures.[5a]

If catalyst **4** indeed promotes the controlled living polymerization of norbornenes and 7-oxonorbornene derivatives, it should produce block copolymers from sequential additions of monomer. Monomer **7** (200 equivalents) was treated with catalyst **4** followed by the addition of monomer **5** (200 equivalents) after 30 minutes (Table 3, entry 1). The final polymer with about twice M_n of initial homopolymer **7** and PDI of 1.10 was obtained. ^{1}H NMR spectrum showed only two sets of overlaying peaks identical to those of two homopolymers. To show that the product was truly a diblock copolymer, another block copolymer was synthesized using 50 equivalents of monomer **6** followed by 200 equivalents of monomer **7**. Figure 4a clearly shows well resolved GPC traces for the diblock copolymer of entry 2 (Table 3) where the signal of the first monomer is wholly shifted to higher molecular weight region. The M_n value of the final copolymer (73k) agrees with the sum of the M_ns of individually synthesized homopolymers of **6** and **7** (10k + 60k = 70k). ABC-Triblock copolymers by sequential addition of three different monomers (entry 3) can be also made. Figure 4b displays well resolved GPC traces of for the narrow polydisperse triblock copolymer. No fractions are observed in the low molecular weight regions indicating that no termination occurred during the course of the two sequential additions of monomers. In all cases, the observed ratios of the monomers by ^{1}H NMR of the final block copolymers are in good agreement with the added feed ratios.

Table 3. Synthesis of block copolymers[a]

entry	1st monomer	M/C	M_n[b](X 10^3)	2nd monomer	M/C	M_n[b](X 10^3)	yield [%]	PDI[b]
1		200	60.6		200	115.1	90	1.10
2		50	10.0		200	72.7	86	1.07
3		15	5.1		75	37.4	-	1.06
			3rd monomer		370	154.8	90	1.05

[a] 0.2 M in CH_2Cl_2 at 23 °C 30 min for each monomer. [b] Determined by CH_2Cl_2 GPC relative to polystyrene standards.
[c] Yield of product isolated by precipitation into methanol.

Conclusion

In this section, we have demonstrated that catalyst **4**, bearing an N-heterocyclic carbene which greatly enhances the activity and 3-bromopyridine ligands which increase the initiation rate tremendously, shows controlled living polymerization of norbornene and oxo-norbornene derivatives. Catalyst **4** expands the substrate scope including those that do not show living polymerization with the previous catalysts. Block copolymers were also successfully prepared.

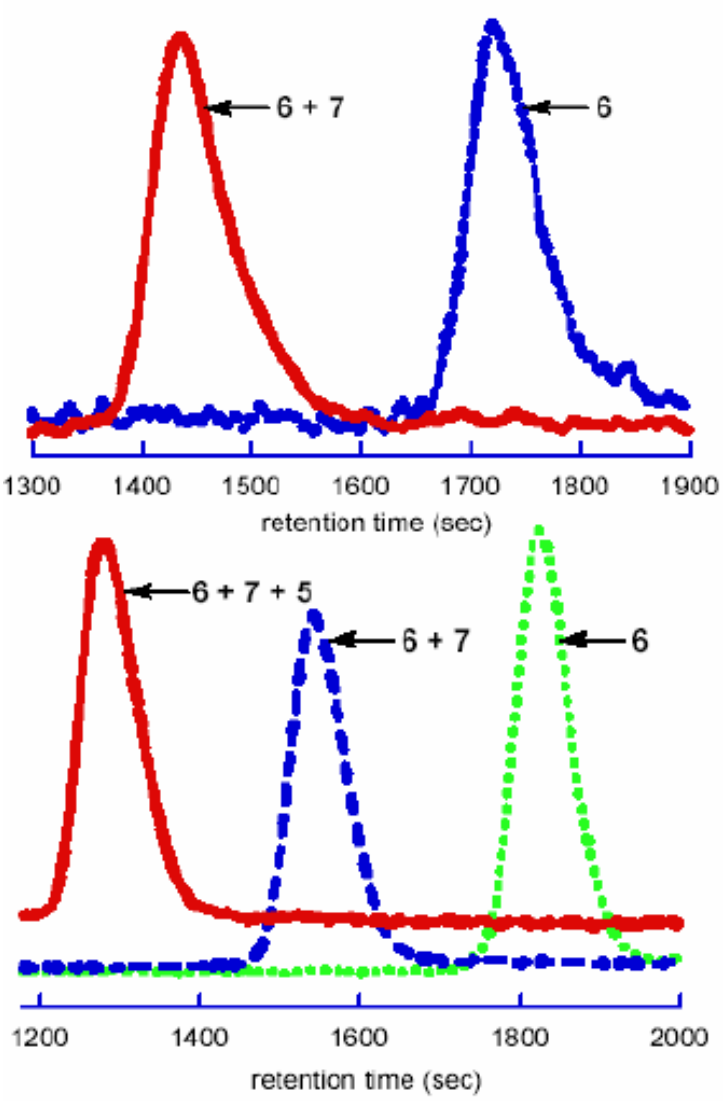


Figure 4. GPC traces of di- and triblock copolymers

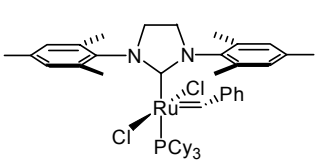
Part II. Mild Synthesis of Polymeric Nanoparticles by Living ROMP

Introduction

Polymeric micelles have attracted great attention due to their novel structures resembling dendrimers[17] and their potential applications towards drug delivery[18] and supporting catalysts.[19] Generally, polymeric micelles are prepared from block copolymers in selective solvents, where the solvent acts as a good solvent for one block (shell) and a bad solvent for the other block resulting in self-assembly to make a core. From the resulting polymeric micelles, polymeric

nanoparticles are prepared by covalently cross-linking the core[20] or the shell.[21] Many methods exist for the synthesis of core-shell micelles and nanoparticles, but a more functional group tolerant, user friendly, and milder method exhibiting good control on particle sizes would be valuable.

Ring-opening metathesis polymerization (ROMP) has expanded the realm of polymer synthesis.[1] With the developments of well-defined olefin metathesis catalysts such as (t-BuO)$_2$(ArN)-Mo=CH(*t*-Bu) (**1**)[3] and $Cl_2(PCy_3)_2Ru$=CHPh (**2**),[9] living polymerization became possible, making ROMP a novel method to synthesize polymer with various architectures. However, these catalysts suffer from either lack of the functional group tolerance (**1**) or the decreased activity and relatively broader polydispersity of 1.2 (**2**). Recently developed N-heterocyclic carbene ruthenium catalyst **3**,[10] solved some of the problems by exhibiting activity comparable to or higher than **1** while retaining the functional group tolerance of **2**. However, **3** has drawbacks such as poor molecular weight control and broad PDIs.[5a]



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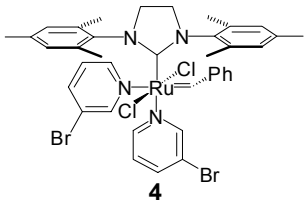

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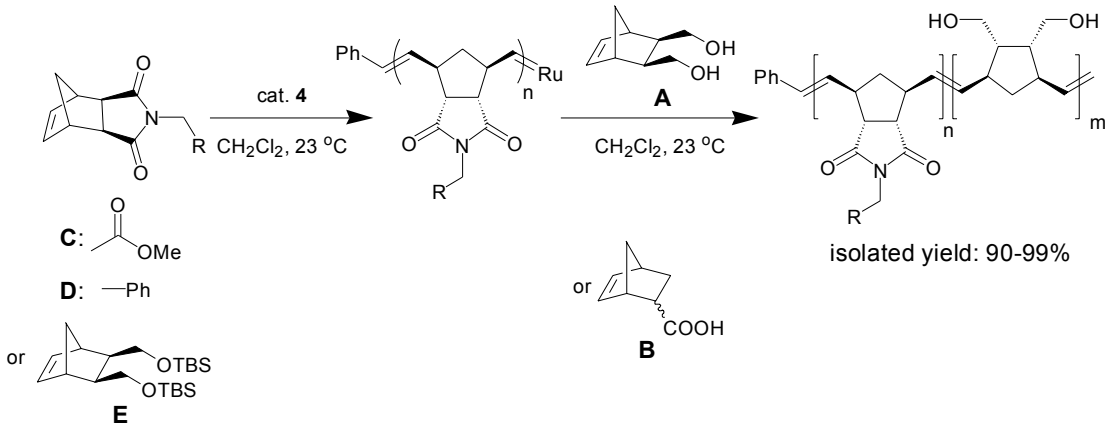
The most recent development of ultra-fast initiating ruthenium catalyst **4**[15] showed improvements over the previous catalysts by exhibiting high activity but still retaining the functional group tolerance of **2** and producing polymers with narrow polydispersity less than 1.1.[8] Herein we report a convenient and mild synthesis of diblock copolymers by ROMP by **4** which self-assemble into stable core-shell nanoparticles even without cross-linking.

Results and Discussion

Previous report from our group showed that catalyst **4** produced di- and triblock copolymers with narrow PDI by living ROMP (Part I of this chapter).[8] With this catalyst in hand,

we tried ROMP of protic monomers that had not been reported in the literature (for example, 5-norbornene-2-*exo*,3-*exo*-dimethanol (**A**) and 5-norborene-2-carboxylic acid (**B**)). As soon as monomer **A** was added to a CH_2Cl_2 solution of catalyst **4**, ROMP polymer immediately precipitated out of the reaction solution. The resulting polymer, which was insoluble in CH_2Cl_2, but soluble in DMSO, had an average degree of polymerization (DP) of 20. Another monomer with a protic functional group, 5-norborene-2-carboxylic acid (**B**) also showed similar result as monomer **A**. These results implied that catalyst **4** is tolerant of protic functional groups such as alcohols, diols and carboxylic acids functional groups. Encouraged by these results, we pursued the synthesis of diblock copolymers whereby one monomers would produce a block well solvated by the reaction solution, CH_2Cl_2 (**C**- **E**), and the other, protic monomers capable of hydrogen bond (**A** and **B**).



Scheme 2. Preparation of diblock copolymers

The synthetic procedure for block copolymers is very simple (Scheme 2). A solution of monomer **C**, **D**, or **E** in CH_2Cl_2 was quickly added to a solution of catalyst **4** via syringe. After 20 minutes, a solution of protic monomer **A** or **B** in CH_2Cl_2 was quickly added to the reaction. The solution immediately became viscous. After 40 minutes the ROMP was quenched with excess ethyl vinyl ether and isolated by precipitation into methanol (or hexane for block copolymers containing **B**). The resulting diblock copolymers were obtained in good yields greater than 90% and formed clear solution in methylene chloride and chloroform upon redissolving. One of the

advantages of the ROMP procedure is the mild conditions, such as room temperature, bench-top reaction where no rigorous techniques or equipment are required and short reaction time typically less than an hour. Also, due to the living nature, the DP of each block can be easily controlled by changing the monomer to catalyst ratio.

Characterizing the block copolymers by NMR spectroscopy provides insight into the polymer's structure. For example, a block copolymer of monomers **A** and **C** was examined by ^{1}H and ^{13}C NMR in $CDCl_3$ and spectra showed only one set of peaks corresponding to homopolymer of **C** and none for the block corresponding to **A** (Figure 5). However, when dissolved in a hydrogen bonding solvent such as $DMSO_{d\text{-}6}$, which is a good solvent for both block, all of the peaks expected for both blocks were visible by ^{1}H and ^{13}C NMR (Figure 6). Solid state NMR further confirmed the presence of both blocks. Furthermore, a gradual appearance of broad peaks corresponding to the diol block **A** was noticed when a small amount of $DMSO_{d\text{-}6}$ was added to the polymer solution in $CDCl_3$ and finally, the new peaks sharpened at 9% by volume $DMSO_{d\text{-}6}$. The similar broad peaks for the diol block were observed in another hydrogen bonding solvent $THF_{d\text{-}8}$ at room temperature and at 60 ^{o}C, the peaks sharpened again. These observations suggest that the diblock copolymer was undergoing some type of aggregation such as a core-shell micelle formation where methylene chloride and chloroform act as selective solvents for blocks **C** (shell) and bad solvents for **A** (core). Therefore the peaks for the non-solvated, thus self-assembled core **4** with low mobility, can be regarded as semi-solid whose peaks greatly broaden and disappear in NMR spectra,[22] whereas in $DMSO_{d\text{-}6}$ all the peaks for the block copolymer are observed. Apparently, diol functionality in the second block provides strong driving force for the self-assembly process. As a result, a small amount of hydrogen bond breaking $DMSO_{d\text{-}6}$ added to the $CDCl_3$ solution of the block copolymer can efficiently disrupts the self-assembly.

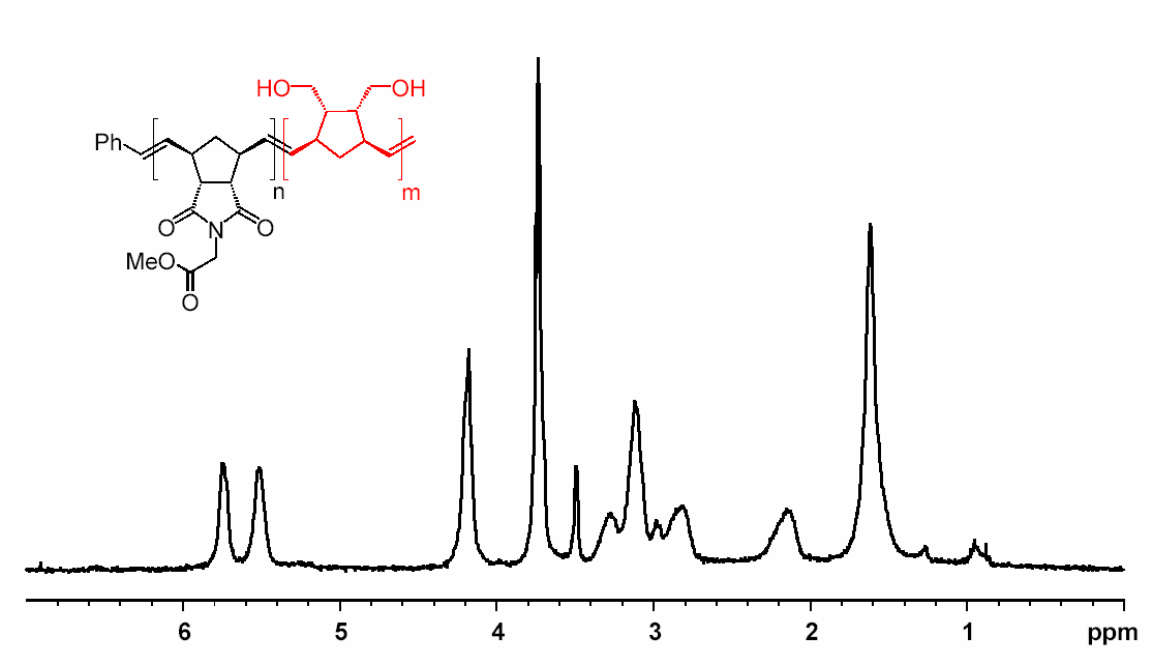


Figure 5. ^{1}H NMR spectrum for an amphiphilic block copolymer in $CDCl_3$

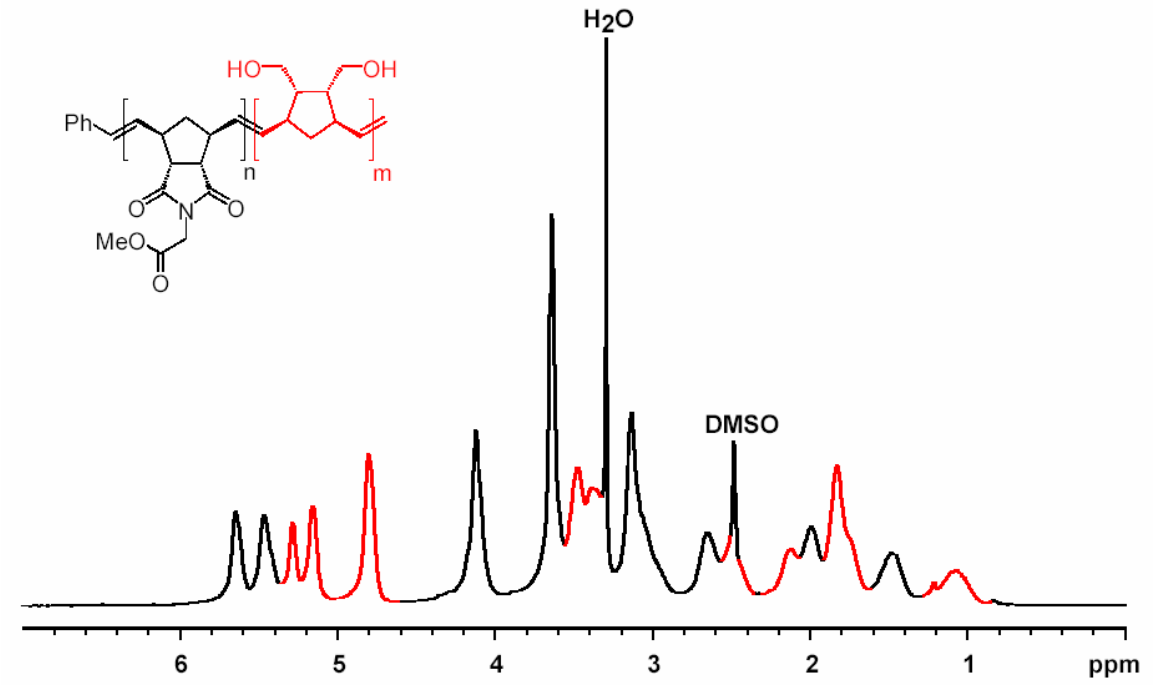


Figure 6. ^{1}H NMR spectrum for an amphiphilic block copolymer in $DMSO_{d\text{-}6}$

Molecular weight analysis by GPC using non-hydrogen bonding CH_2Cl_2 mobile phase strongly supports the formation of hydrogen-bonded self-assembled supramolecules. GPC analysis of a diblock copolymer shown in Figure 7 shows majority of high molecular weight

material (nearly 1.3 x 10^6 g/mol) and a minor fraction of low molecular weight material (26,000 g/mol). Since the theoretical M_n of the block copolymer is about 31,000 g/mol, the self-assembled supramolecule formation must be responsible for the major high molecular weight trace while the minor peak corresponds to the homopolymer of **C**. The high molecular weight polymer is not due to cross-linking or other covalent bond formation because GPC analysis eluted by THF shows a major trace at low molecular weight. Also, a random copolymer of 1: 1 mixture of **C** and **A** prepared by catalyst **4** shows a major trace at low molecular weight fraction. It is notable that the self-assembled diblock copolymers are so tightly bound that supramolecules are not dissociated under the shear pressures of GPC condition. In other words, if the binding force of the self-assembly were weak, or in dynamic equilibrium as in micelles, GPC analysis would show a major trace corresponding to a single polymer chain. The observation of such high molecular weight supramolecules by GPC implies that the diblock copolymers undergo self-assembly to form stable polymeric nanoparticles even without covalent cross-linking. The stability of the polymeric nanopaticles is likely due to the strong interchain hydrogen bonding from the protic blocks which collapse into well-organized cores of the nanoparticles. For the random copolymer, such a strong association between the polymer chains is less likely since the self-assembling protic monomers are randomly incorporated into the polymer chains, thus the interaction of the dispersed hydrogen bond is weak. Also, no stable nanoparticle was observed by GPC analysis (the absence of high molecular weight trace) for the diblock copolymers with DP of the diol block **A** less than 15, as fewer numbers of hydrogen-bond interactions weakens the self-assembling interaction.

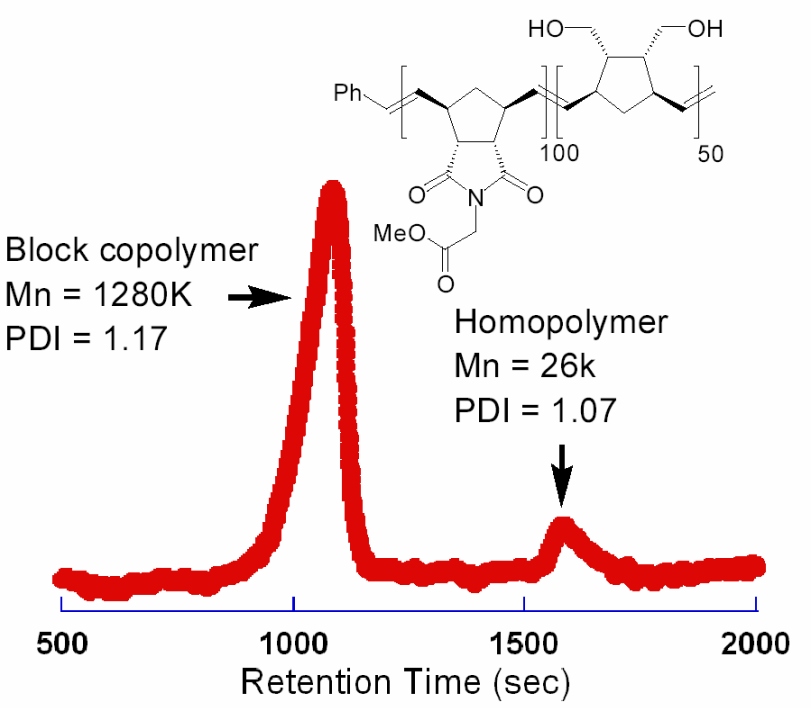


Figure 7. GPC traces of stable supramolecules eluted by CH_2Cl_2

To examine the dimensions of the self-assembled nanoparticles in CH_2Cl_2 solution, dynamic light scattering (DLS) was used to measure hydrodynamic radius (R_h) of the nanoparticles. DLS analysis was conducted with 0.015 wt% of block copolymers in CH_2Cl_2 at 20 ^oC. Representative DLS data for a self-assembled block copolymer of **C** (100eq) and **A** (25eq) is plotted in Figure 8 showing almost monodisperse distribution (polydispersity of 0.03) of particle size with R_h of 23.6 nm. Other block copolymers from difference monomers with various composites were synthesized and their DLS data are listed in Table 4 showing R_h values ranging from 10 to 50 nm and narrow distribution of the particle sizes (polydispersity below 0.09). As expected from the living nature of ROMP by catalyst **4**, the sizes of the nanoparticles increase with the larger DP of the each block. Therefore, the nanoparticle sizes can be easily controlled by changing the monomer to catalyst ratio during the synthesis of the diblock copolymers. The narrow polydispersity (below 0.1) of the particle sizes calculated by DLS reflects the ability of catalyst **4** to produce polymers with narrow PDI. It is quite remarkable that low molecular weight diblock copolymers with a total DP of 30 can self-assemble into the stable nanoparticles (Table 4,

entry 1).

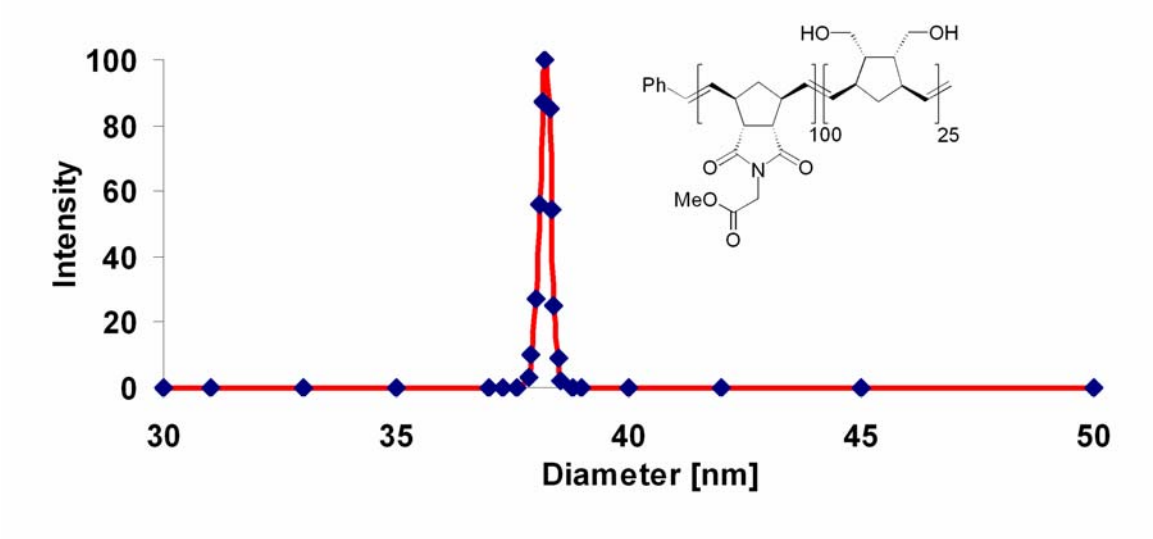
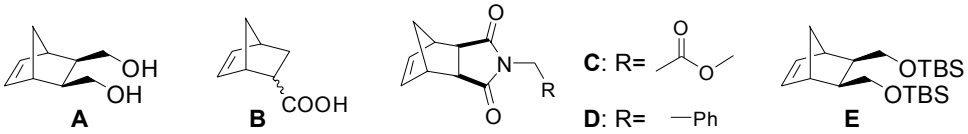


Figure 8. DLS analysis to show R_h in solution

Table 4. DLS data for various polymeric nanoparticles

entry	1st block (DP)	2nd block (DP)	M_n (PDI)[a]	R_h [nm][b]	polydispersity[b]
1	**C** (10)	**A** (20)	508K (1.75)	10.9	0.04
2	**C** (25)	**A** (25)	919K (1.47)	13.3	0.02
3	**C** (50)	**A** (25)	1170K (1.32)	19.1	0.03
4	**C** (100)	**A** (25)	1100K (1.12)	23.8	0.03
5	**C** (100)	**A** (50)	1280K (1.17)	27.5	0.01
6	**D** (35)	**A** (35)	1300K (1.42)	16.1	0.05
7	**D**(100)	**A** (50)	1350K (1.11)	33.1	0.05
8	**E** (50)	**A** (25)	747K (1.11)	18.7	0.06
9	**E** (100)	**A** (50)	1880K (1.15)	34.3	0.02
10	**C** (20)	**B** (20)	1300K (2.00)	16.0	0.05
11	**E** (100)	**B** (30)	967K (1.31)	47.9	0.09

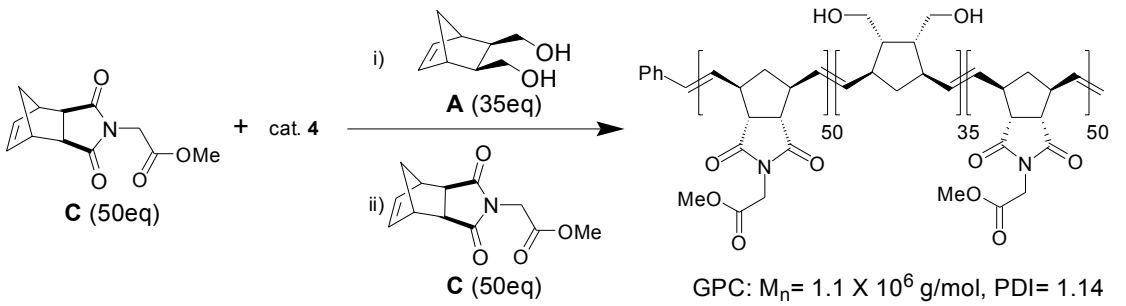
[a] CH_2Cl_2 GPC relative to PS standard [b] Determined by DLS, 0.015 wt % in CH_2Cl_2



Concentration effects of the nanoparticles on particle sizes were also investigated. A diblock copolymer from **C** (50) and **A** (25) (Table 4, entry 3) was dissolved in three different concentrations, 0.015 wt%, 0.15 wt% and 0.75 wt% and their R_h were measured to be 19.1 nm, 16.3 nm and 13.2 nm respectively. Slight decrease in particle sizes (30%) with retained narrow size distributions was observed with large increases (50 times) in the concentration. Compared to micelles where size is highly concentration dependent, concentration effect for the polymeric nanoparticles is less significant. Slight decrease in particle sizes may be due to the perturbations in viscosity and refractive index, to which DLS measurements are sensitive, during the large changes in concentrations.

Not surprisingly, homopolymers of **C** and **D** gives poor DLS data because small particles of single random coils are poor scatters of light. Also the block copolymers dissolved in hydrogen-bonding solvents such as DMSO and THF responded poorly by DLS analysis, indicating that the hydrogen-bonding driven self-assembly was disrupted. These observation along with NMR and GPC analysis, strongly support that the amphiphilic diblock copolymers undergoes self-assembly into stable nanoparticles in non-hydrogen bonding solvent, but are disassembled into random coils in hydrogen-bonding solvents.

A triblock copolymer was synthesized with the similar procedure (Scheme 3). The resulting polymer behaved similarly to the diblock copolymers, showing a high molecular weight trace (M_n= 1.1x 10^6 g/mol) by CH_2Cl_2 GPC and an R_h of 24.8 nm with narrow polydispersity by DSL analysis. Triblock copolymers can be more advantageous since they can contain more functionality compared to diblock copolymers.



Scheme 3. Preparation of nanoparticles from a triblock copolymer

Solid-state structures of polymeric nanoparticles were visualized by high-resolution scanning electron microscopy (SEM). A small amount of powder of the diblock copolymer was mounted on the carbon tape. Shown in Figure 9 is the polymeric nanoparticles from **E** (100) and **A** (50) obtained after precipitation into hexane (Table 4 entry 9). Sphere-like nanoparticles of around 40 nm in diameter can be identified by SEM analysis. Typically the sizes for the solid state (eg. 40 nm) is smaller than that obtained by a solution method, such as DSL (eg. 69 nm) because well solvated polymers tend to swell in solution, giving larger sizes.

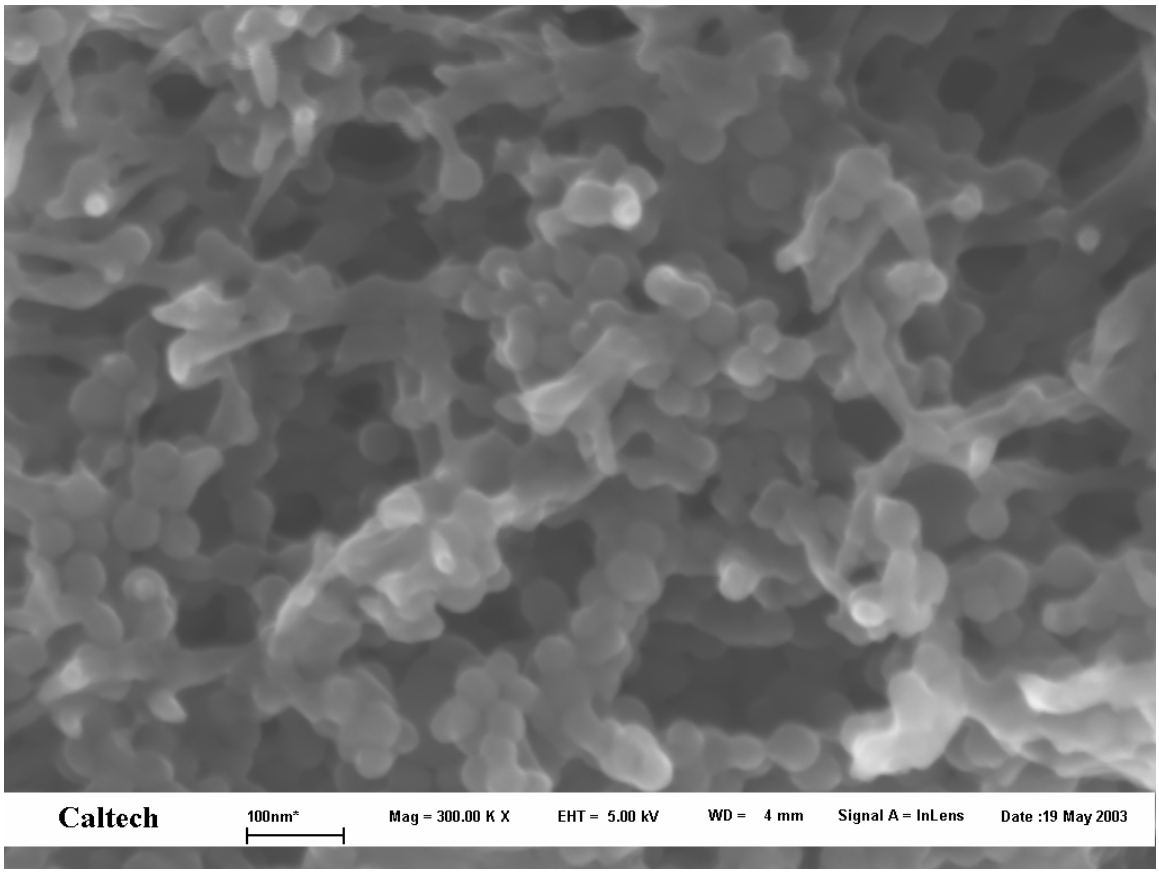


Figure 9. SEM image of polymeric nanoparticles

When a dilute CH_2Cl_2 solution of the nanoparticles prepared from **C** (20) and **B** (20) (Table 4, entry 10) was cast onto the surface of a silicon wafer and dried in humid air, a film of honey-comb structures was obtained as visualized by SEM (Figure 10). The well-ordered honey-comb with 1 *u*m pore and 250 nm thick walls can be observed. It has been proposed that when a film of polymers is casted in humid air, solvent evaporates and water droplets condense in the film to form honey-comb structure (Figure 11).[23] It seems that self-assembled block copolymer solution improves the quality of the honey-comb structures since the film cast by homopolymers or conventional block copolymers produce poorly ordered structure.

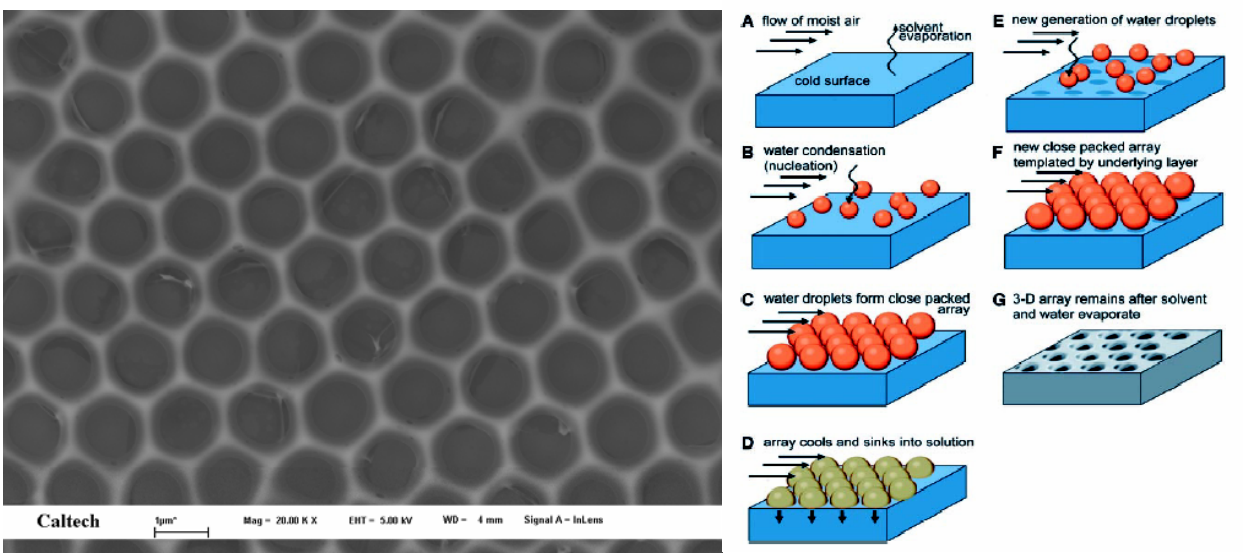


Figure 10. SEM image of honey-comb structures and the proposed mechanism of formation

Conclusion

We have demonstrated that catalyst **4** can be used to synthesize diblock and triblock copolymers that spontaneously self-assemble into stable nanoparticles. Living ROMP allows the preparation of the polymeric nanoparticles under mild conditions with good control of the particle sizes by varying the monomers to catalyst ratio for each block. Nanoparticles with R_h as low as 10.9 nm and narrow size distribution were prepared. NMR experiments gave the indication of self-assembly process, DLS provided information on the sizes and size distribution of the particles in solution, and GPC analysis showed that the hydrogen-bond-driven self-assembly yields stable polymeric nanoparticles. Finally, visualization of the nanoparticles in the solid state was possible by SEM.

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Experimental Section

Instrumentation. NMR spectra were recorded on Varian Mercury-300 NMR (300 MHz for ^{1}H and 74.5 MHz for ^{13}C). Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) with reference to internal solvent. Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), and multiplet (m). The reported ^{1}H NMR data refer to the major olefin isomer unless stated otherwise. The reported ^{13}C NMR data include all peaks observed and no peak assignments were made. Gel permeation chromatography (GPC) analysis in CH_2Cl_2 was obtained on a HPLC system using a Shimadzu LC-10AP_{vp} pump, Shimadzu DGU-14A degasser, a Rheodyne model 7125 injector with a 100 *u*l injection loop through Polymer Standard 10 micron mixed bed columns, and a Knauer differential-refractometer. Molecular weights and molecular weight distributions, M_w/ M_n, are reported relative to narrow disperse polystyrene standards (Showa Denko). Another GPC system was eluted by THF through two PLgel 5 mm mixed-C columns (Polymer Labs) connected in series with a DAWN EOS multiangel laser light scattering (MALLS) detector and an Optilab DSP differential refractometer both from Wyatt Technology. The dn/dc values were obtained for each injection assuming 100% mass elution from the columns. Dynamic light scattering (DLS) data was obtained from Brookhaven 90Plus using ZetaPALS particle sizing software. High resolution SEM images were obtained from LEO 1550VP.

General Procedure for ROMP of norbornenes: To a vial charged with a solution of catalyst **4** in 1 ml of CH_2Cl_2 under argon atmosphere, a solution of monomers in 0.5 ml of CH_2Cl_2 was added rapidly via syringe at room temperature. Quick degassing by dynamic vacuum was conducted. After 30 minutes, the reaction was quenched by addition of excess ethyl vinyl ether. The polymer product was obtained by precipitation into methanol, and dried overnight.

Procedure for ROMP of monomer 7: To a vial charged with catalyst **4** (1.0 mg, 1.1 *u*mol) in 1

ml of CH_2Cl_2 under argon atmosphere, solution of **7** (150 mg, 0.45 mmol) in 0.5 ml of CH_2Cl_2 was added rapidly via syringe at room temperature. After 30 minutes, the product (135 mg, 90% yield, 59% *cis* olefin) was obtained by precipitation into methanol. ^{1}H NMR (300MHz, $CDCl_3$, ppm): δ 7.25 (10H, bs), 5.25 (2H, bm), 4.30 (4H, bm), 3.45 (4H, bs), 2.76 (1.2H for *cis*, bs), 2.38 (0.8H for *trans*, bs), 2.03 (3H, bm), 1.12 (1H, bs). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 138.9(b), 134.0(b), 128.5, 127.7, 127.6, 73.2, 70.7, 70.4, 48.0, 47.7, 45.4 (bm), 41.3 (bm), 40.3. Other homopolymers are all known and well characterized.[9]

Procedure for ROMP of monomer A: To a vial charged with catalyst **4** (2.6 mg, 2.9 *u*mol) in 1 ml of CH_2Cl_2 under argon atmosphere, solution of **A** (22.5 mg, 0.15 mmol) in 0.5 ml of CH_2Cl_2 was added rapidly via syringe at room temperature. Immediately, the product (14 mg, 62% yield, 56% *cis* olefin) was obtained. ^{1}H NMR (300MHz, $DMSO_{d\text{-}6}$, ppm): δ 5.27 (0.9H for *trans*, bs), 5.15 (1.1H for *cis*, bs), 4.83 (2H, bs), 3.44 (4H, br), 2.45 (1.1H for *cis*, bs), 2.10 (0.9H for *trans*, bs), 1.82 (3H, bm), 1.07 (1H, bm).

Procedure for ROMP of monomer B: To a vial charged with catalyst **4** (3.4 mg, 3.9 *u*mol) in 1 ml of CH_2Cl_2 under argon atmosphere, solution of **A** (23 mg, 0.15 mmol) in 0.5 ml of CH_2Cl_2 was added rapidly via syringe at room temperature. Immediately, the product (14 mg, 61%,) was obtained. ^{1}H NMR (300MHz, CD_3OD, ppm): δ 5.35 (2H, bm), 2.9 (1H, bm), 2.52 (1H, bm), 1.98 (2H, bm), 1.7 (1H, bm), 1.3 (1H, bm).

Representative Procedure for amphiphilic diblock synthesis: To a vial charged with catalyst **4** (2.0 mg, 2.3 *u*mol) in 0.5 ml of CH_2Cl_2 under argon atmosphere, solution of **D** (57 mg, 0.23 mmol) in 0.5 ml of CH_2Cl_2 was added rapidly at room temperature. After 20 minutes, another solution of **A** (18 mg, 0.12 mmol) in 0.5 ml of CH_2Cl_2 was added rapidly. After 30 minutes, ROMP was quenched by addition of excess ethyl vinyl ether. The product (73 mg, 98%) was obtained by precipitation into methanol and drying on vacuum pump for overnight. ^{1}H NMR (300MHz, $DMSO_{d\text{-}6}$, ppm): δ 7.20 (5H, bs), 5.61 (0.8H for trans, bs), 5.43 (1.2H for cis, bm), 5.29 (0.8H for

trans, bs), 5.15 (1.2H for cis), 4.81 (2H, bs), 4.46 (2H, bm), 2.50- 3.35 (4H, bm), 1.0- 2.0 (6H, bm). ^{13}C NMR (75 MHz, $DMSO_{d-6}$, ppm): δ 178.6, 178.3, 136.9, 134.3, 133.7, 132.8, 132.1, 129.1, 128.0, 61.1, 53.1, 52.6, 51.3, 50.7, 49.5, 45.6, 42.0. 40 (br).

Reference:

1. For recent reviews on ROMP, see: a) Novak, B. M.; Risse, W.; Grubbs, R. H. *Adv. Polym. Sci.* **1992**, *102*, 47; b) Ivin, K. J.; Mol, J. C. *Olefin Metathesis and Metathesis Polymerization*, Academic Press, San Diego, CA, **1997**; c) Grubbs, R. H.; Khosravi, E. *Material Science and Technology*, **1999**, *20*, 65; d) Buchmeiser, M. R. *Chem. Rev.* **2000**, *100*, 1565.
2. Lehman, S. E.; Wagener, K. B. *Macromolecules* **2002**, *35*, 48.
3. a) Schrock, R. R. *Acc. Chem. Res.* **1990**, *23*, 158; b) Bazan, G. C.; Schrock, R. R.; Cho, H. N.; Gibson, V. C. *Macromolecules* **1991**, *24*, 4495.
4. Grubbs, R. H.; Tumas, W. *Science* **1989**, *243,* 907
5. a) Bielawski, C. W.; Grubbs, R. H. *Angew. Chem, Int. Ed.* **2000**, *39*, 2903; b) Bielawski, C. W.; Benitez, D.; Grubbs, R. H. *Macromolecules* **2001**, *34*, 8610; c) Scherman, O. A.; Kim, H. M.; Grubbs, R. H. *Macromolecules* **2002**, *35*, 5366.
6. Bielawski, C. W.; Louie, J.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 2872.
7. a) Bielawski, C. W.; Benitez, D.; Grubbs, R. H. *Science* **2003**, *297*, 2041; b) Bielawski, C. W.; Benitez, D.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 8424.
8. This portion of the work is published; Choi, T.-L.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **2003**, *42*, 1743.
9. a) Kanaoka, S.; Grubbs, R. H. *Macromolecules* **1995**, *28*, 4707; b) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100; c) Weck, M.; Schwab, P.; Grubbs, R. H. *Macromolecules* **1996**, *29*, 1789.

10. Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.

11. a) Chatterjee, A. K.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 1751; b) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783; c) Choi, T.-L.; Chatterjee, A. K.; Grubbs R. H. *Angew. Chem.* **2001***, 113*, 1317; *Angew. Chem, Int. Ed.* **2001**, *40*, 1277; d) Chatterjee, A. K.; Choi, T.-L.; Grubbs R. H. *Synlett*. **2001**, 1034; e) Choi, T.-L.; Lee, C. W.; Chatterjee, A. K.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 10417; f) Choi, T.-L.; Grubbs, R. H. *Chem. Commun.* **2001**, 2648; g) Lee. C. W.; Choi, T.-L.; Grubbs, R. H. *J. Am. Chem. Soc.* **2002**, *124*, 3224.

12. a) Sanford, M. S.; Ulman, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 749; b) Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543.

13. Choi, T.-L.; Rutenberg, I. M.; Grubbs, R. H. *Angew. Chem, Int. Ed.* **2002**, *41*, 3839.

14. ROMP with catalyst **3** gives extremely high molecular weight polymers that are often insoluble, but low PDIs have been observed, see: Maynard, H. D.; Okada, S. Y.; Grubbs, R. H. *Macromolecules*, **2000**, *33*, 6239.

15. Love, J. A.; Morgan, J. P.; Trnka, T. M.; Grubbs, R. H. *Angew. Chem, Int. Ed.* **2002**, *41*, 4035.

16. Khosravi, E.; Feast, W. J.; Al-Hajaji, A. A.; Leejarkpai, T. *J. Mol. Catal. A: Chemical* **2000**, *160*, 1.

17. Moffitt, M.; Khougas, K.; Eisenberg, A. *Acc. Chem. Res.* **1996**, *29*, 95.

18. Kataoka, K.; Harada, A.; Nagasaki, Y. *Adv. Drug Delivery Rev.* **2001**, *47*, 113.

19. a) Moffitt, M.; Vali, H.; Eisenberg, A. *Chem, Mater.* **1998**, *10*, 1021; b) Klingelhofer, S.; Heitz, W.; Greiner, A.; Oestreich, S.; Forster, S.; Antonietti, M. *J. Am. Chem. Soc.* **1997**, *119*, 10116.

20. a) Saito, R.; Kotsubo, H.; Ishizu, K. *Polymer*, **1991**, *27*, 1153; b) Guo, A.; Liu, G.; Tao, J. *Macromolecules* **1996**, *29*, 2487.

21. For a recent review, see: Wooley, K. L. *J. Polym. Sci. Part A: Polym Chem.* **2000**, *38*,

1397.

22. Butun, V.; Armes, S. P.; Billingham, N. C. *Macromolecules* **2001**, *34*, 1148.

23. a) Widawski, G.; Rawiso, M.; Francois, B. *Nature* **1994**, *369*, 387; b) Jenekhe S. A.; Chen, X. L. *Science* **1999**, *283*, 372; c) Srinivasarao, M.; Collings, D.; Philips, A.; Patel, S. *Science* **2001**, *292*, 79.