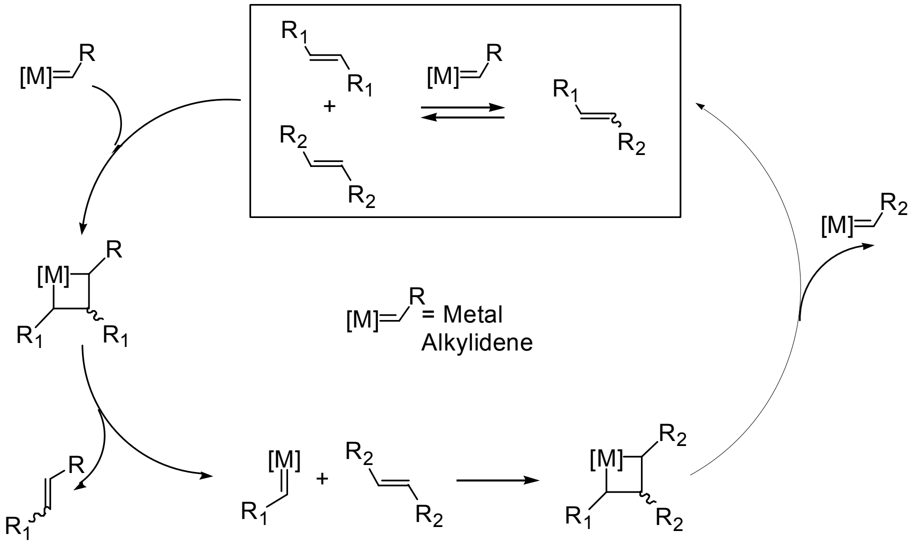
Chapter 1:

Introduction to Olefin Metathesis

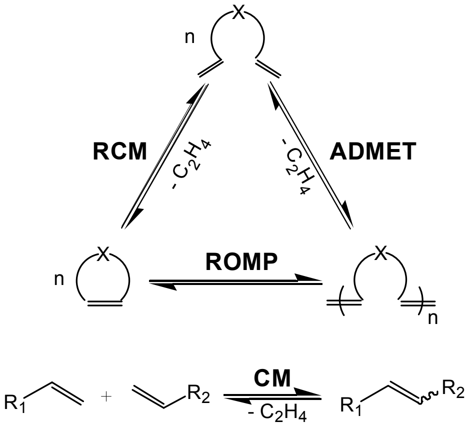
Brief History of Olefin Metathesis

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.

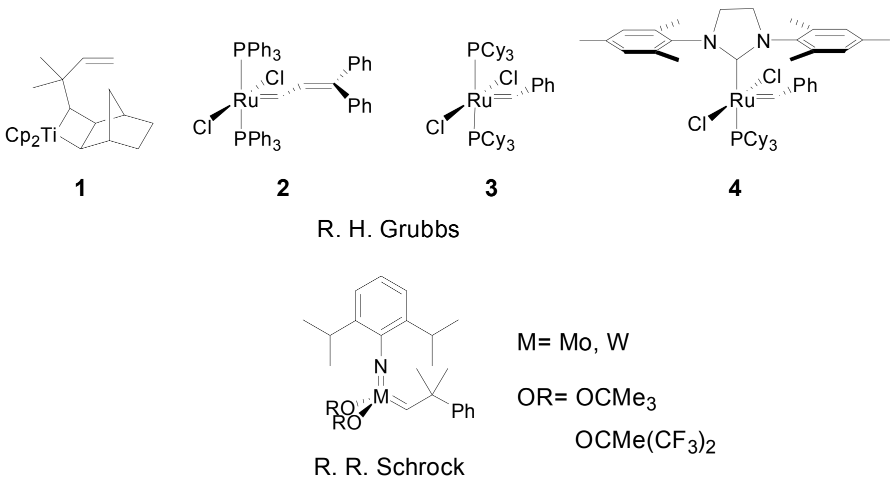
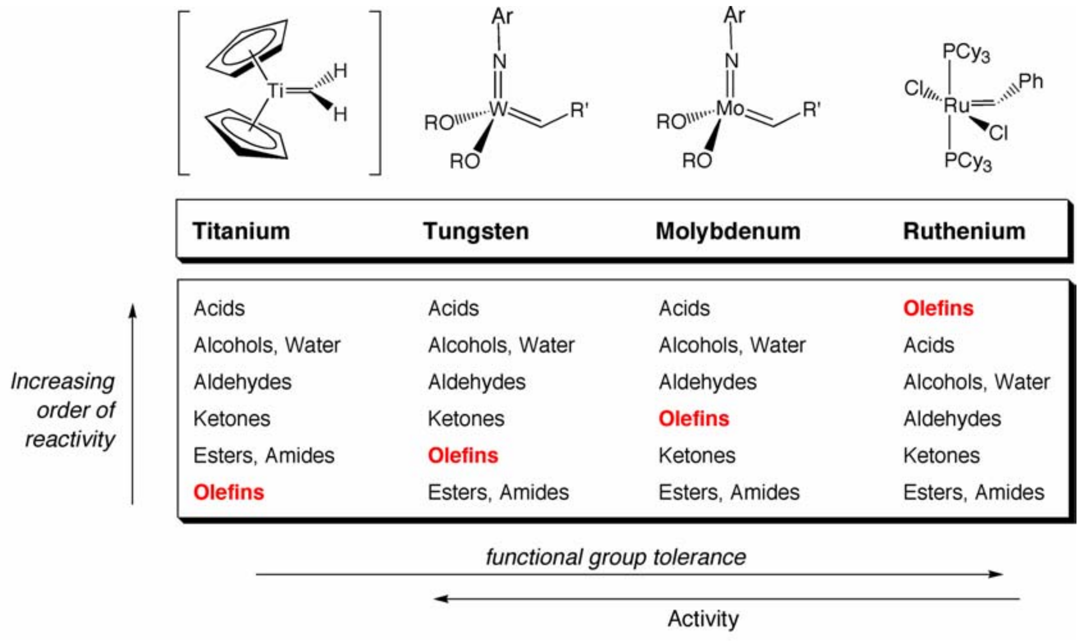


Figure 1. Representative examples of well-defined olefin metathesis catalysts

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.

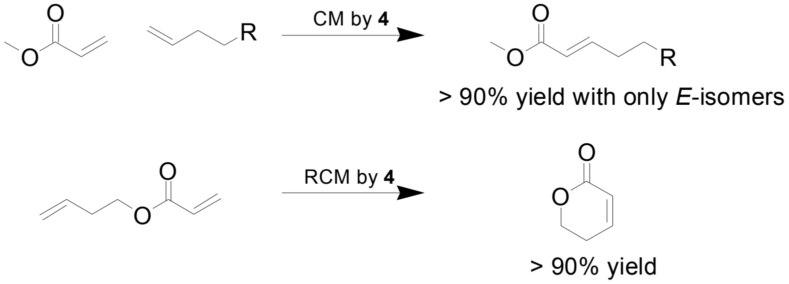
Table 1. Summary of properties for various catalysts



Titanium	Tungsten	Molybdenum	Ruthenium
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

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 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 slowed the metathesis activity of catalyst **4** was observed for electron rich amides. Also direct generation of enoic carbenes by catalyst **4** was possible from acrylates, acrylic acid and vinyl ketones. Enoic carbenes were shown to efficiently ring-open cyclohexene. 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 catalyst **4**. Tandem ring-opening/ring-closing metathesis and tandem enyne RCM provided bicyclic compounds with good yields. Also 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 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 self-assembly to produce stable nanoparticles even without cross-linking.

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.