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RECENT ADVANCES OF OLEFIN METATHESIS AND IT'S APPLICATIONS IN ORGANIC SYNTHESIS

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Abstract

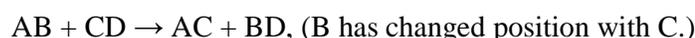
Olefin metathesis has become a tool for synthetic organic and polymer chemists. Well-defined, functional group tolerant catalysts have allowed these advances. A discussion of the evolution of mechanistic understanding and early catalyst development is followed by a description of recent advances in ruthenium based olefin metathesis catalyst. Catalyst improvements have led to new applications in ring closing metathesis, cross metathesis and material synthesis. A water-soluble ruthenium based olefin metathesis catalyst supported by a poly (ethylene glycol) conjugated *N- heterocyclic carbene* ligand is reported. The catalyst displaces greater activity in aqueous ring-opening metathesis polymerization (ROMP) reactions than previously reported water-soluble metathesis catalyst. Olefin metathesis is a unique carbon- carbon bond breaking or making process that has enormously added to the chemist's capabilities at making a broad range of drugs and other useful complex molecules, improved rubbers, and plastics for laboratory and commercial applications.

Key words: olefin metathesis; polymerization; carbene; aqueous metathesis; ruthenium; *N-heterocyclic carbene*.

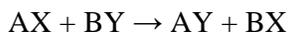
INTRODUCTION TO METATHESIS:

METATHESIS:

Actually the word metathesis is derived from the Greek *are/meta* (change) and *thesis* (position), metathesis is the exchange of parts of two substances. In the reaction.



Metathesis is a molecular process involving the exchange of bonds between the two reacting chemical species, which results in the creation of products with similar or identical bonding affiliations. The general reaction scheme:



These chemical species can either be ionic or covalent.

In metathesis reactions, double bonds are broken and made between carbon atoms in ways that cause atom groups to change places. This happens with the assistance of special catalyst molecules.

Metathesis is used daily in the chemical industry, mainly in the development of pharmaceuticals and of advanced plastic materials. By using metathesis methods have been developed that are

- More efficient (fewer reaction steps, fewer resources required, less wastage)
- Simpler to use (stable in air, at normal temperatures and pressures) and
- Environmentally friendlier (non-injurious solvents, less hazardous waste products).

This represents a great step forward for "green chemistry", reducing potentially hazardous waste through smarter production. Metathesis is an example of how important basic science has been applied for the benefit of man, society and the environment.

PRINCIPLES OF METATHESIS:

1. A water-soluble ruthenium-based olefin metathesis catalyst supported by a (poly ethylene glycol) conjugated N-heterocyclic carbene ligand displays greater activity in aqueous ring-opening metathesis polymerization (ROMP) reactions than previously reported water-soluble metathesis catalysts.

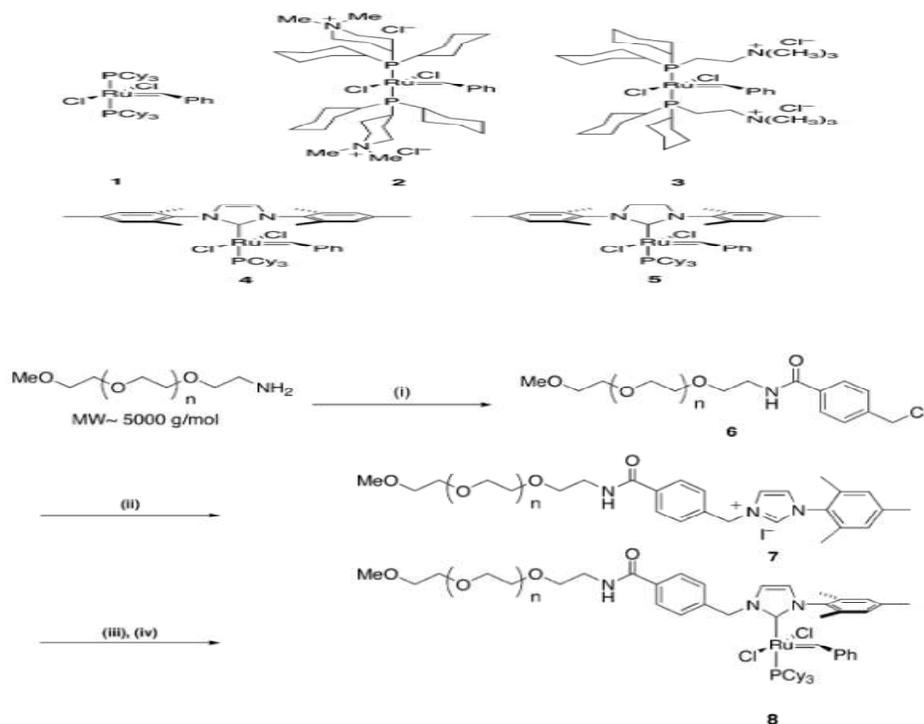
The olefin metathesis reaction is a powerful method for carbon-carbon bond formation in both polymer and small molecule synthesis^{1,2}. In particular, ruthenium based olefin metathesis catalysts are well suited for applications in organic synthesis because they are remarkably tolerant of air, moisture, and a large variety of functional groups.³ The high tolerance of **1** toward water inspired the development of water-soluble analogs **2** and **3** that catalyze olefin metathesis reactions in water and protic organic solvents^{4,5}.

Ruthenium-based olefin metathesis catalysts incorporating N-heterocyclic carbene ligands (**4** and **5**) display increased metathesis activity relative to **1** and retain the functional group tolerance that is a hallmark of **1**¹⁻

⁵. With the goal of developing a homogenous aqueous catalyst that displays increased activity relative to bis (phosphine) analogs **2** and **3** synthesized the (poly ethylene glycol) (PEG) conjugated N-heterocyclic carbene-containing ruthenium benzylidene catalyst was synthesized. This solubility profile could prove useful in the separation of catalyst **8** from organic products.

For example, the catalyst could be removed from organic-soluble material by precipitation from diethyl ether. Additionally, in contrast to other polymer displayed metathesis catalysts,⁶⁻¹² pending PEG to the non-dissociating N-heterocyclic carbene ligand allows catalyst **8** to remain in solution throughout the entire metathesis reaction.

In conclusion, PEG incorporated into the first example of a homogenous olefin metathesis catalyst coordinated with a N-heterocyclic carbene ligand. Catalyst **8** initiates the ring-opening metathesis polymerization of strained cyclic olefins in both water and methanol. Furthermore, direct comparison of the activity of **8** relative to a previously reported water-soluble bis (phosphine) catalyst **8** is more active for the polymerization of hindered monomers in water. In addition to **ROMP**, **8** also catalyze the ring-opening metathesis of organic substrates in methanol. These results show that ruthenium olefin metathesis catalyst containing a N-heterocyclic quite active in water.



Reagents and conditions: (i) 4-(chloromethyl) benzoyl chloride, DMAP, pyr, CH₂Cl₂, 25 °C, 4 h (87 %),

(ii) mesityl imidazole, NaI, acetone, 60 °C, 14 h (98%), (iii) KOtBu, toluene, 25 °C, 15 min, (iv) 1, toluene, 25 °C, 20 min (58%).

THEORY OF METATHESIS:

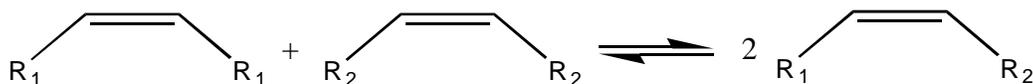
Olefins:

These are the hydrocarbons containing double bonds. These are also called as alkenes. An **alkene**, **olefin**, or **olefine** is an unsaturated chemical compound containing at least one carbon-to-carbon double bond. The simplest acyclic alkenes, with only one double bond and no other functional groups, form an homologous series of hydrocarbons with the general formula **C_nH_{2n}**.

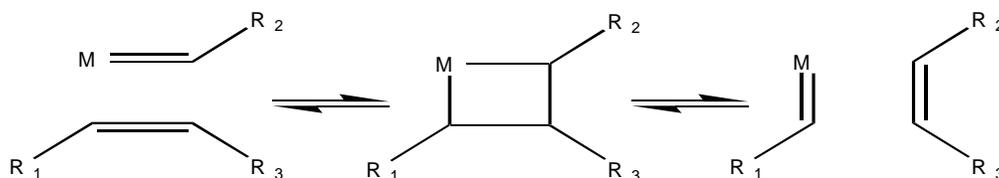
The simplest alkene is ethylene (C₂H₄), which has the International Union of Pure and Applied Chemistry (IUPAC) name *ethene*. Alkenes are also called *olefins* (an archaic synonym, widely used in the petrochemical industry).

Olefin metathesis:

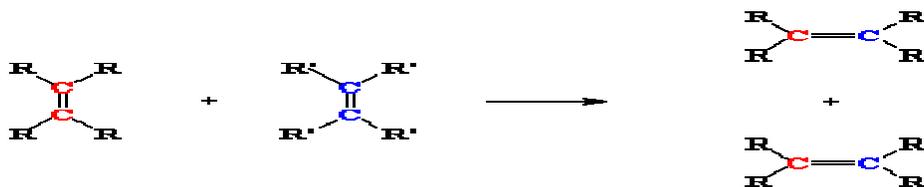
The general Olefin metathesis reaction



Catalysts based Olefin metathesis reactions



An olefin is the same thing as an alkene that is a molecule with a carbon-carbon double bond. Olefin metathesis is of course a reaction involving olefins. Two olefins, to be exact. And here's what they do: the double bond carbons change partners, to form two new olefins,



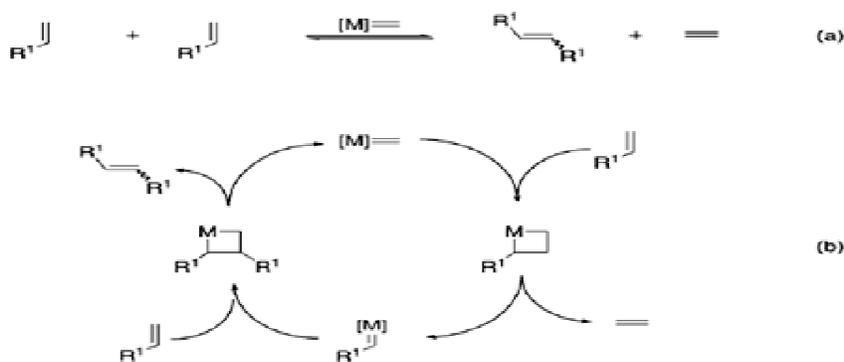
THE DISCOVERY OF THE OLEFIN METATHESIS REACTION:

Catalyzed metathesis was discovered by Ziegler in 1957. It describe the formation of unsaturated polymers. Such a polymer was obtained from the highly-strained starting material norbornene when it was added to molybdenum oxide on alumina combined with lithium aluminium hydride.^{14a}

In the same year another patent application claimed an additional and seemingly novel transformation – disproportionation of olefins – as evidenced by the conversion of propene into ethene and butene upon treatment with a mixture of triisobutylaluminum and molybdenum oxide on alumina.^{14b, c}

DEVELOPMENT OF THE METATHESIS METHOD IN ORGANIC SYNTHESIS:

An olefin metathesis reaction is shown through carbene (alkylidenes) exchange between the two starting olefins two new olefins have been formed.

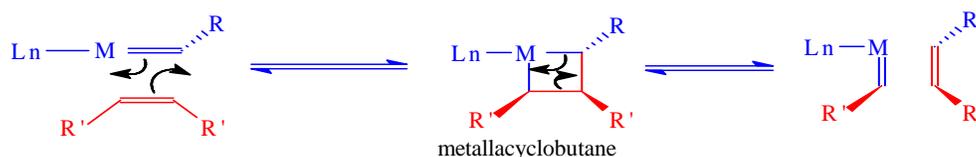


All involve the carbon-carbon bond – its construction and chemistry. This is not surprising given the importance of carbon-carbon bonds, and the enabling nature of organic synthesis⁴.

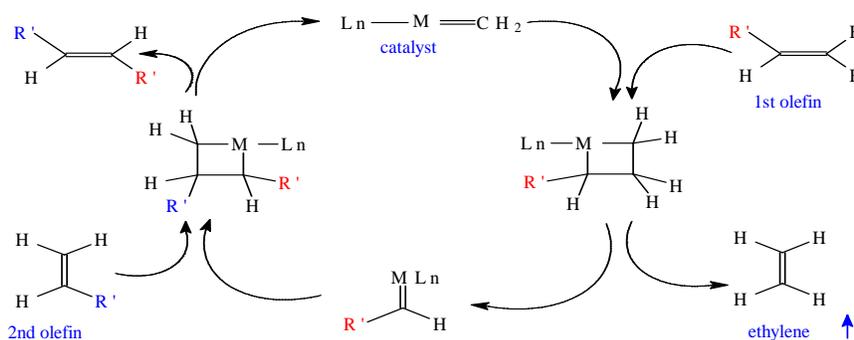
V.Grignard and P. Sabatier recognized the importance of the Grignard reagents in forming carbon-carbon bonds for the construction of molecular frameworks and the use of metals in catalytic hydrogenation of unsaturated compounds.

MECHANISM OF OLIFENE METATHESIS:**CHAUVINS MECHANIM:**

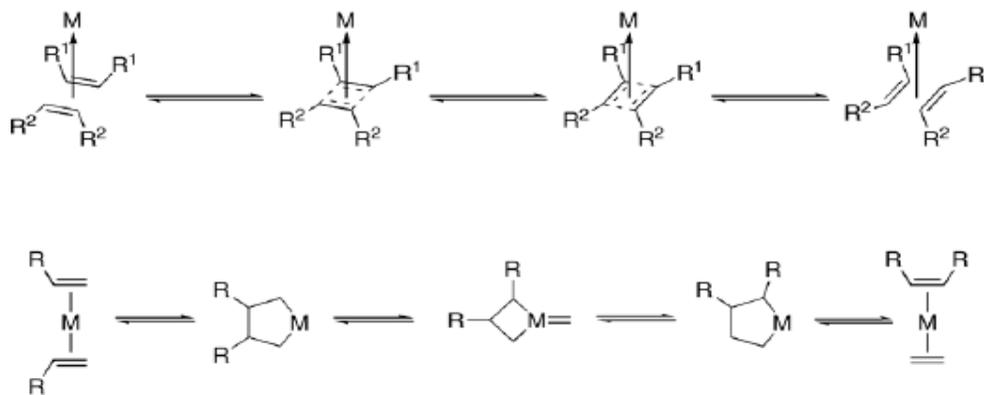
Chauvin's Mechanism of olefine metathesis by "Forbidden" [2+2] Cycloadditions The commonly accepted mechanism for the olefine metathesis reaction was proposed by Chauvin and involves a [2+2] cycloaddition reaction between a transition metal alkylidenes complex and the olefine to form an intermediate metallacyclobutane. This metallacycle then breaks up in the opposite fashion to afford a new alkylidenes and new olefine. If this process is repeated enough, eventually an equilibrium mixture of olefins will be obtained.



Such cycloaddition reaction between two alkenes to give cyclobutanes is symmetry forbidden and occurs only photo chemically. However, the presence of d-orbitals on the metal alkylidenes fragment breaks this symmetry and the reaction is quite facile.

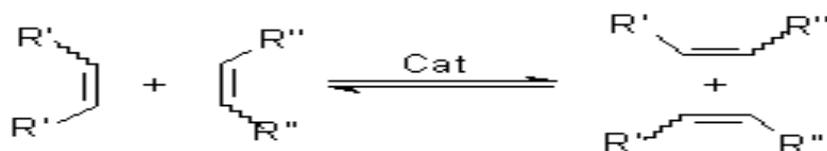


Several mechanistic hypotheses were in existence during this early period of olefine metathesis exploration. At first it was questioned whether olefine metathesis exchanged alkyl or alkylidenes groups. Experiments by Calderon and by J.C. Mol using isotopically labelled alkenes demonstrated that the groups interchanged in olefine metathesis were alkylidenes.^{15a, b} But the mechanism by which interchange occurred and the role played by the metal species remained mere guesswork. Among several ideas about the mechanism circulating at the time to explain alkylidenes exchange were the metal-coordinated cyclobutane model of Calderon^{15d}, and later the metallocyclopentane model of Grubbs¹⁶.



GRUBB'S REACTION:

Olefin Metathesis allows the exchange of substituent's between different olefins - a transalkylidenation.

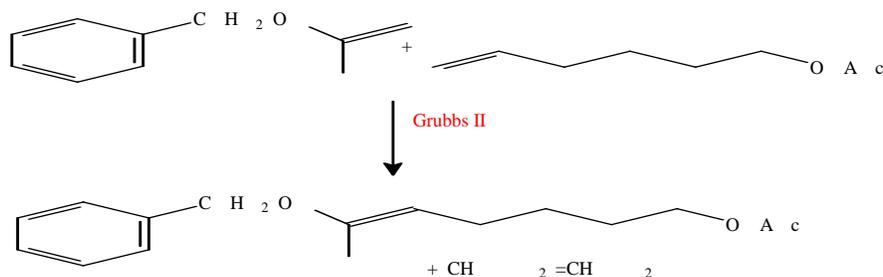


This reaction was first used in petroleum reformation for the synthesis of higher olefins (Shell higher olefin process - SHOP), with nickel catalysts under high pressure and high temperatures. Nowadays, even polyenes with MW > 2,50,000 are produced industrially in this way. All of these applications have been made possible by the development of new homogeneous catalysts. Shown below are some of these catalysts, which tolerate more functional groups and are more stable and easy to handle.³⁰

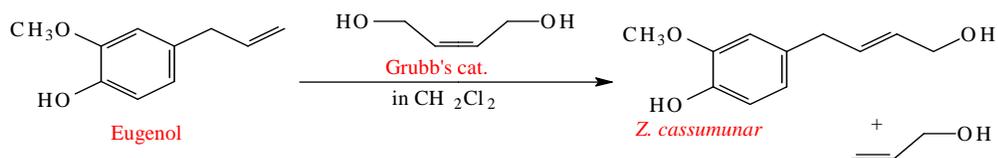
TYPES OF OLEFIN METATHESIS REACTIONS:

A. CROSS METATHESIS:

Example of this reaction



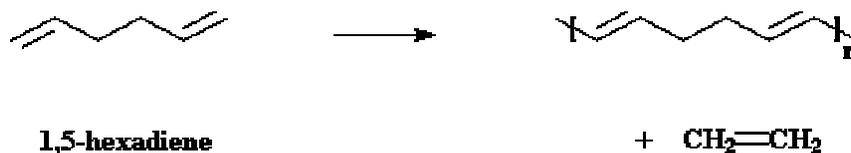
Formation of Z-cassumunar from the eugenol by using grubbs catalysts is one of the examples for this cross metathesis reaction.



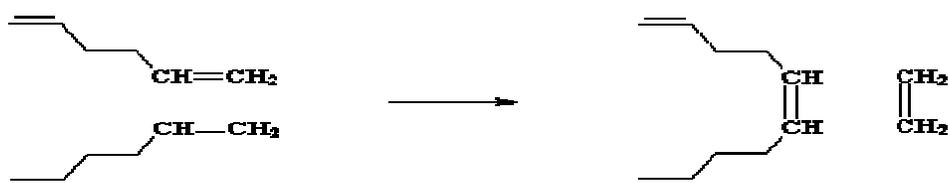
Like other cross metathesis reactions, the formation of E/Z mixtures results in diastereomers relative to the cyclohexene configuration. However, a simultaneous cleavage of the acetates and equilibration to the more stable trans-configuration occurs using NaOMe in MeOH–THF. This strategy was also applied to the synthesis of pipercolic acid derivatives using an aza-Diels–Alder (e.g., X = N; Acc = Ts). This technique allows the preparation of carbohydrate-containing molecules with great structural and functional diversity, which means that metathesis is indeed sweet.

B. ACYCLIC DIENE METATHESIS POLYMERIZATION / ADMET:

Acyclic diene metathesis polymerization or ADMET. Is very simple. It starts with an acyclic diene, such as 1, 5-hexadiene, and end up with a polymer with a double bond in the backbone chain, plus by-product ethylene gas.

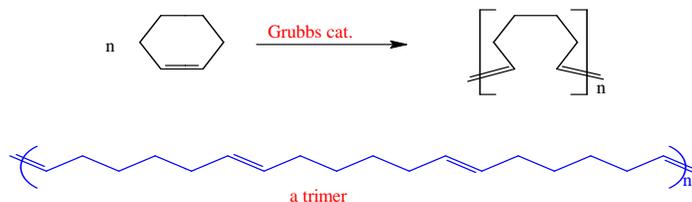


Using the example of two molecules of 1,5-hexadiene reacting together:



The double bonds at the ends of the new molecule can have a little metathesis and the polymer grows. Usually both cis- and trans- isomers can form, and there's usually room for both in the polymer that we end up with.

C. RING OPENING METATHESIS POLYMERIZATION /ROMP:

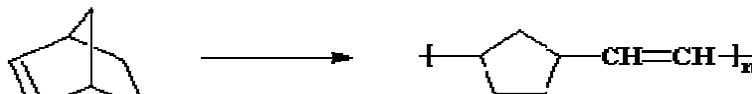


Polymers can be obtained from cyclic olefins. A cyclic olefin; cyclopentene in this case, is used to make a polymer which doesn't have cyclic structures in its backbone.



cyclopentene

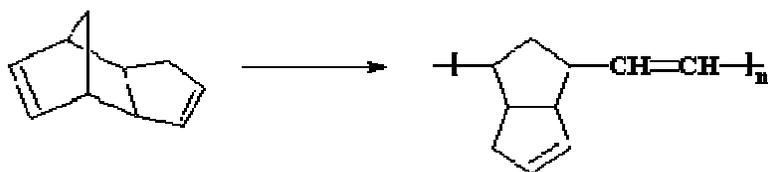
So this is called as "ring-opening metathesis polymerization". ROMP is, used to make some useful products. A little molecule, norbornene, is polymerized by ROMP to get polynorbornene. It's a kind of rubber used to make auto parts, the little body-mount parts that keep things from vibrating and such.



norbornene

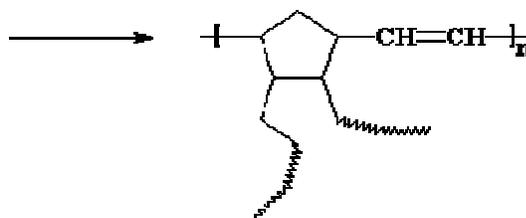
polynorbornene

Another molecule which can be made by using ROMP is endo-dicyclopentadiene is formed. When the polymerization occurs a cyclic olefin in a pendant group. This polymer is polydicyclopentadiene.



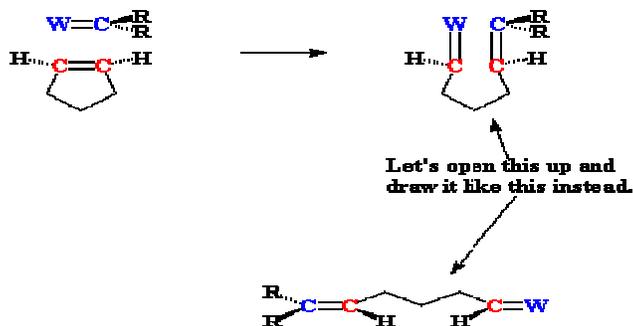
endo-dicyclopentadiene

poly(endo-dicyclopentadiene)

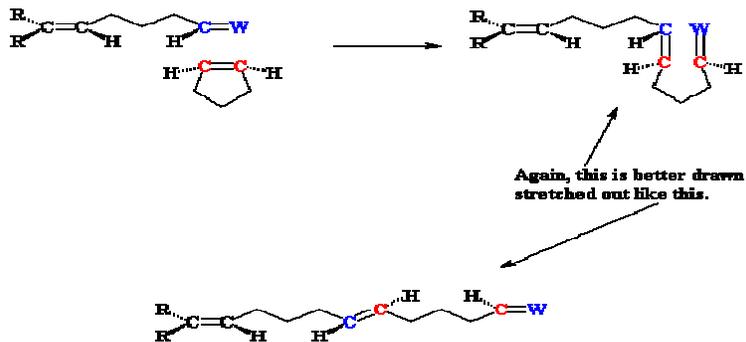


crosslinked polymer

The initiator in this case is usually a compound with a carbon atom double bonded to a metal atom, like tungsten or molybdenum. So the initiator reacts with a molecule of cyclopentene in a metathesis reaction to get a molecule with a carbon-carbon double bond at one end, and a carbon-metal double bond at the other.



That carbon-metal double bond can react with another molecule of cyclopentene in the exact same way



And in this way the polymer grows, until we get this:

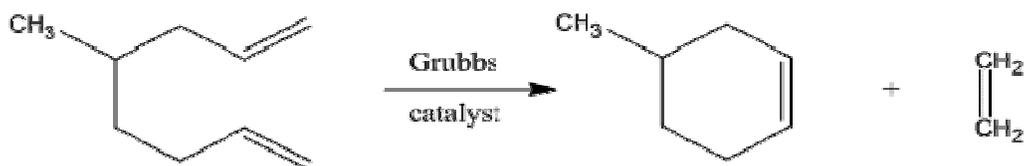


Here some Olefin Metathesis Catalysts are used. Those are

Schrock and Grubbs catalysts

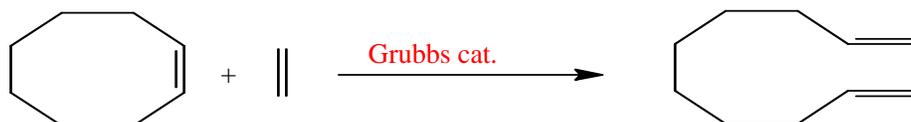
- Air sensitive.
- Initially were molybdenum and ruthenium based, respectively.

D. INTRAMOLECULAR METATHESIS OF A DIENE:



Intermolecular metathesis using 4-methyl-1,7-octadiene. Ring formation occurs when a diene is used as the starting material. Any size ring is possible to make with metathesis of a diene. For example, in the presence of a metal catalyst, usually Grubbs' catalyst, 4-methyl-1, 7-octadiene forms 4-methylcyclohexene. When using terminal alkenes the by-product is always gaseous ethene.

E. RING OPENING CROSS METATHESIS:



Example of this reaction is shown above. Here cyclic compounds are modified into acyclic molecule with additional cross metathesis.

INSTRUMENTATION/EQUIPMENT:

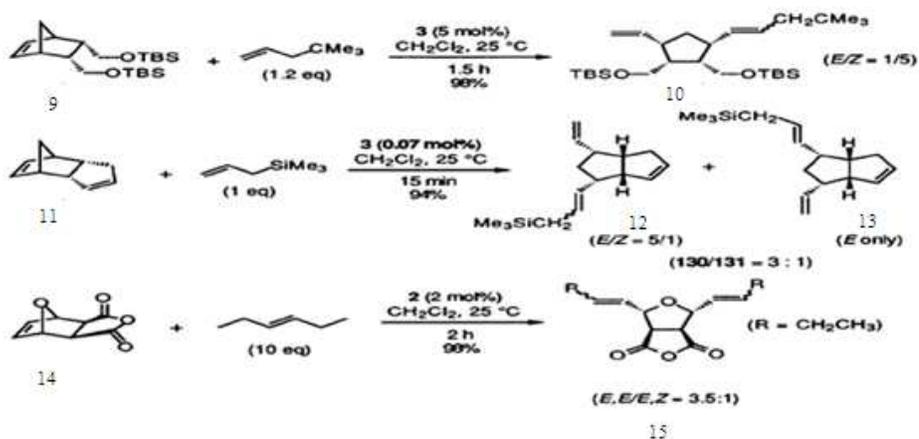


LARGE SCALE Olefin metathesis is key in the production of linear olefins at the

Ring-Opening Cross Metathesis:

Ring opening metathesis of strained ring systems and subsequent coupling with acyclic alkenes provides new types of diene products. To avoid polymerization of the cyclic olefins, the reaction is usually performed in relatively dilute concentrations (0.1 M) and an excess of acyclic alkenes is added. This modified cross metathesis uses the ring-opening of strained cyclic olefins as a driving force for the reaction. The recent successful application of these reactions is surprising in light of the rapid equilibration of the end groups in cross metathesis reactions with classical catalysts. In fact the formation of scrambled cross products as the kinetic products with classical catalysts was one of the fonts' clues implying that the mechanism involves carbenoid intermediates.¹⁶

Ring-opening cross metathesis of strained norbornene derivatives with various types of olefins has been illustrated by Biechert and co-workers¹⁸ with symmetrical norbornenes such as 9, reaction with a slight excess of terminal alkene produced only one regioproduct 10 in excellent yield using the Ru catalyst 3. Two regioisomeric products, however, would be formed from the reaction of unsymmetrical norbornenes. Indeed, reaction of dicyclopentadiene 11 with allylsilane afforded a 3:1 mixture of two regioisomeric products 12 and 13. The efficiency of the reaction is remarkable, with only 0.07 mol% of the Ru-catalyst 3 being sufficient to complete the reaction in 15 min at room temperature.¹⁹

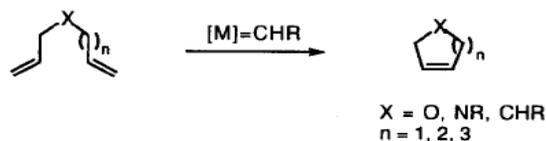


Scheme -1

Regio - and stereo selective ring-opening cross metathesis of cyclobutene-containing substrates with suitable terminal olefins has been recently investigated by Snapper and co-workers.^{20,21}

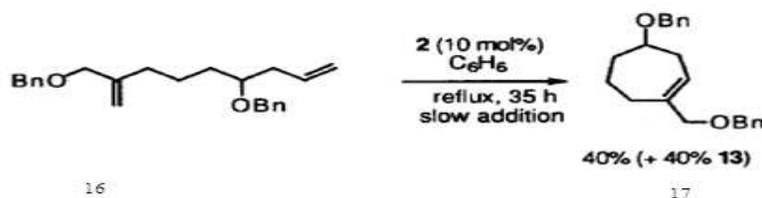
Medium Sized (5-8) Ring Formation:

The modern use of olefin metathesis can be tracked to the series of papers²² that demonstrated the high yielding closure of diolefins to provide 5, 6 and 7 membered rings with a diverse functionality and double bond Substitution.



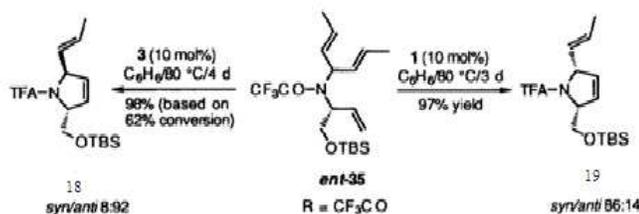
RCM was utilized for the formation of 1, 4-difunctionalized cycloheptenes for eventual use in an enediyne system synthesis²³ while the Mo-catalyst I rendered only intermolecular dimer, the Ru-carbene 2 was able to

convert diene **13** to cycloheptene **14**. The cyclization yield was increased by slow addition of the catalyst and the substrate.



Stereo selective RCM:

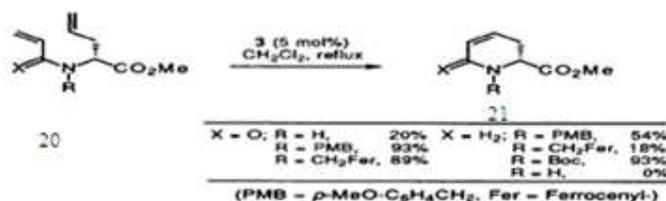
Diastereoselective ring-closing metathesis reactions have been recently described in which an existing chiral center controls the direction of cyclization of prochiral dienes.²⁴ This strategy requires that initial metathesis occurs at the double bond of the chiral center and that the olefins of the prochiral center do not react with each other. This is possible by a modification of the prochiral olefins from terminal to internal position so that the likelihood of ring closure between the sterically crowded double bonds at the prochiral center is minimized. It was found that cyclization of enantiopure **18** did indeed proceed with a significant diastereoselectivity.²⁵



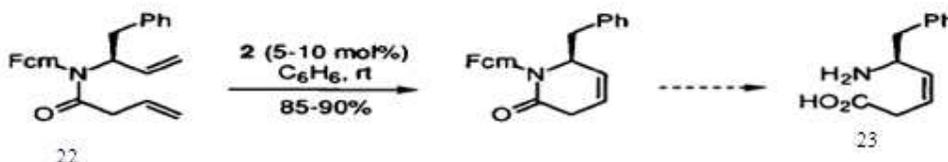
Ru-catalyst **3** provided the remarkably high i.e., whereas the syn-product **19** was preferentially obtained with the Mo-carbene **1**.

Application to Peptide Chemistry:

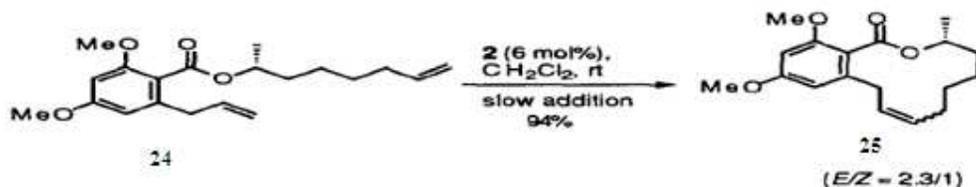
Due to the high activity and functional group tolerance of the metathesis catalysts 1-3, RCM has recently extended its utility to the area of peptide chemistry. Highly functionalized 6- and 7-membered amino esters or acrylic amides 21 were prepared from enantiopure amino acid-derived dienes 20 with the Ru-catalyst 3.²⁶



RCM of a dienic amide 22 with the Ru-catalyst 2 led to a dehydro lactam 23, a direct precursor of the Zethylenic dipeptide isostere 23.²⁷ It is interesting that the ferrocenylmethyl (Fcm) group was selected for nitrogen protection of the amide bond in the substrate 22 because apparently the steric bulk leads to the formation of the favorable conformation for closure.

**Macrocyclization Using RCM:**

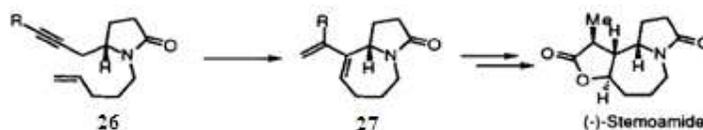
One of the major considerations for RCM in the synthesis of highly flexible large (>9) ring systems is the conformational predisposition of starting material for favorable intramolecular cyclization. However, it has been demonstrated that macrocyclization metathesis is highly efficient not only with substrates having suitable restrictions but also with substrates devoid of any rigorous conformational constraints by modification of the reaction conditions (usually by slow addition). Therefore, RCM is becoming recognized as one of the most straightforward and reliable methods for the formation of large ring systems and compares favorably to all current synthetic alternatives.



Tandem Reactions:

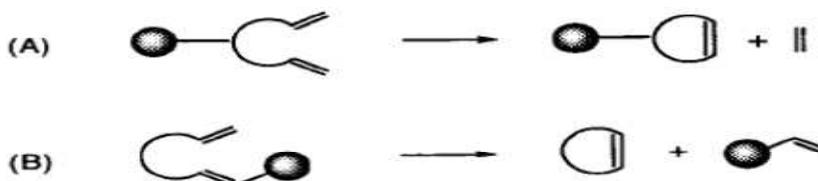
In addition to the ring-closing metathesis (RCM) of acyclic dienes, Mo- and Ru-carbene complexes 1-3 also promote the ring opening metathesis of strained cyclic olefins.

Ex: Intramolecular enyne metathesis has been applied in the total synthesis of a natural product, stemoamide²⁸. Cyclic enynes **26** were smoothly converted to the 5,7-fused compounds **27** in the presence of Ru-carbene catalysts 2 or 3.



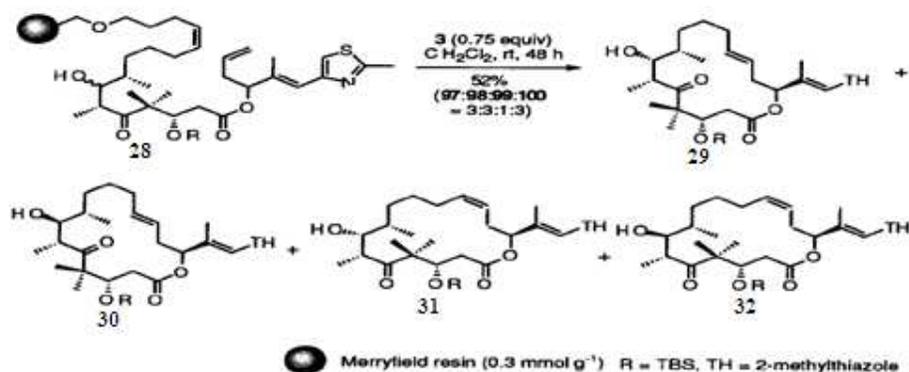
RCM of Solid Supported Substrates:

Performing organic transformations on a solid support has seen increased uses during the past few years. Olefin metathesis methodology has been also shown to be compatible on solid support bound substrates. There are two potential strategies depending on the olefin's position on the solid support as depicted. A diene which contains a variety of functional groups (for instance, alcohol, carboxylic acid, amine etc.) may be covalently bound by a linker to a solid support and heterogeneous RCM can be carried out on the resultant solid bound substrates (equation A). A different approach (B) is the "cyclization/cleavage method" in which the desired cyclic olefin is directly liberated from RCM of a diene attached at one end to solid support and therefore no additional step for removing the linker from the resin is necessary.



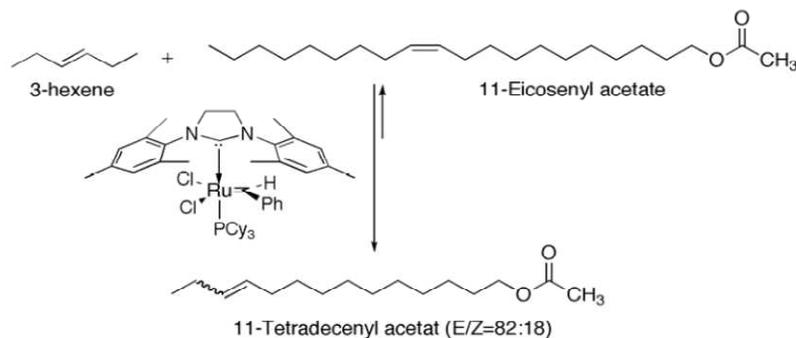
Nikolaou and co-workers have reported a solid-phase synthesis of epothilone A incorporating RCM²⁹

Upon treating solid support bound olefin 28 with 0.75 equiv of catalyst in methylene chloride, 4 olefinic compounds 29-32 were released from the resin in total 52% yield as a separable mixture of 4 diastereomers. Desilylation and epoxidation of the cyclic olefins affords the biologically important epothilone A and its derivatives.



5. APPLICATIONS OF METATHESIS:

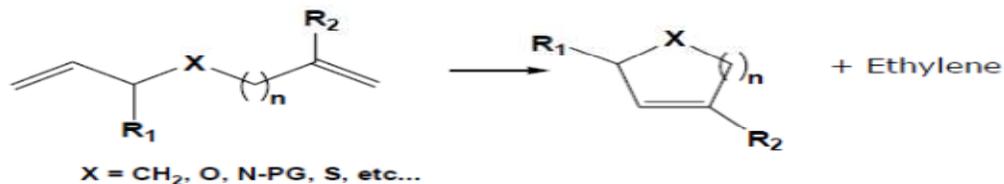
1. The omnivorous leafroller (OLR) is a pest of apples, pears, peaches, and nectarines. The OLR pheromone is an 82:18 ratio of *E* to *Z*-tetradecenyl acetate isomers. The synthesis of OLR pheromone is a particularly attractive target for metathesis because this CM reaction, using the second generation Grubbs' catalyst, produces the desired isomeric ratio¹⁷.



2. Ring Closing Metathesis in Pharmaceutical Applications:

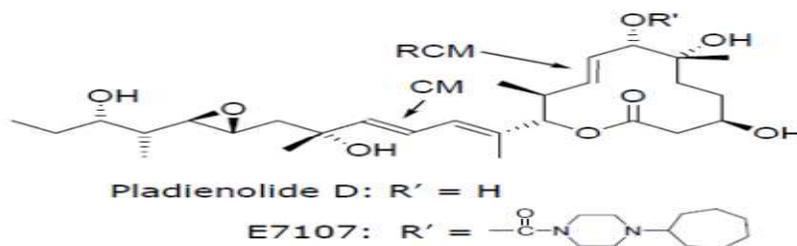
- RCM is an efficient method in the formation of medium to large rings
- Medium rings yield *cis*-double bonds and can be run more concentrated
- Large rings yield *trans*-double bonds and need to be run more dilute

- Ring low strain facilitates otherwise non-favourable metathesis reactions



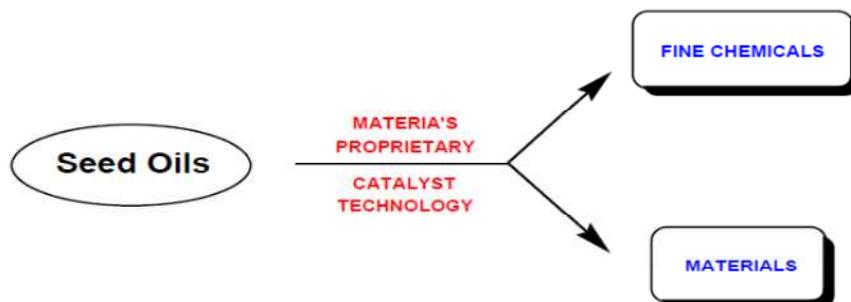
3. Application of cross metathesis:

Produce Pladienolide D and E7107 by cross metathesis, traditional Julia-Kocienski olefination techniques failed.



4. Conversion of Seed Oils to Chemicals

Opportunities to use metathesized seed oils to displace petroleum based products.



5. Insect Pheromones from Seed Oils:



6. Pheromones from Jojoba Oil:



7. Industrial production of olefins is based on cross-metathesis using heterogeneous catalysts. From 1966 to 1972, Phillips Petroleum was making ethylene and 2-butene from propylene, a process known as the Phillips trioolefin process. Because olefin metathesis is a reversible reaction, propylene can be produced from ethylene and 2-butene. The process, known as olefins conversion technology (OCT).³¹

8. 1-Hexene and neohexene (3,3-dimethyl-1-butene) are also made by cross-metathesis.³¹

9. Most olefin-metathesis-derived polymers are made with complex homogeneous systems. Commercial polymers produced industrially by ring-opening metathesis polymerization include polyoctenamer, polynorbornene, and polydicyclopentadiene (PDCP).³¹

6. CONCLUSION AND SUMMARY:

Olefin metathesis is quickly emerging as one of the most powerful strategies for carbon-carbon bond formation. With the advent of the well defined [Mo] and [Ru] catalyst the early promise of olefin metathesis as a new synthetic strategy is being realized and numerous new aspects of this chemistry have been discovered. Ring-closing metathesis (RCM) reactions are simple, high-yielding and truly friendly to the environment. The examples discussed above demonstrate that RCM catalysts show the scope and activity required for a generally useful synthetic approach to complex molecules. Although control of stereo selectivity macrocyclization and cross metathesis is one issue that is yet to be addressed in order to make this strategy more valuable, some reaction conditions have been disclosed that reduce this selectivity problem.

7. FUTURE OUTLOOK:

The successful application of olefin is metathesis reactions hinges on the selectivity of the carbon-carbon bond formation, more significantly in reactions involving cross metathesis. Although introduction of substituent's on the substrates results in different degrees of cis trans preferences, it is too early to correctly predict the outcomes of the stereo selectivity. However, considering the remarkable speed of progress in the area of RCM in the recent years, this selectivity issue should find its solution, through either development of new selective catalyst systems or discovering more optimized reaction conditions including modification of substrate types.

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