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Open Access Journal of Agricultural Research
ISSN: 2474-8846

An Overview on Ring Closing Metathesis Reaction and its Applications

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Mini Review

Volume 3 Issue 10

Received Date: October 16, 2018

Published Date: October 25, 2018

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Introduction

Carbon-carbon bond forming reactions are the most important class of reactions in organic synthesis. Among them, in recent years, ring-closing metathesis (RCM) has gained much of attention due to its success for the synthesis of macro lactones. In many cases, ring closing metathesis has been used as the key step, owing to its fundamentally convergent character [1]. Therefore, RCM reaction is documented as one of the most straight-forward and reliable method for the formation of large ring systems and compares favorably to all current synthetic alternatives. In this review, a brief description of ring-closing metathesis (RCM) reaction has been discussed.

Olefin metathesis is an organic reaction that entails the union of fragments of alkenes (olefins) by the scission and regeneration of carbon-carbon double bonds [1]. Olefin metathesis has become a strong and potent synthetic technique and is a powerful method for the clean construction of innumerable classes of chemical architectures [1-8]. The successful applicability of the reaction in the total synthesis of natural products and in commercial scale led to the awarding of Nobel Prize in Chemistry to the pioneers in olefin metathesis: Prof. Yves Chauvin, Prof. Robert H. Grubbs, and Prof. Richard R. Schrock. The salient features of the these catalyst are functional group tolerance, shelf stable and their ability to be handled without inert atmosphere, have propelled this synthetic methodology in to the front runner of carbon-carbon bond forming methods. Therefore herein, we willdiscusse briefly about the ruthenium alkylidenes participation in olefin metathesis reaction [2-8].

Metathesis reaction represents a bimolecular process involving the exchange of bonds between the two reacting chemical species and the olefin metathesis is a reaction which involves the redistribution of olefin bond. The term metathesis was first introduced by Colderon in 1967 although this reaction was initially observed in 1950 during the study on Ziegler-Natta polymerization process. The first report of the process involving olefin metathesis was reported by Eleuterio. Traditional catalysts are prepared by a reaction of the metal halides with alkylatiing agents. Historically, olefin metathesis has been studied both from a mechanistic viewpoint and in the context of polymer synthesis [9-11].

Modification of Catalyst

Modern catalysts are well-defined organometallic compounds that come in to two main categories, commonly known as Schrock catalysts and Grubbs' catalysts. Schrock catalysts are molybdenum (VI) and tungsten(VI) based alkylidenes. Schrock entered the olefin metathesis field in 1979 as an extension of work on tantalum alkylidenes [12]. Schrock in 1990, prepared the alkylidenes for olefin metathesis and in 1993, prepared the asymmetric catalyst in which the saturated part was replaced with a binol ligand (Figure 1) [13].

Utilization of the so called catalyst in different type of metathesis reactions, resulted several types of olefin metathesis processes.

Some important classes of olefin metathesis include:

- Cross Metathesis (CM)
- Ring-Opening Metathesis (ROM)
- Ring-Closing Metathesis (RCM)
- Ring opening metathesis polymerisation (ROMP)
- Acyclic diene metathesis (ADMET)
- Ethenolysis

Cross-metathesis (CM) and Ring closing metathesis (RCM) reactions are widely used in total synthesis of many complex bioactive natural products. Herein, a brief discussion about CM and RCM reactions has been given.

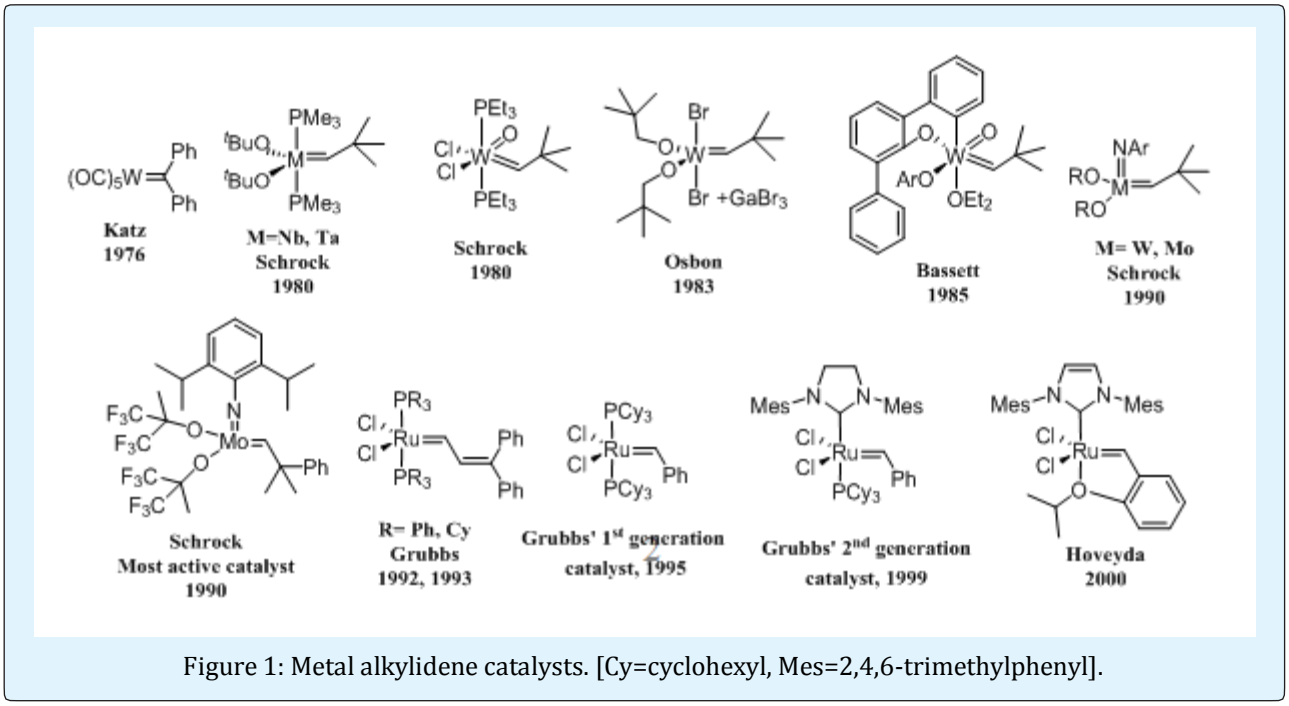

Figure 1: Metal alkylidene catalysts. [Cy=cyclohexyl, Mes=2,4,6-trimethylphenyl].

Cross-Metathesis (CM)

Carbon-carbon bond construction is an interesting part of organic chemistry. Number of protocols are reported for the construct C-C bond. Olefin metathesis has come to the fore in recent years owing to the wide range of transformations that are possible with commercially available and easily accessible catalysts. Consequently, olefin metathesis is now widely considered as one of the most powerful synthetic tool in organic chemistry. Until recently the intermolecular variant of this reaction, cross-metathesis, has been neglected despite its potential. With the evolution of new catalysts, the selectivity, efficiency, and functional-group compatibility of this reaction has improved to a level that was unimaginable just a few years ago. These advances, together with a better understanding of the mechanism and catalyst–substrate interactions, have brought to a stage where more and more researchers are employing cross-metathesis reactions in multistep procedures and in the synthesis of natural products. The recent inclusion of alkynes and hindered bi-cyclic olefins as viable substrates for bimolecular metathesis coupling, the discovery of enantioselective cross-metathesis and cross-metathesis in water was also reported. Progress in the development of the metathesis reaction has been directly correlated to improvements in the functional group compatibility and the reactivity of the catalysts. Cross metathesis reactions have numerous advantages, typical of modern olefin-metathesis reactions *i.e.* to carry out this reaction 1–5 mol% of catalyst required and high yields can obtain under mild conditions in relatively short reaction times, a wide range of functional groups are tolerated, with minimal substrate protection necessary, this is a well adoptable process for industrial applications due to its reversibility character and relatively atom-economic and ethylene is usually the only by product which is a gas, the olefin substrates are generally easier and less expensive to prepare than those associated with other common catalytic C-C bond-forming reactions (e.g. unsaturated

boranes, stannanes, halides, triflates), the olefinic products are suitable for further structural elaboration (e.g. hydrogenation, epoxidation, halogenation, cycloaddition), high levels of chemo, regio and stereoselectivity can be attained.

Cross-metathesis between two acyclic olefins offers interesting possibilities for synthesizing higher-substituted alkenes. The use of highly substituted asymmetric olefins is not practical because of the expected complex spectrum of products. Use of terminal olefins in the formation of volatile ethylene as a byproduct provides the driving force for the reaction. The volume of work reported in the areas of RCM, ROMP, and novel combinations thereof has dramatically over shadowed that reported for olefin cross-metathesis (CM). This unique method for the intermolecular formation of carbon-carbon double bonds has not yet found wide spread application in organic synthesis because general reaction conditions that give high product and *trans/cis* selectivity have not been developed. The simplified CM reaction between two terminal olefins is depicted below.

Mechanism of Cross-Metathesis

Hérisson and Chauvin first proposed the widely accepted mechanism of transition metal alkene metathesis. The direct [2+2] cycloaddition of two alkenes is formally symmetry forbidden and thus has high activation energy. The Chauvin mechanism involves the [2+2] cycloaddition of an alkene double bond to a transition metal alkylidene to form a metal-cyclobutane intermediate. The metal-cyclobutane produced then cyclorevert to give either the original species or a new alkene and alkylidene (Figure 2). Interaction with the d-orbitals on the metal catalyst lowers the activation energy enough that the reaction can proceed rapidly at modest temperatures.

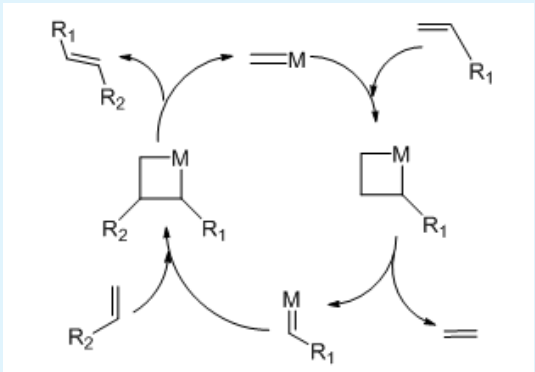

Figure 2: General mechanism of alkene metathesis reactions.

Cross-metathesis is a powerful method for the rapid synthesis of simple and complex olefinic building blocks. Grubbs catalyst and Hoveyda-Grubbs catalyst are generally used for this reaction to lead high yield of desired product. Some examples by using Grubbs II generation catalyst were shown figure 3.

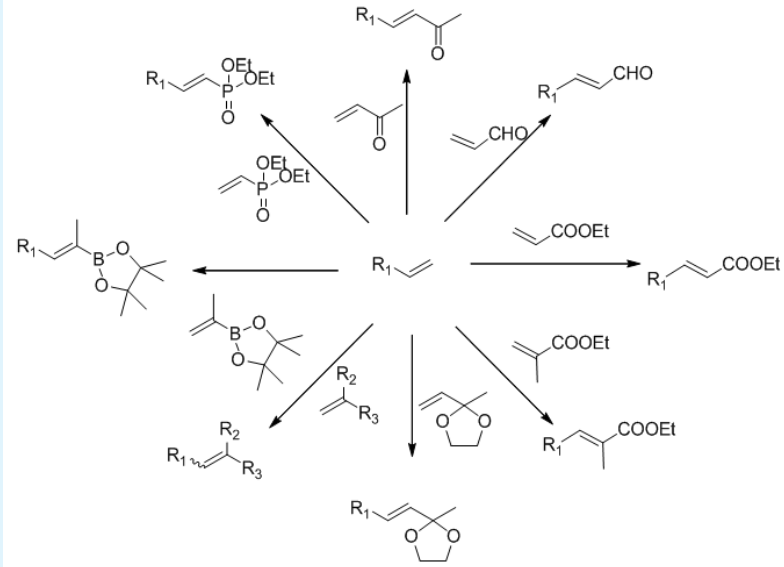

Figure 3: Examples by using Grubbs II generation catalyst.

Ring-Closing Metathesis (RCM)

The olefin metathesis reaction has been known since the 1960s, but it was not until the early 1990s that this transformation became an important tool in synthetic organic chemistry. It was thus in 1992 that Grubbs and Fu published two seminal papers describing the application of ring-closing metathesis (RCM) to the synthesis of simple five, six, and seven memebered monocyclic systems containing oxygen and nitrogen atoms using a molybdenum catalyst that has been first prepared by Schrock [14,15]. RCM became an interesting and exciting protocol for total synthesis of number of natural products after its discovery. Ruthenium and the molybdenum catalysts are very reactive and well tolerance behavior towards all types of functional groups, but the Mo-based complexes suffer the potential disadvantage of being more air and moisture sensitive. Therefore ruthenium-based catalysts were treated as ideal catalyst worldwide.

The high selectivity and reactivity of all ruthenium catalyst for carbon-carbon π-bonds reduces protecting group manipulations while enabling the use of RCM as an excellent alternative to other ring-forming reactions for the efficient construction of complex cyclic targets having a variety of ring sizes. The ring-closing metathesis allows synthesis of 5- to 30-membered cyclic alkenes. The *E/Z*-selectivity depends on the ring strain.

Chauvin's Mechanism for RCM

Chauvin suggested the following mechanism, which was universally accepted.

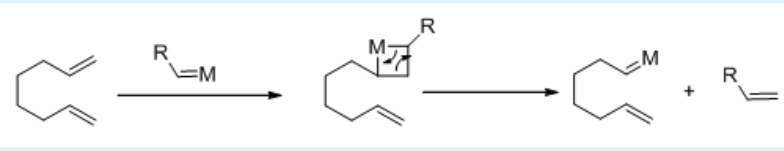

Figure 4: Scheme 1.

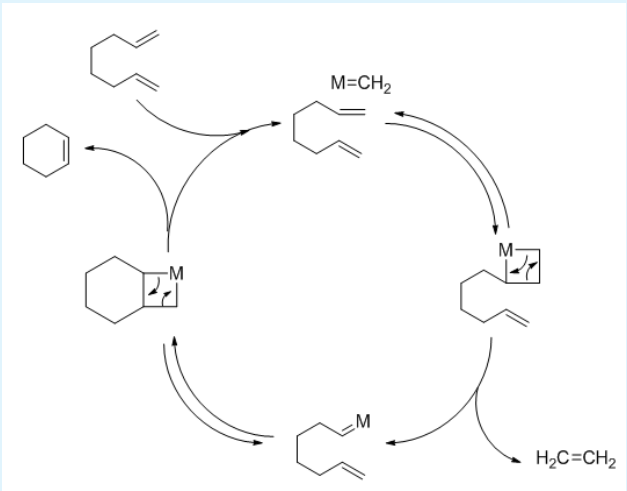

Figure 5: Catalytic cycle.

It is now generally accepted that the mechanism of both cyclic and acyclic olefin metathesis proceeds through a series of metallacyclobutanes and carbene complexes. Although the relative stabilities of the carbenes and metallacyclo butanes can change with (Diagram for most commonly employed different types of alkene metathesis reactions.)reaction conditions, catalyst composition and alkene substitution, the mechanism of olefin metathesis appears to be the same for all catalysts (Figure 4) [14,15]. The key intermediate is a metallacyclobutane, which can undergo cycloreversion either towards products or back to starting materials.

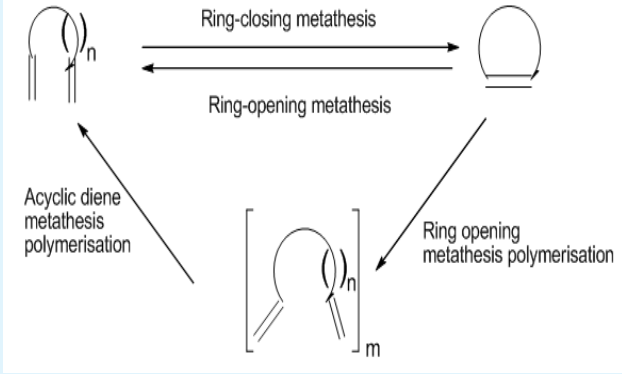

Figure 6: Scheme 2.

As with any other cyclization method, the synthetic efficiency of RCM is limited by the competition between intramolecular ring-closing and intermolecular oligomerization reactions. Olefin metathesis is represented as a fully reversible set of [2 + 2] cyclo-addition-cycloreversion equilibria, employing a thermodynamic distribution of "living" metathesis products [16]. The emergence of metathesis reactions in chemical synthesis over the last few years has been dramatic. It has been delightful to review the field and highlight some of its most exciting applications in total synthesis. Some excellent use of ring closing metathesis has been demonstrated bellow.

Olefin ring closing metathesis and hydrosilylation reaction in aqueous medium by Grubbs second generation ruthenium catalyst was demonstrated by Verma, et al. (Scheme 3) [17].

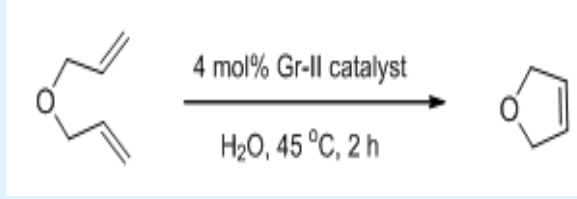

Figure 7: Scheme 3.

The total synthesis of (−)-muricatacin has been achieved *via* highly regioselective and stereoselective tandem ring-closing/cross metathesis reaction in which both lactone formation and chain extension was accomplished (Scheme 4) [18].

Figure 8: Scheme 4.

A straightforward total synthesis of the cyclooctenoidsesquiterpenedactylol has been achieved *via*ring-closing metathesis (RCM) of the resulting dienes to form the cyclooctene ring using Schrocks molybdenum carbene as a precatalyst (Scheme 5) [18].

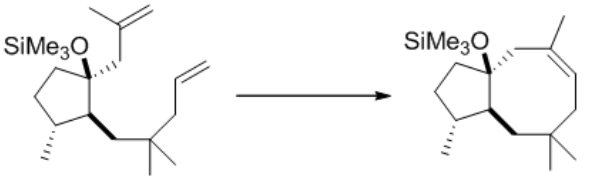

Figure 9: Scheme 5.

The first total synthesis of elatol which is a halogenated sesquiterpene in the chamigrene natural product family has been achieved a ring-closing olefin metathesis to concomitantly form the spirocyclic core as well as the fully substituted chlorinated olefin (Scheme 6) [19].

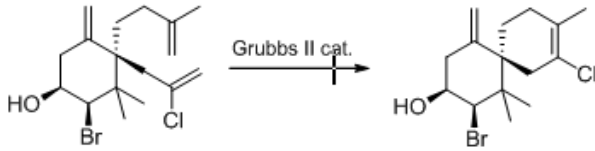

Figure 10: Scheme 6.

The total synthesis of the novel lactone natural product octalactin A was done. The key step involves the facile construction of the eight-membered lactone core via ring-closing metathesis (RCM) (Scheme 7) [19].

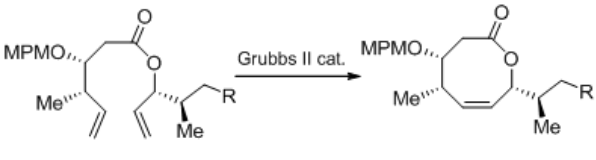

Figure 11: Scheme 7.

Racemic and enantiopure targets containing the 6,8-dioxabicyclo [3.2.1] octaine skeleton, was conveniently synthesized from monocyclic diene precursors using an intramolecular ruthenium-catalyzed ring-closing metathesis reaction as the key step (Scheme 8) [20].

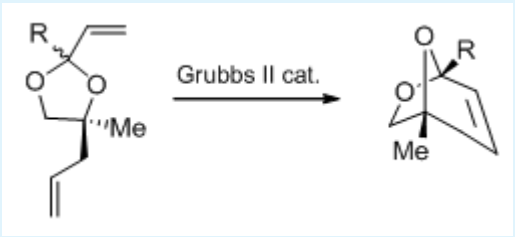

Figure 12: Scheme 8.

The ring closing reaction was widely demonstrated in 10 membered lactones. In this context, we are going to discuss about some similar lactones. The total syntheses of stagonolide B and its 4-epimer were carried out to probe into how the relative stereochemistry of allylic hydroxy groups and their protecting groups influence the efficiency of the ring closing metathesis (Scheme 9) [21].

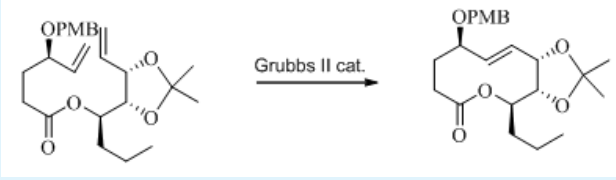

Figure 13: Scheme 9.

Ring-closing metathesis to form a diene system in the total synthesis of pochonin C was completed by Winssinger and co-workers in 2004 (Scheme 10) [22].

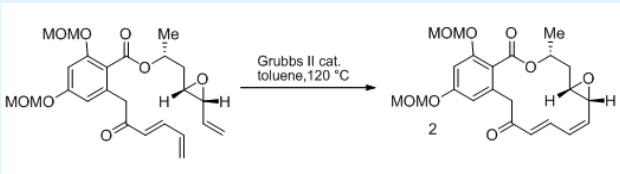

Figure 14: Scheme 10.

Wood and co-workers in 2004 had reported the total synthesis of Ingenol via ring-closing-metathesis reaction (Scheme 11) [23].

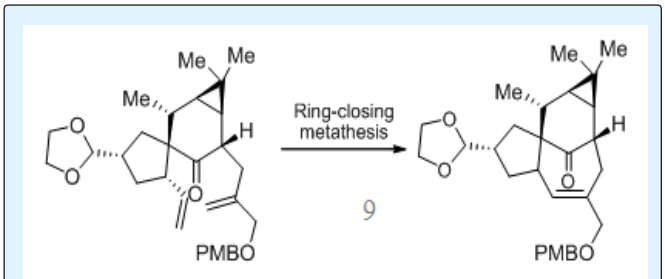

Figure 15: Scheme 11.

Ring-closing-metathesis reactions in the total synthesis of amphidinolide A and its stereoisomers was successfully demonstrated by Maleczka and co-workers (Scheme 12) [24].

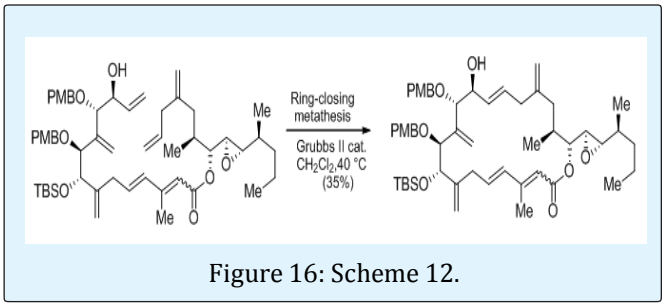

Figure 16: Scheme 12.

Raghavan and Ganapathy Subramanian demonstrated the power of protecting groups in the product distribution using ring closing metathesis to obtain a key fragment of (-)-mucocin(Scheme 13) [25].

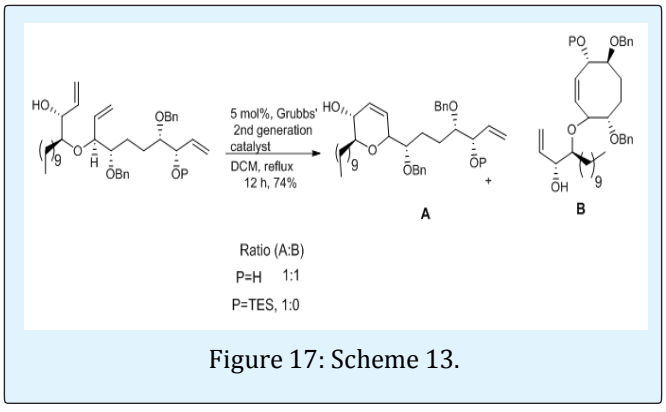

Figure 17: Scheme 13.

In 2016, Raghavan and coworkers reported the synthesis of (+) and (-)-cyclophellitol, Conduritol and conduramine from a common intermediate obtained using stereoselective alkylation followed by ring closing metathesis approach (Scheme 14) [26].

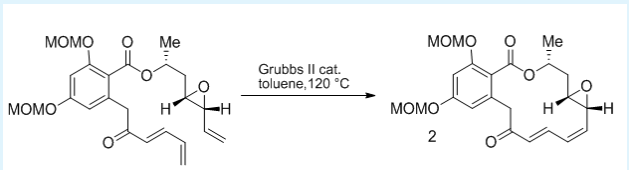

Figure 18: Scheme 14.

Conclusion

The ring closing metathesis approach has emerged as a powerful tool for organic chemists to achieve their targets in an elegant way. Using this technique in synergy with creativity and mechanistic understandings have helped them in accomplishing many total synthesis, advanced intermediates in drug discovery. More discoveries in natural product synthesis can be realized and will be reported in future using this approach by chemists from all over the world.

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