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SYNTHESIS OF FIVE- AND SIX-MEMBERED HETEROCYCLIC COMPOUNDS BY THE APPLICATION OF THE METATHESIS REACTIONS

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Abstract - This review describes the formation of five- and six-membered heterocyclic rings in various compounds by ring closing diene and enyne metathesis.

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1. INTRODUCTION

Since the 1960s the famous olefin metathesis has been known, but it was not the early 1990s that this conversion became an important tool in synthetic organic chemistry. Grubbs and Fu published two significant papers¹ indicating the application of ring-closing metathesis (RCM) for the synthesis of simple five- six- and seven-membered monocyclic systems bearing oxygen and nitrogen atoms by utilizing a molybdenum catalyst that had been first prepared by Schrock. Metathesis is the exchange of parts of two substances. In the generic reaction,



B has changed position with C. The name “olefin metathesis” was first given by Calderon.² Olefin metathesis is truly an amazing reaction in which the strongest bond in an alkene, the C=C double bond, is broken and remade. In 1971, Chauvin proposed³ a mechanism for the olefin metathesis that is beautiful in its simplicity: a metal carbene comes together with an alkene to reversibly form a four-membered ring metallocycle. This metallocyclobutane ring can open in a different way to generate a new carbene complex and a new alkene (Figure 1).

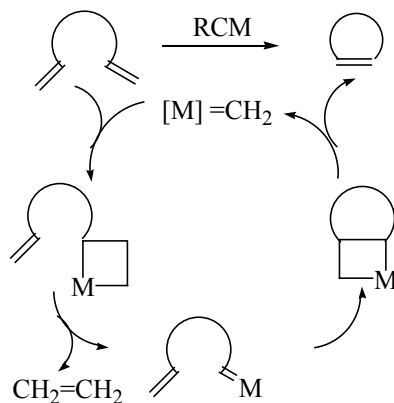


Figure 1 Chauvin proposed mechanism.

Other supports for Chauvin's metallocyclobutane mechanism came from the research group of Robert H. Grubbs.⁴ With understanding of the basic mechanism of olefin metathesis the new challenge was to construct efficient catalyst that would tolerate the various functional groups in the typical organic molecules. Though olefin metathesis has been known since 1960's, but this area of research became familiar to us after the discovery of the air stable Grubbs' catalysts (1992 and 1995). The number of applications of this reaction has dramatically increased in the past few years due to tremendous improvements in the functional group compatibility and reactivity of the catalysts.

2. GENERAL ASPECTS OF METATHESIS REACTION

Olefin metathesis is a unique carbon skeleton redistribution in which unsaturated carbon- carbon bonds are rearranged in the presence of metal carbene complexes. With the advent of efficient catalysts, this

reaction has emerged as a powerful tool for the formation of C-C bonds in synthetic organic chemistry. Although alkene metathesis constitutes, for example, the most widely utilized type of metathesis reaction, recent years have witnessed the discovery and development of a number of related processes employing a broader range of substrates. Prominent amongst these are the enyne metathesis, which involves the union of an alkyne with an alkene to form 1,3-diene system. Enyne metatheses are wholly atom economical and are, therefore, driven by enthalpic rather than entropic factors. On the basis of mechanistic studies on enyne metathesis, a Chauvin-type³ mechanism involving an 'yne-then-ene' (Figure 2) sequence was proposed. Very recently Lloyd-Jones⁵ reported an alternative 'ene-then-yne' mechanism for Ru-catalyzed enyne ring closing metathesis reaction for which ethylene can catalyze the reaction.

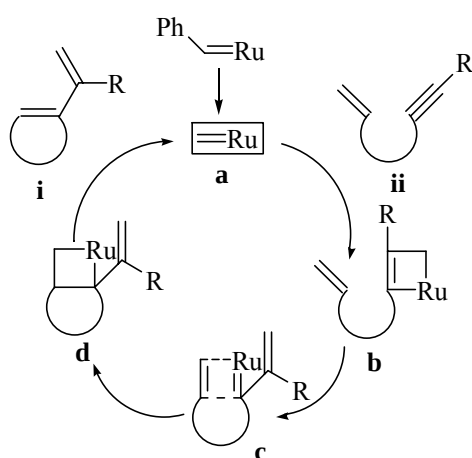


Figure 2 'Yne-then-ene' mechanism for Ru-catalyzed enyne ring closing metathesis.

Ring closing metathesis has been developed into one of the most powerful and reliable method for ring formation. A variety of ring systems,⁶⁻⁸ such as regular, medium and large carbo- or heterocyclic, can be constructed by the application of ring-closing metathesis reaction. Selectivity issues can arise in the metathesis chemistry when more than one ring is formed during a ring closing process. Recently, relay RCM has been developed as a method to overcome both the reactivity and selectivity issues in the metathesis chemistry.⁹ The presence of heteroatom in the substrate leads to a variety of results.¹⁰⁻¹⁹ Nitrogen is generally not tolerated unless non basic functional groups such as tosylamides are used. Certain metathesis reactions of amine-containing compounds were carried out with one equivalent of *p*-toluenesulfonic acid to prevent coordination of the electron pair on the nitrogen atom to the catalysts.¹⁴ Oxygen appears to be beneficial for the metathesis reactions.¹⁵ Surprisingly, however, very limited examples¹⁹ of substrates containing sulfur atom have so far been reported. The limited number of examples of metathesis with sulfur containing substrates can be partly explained by the fact that middle to late transition metals used as catalyst may interact favorably with the soft sulfur atom.

A number of reviews²⁰⁻²³ on RCM have been published to date, but none of these focuses solely on the formation of five- and six-membered heterocyclic compounds.^{24,25} In this review, important recent advances related to the formation of regular rings *via* RCM is discussed based on the reports published in

the literature from 2004 to 2006. An attempt has been made to summarize the reaction conditions, such as choice of catalyst, solvent, temperature, concentration and reaction time, which are crucial for ring closing metathesis reactions. In general this review is organized into oxygen and nitrogen categories and further divided according to the each functional group subclass. It is designed to illustrate typical examples and situations where olefin metathesis was, and can be, used to construct various five- and six-membered heterocyclic compounds.

2.1 CATALYSTS USED FOR THE METATHESIS AND THEIR RECENT MODIFICATIONS

The success of metathesis reaction is largely due to the advent of today's readily available catalyst systems that display high activity and excellent functional group tolerance. The three catalysts most routinely used by organic chemists (all of which are commercially available) are shown in Figure 3.

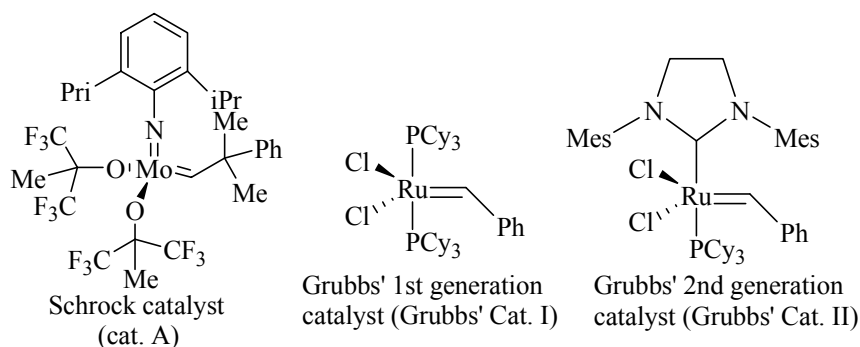


Figure 3 Three important catalysts for RCM reaction.

One of the most important catalyst systems developed by Schrock and co-workers is the alkoxyimido-molybdenum complex represented by **A**²⁶ in Figure 3. Major advances of this system are its high reactivity towards a broad range of substrates with many steric and electronic variations. The alkoxides in the [Mo] system can readily be altered to adjust their activities. Critical drawbacks of this Mo-based carbene complexes are however its moderate to poor functional group tolerance, high sensitivity to air, moisture or even to trace of impurities present in solvents, thermal instability on storage and expenses. Grubbs and coworkers subsequently introduced ruthenium-based carbene complexes, initially optimized to Grubbs' catalyst I, as general and practical catalysts for metathesis. Although less reactive than the Schrock Mo-based system **A**, the first generation Grubbs' catalyst exhibits much greater functional group tolerance and expanded the scope of olefin metathesis. In particular, the replacement of one of the phosphine ligand in Grubbs' catalyst I with *N*-heterocyclic carbene ligands,²⁷ increases the catalytic activity, thermal stability and functional group tolerance of the complex. The second generation Grubbs' catalyst engenders metathesis reaction with particularly high levels of activity, in certain cases approaching that the Schrock system **A**, and with a unique reactivity profile that nicely complements both earlier Grubbs' catalysts I and II. Grubbs' detailed mechanistic studies provided evidence that phosphine dissociation to give a reactive 14-electron ruthenium intermediate was required for reaction with alkene. Highly active NHC catalysts were synthesized by the groups of Herrmann,²⁸ Nolan,²⁹ and Fürstner.³⁰

Along this line Hoveyda,³¹ Hoffmann,³² and Blechert^{33,34} reported other related, very active, stable and functional group tolerant ruthenium metathesis catalysts. The first Hoveyda metathesis catalyst is derived from Grubbs' 1st generation catalyst. It bears only one phosphine and a chelating carbene ligand. The second one bears in addition, an *N*-heterocyclic carbene ligand instead of the phosphine (Figure 4).

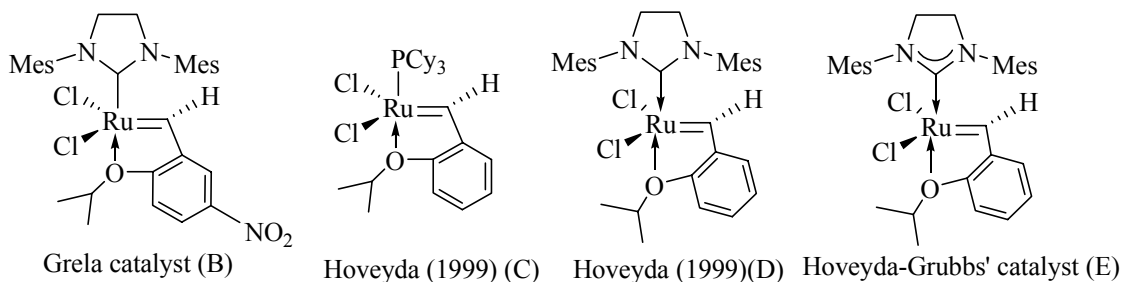


Figure 4 Different types of Ru catalysts used in the RCM/RCEM reactions.

The family of Hoveyda catalysts whose activity compares with that of the 2nd generation Grubbs' catalyst are especially useful for difficult cases of metathesis of polysubstituted olefins and selective cross metathesis in which homo coupling needs to be avoided.^{35,36} Grela *et al.* reported³⁷ variations of the Hoveyda catalyst with increased efficiency (active even at 0 °C) when aryl group of the benzylidene ligand bears a nitro group in the meta or para positions or two methoxy substituents. Grela's group has recently introduced³⁸ a new air stable ruthenium olefin metathesis catalyst derived from inexpensive bisphenol-S with Hoveyda-Grubbs' catalyst. Grela's successful idea was based on the destabilization of the Ru-O(ether) chelation that generates the catalytically active 14-electron species. They have also developed³⁹ a novel pyridinium-tagged ruthenium complex to perform metathesis reaction in aqueous as well as ionic medium. Following the discovery of the original Grubbs' catalyst, much of research^{40,41} in this area has focused on increasing the stability, selectivity and particularly the activity of ruthenium olefin metathesis catalysts. Grubbs' recently developed⁴² a ruthenium based asymmetric olefin metathesis catalyst, containing chiral, and monodentate *N*-heterocyclic carbene ligands. These are shown to be promising due to their high activity, low catalyst loading, ease of handling and different functional group tolerance relative to that of the molybdenum catalysts. Grubbs's success story has encouraged the search for ruthenium metathesis catalyst and other ruthenium structures and variations have been published,⁴³⁻⁴⁵ including water-soluble ones,⁴⁶ reaction carried out in ionic liquids^{47,48} and on solid supports.⁴⁹⁻⁵² Another successful variation of the Ru-benzylidene catalysts was reported by Blechert⁵³ whose strategy to sterically destabilize the Ru-O (ether) bond was to introduce an aryl (phenyl or naphthyl) substituent on the benzylidene aryl in the *ortho*-position relative to the O-(ether). Very recently Buchmeiser *et al.*⁵⁴ also reported a derivative of Schrock catalyst containing fluorinated carboxylates which displays moderate metathesis activity in ROMP, cyclopolymerization and RCM upon addition of quinuclidine as a base. Though various ruthenium catalysts have been widely used for ring closing olefin metathesis (RCM), ring opening metathesis polymerization (ROMP) and acyclic cross metathesis, one major concern is the

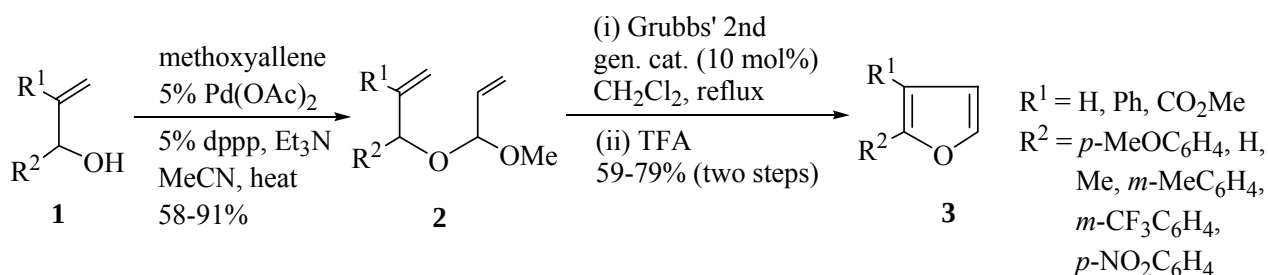
removal of colored, toxic ruthenium metal byproducts from the desired products even after purification on silica gel column chromatography several times. Kim *et al.*⁵⁵ introduced an efficient method for the removal of dark brown ruthenium byproducts from the reaction mixture. Grela *et al.* recently reported their new metathesis catalyst⁵⁶ which exhibited high affinity for silica gel compared to the parent Hoveyda-Grubbs' catalyst when CH_2Cl_2 is used as eluant. Utilizing this advantage, they have designed⁵⁷ an efficient new strategy for homogenous Ru-catalyst phase-separation and recovery, which provided products of excellent purity. The ruthenium complex induces both the metathesis and non-metathesis processes,⁵⁸ being active in non-metathesis as a result of a simple conversion of Ru-alkylidene into Ru-hydride species. Grubbs' and co-workers have recently observed⁵⁹ that decomposition of the catalyst to a hydride dinuclear carbene complex (HRuCRu) could be responsible for the undesirable isomerization during difficult olefin metathesis. When a substrate cannot give a product by metathesis, non-metathetic reactions proceed efficiently or complete recovery of the starting materials was observed. These discoveries actually expanded the synthetic utility of these catalysts beyond olefin metathesis.^{60,61} Presence of NHC (*N*-heterocyclic carbene ligand) in the ruthenium carbene complex could also be the key component for cycloisomerization.⁶¹

3. SYNTHESIS OF OXYGEN HETEROCYCLES

In recent years significant activities have been observed in the synthesis of oxygen heterocycles. The versatility of the molybdenum and ruthenium catalysts in cyclization of different ring sizes was amply demonstrated even in the presence of diverse functionalities. Substrates containing oxygen are found to be beneficial for the metathesis in some studies,^{15,16} while in other cases no influence is observed.

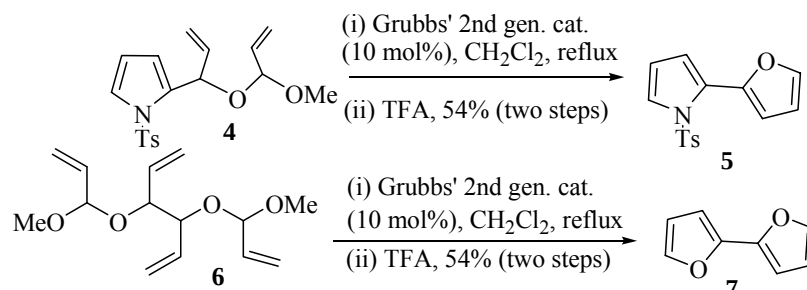
3.1 SYNTHESIS OF FIVE-MEMBERED CYCLIC ETHERS

Synthesis of substituted furans by ring closing metathesis was described by Donohoe *et al.*⁶² Precursors **2** were cyclized by Grubbs' catalyst II (10 mol%) and these heterocycles were finally aromatized to **3** simply by adding trifluoroacetic acid (Scheme 1). To avoid the purification problem due to the non-polar phosphane residue from the catalyst and non-polar aromatic products, the RCM reaction was quenched and more polar dihydrofuran product was first purified by chromatography and finally aromatized by the reaction with TFA (Scheme 1).



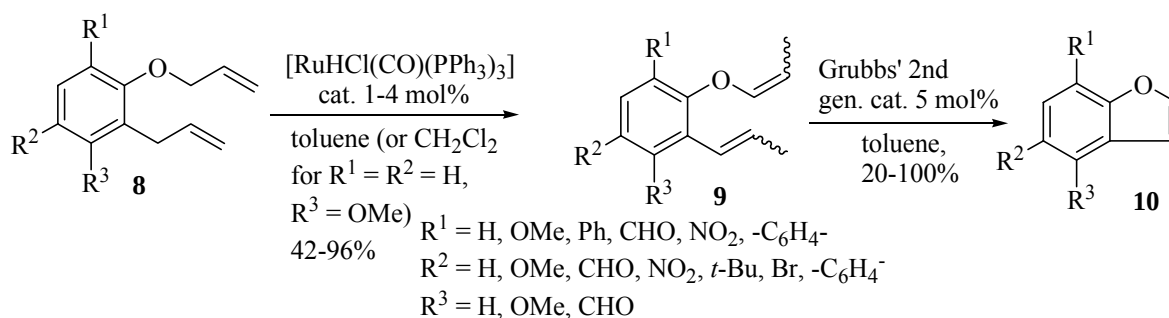
Scheme 1 RCM for the synthesis of 2,3-disubstituted furan derivatives.

Extension of this strategy towards the synthesis of some linked biaryl system was attempted and successfully synthesized pyrrole-furan biaryls **5**. Further, a fully aromatized bis-furan system **7** has been synthesized by extending the same protocol (Scheme 2).



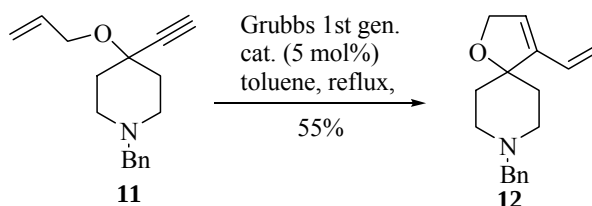
Scheme 2 RCM for the synthesis of pyrrole-furan and bis-furan system.

Benzofuran skeleton is a well-known structural unit in naturally occurring compounds possessing medicinal values. van Otterlo group⁶³ reported that benzofurans **10** could also be accessible from the corresponding *O*- and *C*-allyl phenols **8** using the isomerization technique prior to RCM as reported previously for the synthesis of 2*H*-chromenes in moderate to excellent yields.⁶⁴ They also reported the synthesis of substituted benzofurans from the corresponding *O,C*-diallyl benzenes **8** using 5 mol% ruthenium catalyst-mediated isomerization followed by ring closing metathesis with Grubbs' catalyst II (Scheme 3). Using the same isomerization-RCM strategy the synthesis of benzodioxene⁶⁴ starting from catechol was also reported.



Scheme 3 Variously substituted benzofuran synthesis by RCM.

Recently, Pujol *et al.* reported⁶⁵ the synthesis of spiro-piperidines **12** as potentially valuable functionalized 1,3-dienes starting from *N*-benzyl piperidone. The dihydrofuran ring of **12** could be constructed at the last stage of the synthesis by intramolecular RCM. Incidentally, this is the first report of the synthesis of spiro furo piperidines using metathesis reaction (Scheme 4).



Scheme 4 Synthesis of spiro-piperidines by RCM.

The synthesis of Solamin (**13**) has attracted great attention to the synthetic chemists due to its marked antitumor, antimalarial, pesticidal and immunosuppressive properties. The synthesis of central tetrahydro-

furan core was achieved⁶⁶ by means of a ring closing metathesis using Grubbs' catalyst I or II (Figure 5).

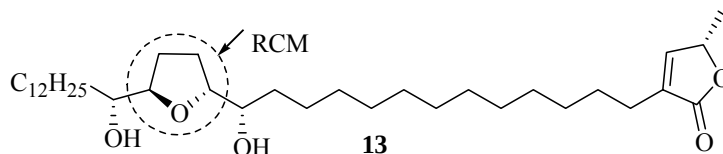
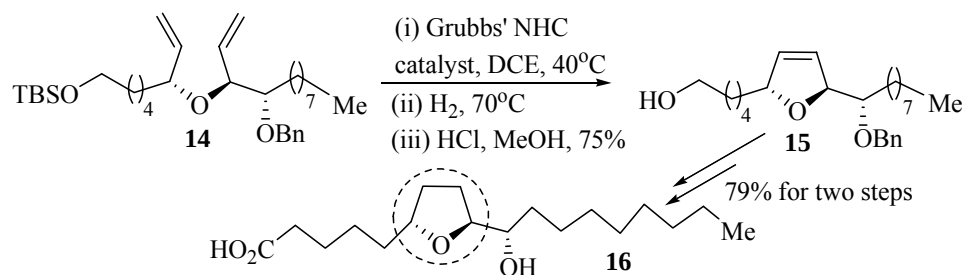


Figure 5 solamin

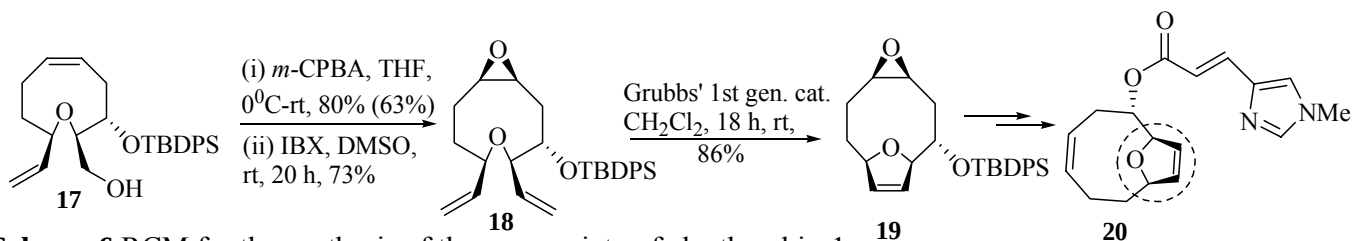
Another structurally related natural product squamostolide was also recently synthesized⁶⁷ via highly selective tandem ring-closing/cross metathesis step in which lactone formation and fragment coupling were accomplished.

Evans *et al.*⁶⁸ reported the stereospecific rhodium catalyzed allylic etherification with secondary alkenyl alcohols along with ring closing metathesis to provide a stereospecific route to the synthesis of *cis*- and *trans*-2,5-disubstituted tetrahydrofuran **15**. This study also demonstrated that a dramatic enhancement of the stereospecificity is possible by the modification of the Cu(I) alkoxide with trimethylphosphite. The potential of this protocol has been demonstrated by a seven step total synthesis of gaur acid **16** of which RCM is the key step (Scheme 5).



Scheme 5 RCM as the key step for the synthesis of the core moiety gaur acid.

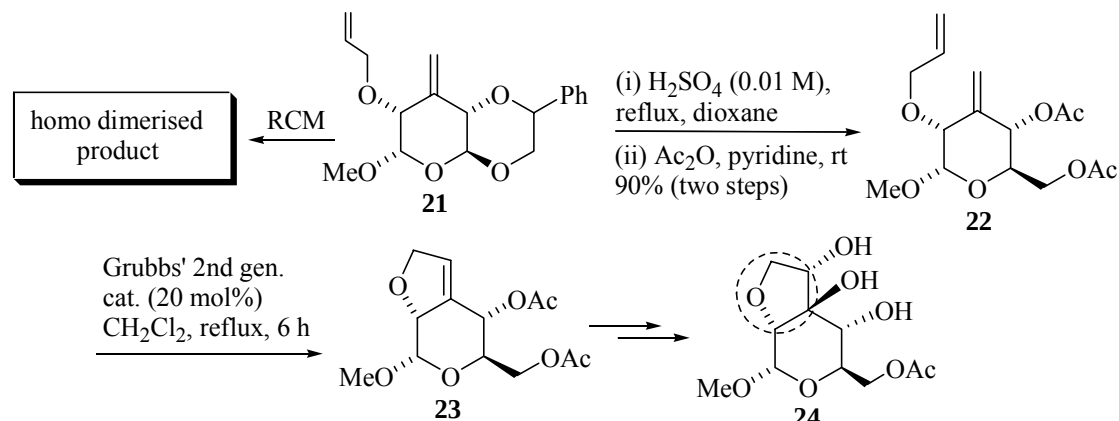
The synthesis of structurally diverse uronic acid side chain attached to the bicycle core **20** was reported by Holmes *et al.*⁶⁹ by the application of sequential Claisen rearrangements and ring closing metathesis strategy (Scheme 6). The epoxide protected RCM precursor **18** on treatment with Grubbs' catalyst I gave the desired ring-closing product **19** which after two steps gave the targeted bicyclic core **20** in moderate yield.



Scheme 6 RCM for the synthesis of the core moiety of eleutherobin-1.

Miharamycins are the nucleoside antibiotics, which show good activity against the rice blast and other fungal diseases. Etheve-Quelquejeu *et al.*⁷⁰ reported the synthesis of the bicyclic core of the molecule by utilizing ring closing metathesis from 2-*O*-allyl-3-allyl-*C*-ene-ethylene sugar **22**. Replacement of the 4,6-*O*-benzylidene group by protecting acetyl group of the substrates followed by ring closing metathesis with Grubbs' catalyst II afforded the compound **23** which after a sequence of reaction steps gave the

bicyclic moiety of the miharamycin **24** in good yield. Interestingly, 4,6-*O*-benzylidene protected sugar **21** on ring closing metathesis with Grubbs' catalyst I / II gave only the homodimer as a mixture of *cis*- and *trans*-isomer which may be due to intramolecular constrain during the RCM process (Scheme 7).

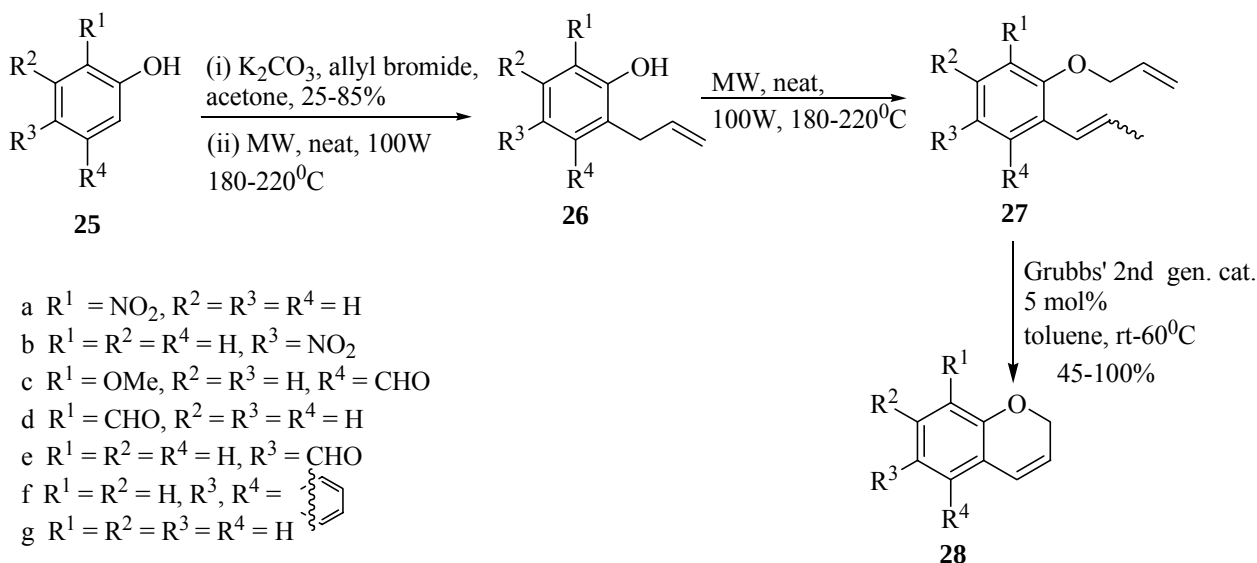


Scheme 7 RCM for the synthesis of the bicyclic core of the miharamycins.

3.2 SYNTHESIS OF SIX-MEMBERED CYCLIC ETHERS

Benzo-fused oxa-bicyclic compounds are ubiquitous in nature and exhibit interesting biological properties. Hence they are interesting scaffolds for drug design. Chromene is one of the subclass of benzo-fused bicyclic compounds, which have potent biological activity and spread over natural products. Grubbs reported the synthesis of 2-*H*-chromenes from 6-allyloxystyrene ring closing metathesis using Grubbs' catalyst I.⁷¹

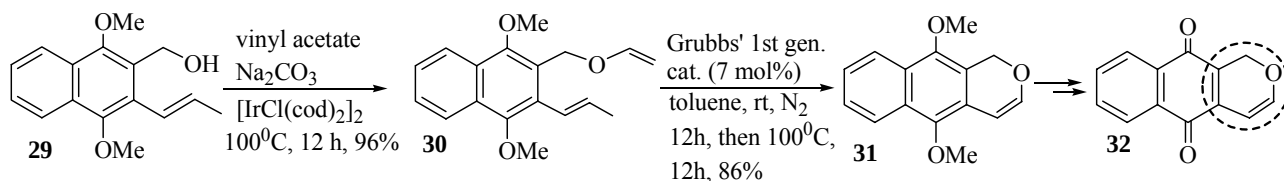
Recently, van Otterlo⁷²⁻⁷⁴ reported the synthesis of 2*H*-chromenes **28** involving an allyl aryl isomerization **27** as one of the key step followed by usual RCM reaction. Modification of the 2-*H*-chromenes skeleton could be readily attainable due to the presence of versatile aldehyde substituents and NO₂ group which can be reduced to amine and makes this procedure a valuable one (Scheme 8).



Scheme 8 Synthesis of 2*H*-chromenes involving an aryl allyl isomerization and RCM.

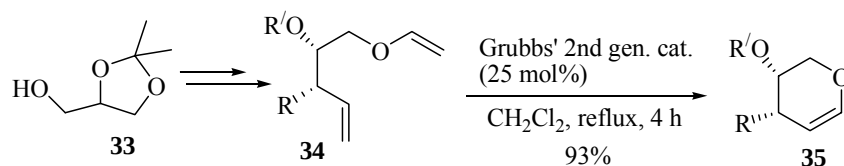
A new synthetic protocol described for the synthesis of naturally occurring antibiotics pentalogin **32** using ring closing metathesis was reported by de Kimpe *et al.*⁷⁵ This was achieved from the precursor **30** by

ring-closing metathesis with Grubbs' catalyst I to afford compound **31** and further oxidation of **31** afforded the target molecule **32** (Scheme 9). The protocol opens a new way for the synthesis of other pyranonaphthoquinone antibiotics.



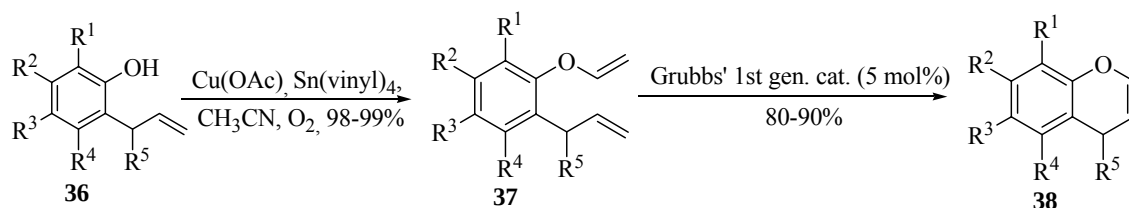
Scheme 9 Synthesis of pentalogin by RCM.

Highly enantioenriched cyclic β -hydroxyallylsilanes have been prepared by Ghosez *et al.*⁷⁶ via enantioselective allylation of unsaturated aldehydes using a chiral allyltitanium reagent followed by ring closing metathesis. This strategy has been successfully demonstrated through enantioselective synthesis of dihydropyrans. The RCM precursor **34** was synthesized starting from (+/-) solketal **33**. A huge consumption of Grubbs' catalyst II (25 mol %) afforded the cyclic vinyl ether **35** (Scheme 10). These dihydropyrans could be useful intermediate for the synthesis of glycomimetics.



Scheme 10 Enantioselective synthesis of dihydropyran by RCM.

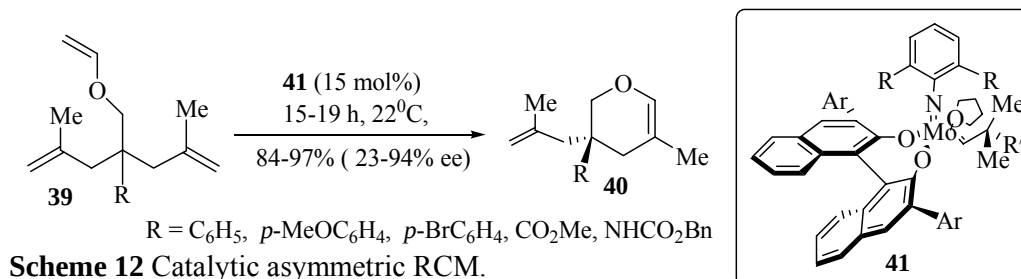
4*H*-chromenes are found as structural units in many natural products. Synthesis of 4*H*-chromenes **38** by RCM using Grubbs' catalyst from substrates having electron rich vinylic olefins is known to be problematic.⁷⁷ van Otterlo reported⁷⁸ the synthesis of this class of compounds by metathesis reaction with phenyl vinyl ethers **37** (Scheme 11).



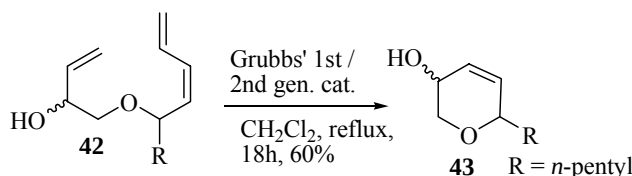
Scheme 11 Synthesis of 4*H*-chromenes **38** by RCM.

Recently, enantioselective synthesis of cyclic enol ether and all carbon quaternary stereogenic centres through catalytic asymmetric ring closing metathesis was reported by Hoveyda *et al.*⁷⁹ Various chiral Mo- and Ru-based catalysts to identify the most effective one was examined. It was found that the Mo-catalyst **41** (15 mol% in benzene) effectively promoted the enantioselective transformation to access various five- and six- membered cyclic enol ethers in up to 94% ee from readily available achiral starting materials. Representative examples of the formation of the cyclic enol ethers through catalytic asymmetric ring-closing metathesis are shown in Scheme 12. Interestingly, these are the first examples of catalytic asymmetric RCM. This protocol was also utilized for the formation of all carbon quaternary stereogenic

centers.

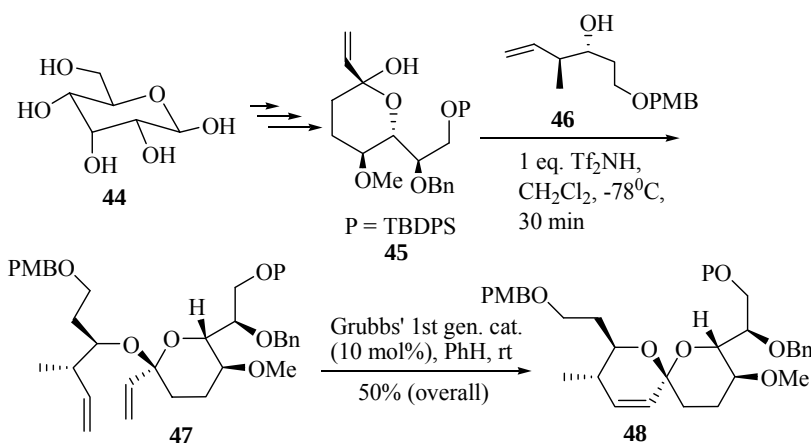


Recently, an interesting example of the formation of small size ring by diene-ene ring closing metathesis of differently substituted pentadienyl ethers and their competition to give either a medium- or small-sized cyclic ethers has been reported by Waldmann *et al* (Scheme 13).⁸⁰ The preference for the formation of smaller ring indicates that the reaction is initiated *via* ruthenium carbene complex formation at the site of the isolated double bond. Further experiments were carried out and observed that small-sized cyclic ethers **43** are thermodynamically controlled and the free hydroxyl group of the diene-ene system **42** does not affect the RCM process. Only six-membered product was obtained. No eight-membered product was isolated.



Scheme 13 Competitive synthesis of five- and six-membered oxa-cycles by RCM.

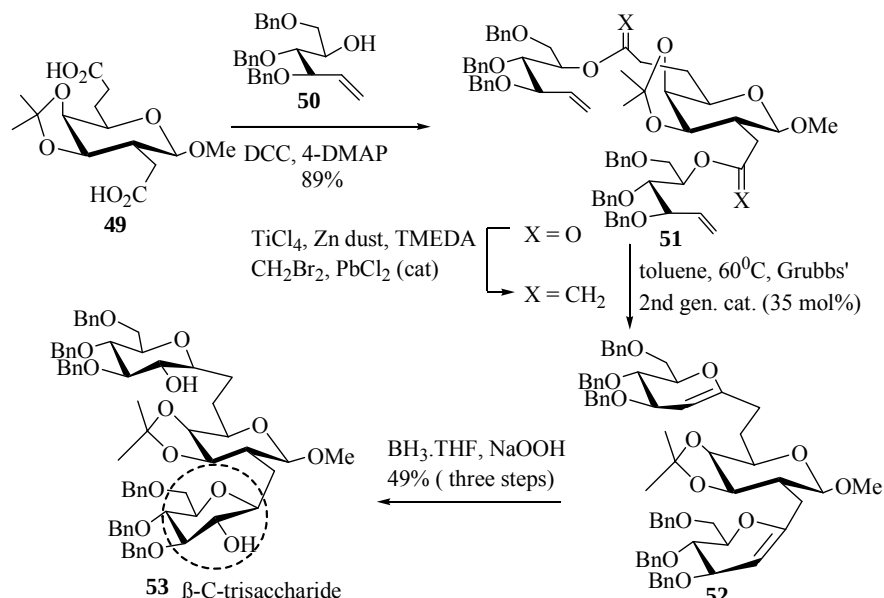
A ketal-tethered ring closing metathesis approach to the construction of spiroketals have been reported by Hsung^{81,82} in the synthesis of C11-C23 fragment of Spirastrellolide A, a novel macrolide from the marine sponge *spirastrellolide coccinea*. In addition to its ability to cause a timely mitotic arrest in cells, spirastrellolide A was shown to exhibit potent inhibitory activity against protein phosphatase 2A. The ring closing metathesis of the precursor **47** was performed by Grubbs' catalyst I (10 mol%) to give the spiroketal **48** (Scheme 14).



C11-C23 fragments of spirastrellolide A

Scheme 14 Ketal-tethered RCM to construct C11-C23 fragments of spirastrellolide.

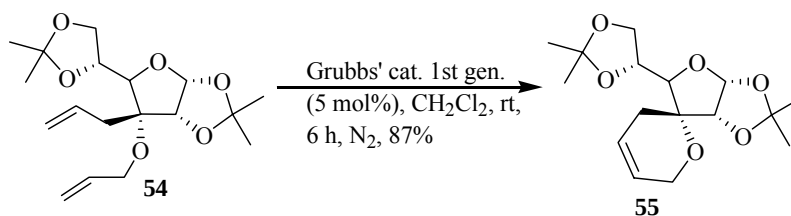
The synthesis of C-glycosides has received considerable attention from both the synthetic and biological point of view. Ring closing metathesis approach is flexible enough to deliver a wide variety of C-glycoside type structure.⁸³



Scheme 15 Enol-ether-olefin RCM approach for the preparation of β -C-trisaccharides.

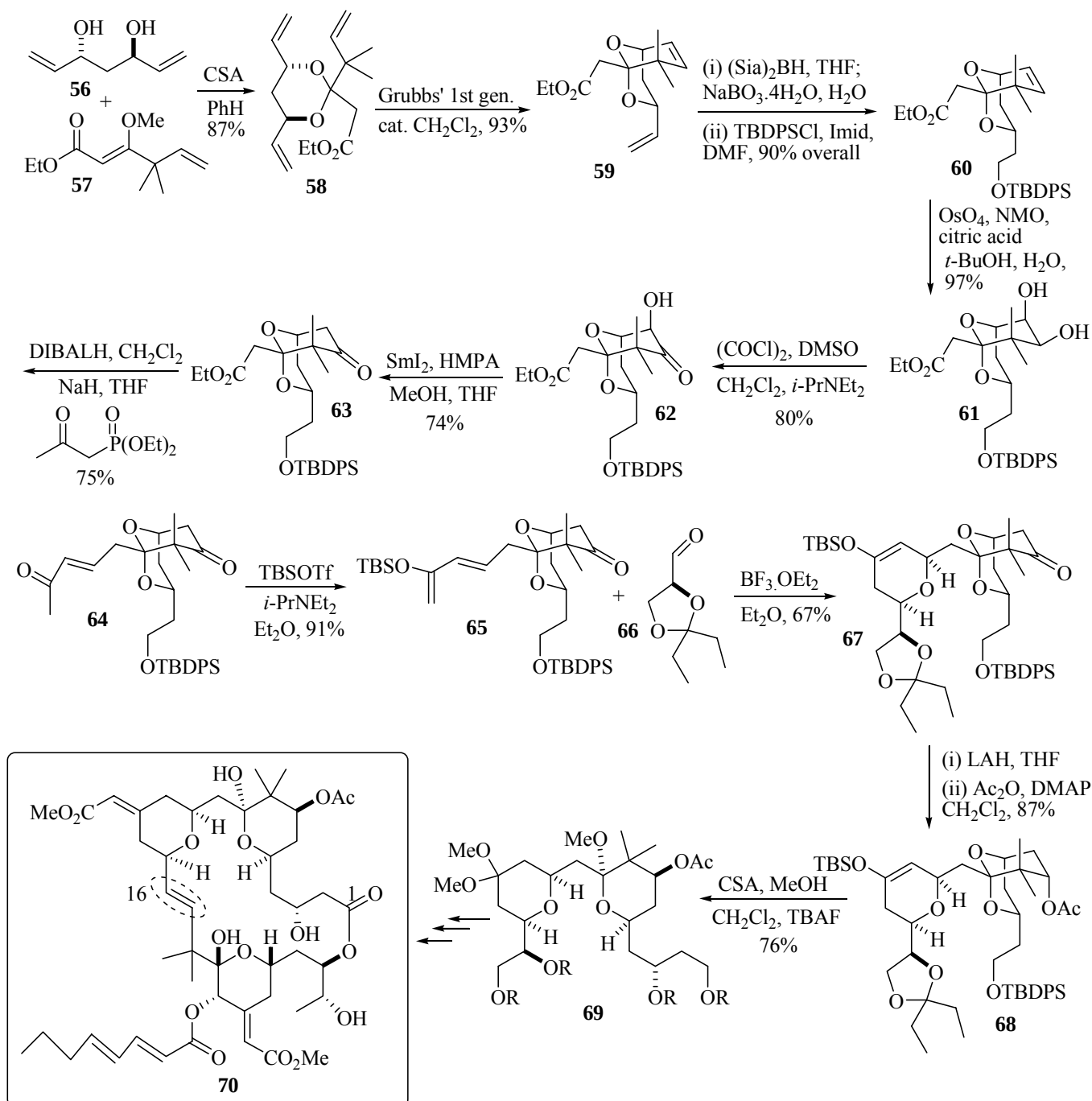
Postema *et al.* reported⁸⁴ a metathesis based approach to synthesize β -C-trisaccharides **53** which involved a highly efficient enol-ether-olefin ring closing metathesis cyclization. Precursor **51** on a double ring closing metathesis gave the C-glycal **52**. Functionalization of the bis-glycal double bond afforded the β -C-trisaccharides **53**. Using this reaction sequence, eight different β -C-trisaccharides were prepared by the same group. β -C-glycosides, which are also convertible to β -C-glycoglycerolipids with potent anti-tumor activity were also synthesized (Scheme 15).

Various synthetic approaches have been reported in recent years to generate nucleoside analogues particularly in search of effective and non-toxic anti-viral and anti-tumor agents. A new family of spiro-annulated carbocyclic nucleosides and conformationally locked bicyclic nucleoside analogues from sugar based substrates has recently been reported by Mandal *et al.*⁸⁵ by ring closing metathesis and intramolecular nitron cycloaddition reaction as the key steps. Diallylated compound **54**, generated from D-glucose-derived substrate through *O*-allylation, underwent ring closing metathesis reaction with Grubbs' catalyst I to afford the 6/5 spirocycle **55** (Scheme 16). The spiroheterocycle **55** was further elaborated through a sequence of reactions, notably, a nonisolable nitron intermediate at C1 to afford isooxazolidinospiroheterocycle.



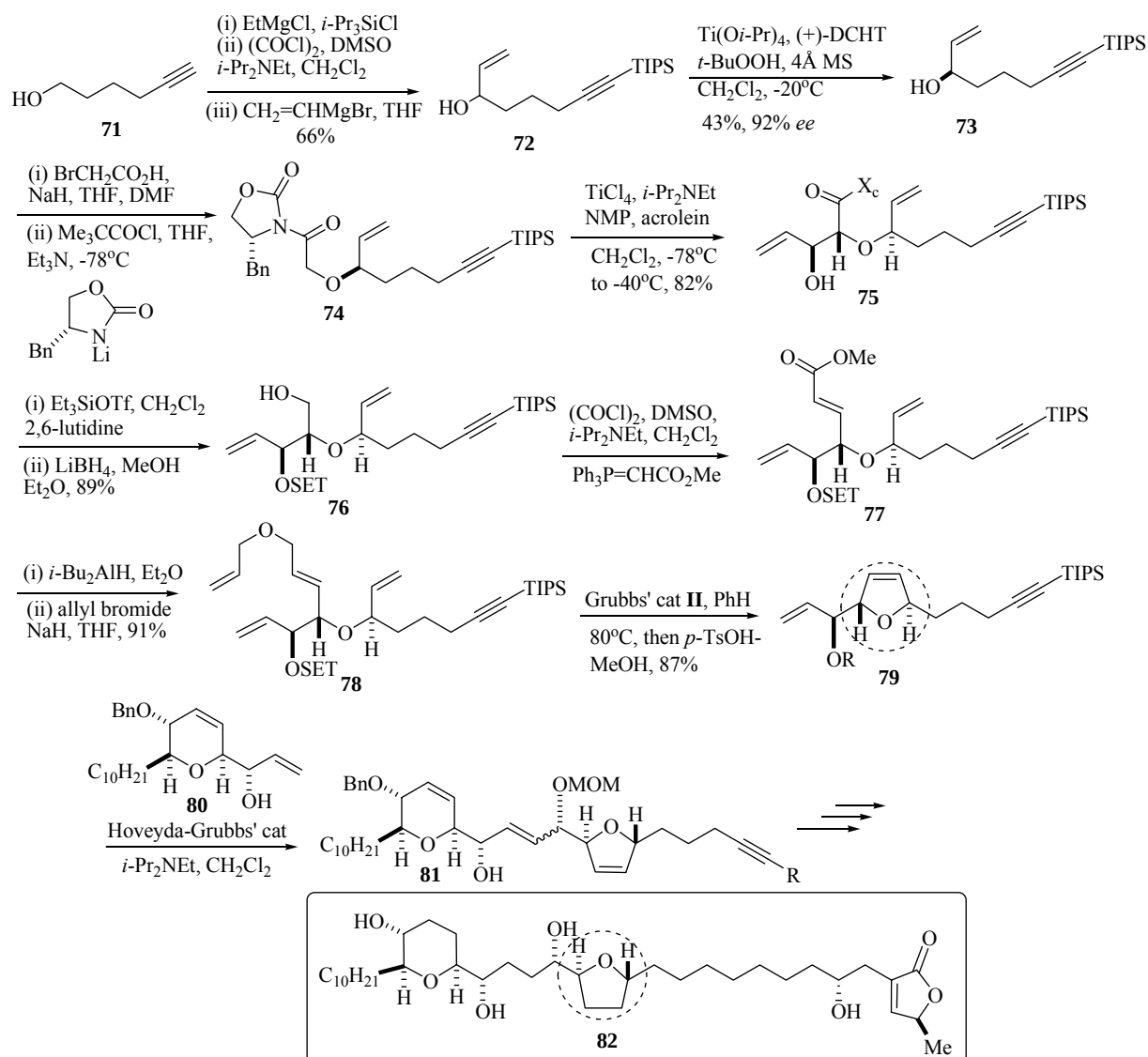
Scheme 16 Synthesis of spirocycle by RCM.

Owing to the potent anticancer activity of bryostatin **70** (Scheme 17), a considerable activity towards the total synthesis of this class of compounds and analogues was displayed.⁸⁶ An efficient and general synthetic approach towards the synthesis of C1-C16 part of bryostatin **70** was reported by Burke *et al.*⁸⁷ utilizing desymmetrization by ketalization and a ring closing metathesis step.



Scheme 17 Synthesis of bryostatin by RCM strategy.

In another approach of enantioselective total synthesis of (-)-mucocin **82**, the first member of the acetogenin family bearing a tetrahydropyran (THP) ring along with a tetrahydrofuran (THF) ring was reported recently by Crimmins *et al.*⁸⁸ This was achieved by ring closing metathesis as one of the key steps with Grubbs' catalyst II (Scheme 18).

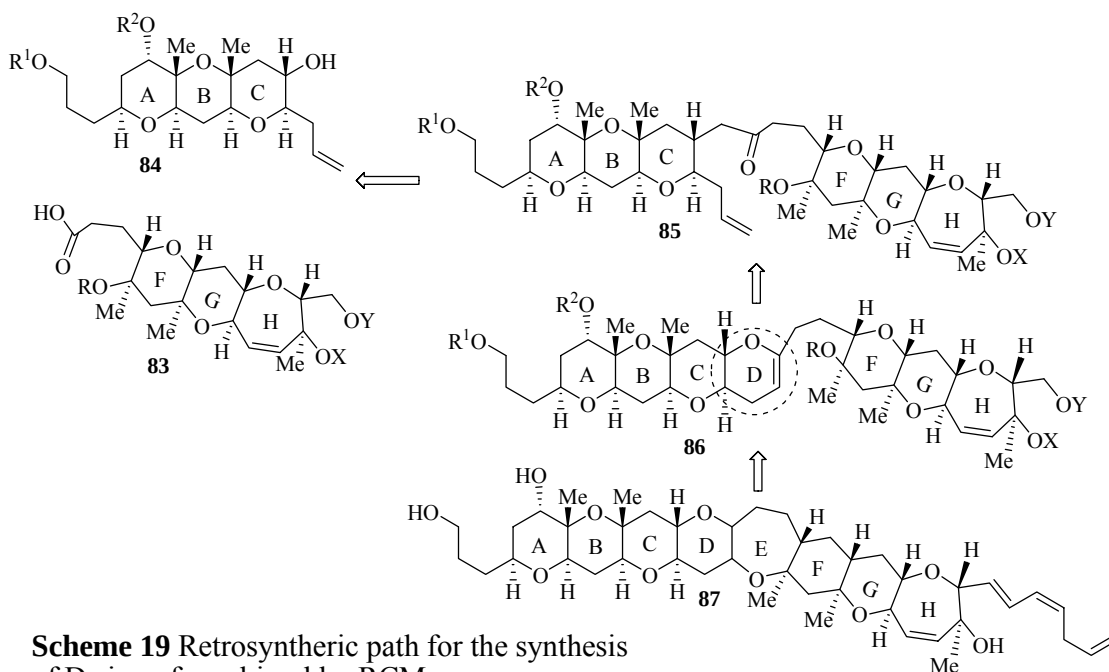


Scheme 18 Synthesis of (-)-mucocin by ring-closing metathesis.

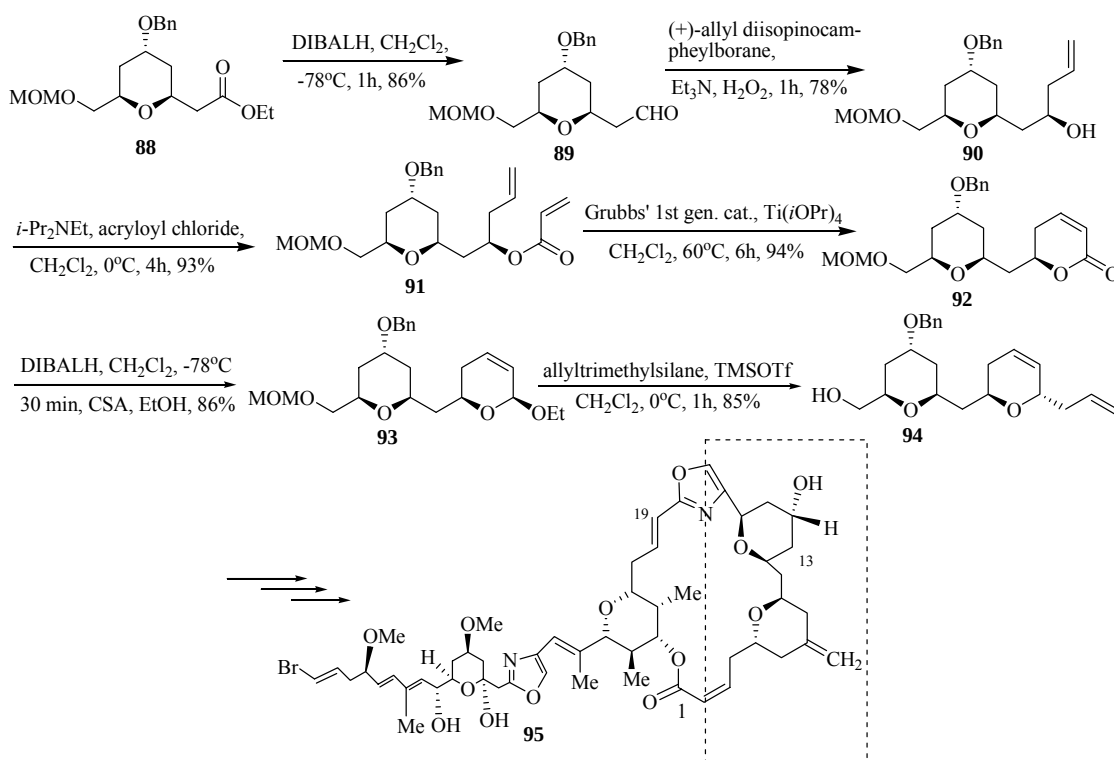
2,5-Disubstituted tetrahydropyran is an important structural motif in a number of natural product and possesses various biological activities. Schmidt and Nave recently⁸⁹ reported the regio- and stereoselective synthesis of this class of compounds based on the combination of Grubbs' catalyst mediated olefin metathesis with either a Claisen rearrangement or Pd-catalyzed allylic substitution as one of the key steps. In continuation of their work on ring closing metathesis, they also reported⁹⁰ a novel ruthenium catalyzed tandem ring closing metathesis and double bond isomerization reaction for the synthesis of cyclic enol ether in which the metathesis active catalyst ruthenium carbene complex was converted *in situ* to an isomerization active ruthenium hydride species. Based on this idea, they have synthesized various cyclic enol ethers in moderate-to-good yields.

Large fused polycyclic ether natural products of marine origin are some of the most complex and formidable synthetic targets found in nature and they continue to fascinate and inspire those who are involved in the target oriented synthesis and developments of new synthetic methods.⁹¹ Gambierol is a representative marine ladder toxin family with a relatively complex structure. Recently, Rainier *et al.*

reported^{92,93} the total synthesis of Gambierol **87** in 44 steps in which few key features is enol ether olefin metathesis chemistry, Claisen rearrangement, generation of glycosyl anhydride and C-ketoxide. The D-ring was constructed using Grubbs' catalyst II (20 mol%) (Scheme 19).

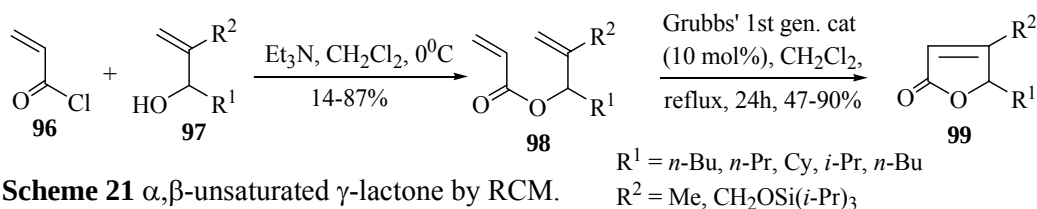


A chiral methylene bis-pyran fragment (C2 – C16 fragment of Phorboxazole A **95**) was successfully synthesized by Yadav and co-workers.⁹⁴ The synthetic route involved the use of an oxy-anion intramolecular Michael addition, Brown's asymmetric allylation and Grubbs' ring closing metathesis reaction in a stereoselective manner (Scheme 20).



3.3 SYNTHESIS OF FIVE-AND SIX-MEMBERED LACTONES

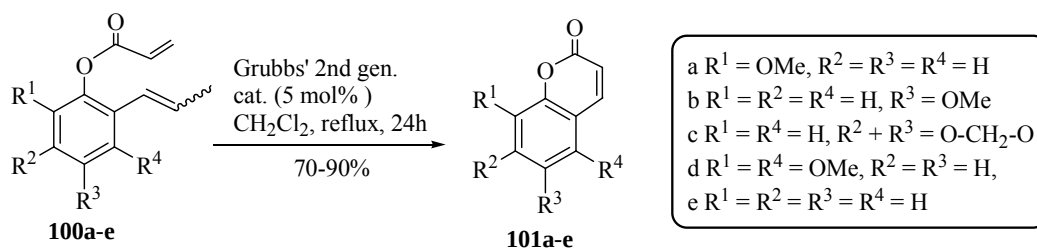
Despite the electronic deficiency of the conjugated double bond of the *gem*-disubstituted allylic alkene unit in the starting acrylates **98**, Grubbs' catalyst I proved to be an effective promoter of the RCM affording the α,β -unsaturated γ -lactones.⁹⁵ Variation of concentrations of the substrates and /or catalyst showed a positive effect on the yields of the RCM product. The optimized experimental condition was applied on the diolefin **98** with Grubbs' catalyst I to afford differently alkyl substituted butenolides **99** and the positive effect of dilution on reactivity was attributed to the fact that low substrate concentration can indeed minimize the formation of undesired cross metathesis product, and also imply a longer lifetime of the catalyst (Scheme 21).



Scheme 21 α,β -unsaturated γ -lactone by RCM.

Fujii and co-workers reported⁹⁶ a two-steps synthesis of highly optically active γ -alkyl- γ -butenolides from commercially available racemic hept-1-en-3-ol by the combination of lipase catalyzed transesterification and ring closing metathesis reaction. Grubbs' catalyst II was found to be an effective one for the asymmetric synthesis of γ -substituted- γ -butenolides in high yields.

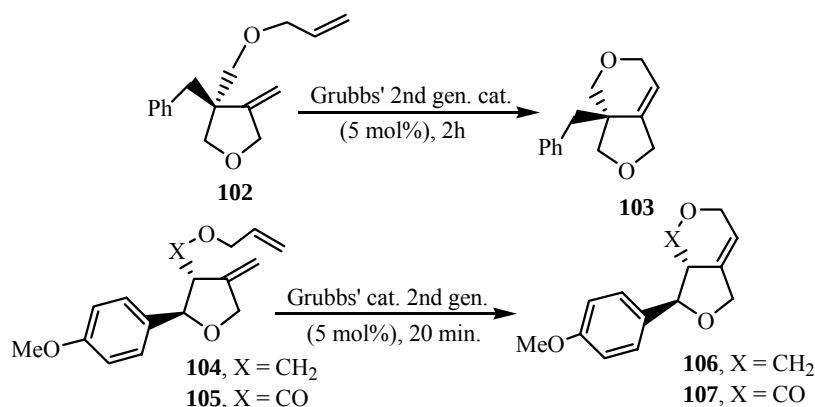
The disadvantages (harsh reaction conditions, use of toxic reagents, low yields) of the synthesis of coumarins by classical methods have been overcome by the use of ring closing metathesis.⁹⁷ Kimpe *et al.* reported⁹⁸ a novel synthesis of substituted coumarins **101** from the compounds **100** by ring-closing metathesis with Grubbs' catalyst II (Scheme 22).



Scheme 22 Synthesis of substituted coumarins by RCM.

Synthesis of coumarins having substitution both at the aromatic ring and the α,β -unsaturated lactone ring was also developed⁹⁹ by Lay *et al.* which can be used as molecular scaffolds suitable for further diversification through a combinatorial approach. Similarly, 3-fluorocoumarin¹⁰⁰ has also been prepared by ring closing metathesis with Grubbs' catalyst II starting from (2-vinylphenyl)- α -fluoroacrylate.

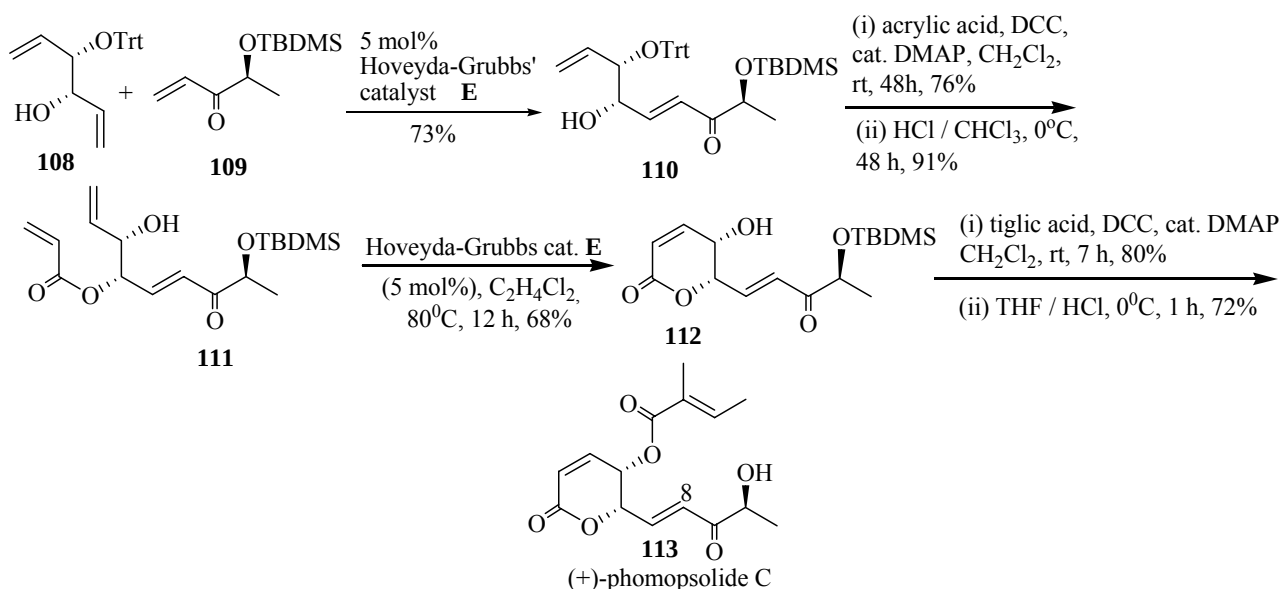
RCM reaction of an *exo*-methylene unit of a cyclic compound with double bond of suitably tethered allyl ether leading to the formation of furo-[3,4-*c*]pyran skeleton has been reported.¹⁰¹ The substrates **102**, **104** and **105** on treatment with Grubbs' catalyst II (5 mol %) in CH₂Cl₂ afforded the furopyrans **103**, **106** and **107** in 48-92% yields respectively (Scheme 23).



Scheme 23 RCM for the formation of furo-[3,4-c]pyran skeleton.

Substitution either in the allylic part or in the tetrahydrofuran ring of the substrates led to the self-metathesis product rather than the cyclized product. Propargyl ether of the substrate **102** with Grubbs' catalyst, once again demonstrated the deprotection methodology affording the corresponding alcohol.¹⁰²

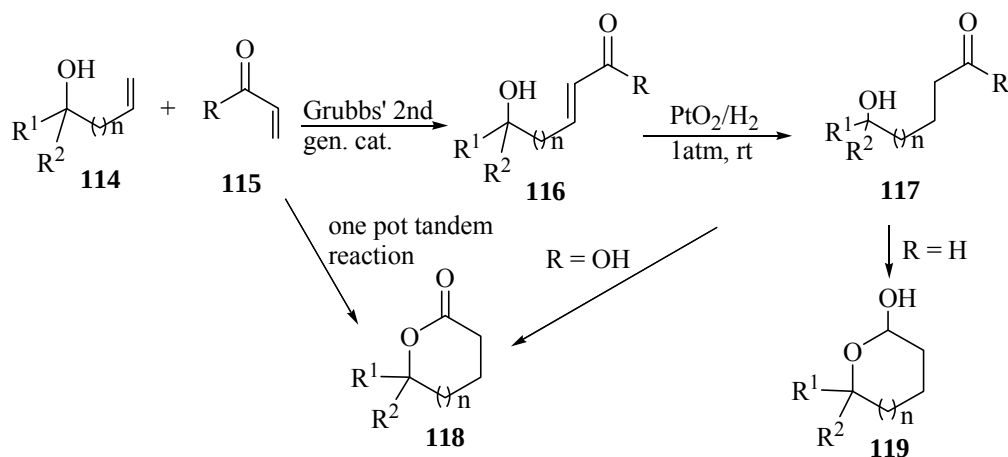
A new strategy for the total synthesis of phomopsolide C by ring-size selective ring closing metathesis and chemoselective cross metathesis was reported¹⁰³ by Blechert and Michaelis. Cross metathesis of the compounds **108** and **109** with Grubbs-Hoveyda catalyst **E** (5 mol%) gave the desired regioisomer **110** exclusively in 73% yield which on further acroylation with acrylic acid and deprotection of the trityl group afforded the precursors **75** for the ring closing metathesis. Possibility of migration of the acyl group during the deprotection process was suppressed with HCl solution in CHCl_3 by controlling either too acidic or basic conditions. The substrates **111** with 5 mol% Hoveyda-Grubbs' catalyst **E** in dichloroethane at 80 °C for 12 h gave the substituted 5,6-dihydro-5-hydroxypyran-2-ones **112** in 68% yield. Further esterification and subsequent deprotection yielded the desired phomopsolide C **113** (Scheme 24).



Scheme 24 RCM is the key step for the total synthesis of phomopsolide C.

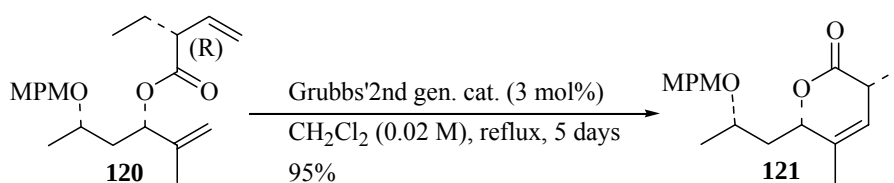
In the ring closing metathesis step exclusive formation of the six-membered rather than five-membered lactone was achieved by the installation of more electron withdrawing enone moiety at the position-8, directing the metathesis process to the sterically less hindered more electron rich double bond of the allylic alcohol.

Substituted lactols are useful intermediates in organic synthesis as these synthetic equivalents of ω -hydroxyaldehydes. Using a three-step one-pot reaction, five-membered and six-membered ring lactones **118** and lactols **119** were devised¹⁰⁴ by Cossy *et al.* The procedure consisted of a one-pot tandem cross metathesis / hydrogenation / cyclization at room temperature under 1 atm of hydrogen in the presence of Grubbs' catalyst II and PtO_2 . The first step was accomplished by Grubbs' catalyst II and the second step involved hydrogenation, which was achieved in the presence of PtO_2 to give the ω -hydroxyacid **116** or ω -hydroxyaldehydes **117** which immediately cyclized to the corresponding lactones **118** and lactols **119**. The catalyst II was found to be tolerant to all the aforesaid reactions and effective for the first step to afford a number of lactols and lactones in 45-70% yields (Scheme 25).



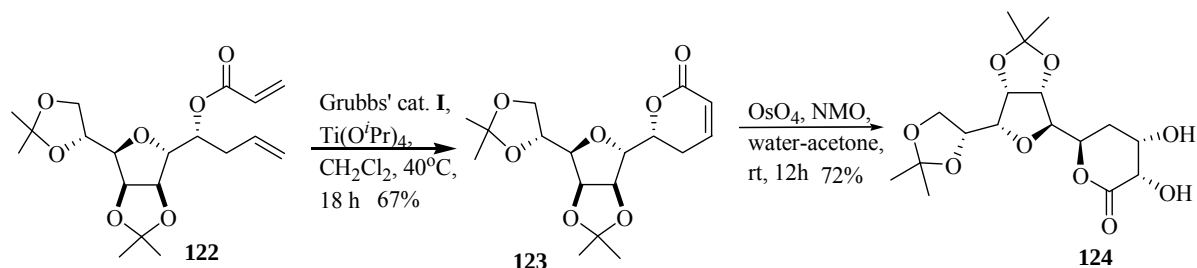
Scheme 25 Tandem cross RCM for the synthesis of lactones.

Peloruside A is a 16-membered macrolide with potent taxol-like cytotoxic properties acting on the cell mitotic process at the G2 stage through a mechanism blocking microtubule depolymerization.¹⁰⁵ A short and efficient synthesis of the C12-C19 fragment of the cytotoxic macrolide peloruside has been achieved by Ermolenko *et al.*¹⁰⁶ One of the key step of this synthesis is the formation of the six-membered lactone **121** (Scheme 26) and that was accomplished by the RCM reaction with the diene **120** and Grubbs' catalyst II (10 mol%) for an extended reaction time. The unprecedented diastereomer-discriminating ring closing metathesis reaction leading to the lactone **121** is the vital step for the synthesis of polyketide natural products.



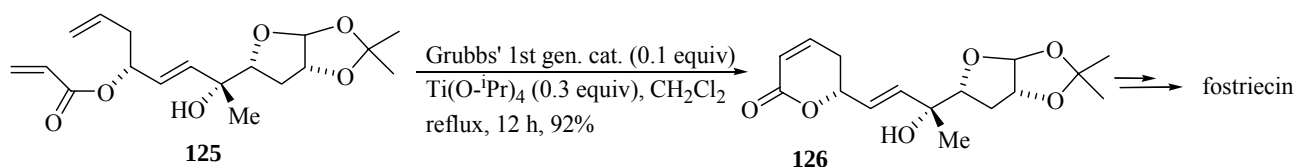
Scheme 26 RCM for the synthesis of the lactone **121**.

Sharma *et al.* described¹⁰⁷ the stereoselective synthesis of C1-C5 and C4-C5 linked deoxy disaccharides using RCM strategy. The RCM is the key step, which is depicted in Scheme 27.



Scheme 27 Stereoselective synthesis of C1-C5 and C4-C5 link of deoxy disaccharides by RCM as the key step.

The synthesis of fostriecin starting from D-glucose, involves chelation-controlled addition, Wittig rearrangement, ring closing metathesis and iodomethylation. The key intermediate **126** was accessed¹⁰⁸ by ring closing metathesis as one of the key steps. Ester alcohol **125** was subjected to ring closing metathesis with Grubbs' catalyst I (0.1 equiv) in the presence of $\text{Ti}(\text{O}^i\text{Pr})_4$ (0.3 equiv) in refluxing CH_2Cl_2 for 12 h to afford the lactone **126** from which fostriecin was synthesized in several steps (Scheme 28).



Scheme 28 Formal synthesis of fostriecin's core moiety by RCM.

Lactone rings constitute structural features of many natural products. A good deal of naturally occurring lactones, most particularly those being α,β -unsaturated lactones display wide range of pharmacological properties. Total synthesis of various natural product having lactone moiety *i.e.* (-)-malyngolide (**127**), (5*S*,7*S*,9*S*,11*S*)-tetrahydroxyhexacos-2-enoic acid (**128**), (5*R*,7*S*,9*S*,11*S*)-tetrahydroxyhexacos-2-enoic acid (**129**), (+)-boronolide (**130**), (+)-triacetoxyniotriol (**131**), spicigerolide (**132**), (6*S*)-5,6-dihydro-6-[(2*R*)-2-hydroxy-6-phenylhexyl]-2*H*-pyran-2-one (**133**), cryptocaryadiacetate (**134**), (*R*)-(+)-gonithalamin (**135**) and (*R*)-(+)-gonithalamin oxide (**136**) have been synthesized by various groups¹⁰⁹⁻¹¹⁶ using ring closing metathesis as one of the key steps (Figure 6).

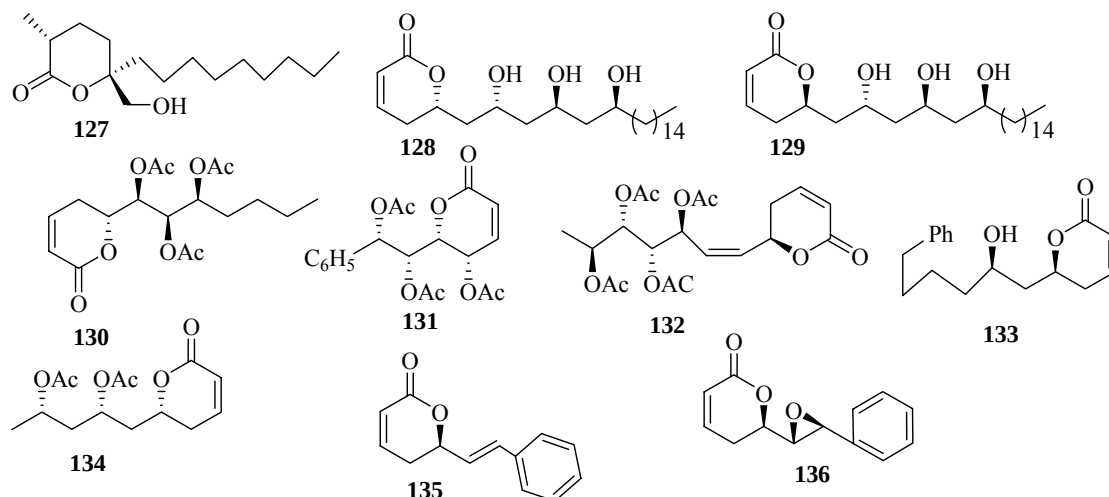


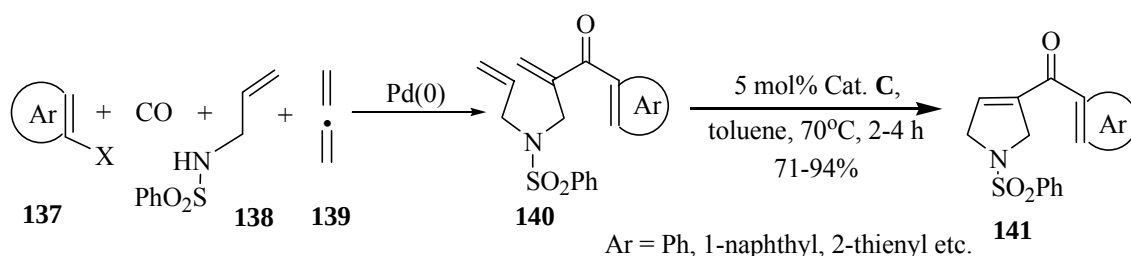
Figure 6 Naturally occurring important lactones.

4. Synthesis of nitrogen heterocycles

A number of research groups in recent years have demonstrated the usefulness of RCM for constructing *N*-heterocycles. Due to the importance of nitrogen-containing compounds, for instance in the synthesis of alkaloids and other biologically active substances, the RCM protocol is an enrichment of synthetic chemistry.

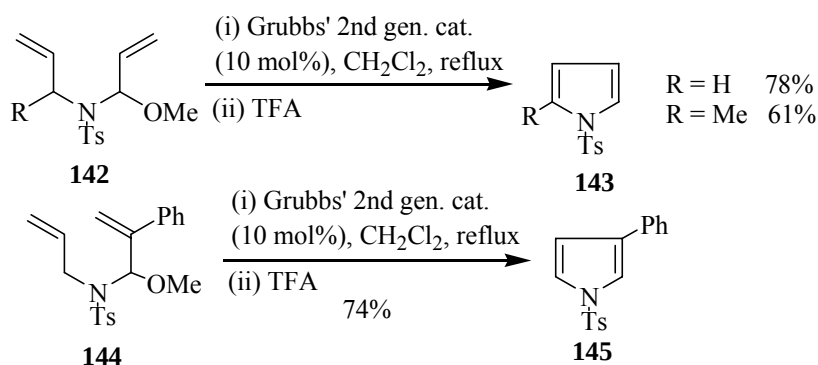
4.1 SYNTHESIS OF FIVE-MEMBERED NITROGEN HETEROCYCLES

A novel sequential palladium/ruthenium-catalyzed four-component process for the synthesis of *C*-allyl-*N*-heterocycles was developed by Grigg and coworkers,¹¹⁷ in good yield which in turn can be used as an active dipolarophiles in 1,3-dipolar cycloaddition. 1,6-Dienes **140** underwent ruthenium-catalyzed RCM to give Δ^3 -pyrrolines **141** (Scheme 29).



Scheme 29 RCM for the synthesis of pyrrolines.

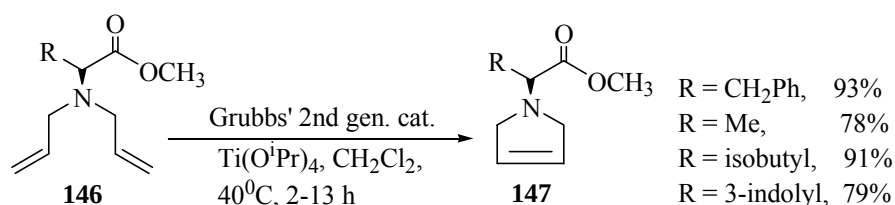
The use of RCM to form heteroaromatic compounds has only been recently reported.¹¹⁸ Donohoe *et al.* reported¹¹⁹ a novel and versatile approach to the synthesis of pyrroles **143** and **145** that uses ring-closing metathesis as the key C-C bond-forming reaction (Scheme 30).



Scheme 30 2-alkyl and 3-phenyl substituted pyrrole synthesis by RCM.

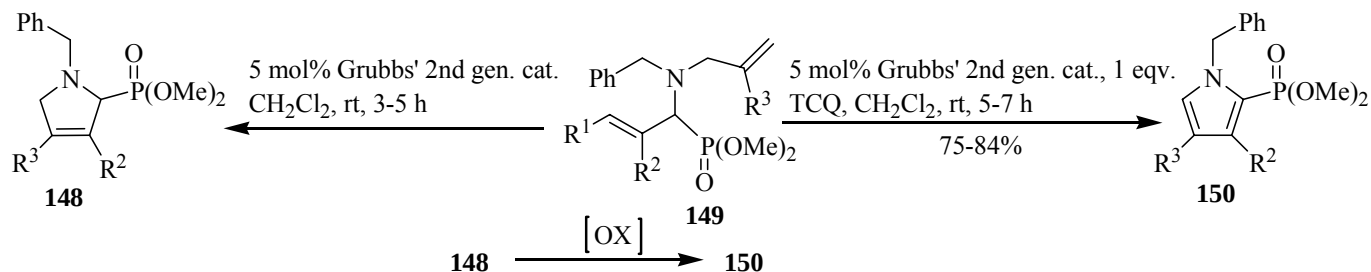
The basicity and nucleophilicity of the *N*-atom played a crucial role in the RCM reaction of diallylamines. The coordination between the nitrogen atom and the ruthenium species may turn down the expected RCM reaction. The metathesis of diallylamine possessing basic and nucleophilic nitrogen atoms has not been successfully carried out to afford pyrrolidines, even under harsh reaction conditions.¹²⁰

Xiao and Yu successfully reported¹²¹ the straightforward method for the synthesis of enantiopure pyrrolidines by Lewis acid-assisted RCM of chiral diallylamine substrates **146**. The RCM reaction of a series of diallylamines **146** were performed using 5-8 mol% Grubbs' catalyst II and 20 mol% $\text{Ti}(\text{O}^i\text{Pr})_4$ in CH_2Cl_2 (10 ml per 1 mmol of diallylamine) at 40°C for 2-13 h to furnish the pyrrolidine derivatives **147** (Scheme 31).



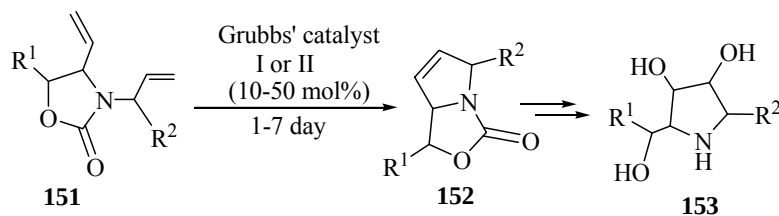
Scheme 31 Synthesis of enantiopure pyrrolidines by Lewis acid-assisted RCM.

This new procedure demonstrated that basic and nucleophilic diallylamines could participate in RCM reactions with the use of Grubbs' catalyst II in the presence of Ti(O^{*i*}Pr)₄ to prevent the coordination of the *N*-atom to the ruthenium carbene intermediate. Recently, Stevens *et al.* reported¹²² the synthesis of *N*-benzyl-2-phosphono-3-pyrrolines via RCM starting from functionalized α -aminoalkenyl phosphonates followed by *in situ* conversion to the corresponding 2-phosphonopyrroles by tetrachloroquinone (TCQ) (Scheme 32).



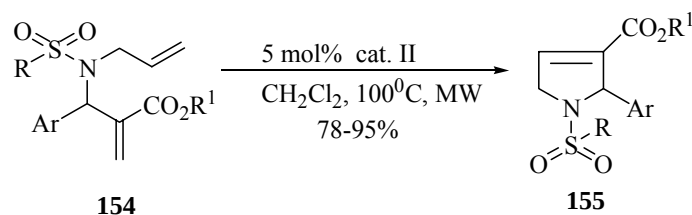
Scheme 32 Synthesis of *N*-benzyl-2-phosphono-3-pyrrolines by RCM.

Pyne *et al.* described¹²³ a new strategy for the synthesis of polyfunctionalized pyrrolidines **153** via the ring closing metathesis reaction of substituted 3-allyl-4-vinyl-2-oxazolidones **151** and subsequent diastereoselective *cis*-hydroxylation of the resulting pyrrolo[1,2-*c*]oxazol-3-ones **152**. These reactions, however required longer reaction times and higher catalyst loading compared to the RCM reaction of their corresponding acyclic diene analogues due to the formation of relatively strained 5,5 hetero-bicyclic system, containing three sp² hybridized centers (Scheme 33).



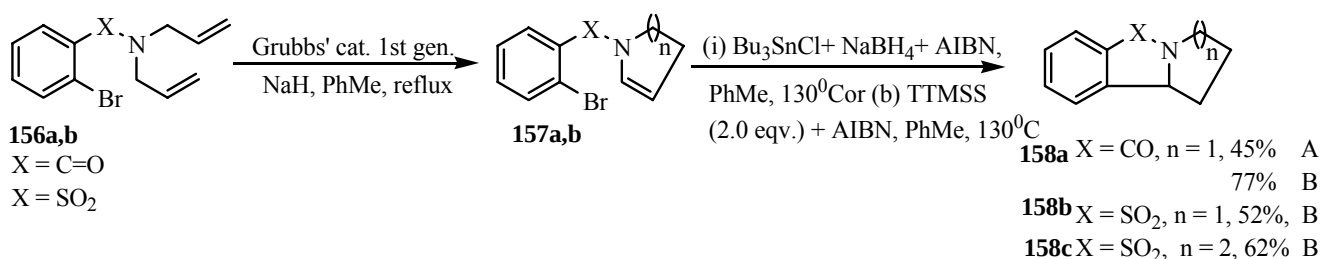
Scheme 33 Synthesis of pyrrolo[1,2-*c*]oxazol-3-ones by RCM.

The increased thermal stability of Grubbs' catalyst II, improved the usefulness of the RCM and allowed efficient performance of this reaction at elevated temperature. A rapid method for the preparation of functionalized 2,5-dihydropyrroles containing electron-withdrawing substituents, using ruthenium-catalyzed ring-closing metathesis under microwave irradiation was reported.¹²⁴ The *N*-alkylated *aza*-Baylis-Hillman adducts **154** were converted to the desired ring closing products 2,5-dihydropyrroles **155** within 1 min. reaction time with one exception of the sterically more congested *tert*-butyl ester which required an additional 60 sec for full conversion (Scheme 34).



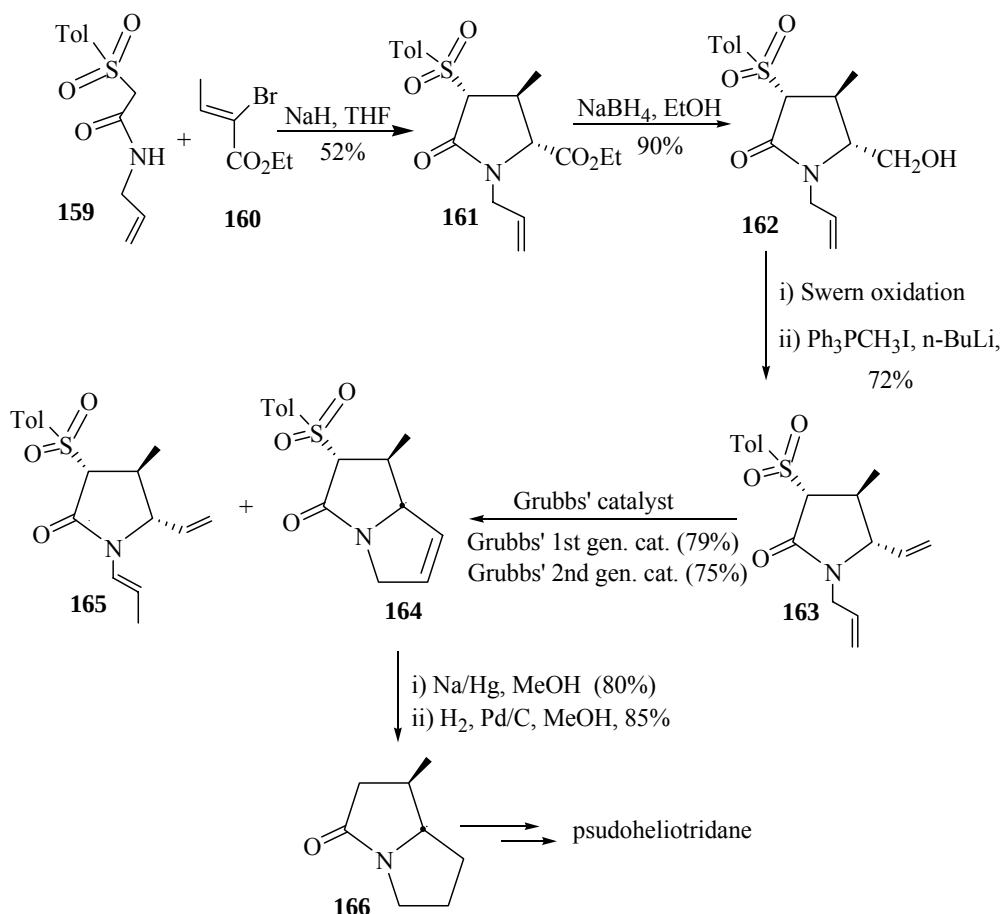
Scheme 34 Synthesis of 2,5-dihydropyrroles by RCM.

Piva *et al.* developed¹²⁵ a one-pot procedure, a tandem RCM/ isomerization followed by a sequential radical cyclization, to prepare polycyclic lactams and sultams **158a-c** from amides **156a** and sulfonamides **156b**. This process was also successfully conducted on bisallylsulfonamide to give the corresponding sultams (Scheme 35).



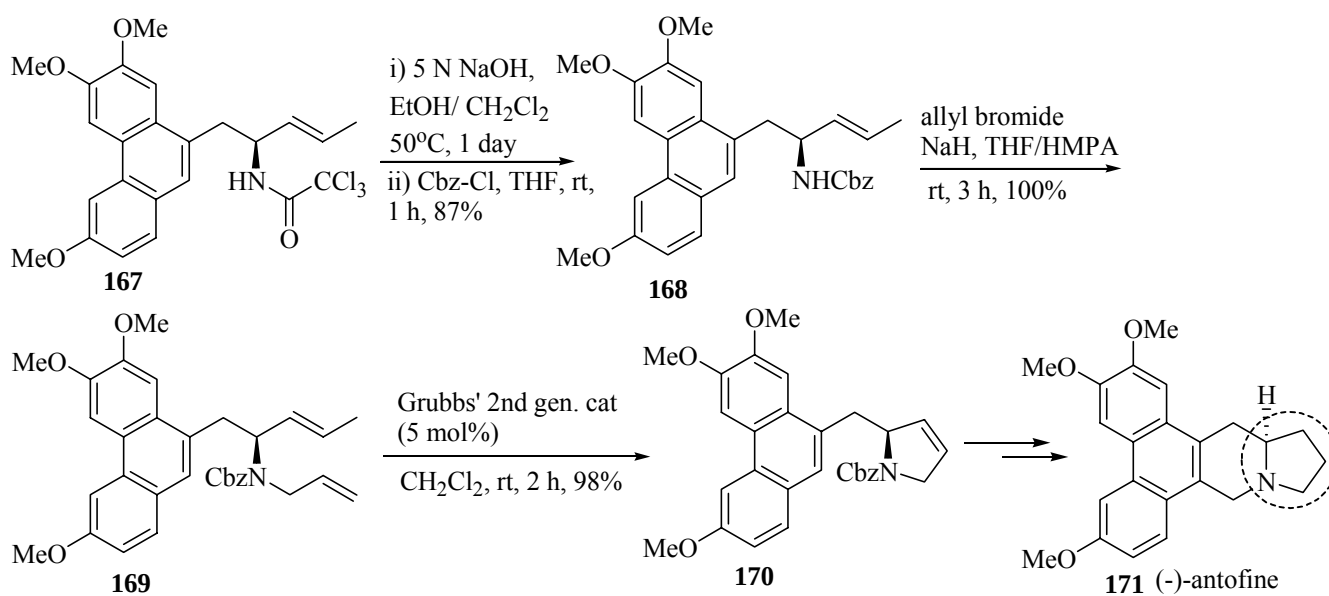
Scheme 35 RCM/isomerization strategy for the preparation of lactams and sulfonamides.

Chang *et al.* recently reported¹²⁶ a formal synthesis of pyrrolizidine alkaloid **166**, pseudoheliotridane in one-pot by efficient intramolecular ring-closing metathesis of **163** to give **164** using Grubbs' catalyst II as one of the key steps. Pseudoheliotridane was obtained from the intermediate **164** in several steps (Scheme 36).



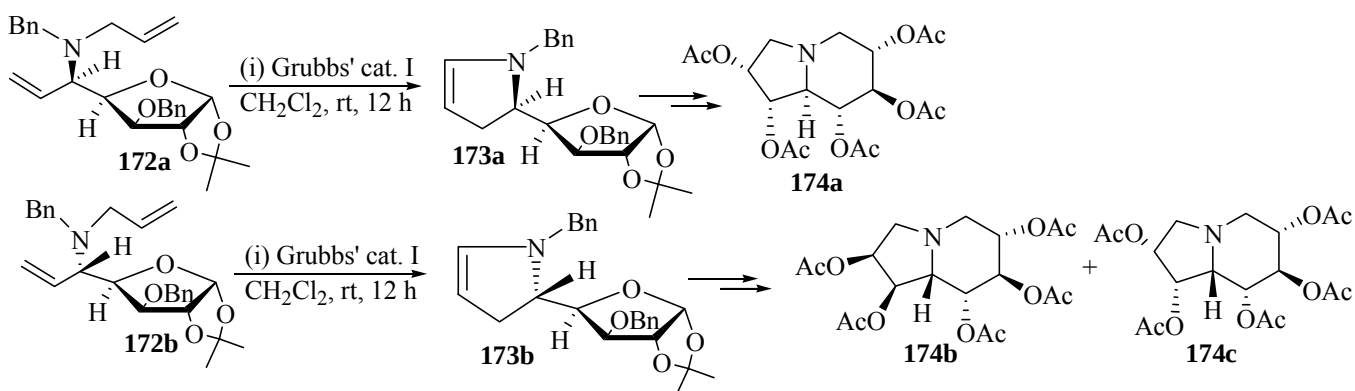
Scheme 36 A formal synthesis of pyrrolizidine alkaloid by RCM.

Kim *et al.* achieved¹²⁷ a new enantioselective synthetic route to (-)-antofine **171** and a representative phenanthroquinolizidine alkaloid (-)-cryptopleurine. The ring-closing metathesis of the bisallylamine **169** was successfully performed with 5 mol% Grubbs' catalyst II in CH₂Cl₂ at room temperature for the construction of the pyrrolidine ring **170** from which (-)-antofine **171** was synthesized in two steps (Scheme 37).



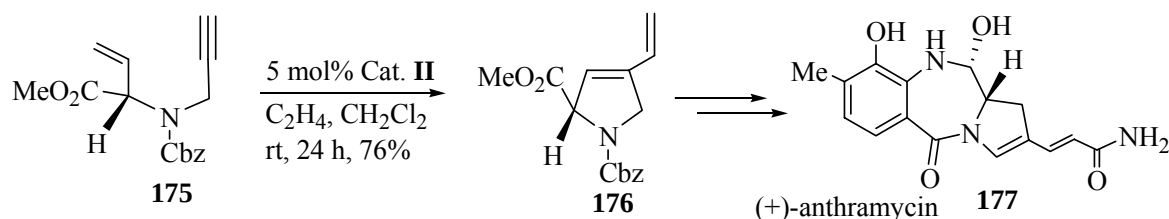
Scheme 37 Synthesis of pyrrolidine ring from bisallylamine.

Another route for the synthesis of pentahydroxy indolizidine derivatives starting from a carbohydrate intermediate having nitrone functionality has been reported.¹²⁸ Ring closing metathesis of the dienes **172a** and **172b** provided sugar substituted dihydropyrrolidine ring systems **173a** and **173b** respectively that could be elaborated to provide different pentahydroxylated indolizidine alkaloids (Scheme 38).



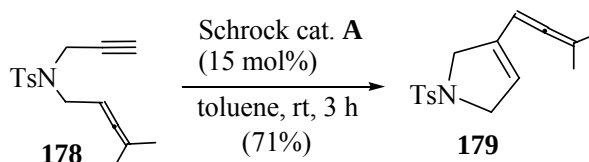
Scheme 38 RCM for the synthesis of the sugar-substituted dihydropyrrolidine derivatives.

(+)-Anthracycline, possessing a pyrrolbenzodiazepine skeleton and a dienamide group conjugated with nitrogen in a pyrrolidine ring, was synthesized by Mori *et al.*¹²⁹ using ring-closing enyne metathesis and cross metathesis followed by isomerization of the resulting double bond. Pyrrolbenzodiazepine skeleton was constructed by reductive cyclization of a nitro group and an ester group of pyrrolidine derivative **177**, which in turn was obtained by enyne metathesis (Scheme 39).



Scheme 39 RCEM for the synthesis of pyrrolidine moiety of (+)-anthramycin.

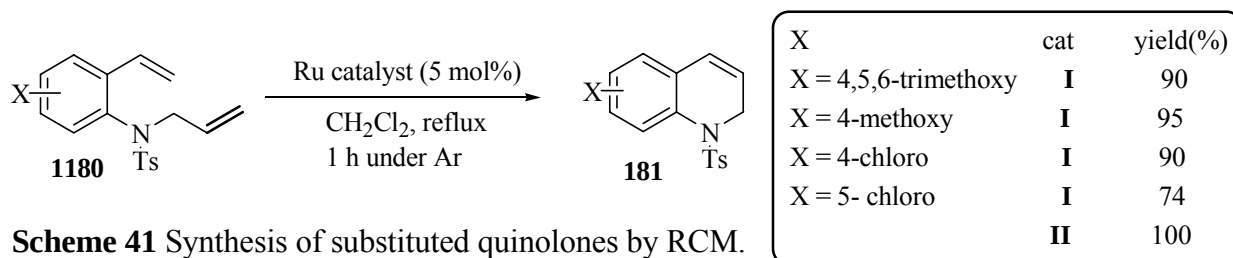
Murakami *et al.* recently reported¹³⁰ the first ring-closing metathesis reaction of allenynes **178** occurred at room temperature in the presence of molybdenum complex to give ring-closed vinyl allenes **179**. Allenynes **178** were treated with Schrock catalyst (15 mol%) in toluene at room temperature for 3 h. Metathesis between the alkyne and the proximal carbon-carbon double bond of the allene moiety took place to afford five-membered ring product with an allene side chain in good yield (Scheme 40).



Scheme 40 First ring-closing metathesis reaction of allenynes occurred at room temperature.

4.2 SYNTHESIS OF SIX-MEMBERED NITROGEN HETEROCYCLES

Quinoline is an important heterocyclic moiety present in many alkaloids and played an important role in the field of natural products and medicinal chemistry. A novel synthesis of substituted quinolines using ring closing metathesis and its application to the synthesis of key intermediates for antimalarial agents has recently been reported.¹³¹ Various α,ω -dienes **180** were prepared from anthranilic acid derivatives and subjected to ring-closing metathesis using 5 mol% Grubbs' catalyst I at reflux condition to afford substituted quinolone derivatives **181** in good-to-excellent yields regardless of the substituent pattern on the aromatic ring (Scheme 41).



Scheme 41 Synthesis of substituted quinolones by RCM.

Effect of the protecting groups on nitrogen was also thoroughly examined. With catalyst I, *N*-benzyl derivative gave the desired product in excellent yield, *N*-acetyl did not give the desired product due to formation of some chelated intermediate **182** (Figure 7) and *N*-*tert*-butoxycarbonyl derivative gave the product in modest yield. On the other hand with catalyst II, yield of the *N*-acetyl and *N*-*tert*-butoxycarbonyl derivatives were dramatically increased to give the desired product in almost quantitative yield.

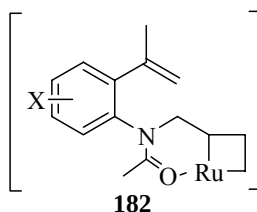
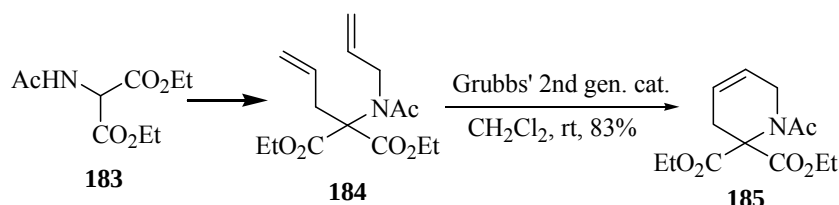


Figure 7 Chelated intermediate with catalyst **I**

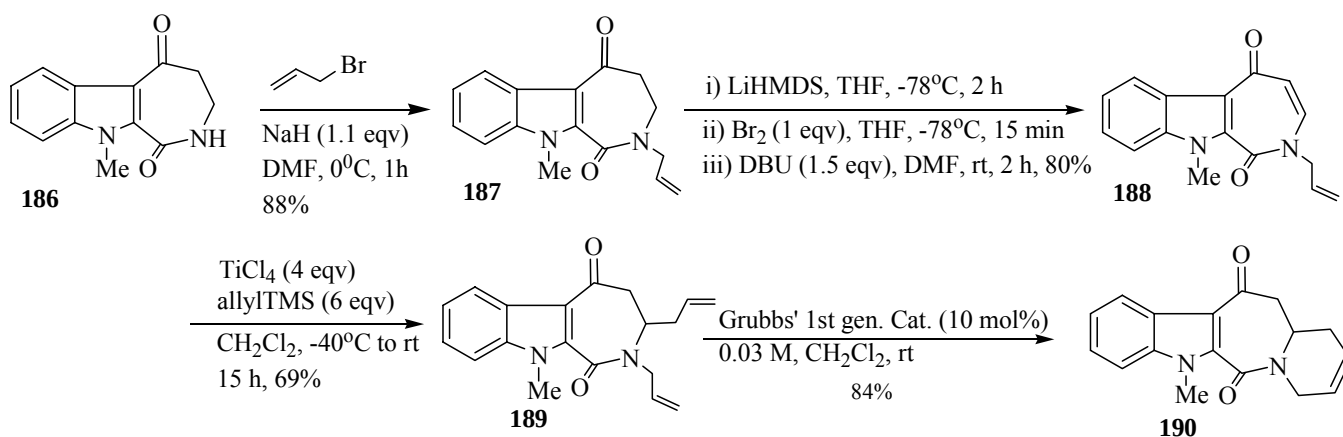
It was shown¹³² that a pure ruthenium hydride complex with *N*-heterocyclic carbene ligand was effectively generated from the reaction of Grubbs' catalyst **II** with vinyloxy trimethyl silane. This ruthenium hydride complex displayed high catalytic activity in the selective isomerization of the terminal olefin and the cycloisomerization of the diene. Substituted 1,2-dihydroquinoline, indole and 3-methylene 2,3-dihydroindole were prepared selectively from the common starting material *N*-allyl-*O*-vinylaniline using Grubbs' catalyst **II** by slight modification of the reaction conditions.

Diethyl acetoamidomalonate (DEAM) has been used to prepare unusual amino acids, which are known to induce unique conformational restrictions when incorporated into biologically active peptides. Kotha¹³³ developed a simple method for the synthesis of nitrogen containing heterocycles incorporating aminomalononic acid derivatives *via* RCM reaction. Dialkylated aminomalononic acid derivative **184** was subjected to ruthenium catalyzed RCM reaction to obtain the corresponding cyclic amino acid derivatives **185** using Grubbs' catalyst **II** in dry CH₂Cl₂ at room temperature under high dilution (Scheme 42).



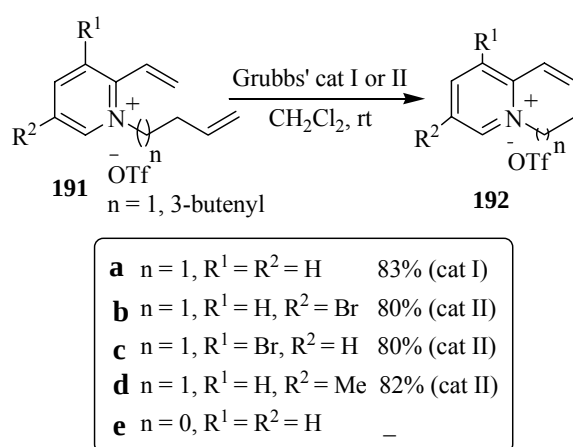
Scheme 42 RCM for the preparation of cyclic aminoacid derivatives.

A new six-membered ring-fused azopino[5,6-*b*]indole derivative **190** *via* ring-closing metathesis was reported by Mérour *et al.*¹³⁴ The RCM of **189** using Grubbs' catalyst **I** in CH₂Cl₂ at room temperature afforded the tetracyclic compound **190** in 84% yield. The same reaction conditions were also applied to get higher ring sized derivatives in excellent yields (Scheme 43).



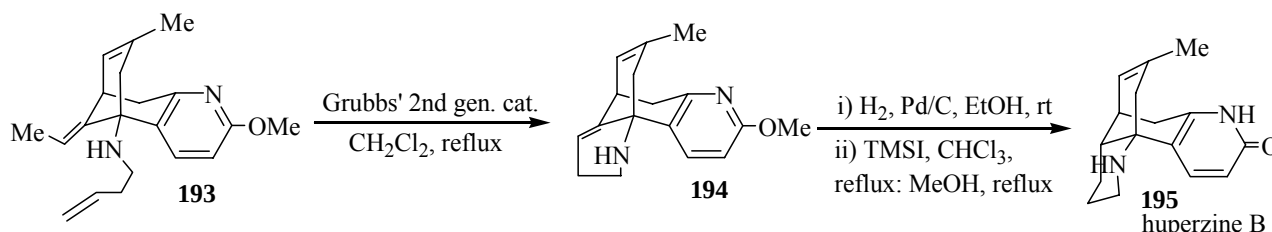
Scheme 43 Azopino[5,6-*b*]indole derivatives by RCM.

Cuadro and Vaquero recently reported¹³⁵ the first example of an olefin ring-closing metathesis reaction on cationic heteroaromatic systems. The appropriate *N*-(3-butenyl)-2-vinyl-pyridinium substrates **191** was reacted selectively under RCM condition with Grubbs' catalyst I (10 mol%) to afford the desired dihydroquinolizinium cations. The quinolizinium system could also be obtained *via* oxidation of the dihydro compound in good yield. Attempts to achieve RCM on substrate (*n* = 1) using Grubbs' catalyst I, II and even with Hoveyda-Grubbs' catalyst in CH₂Cl₂ at room temperature was proved to be unsuccessful. Neither the salt nor the most stable neutral compound indolizine could be isolated even with changed reaction conditions (Scheme 44).



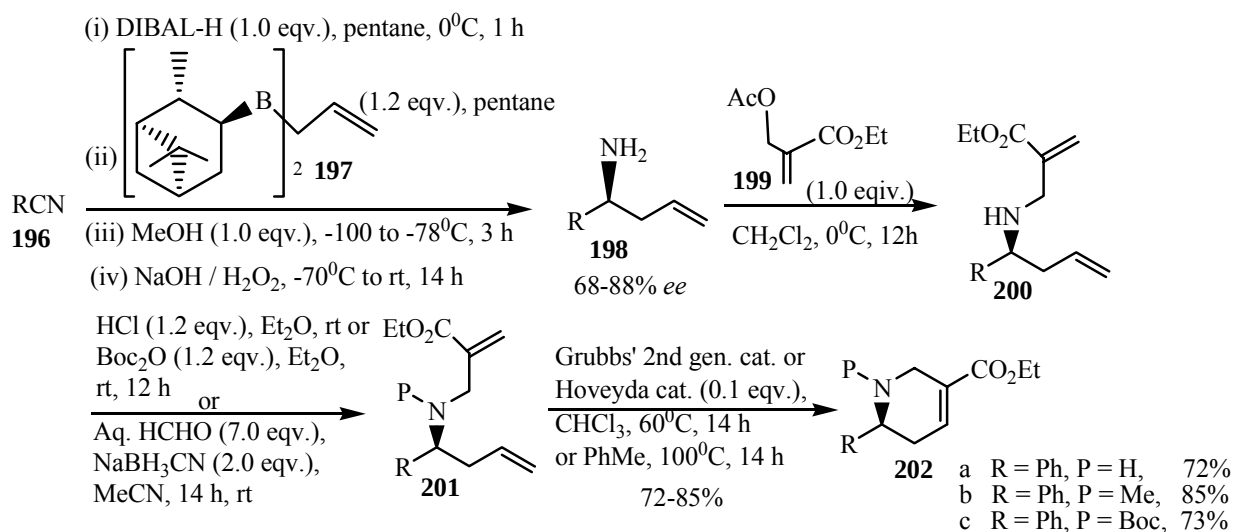
Scheme 44 Synthesis of dihydroquinolizinium cations by RCM.

Another route to the 1-azabicyclic alkaloids using ring-closing metathesis reaction was reported by Barluenga *et al.*¹³⁶ Synthetic route involved the construction of the diene 4-piperidone systems huperzine B (**195**) by an imino-Diels-Alder reaction between the aminotrienes and *N*- ω -vinylimines, in the presence of Yb(OTf)₃, followed by ring closing metathesis reaction of these cyclic dienes under the influence of Grubbs' catalyst I. Lee recently reported¹³⁷ the synthesis of huperzine B *via* ring-closing metathesis of *N*-alkenylamine **193** in the presence of Grubbs' catalyst II followed by selective hydrogenation of the double bond and deprotection with TMSI (Scheme 45).



Scheme 45 Synthesis of the intermediate **194** by RCM towards the the synthesis of huperzine-B.

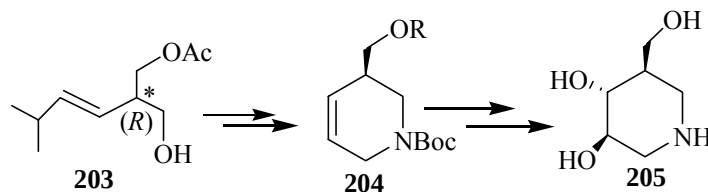
The tetrahydropyridine moiety¹³⁸ has been identified as the pharmacophore for GABA (γ -amino butyric acid), one of the major mammalian inhibitory neurotransmitters. But a systematic study of such compounds has been limited due to cumbersome routes for their preparation.¹³⁹ Ramachandran *et al.* recently developed¹⁴⁰ a conventional preparation of functionalized chiral tetrahydropyridine-3-carboxylate **202** from **201** by ring closing metathesis (Scheme 46).



Scheme 46 Synthesis of chiral tetrahydropyridine-3-carboxylate by RCM.

The RCM reaction using Grubbs' catalyst II on the aminodiene containing free secondary amine failed to provide any cyclized product. The deficiency of RCM was circumvented by conversion of the amine to the ammonium salt, conversion of secondary amine to the tertiary one or by the protection of the amine. This methodology can also be applied to the synthesis of a chiral C₆-substituted tetrahydropyridines with known GABA-inhibitory properties at low concentrations.

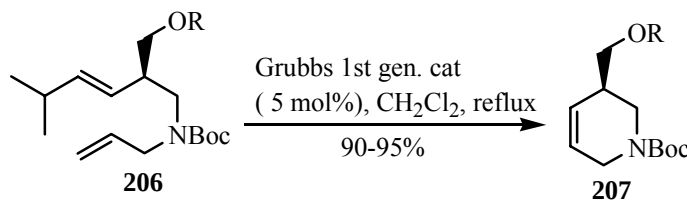
Glycosidases are implicated in various diseases such as diabetes, metastatic cancer, malaria and viral infection making glycosidases good target for drug development. Polyhydroxylated piperidines have the ability to inhibit glycosidases and glycosyl transferases, the carbohydrate processing enzymes, which are responsible for the cleavage of glycosidic bonds. Tetrahydropyridines are useful intermediates for the synthesis of iminosugars and various glycosidase inhibitors. Although different unsaturated six-membered nitrogen heterocycles have been synthesized in the last few years using RCM, syntheses of new enantiopure branched tetrahydropyridines as precursors of the potent glycosidase inhibitors are of great interest in recent years. Isofagomine **205**, a mimic of glucose and its "gulo" isomer, was prepared¹⁴¹ by Riva *et al.* through 8-step sequence in 62% overall yield from chiral THYM* [tris(hydroxymethyl) methane] precursor **203** using ring-closing metathesis for the cyclization step (Scheme 47).



Scheme 47 Isofagomine an important natural product.

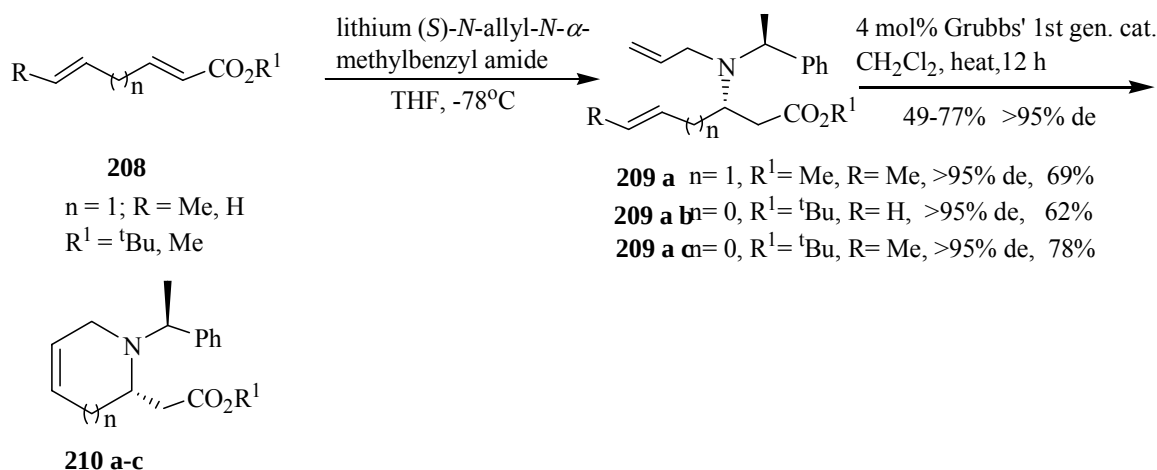
Riva *et al.* also described¹⁴² a novel synthetic application of asymmetrized tris(hydroxymethyl)methane (THYM), obtained in both enantiomeric forms in high ee *via* a chemoenzymatic procedure. Starting from a monoacetate which is a synthetic equivalent of asymmetrized THYM*, six-membered N-heterocycles **207** were prepared exploiting ring-closing metathesis as one of the key steps (Scheme 48).

The *O*-protected carbamates **206** were subjected to RCM in the presence of Grubbs' catalyst I to give the corresponding tetrahydropyridines **207**. However, different behaviors were observed with Cbz-protected dienes, which were transformed into the corresponding tetrahydropyridines only in moderate yields, thus indicating an influence of the *N*-protecting group on the outcome of the reaction. After RCM, the endocyclic double bond can be exploited for different functionalizations and a large variety of artificial sugars and iminosugars such as isofagomine could be accessible.



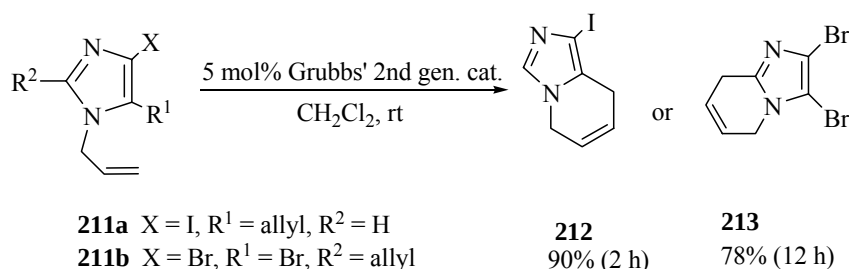
Scheme 48 RCM for the synthesis of six-membered *N*-heterocycle.

Davies and co-workers showed¹⁴³ the efficiency of Grubbs' catalyst I over the others (Nugent catalyst and Schrock catalyst) for the synthesis of *N*-protected heterocyclic amino acids and amines. The protocol is based on the diastereoselective conjugate addition of lithium (*S*)-*N*-allyl-*N*- α -methylbenzylamide to a range of α,β -unsaturated esters **208** followed by ring closing metathesis of β -amino esters **209** with Grubbs' catalyst I to furnish desired *N*- α -methylbenzyl protected pyrrolidine β -amino ester and piperidine β -amino ester **210a-c** as single diastereomer in each case (Scheme 49).



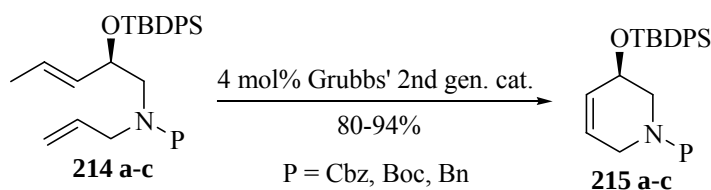
Scheme 49 RCM for the synthesis of *N*- α -methylbenzyl protected pyrrolidine

The utility of a number of dienyl imidazoles in ring-closing metathesis reaction with Grubbs' 2nd generation ruthenium carbene complex, provided that the imidazole *N*-3 atom should remain protonated which was demonstrated by Lovely *et al.*¹⁴⁴ The substrates **211a,b** successfully underwent RCM reaction to afford the cyclic six-membered products **212** and **213**, respectively. Surprisingly, the 4,5 allyl vinyl system did not participate in the metathesis, but 1,5 linked congeners readily provided the cyclic products. Steric effect of 4-iodo-substituent might be important since its removal provided a substrate that participated in the metathesis but with reduced efficiency (Scheme 50).



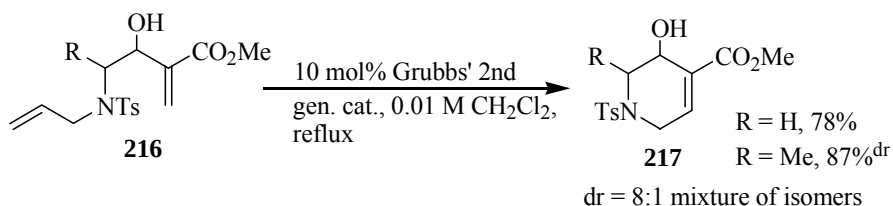
Scheme 50 RCM for the synthesis of imidazole-annulated nitrogen heterocycles.

Chiral non-recemic cyanohydrins are proven expedient starting materials for the synthesis of several classes of compounds. Brussee *et al.* recently reported¹⁴⁵ the synthesis of a set of new chiral unsaturated *N*-heterocycles *via* ring-closing metathesis. Tetrahydropyridines **215** were obtained ring-closing metathesis reaction of *N*-protected bis-olefinic secondary amine **214** with Grubbs' catalyst I in refluxing CH₂Cl₂. The smooth transformation of **214** into **215** is remarkable as the Grubbs' catalyst I is generally ineffective for the conversion of tertiary amines (Scheme 51).



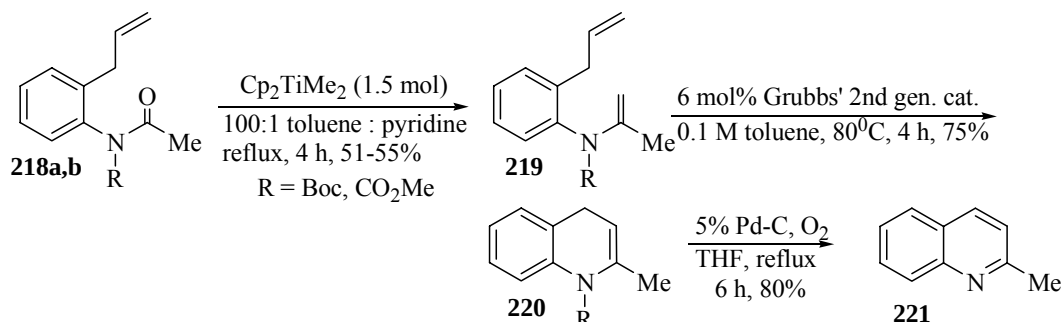
Scheme 51 RCM for the construction of chiral unsaturated *N*-heterocycles.

Tandem Morita-Baylis-Hillman and ring-closing metathesis reaction sequence as a high yielding method for the construction of highly functionalized heterocyclic sulfonamides **217** with high efficiency was utilized by Krafft *et al.* (Scheme 52).¹⁴⁶



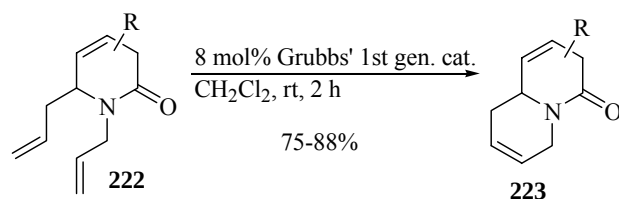
Scheme 52 RCM for the synthesis of highly functionalized sulfonamides.

A new synthetic entry to the 1,4-dihydroquinoline nucleus **220** was reported¹⁴⁷ by Bennasar *et al.* The synthetic strategy involved the amide olefination-enamide RCM sequence for the construction of dihydroquinolines **220** (Scheme 53).



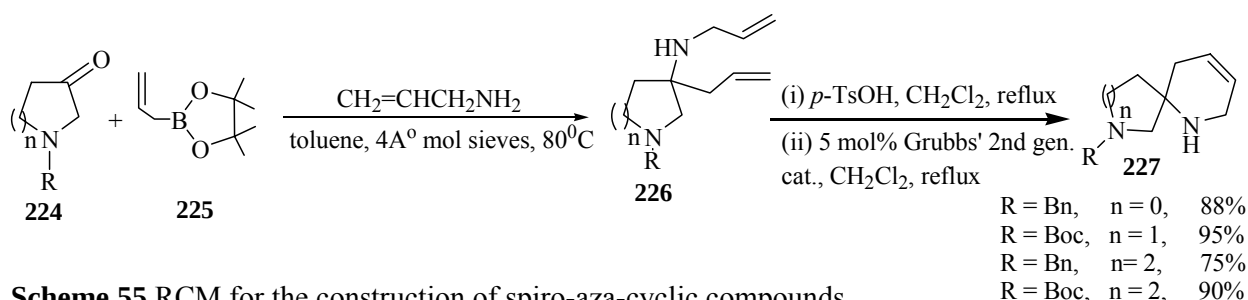
Scheme 53 RCM to construct 1,4-dihydroquinoline.

Organic compounds containing the quinolizidine skeleton are widespread in naturally occurring alkaloids and in biologically active compounds.¹⁴⁸ Recently, Sósnicki reported¹⁴⁹ a new strategy to the synthesis of quinolizidine skeleton with olefinic bonds in both the rings. The substrate **222** was subjected to ring-closing metathesis in a sequential fashion to achieve the desired tetrahydroquinolizin-4-ones **223** (Scheme 54).



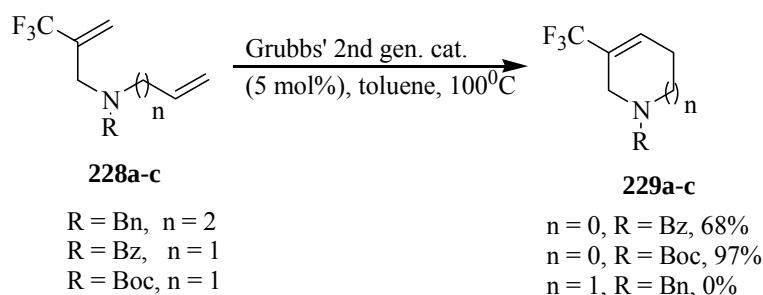
Scheme 54 Synthesis of tetrahydroquinolizin-4-ones by RCM.

Gracias *et al.* recently developed¹⁵⁰ a two-step reaction sequence using a one-pot α -aminoallylation reaction followed by the RCM reaction to afford spirocyclic diamines (Scheme 55). Treatment of the secondary amines **190** with 1.0 equiv of *p*-TsOH in CH_2Cl_2 for 30 min at reflux followed by the addition of the 5 mol% Grubbs' catalyst II gave the desired spirocyclic diamines **227** in excellent yield. In absence of the pretreatment with *p*-TsOH the reaction failed to undergo ring closure.



Scheme 55 RCM for the construction of spiro-aza-cyclic compounds.

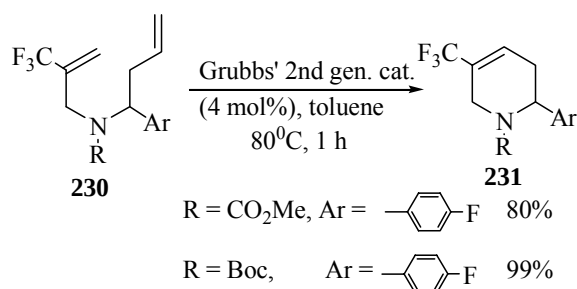
Very recently, another method for the synthesis of trifluoromethyl-containing piperidines **229** by ring-closing metathesis has been developed by Rutjes *et al.*¹⁵¹ (Scheme 56).



Scheme 56 Trifluoro-containing piperidine ring synthesis via RCM.

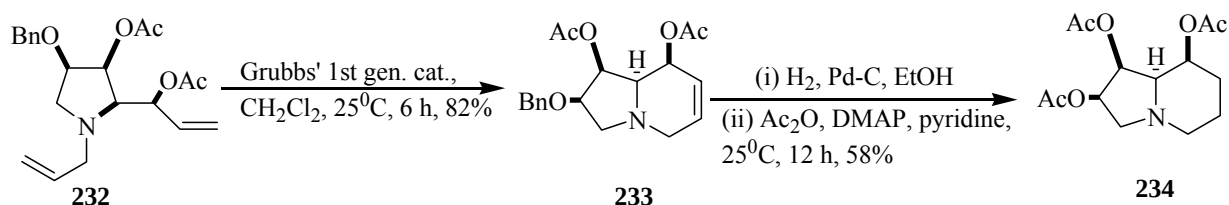
Attempts to cyclize **228a** to tetrahydropyridine **229a** failed under different RCM conditions, probably due to the presence of basic amine functionality. However, substrates **228b,c** were readily cyclized to the corresponding trifluoromethyl substituted cyclic nitrogen heterocycles **229b** and **229c**, respectively.

Similarly, some other substrates **230** were designed and subjected to the same RCM conditions to prepare the corresponding trifluoromethyl substituted tetrahydropyridine derivatives **231** in good-to-excellent yields (Scheme 57). This methodology was also successful towards the synthesis of some cyclic amino acid derivatives in moderate yields.



Scheme 57 RCM for the synthesis trifluoromethyl substituted tetrahydropyridine.

Very recently, Bhattacharjya *et al.* reported¹⁵² an important strategy for the synthesis of azabicyclic ring systems starting from a carbohydrate derivative (Scheme 58). Furanoside proved to be a versatile precursor for the synthesis of differently substituted indolizidine and pyrrolo[1,2-*a*]azepine skeleton.



Scheme 58 RCM for the synthesis of azabicyclic ring system.

The diacetate **232** smoothly underwent ring-closing metathesis with the Grubbs catalyst I to provide the indolizidine derivative **233** in 82% yield. Hydrogenation of **233** followed by acetylation gave the final compound (–)-8-*epi*-swainsonine triacetate **234**.

Recently, Arisawa *et al.* conducted¹⁵³ a thorough synthetic study of nitrogen containing heterocycles using RCM, such as chiral bicyclic lactams, 1,2-dihydroquinolines, 2-quinolines and indoles including the development of silyl-enol-ether ene metathesis and isomerization of the terminal olefins. This methodology was applied to the synthesis of (–)-coniceine **235**, (+)-angustureine **236** and also for the determination of absolute configuration of the angustureine (Figure 8).

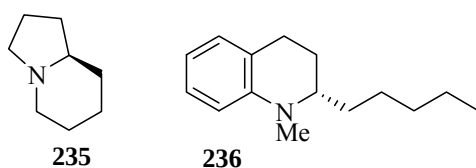
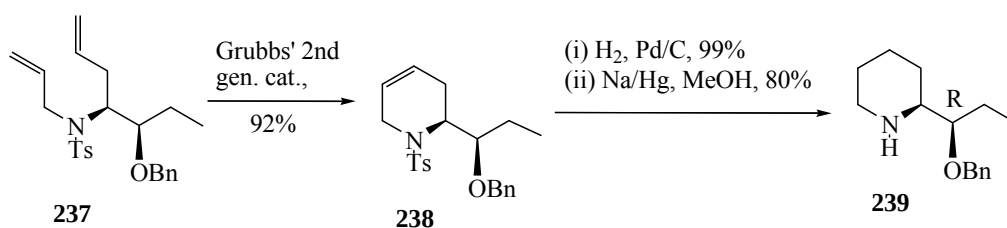


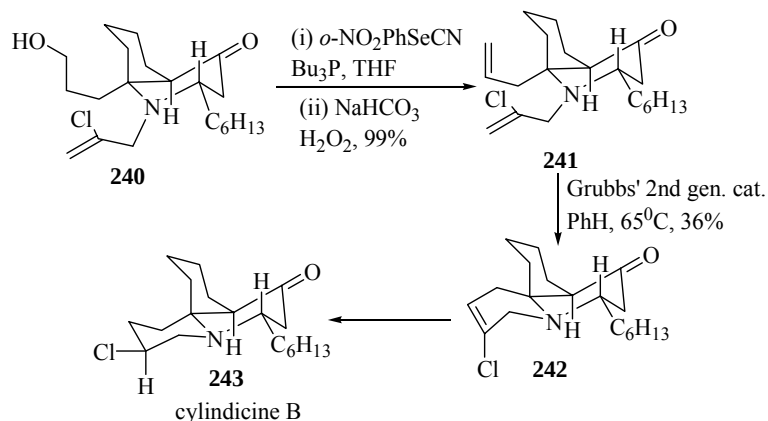
Figure 8 (–)-coniceine and (+)-(S)-angustureine

Chang *et al.* recently accomplished¹⁵⁴ the synthesis of α -conhydrine from *trans*-(2*S*,4*R*)-4-hydroxyproline *via* diastereoselective Grignard addition, regioselective Bayer-Villiger reaction and ring-closing metathesis of **237** to **238** as the key step (Scheme 59).



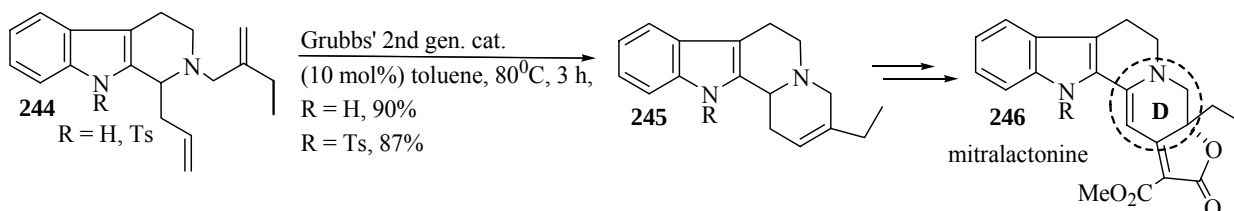
Scheme 59 Synthesis of α -conhydrine from *trans*-(2*S*,4*R*)-4-hydroxyproline.

Recently, Weinreb and co-workers reported¹⁵⁵ the total synthesis of the cylindricine B **243**, a pyridoquinoline subclass of tricyclic marine ascidian alkaloids. The key steps involved the *N*-acylketiminium ion / olefin hetero-Diels-Alder reaction and ring-closing metathesis of vinyl chlorides (Scheme 60).



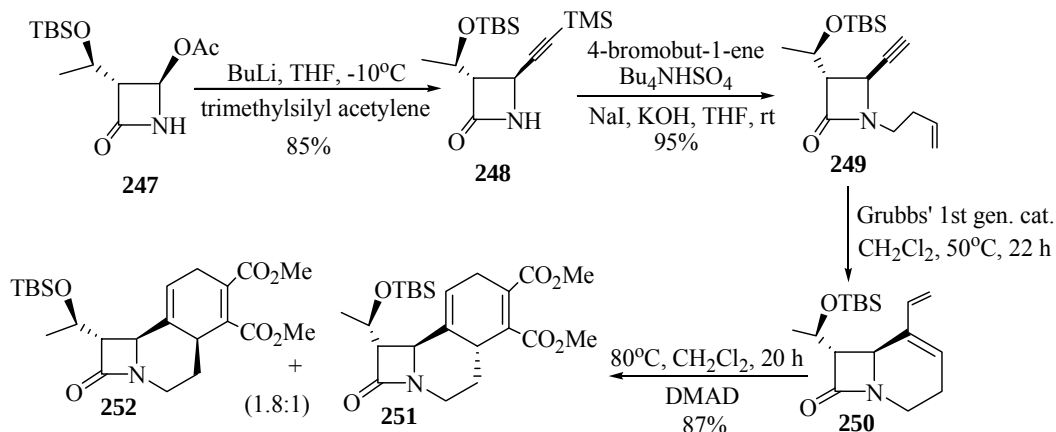
Scheme 60 Total synthesis of the cylindricine B.

Highly functionalized tetracyclic intermediate of pentacyclic indole alkaloid mitralactonine **246** was conveniently synthesized¹⁵⁶ by Chavan *et al.* employing RCM as the pivotal step for the construction of the D-ring (Scheme 61). The diene precursor **244** was subjected to 10 mol% Grubbs' catalyst II in toluene at 80°C for 3 h to afford the desired cyclized product **245** in excellent yield. Easy functionalization of this tetracyclic unit finally gave the indole alkaloid mitralactonine **246**.



Scheme 61 RCM for the synthesis of tetracyclic intermediate of pentacyclic indole alkaloid mitralactonine.

Savignac and Genêt described¹⁵⁷ the synthesis of new tricyclic β -lactams **251** and **252** via one-pot enyne metathesis and Diels-Alder reaction (Scheme 62).

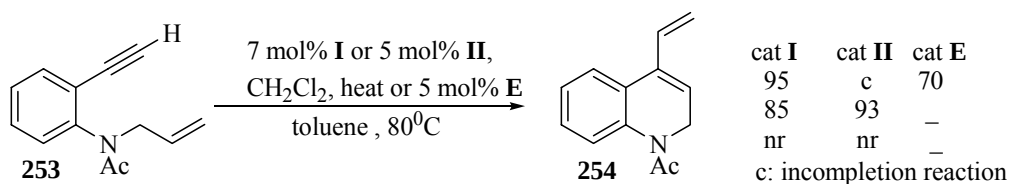


Scheme 62 RCEM for the synthesis of polycyclic β -lactam.

Ring-closing enyne metathesis (RCEM) of **249** with 5 mol% of Grubbs' catalyst I afforded the bicyclic diene compound **250** which upon treatment with dimethylacetylenedicarboxylate (DMAD) gave cycloadducts **251** and **252**. Interestingly, one-pot metathesis-cycloaddition of the enyne **251** gave better

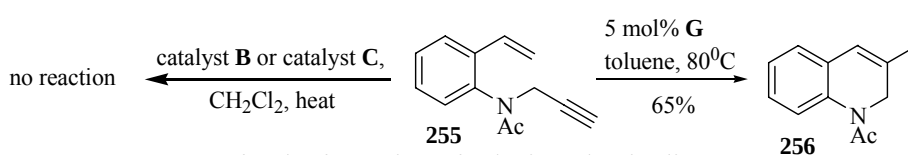
yield of the cycloadducts, compared to stepwise procedure.

Pérez-Castells and co-workers¹⁵⁸ made an exhaustive study on the reactivity of different generations of catalysts on the enyne metathesis reaction course. Substrate **253** was treated with different catalysts in CH₂Cl₂/toluene to give different results. Grubbs' catalyst I afforded the highest yield (95%) of the 4-vinyl-1,2-dihydroquinoline **254**. The reaction was incomplete with Grubbs' catalyst II whereas catalyst **E** furnished the cyclized product **254** in 70% yield. This study was also extended to the synthesis of benzazepine from *N*-acetyl,*N*-homoallyl-2-prop-2-ynyl benzene (Scheme 63).



Scheme 63 RCEM of nitrogen heterocycles with different ring size.

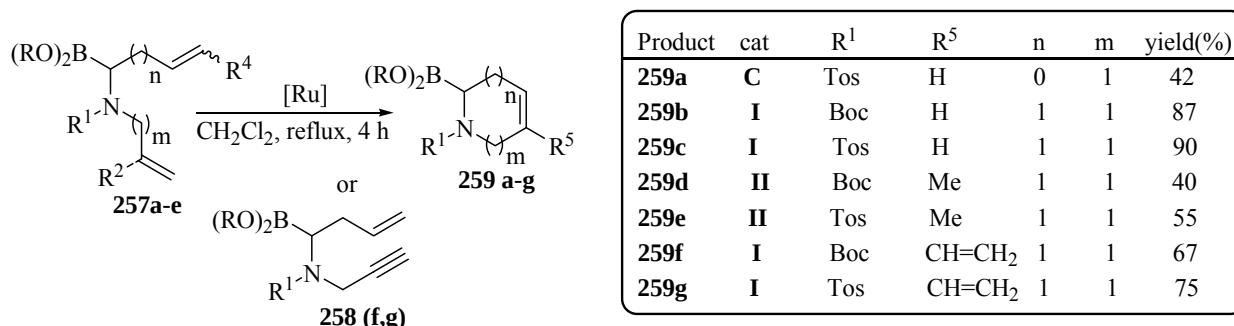
It is quite clear that Grubbs' catalyst II was much more sensitive towards steric hindrance as it improved the yield of the cyclized product with less hindered substrate **263**. It should also be noted that neither Grubbs' catalyst I nor catalyst II were able to catalyze the cyclization of the substrate **255** having double bond conjugated with the aromatic ring. On the other hand such type of compounds **255** underwent complete conversion with 5 mol% Hoveyda-Grubbs' catalyst **E** (Scheme 64).



Scheme 64 RCEM for the formation of substituted quinoline.

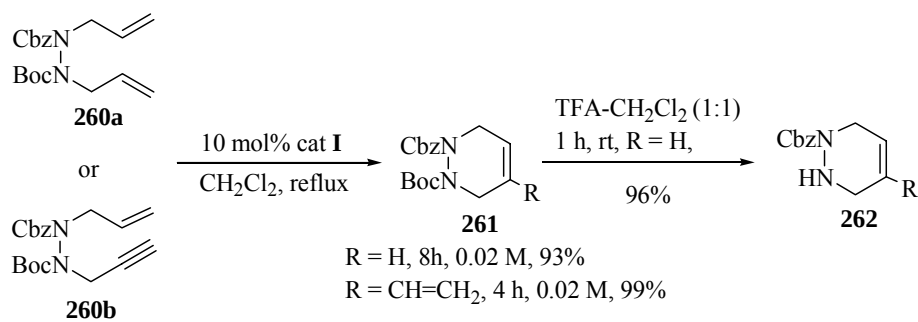
This methodology was also applied to the synthesis of indole nucleus with Hoveyda-Grubbs' catalyst (**E**). The reactivity of the most popular ruthenium complexes were studied but there is no exact rule for their preferential use although Grubbs' catalyst II gave better results with monosubstituted olefins and worse with hindered substrates.

Synthesis of a variety of *N*-protected cyclic α -aminoboronates¹⁵⁹ **259a-g** was achieved by Carboni *et al.* that could be further engaged in boropeptide synthesis. Ruthenium catalyst I was found to be effective for six-membered ring α -amidoboronic esters in 40-90% isolated yield in CH₂Cl₂ at reflux for 4 h. Grubbs' catalyst I or II is unable to cyclize compound **257a** (Scheme 65).



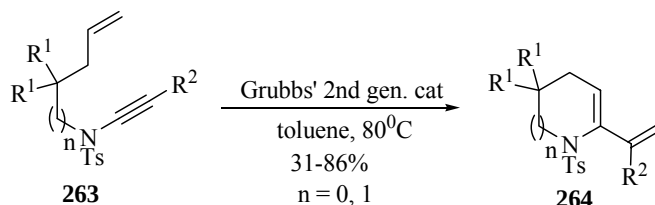
Scheme 65 RCM for the construction of *N*-protected cyclic α -aminoboronates.

Six-membered heterocycles containing an *N-N* bond possess significant biological activity. Piperazic acid and 1-azafagomine are well known six-membered compounds with cyclic hydrazine skeleton. Although a number of methods have been reported for the synthesis of six-membered cyclic hydrazine,¹⁶⁰ Tae and coworkers synthesized¹⁶¹ cyclic hydrazine **261** by ring closing metathesis of dienes and enynes tethered by an *N-N* bond (Scheme 66).



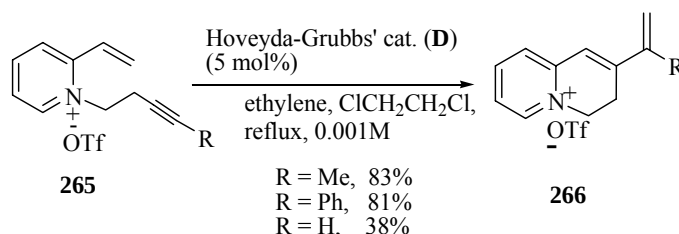
Scheme 66 Synthesis of cyclic hydrazine via RCM/RCM.

Cyclic dienamides are important skeletons of natural products and biologically active substances. Very recently Mori *et al.* synthesized¹⁶² a number of cyclic dienamides **264** using ruthenium catalyzed ring-closing metathesis of ene-ynamides **263**. Substituents on the alkyne part (i.e. Ph group or an electron withdrawing group) were well tolerated under this reaction condition. The cyclic dienamides **264** are also good precursor towards the Diels-Alder reaction and afforded an indole or isoquinoline derivatives under mild conditions in high yield (Scheme 67).



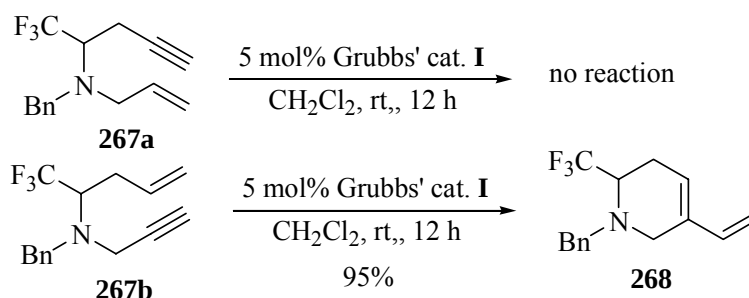
Scheme 67 Cyclic dienamides synthesis by RCEM.

Recently, a new approach to 1- and 2-vinyl substituted 3,4-dihydroquinolizinium cation by ring-closing enyne metathesis (RCEM) reaction from appropriately substituted pyridinium substrates under an atmosphere of ethylene and using the Hoveyda-Grubbs' catalyst (**D**) was reported by Cuadro and Vaquero.¹⁶³ Ring-closing enyne metathesis of the enyne **265** with Hoveyda-Grubbs' catalyst **D** in CH_2Cl_2 gave the desired 2-vinyl-3,4-dihydroquinolizinium salt **266** in 83% yield. Substitution on the vinyl moiety of substrates **265** resulted in failure of the RCEM reaction and formation of cross metathesis products (Scheme 68).



Scheme 68 New approach to 1- and 2-vinyl substituted 3,4-dihydroquinolizinium cation by RCEM.

Allyl-homoallyl adducts in the presence of 5-10 mol% Grubbs' catalyst I easily reacted at room temperature to afford the expected dihydropiperidine derivative. However, RCM of *N*-methallylamines proceeded under reflux and with a longer reaction time. Homopropargyl allylamine **231a** did not undergo cyclization even under reflux condition or with the use of Grubbs' catalyst II (Scheme 69).¹⁶⁴

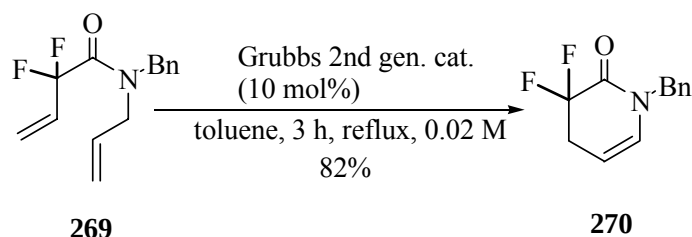


Scheme 69 Studies of RCM of the two substrates.

4.3 SYNTHESIS OF FIVE- AND SIX-MEMBERED LACTAMS

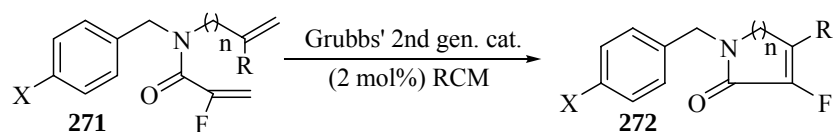
Vinyl fluorides are versatile building blocks and are widely used in organic and medicinal chemistry e.g. isosteres of peptides and amides.¹⁶⁵

Very recently, Fustero *et al.* reported¹⁶⁶ a new example of the tandem RCM-isomerization reaction that allowed the efficient preparation of fluorinated and non-fluorinated unsaturated lactam derivatives of various sizes. Grubbs' catalyst II in refluxing toluene is likely to generate a ruthenium hydride species⁵⁹ *in situ*, without any use of additives which may in turn be responsible for the isomerization reaction. The presence of *gem*-difluoro moiety in the starting materials also exerted a pivotal effect by directing the isomerization step, making the overall transformation a regioselective process (Scheme 70).



Scheme 70 RCM for the synthesis of unsaturated lactam.

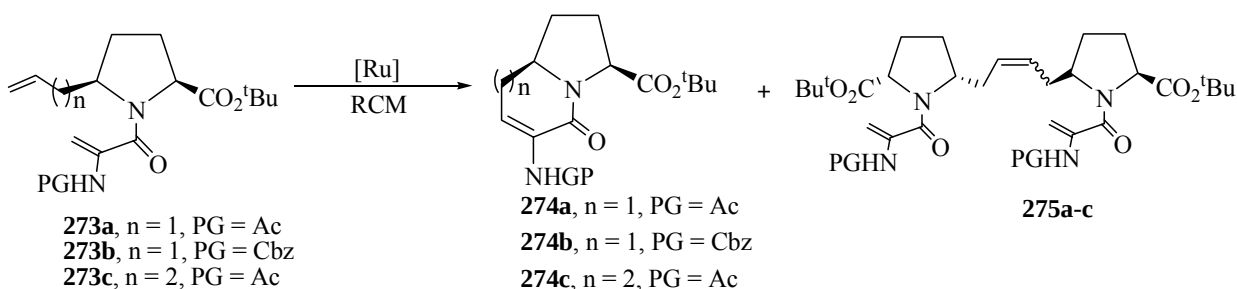
Grubbs and co-workers¹⁶⁷ reported their unsuccessful attempts to cross metathesis reaction of vinyl halides and olefins. The first ring closing metathesis of alkenyl α -fluoroacrylamides incorporating a fluorinated double bond was successfully reported by Haufe and co-workers.¹⁰⁰ They showed that vinyl fluorides that are a part of an α,β -unsaturated carbonyl system to be more suitable for RCM reaction. A number of terminal *N*-alkenyl-*N*-benzyl- α -fluoroacrylamides **271** were synthesized by acylation with α -fluoroacrylic acid. Several *N*-alkenyl- α -fluoroacrylamides **271** were cyclized in the presence of 2 mol% of Grubbs' catalyst II at room temperature to form an unsaturated γ -lactam **272a** and at 80°C to form the corresponding δ -lactam **272b,c** bearing the fluoro vinyl moiety in 76-86% yields. Under the same conditions corresponding seven- and eight-membered *N*-heterocycles were not formed (Scheme 71).



Compound	Time (min)	Temp ($^{\circ}\text{C}$)	Product	Yield (%)
n = 1, 271a , R = H, X = H,	10	rt	272a	79
n = 2, 271b , R = H, X = H	120	80	272b	86
n = 1, 271c , R = CH ₃ , X = H	480	80	272c	46
n = 2, 271d , R = H, X = OMe	240	80	272d	81
n = 2, 271e , R = H, X = F	240	80	272e	76

Scheme 71 Synthesis of *N*-benzyl five-membered lactams via RCM.

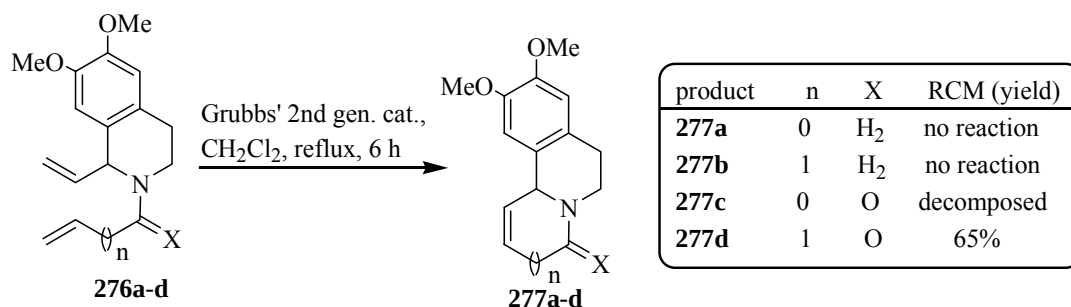
Manzoni *et al.* reported¹⁶⁸ the first example of ring-closing metathesis of dehydroamino acid for the construction of bicyclic lactams. It was observed that both the steric and electronic factors of the *N*-protecting group played an important role to the behavior of ring-closing metathesis reaction.



Scheme 72 RCM for the synthesis of δ -substituted α,β -unsaturated δ -lactams.

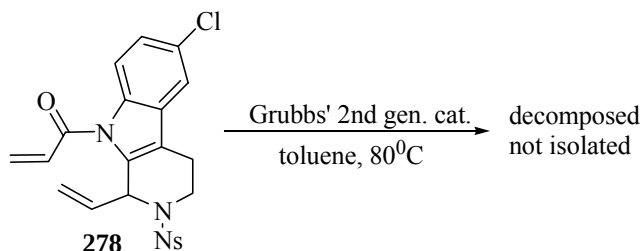
Low yields of metathesis were obtained when the sterically bulky amino acid moiety was hindering the approach of the catalyst ruthenium species to the double bond of the substrate. Substrate **273c**, when subjected to Grubbs' catalyst II at 100 $^{\circ}\text{C}$ in toluene for 72 h gave the cyclized product **274c** in 53% yield along with the bicyclic lactam **274a** (14%) due to isomerisation of double bond followed by ring closure of the isomerized intermediate (Scheme 72).

Hiemstra and Rutjes demonstrated¹⁶⁹ the usefulness of α -vinyl tetrahydroisoquinolines and tetrahydro-1*H*- β -carboline systems for the construction of heterocycles *via* ring-closing metathesis reaction. Sterically more hindered and rigid characteristics of the vinyl moiety compared to the flexible allyl moiety make this functionality less attractive for the metathesis reaction. However, they showed that vinyl moiety could be constructively used in RCM (Scheme 73).



Scheme 73 Synthesis of condensed aza-cycles via RCM.

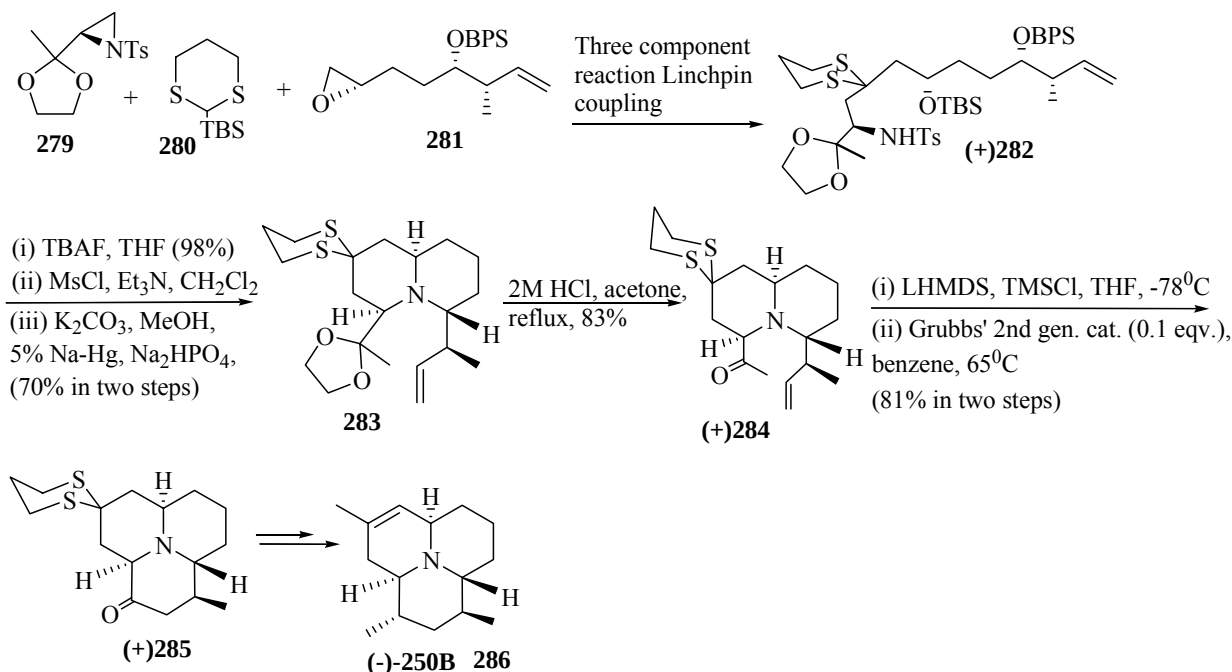
Both the tertiary amines **276a,b** failed to undergo metathesis reaction. However the amides **276c,d** showed good conversion to the metathesis products **277c,d**. 5,6-bicyclic systems **277c** was formed in good yield but isolation of the product was impossible due to rapid decomposition *via* aerial oxidation. Best result was obtained with the longest alkenyl chain on nitrogen atom. The metathesis precursor **278** on treatment with Grubbs' catalyst II in toluene at 80°C afforded the metathesis product but could not be isolated due to aerial oxidation (Scheme 74).



Scheme 74 RCM of the precursor with unsuccessful results.

The stereoselective total synthesis of novel quinolizidiene alkaloid (+)-epiquinamide was presented by Blaauw *et al.*¹⁷⁰ starting from amino acid L-allysine ethylene acetal. Key steps in the synthesis involved highly diastereoselective *N*-acyliminium ion allylation and a ring closing metathesis reaction to provide the bicyclic skeleton.

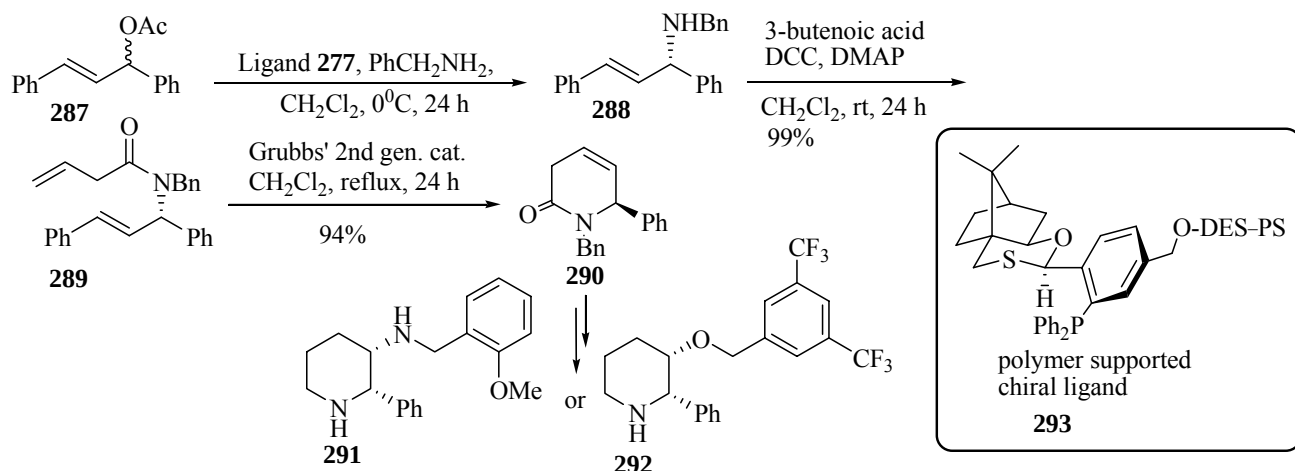
A stereocontrolled total synthesis of an alkaloid (-)-**250B** (**286**), isolated from the skin of neotropical poison-frogs, was reported¹⁷¹ recently by Smith III *et al.* employing a dithiane three component linchpin coupling, a one pot sequential construction of the embedded indolizidine ring and ring closing metathesis reaction of **284** to **285** (Scheme 75).



Scheme 75 RCM-based stereocontrolled total synthesis of an alkaloid (-)-**250B**.

A concise and practical catalytic asymmetric synthesis of (-)-CP-99,994 and (-)-L-733,061 was achieved

by Nakano *et al.*¹⁷² Key steps for these syntheses involved the Pd-catalyzed asymmetric allylic amination and a ring-closing metathesis reaction of **289** to **290** (Scheme 76).



Scheme 76 Catalytic asymmetric synthesis of (-)-CP-99,994 and (-)-L-733,061 via RCM.

Ring-closing metathesis reaction sometimes accompanied by variable amounts of the other compounds that arise as a result of isomerization of the newly created double bond.^{60,173} Several reports indicated that the decomposition products of Ru-metathesis catalyst (generally Ru-hydride complexes) may be responsible for these side reactions and especially for alkene isomerization. Although the side reactions constitute a general problem but it is also true that several authors in specific synthetic strategies used them advantageously.

Martin group recently developed¹⁷⁴ a novel approach to a variety of indole alkaloids from a key intermediate **294** by employing a sequence of two RCM reactions and one zirconocene-catalyzed carbomagnesation. A variety of substituents at C (15) in **294**, can be installed by exploring the 1,4-conjugate addition of various nucleophiles onto α,β -unsaturated lactams to complete the concise total synthesis of corynanthe group of indole alkaloid **295** and also the formal synthesis of other indole alkaloids such as **296**, **297** and **298** (Figure 9).

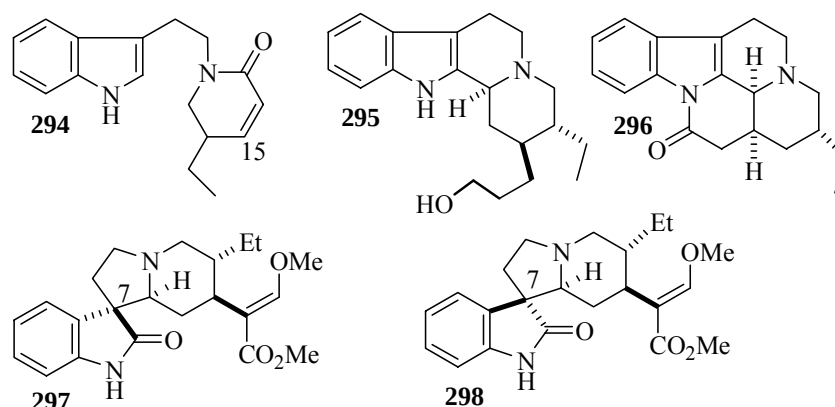


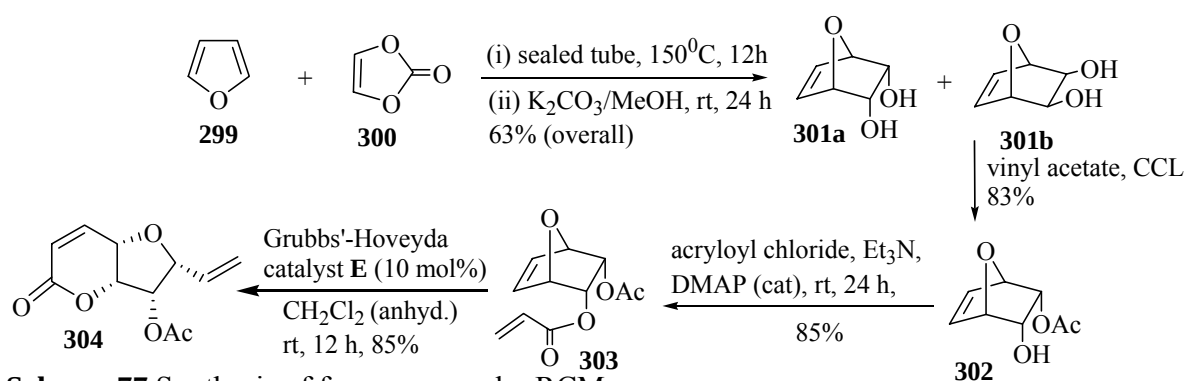
Figure 9 A novel approach to variety of indole alkaloids.

5. SYNTHESIS OF NITROGEN AND OXYGEN HETEROCYCLES BY DOMINO PROCESS VIA RCM

Tandem catalysis can offer unique and powerful strategies for converting simple starting materials into more complex products in a single step generating less waste and minimizing the excessive handling of multistep process. In this regard, ruthenium catalyst *i.e.* Grubbs' catalysts are shown to catalyze two mechanistically distinct transformations to offer unique protocol that effects multiple bond changes in a single operation.

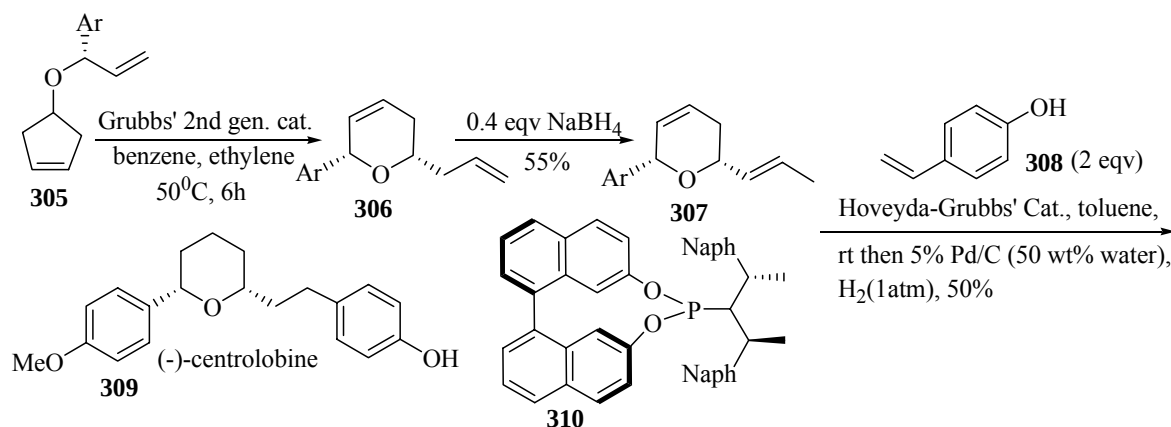
5.1 SYNTHESIS OF HETEROCYCLES BY ROM / RCM STRATEGY

An efficient stereoselective route to the synthesis of dihydrofuropyran skeleton starting from furan using ring-opening, cross and ring-closing metathesis approach was recently described¹⁷⁵ by Plumet *et al.* The RCM precursor **303** on treatment with Hoveyda-Grubbs catalyst **E** (10 mol%) in anhydrous CH₂Cl₂ under ethylene atmosphere afforded the desired furanopyrone **304** in 90% yield (Scheme 77).



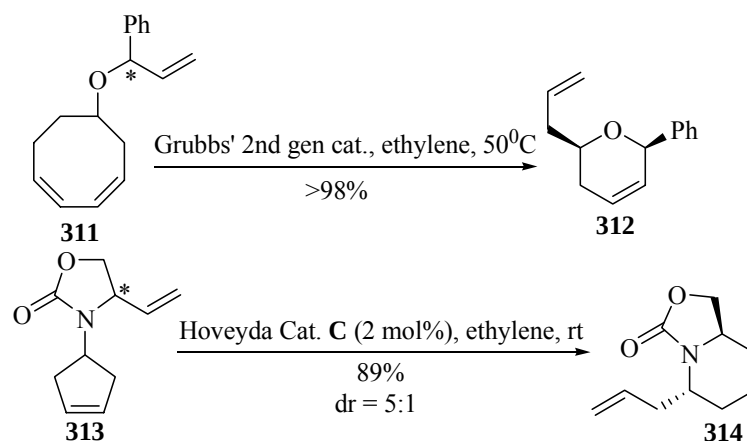
Scheme 77 Synthesis of furanopyrone by RCM.

Among the different types of metathesis reactions, diastereoselective ring rearrangement metathesis (dRRM) is especially powerful in the asymmetric synthesis leading to various natural products. Blechert *et al.* recently reported¹⁷⁶ the stereoselective synthesis of 2,6-disubstituted dihydropyrans to the total synthesis of (-)-centrolobine. During the study of dRRM, different conditions were employed and in the optimized procedure, the dRRM reaction was carried out using Grubbs' catalyst II in benzene, saturated ethylene atmosphere at 50°C in a pressure vessel to furnish the desired product **306**. Isomerization of the dRRM product with 40 mol% NaBH₄ to dihydropyran without affecting the endocyclic double bond followed by cross-metathesis finally afforded the targeted molecule (-)-centrolobine **309** (Scheme 78).



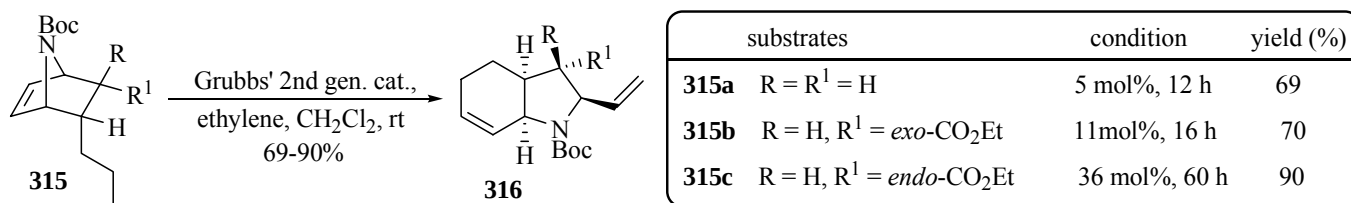
Scheme 78 Stereoselective synthesis of 2,6-disubstituted dihydropyrans to the total synthesis of (-)-centrolobine.

Ring rearrangement metathesis has already proven to be a powerful tool for the synthesis of complex molecules. An interesting methodology to create a new stereogenic centre by RCM was recently reported¹⁷⁷ by Blechert *et al.* They have envisaged that cyclodienes such as **311** would rearrange to give products with an internal double bond in the side chain. However, **311** was converted into the dihydropyran **312** with a diastereomeric mixture 7:2 in favor of the 2,6-*cis* product. Similarly, cyclopentene derivatives of carbamate **313** underwent rearrangement most effectively with Hoveyda catalyst **C** (2 mol%) in 89% yields and good diastereoselectivity (5:1) to give the nitrogen heterocycles (Scheme 79).



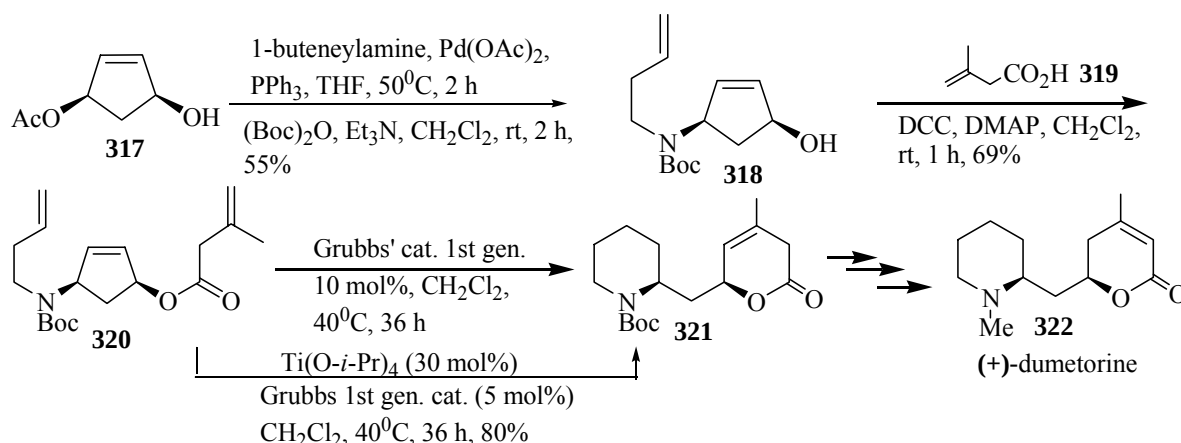
Scheme 79 Ring rearrangement RCM for the synthesis of pyran/furan systems.

Rainier *et al.* also recently utilized¹⁷⁸ 7-azanorbornenes for the synthesis of hexahydroindoline derivatives **316** via ring opening / ring closing metathesis upon treatment with Grubbs' catalyst II (Scheme 80).



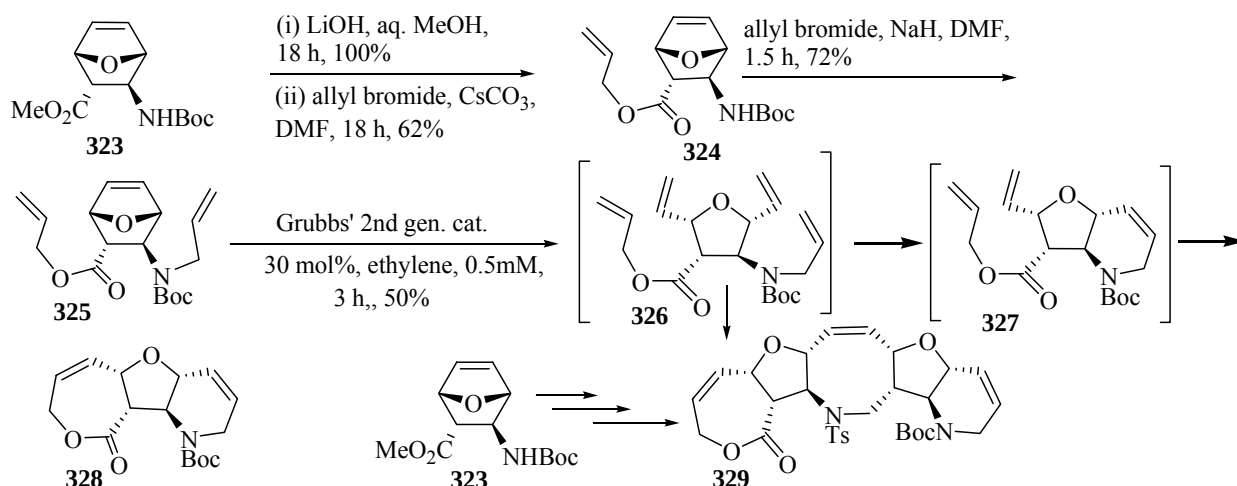
Scheme 80 RCM for the synthesis of synthesis of hexahydroindoline derivatives.

Blechert *et al.* reported¹⁷⁹ the first enantioselective synthesis of naturally occurring alkaloid (+)-dumetorine by the application of ring rearrangement metathesis strategy to convert the intermediate **329** to **322** (Scheme 81).



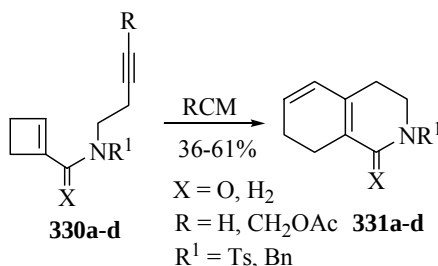
Scheme 81 First enantioselective synthesis of naturally occurring alkaloid (+)-dumetorine.

A tandem metathesis approach has been reported¹⁸⁰ for the synthesis of stereochemically defined tri- and penta-heterocyclic ring system by Winkler *et al.* The RCM precursor **325** on exposure to Grubbs' catalyst II, in ethylene atmosphere initially afforded a ring opening of oxanorbornanene then the six-membered tetrahydropyridine ring intermediate and finally a tricyclic heterocycle **328**. In a similar manner the pentacyclic heterocycle **329** have also been synthesized starting from the basic unit **323** (Scheme 82).



Scheme 82 Stereochemically defined tri- and penta-heterocyclic ring system by RCM.

Ring opening metathesis (ROM)-ring closing metathesis (RCM) is a very attractive method for the synthesis of bicyclic compounds.^{181,182} Utilizing this methodology, Mori *et al.* synthesized¹⁸³ isoquinoline derivatives from cyclobutenylmethyl amine derivatives having an alkenyl moiety in a tether using Grubbs' 2nd generation ruthenium carbene complex under ethylene gas. When cyclobutenylmethylenamines and cyclobutenecarboxamides **330a-d** were treated with 5-10 mol% of Grubbs' catalyst II under suitable condition afforded the desired isoquinoline and isoquinolone derivatives **331a-d** in good yields respectively (Scheme 83).



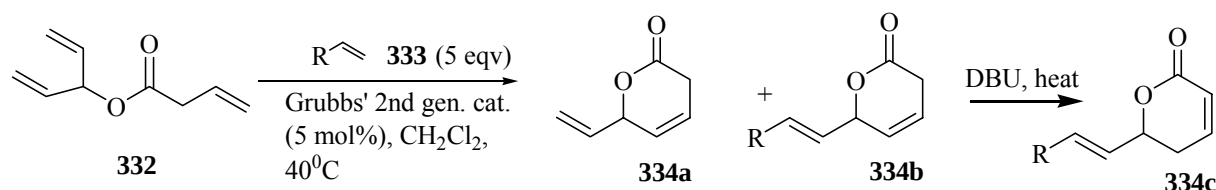
Scheme 83 Construction of isoquinoline derivative.

5.2 SYNTHESIS OF HETEROCYCLES BY TANDEM RCM

A pyrone subunit is found to be present in a large number of natural products. Similarly, butenolide is also a framework of many compounds having interesting biological activity. A direct synthesis of butenolides and β,γ -unsaturated δ -lactones has been devised¹⁸⁴ by Piva *et al.* by combining a ring closing metathesis with cross-metathesis process.

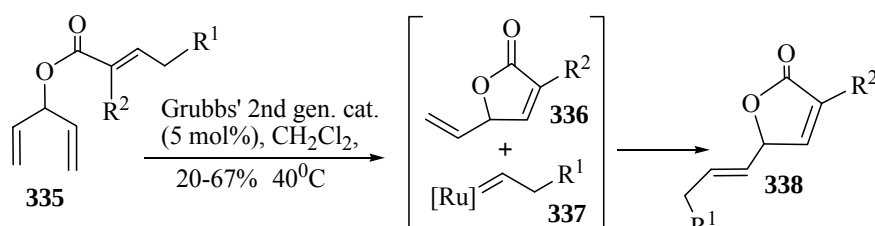
Recently, Piva *et al.* developed an efficient method for the synthesis of pyrones by a tandem ring-closing-cross-coupling metathesis reaction.¹⁸⁵ The approach was based first on a RCM process of

3-*O*-(1,4-pentadienyl)3-butenolate **332** promoted by Grubbs' catalyst II to form compound **334** as an intermediate. In the presence of various alkenes and with the same catalyst, **334a** was converted into functionalized lactones **334b** which were isomerised into α -pyrones **334c** by treatment with a base such as DBU (Scheme 84).¹⁸⁶ The first step of the reaction generates a new carbene group, which is capable of functionalizing the lateral unsaturated chain during the second coupling reaction. Following this route, the transfer of the alkyl group, initially fixed on the acid chain, avoids the use of an alkene partner introduced in large excess. This method also avoids the use of toxic acrylic esters.



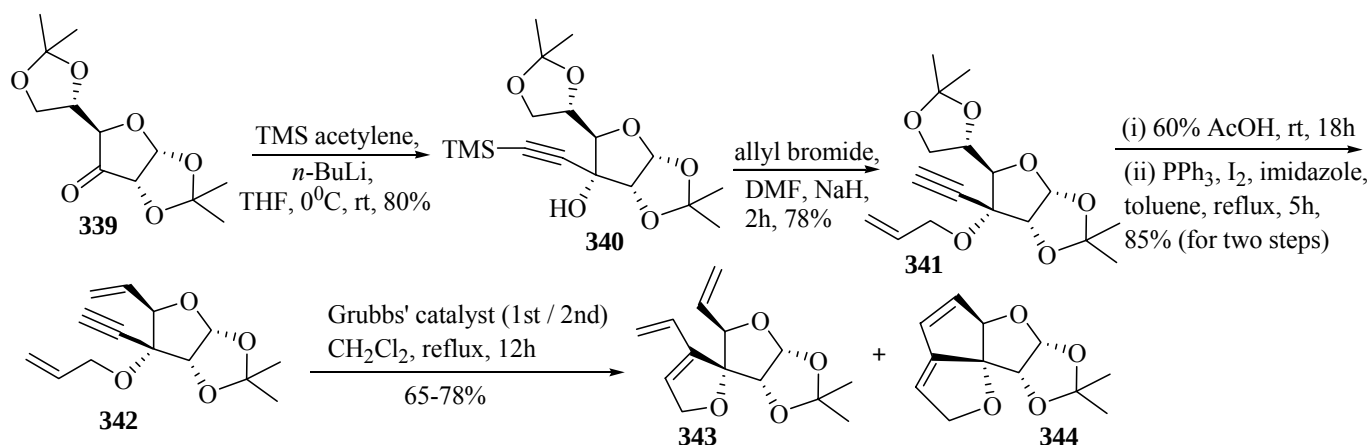
Scheme 84 β,γ -Unsaturated lactone by RCM.

Conjugated esters **298** were converted directly into five-membered ring lactones **338** without the introduction of an additional alkene as a counterpart in the reaction media (Scheme 85).¹⁸⁶



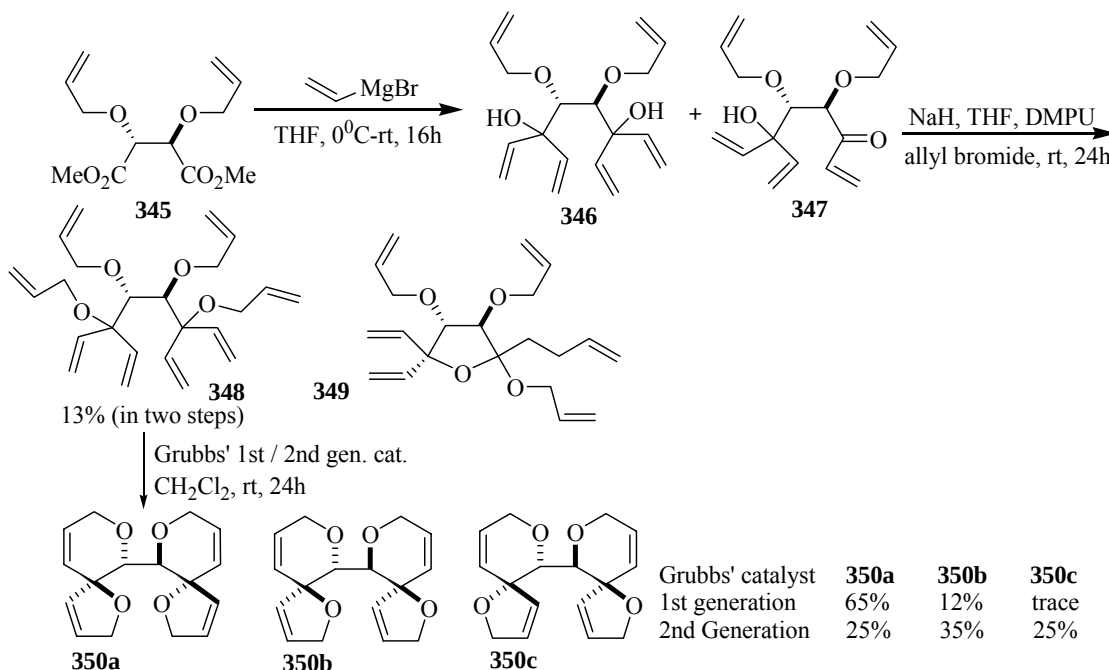
Scheme 85 Substituted α,β -unsaturated five-membered lactone.

A tandem enyne/ring-closing metathesis approach on a sugar template leading to a novel angularly fused dioxatriquinane was achieved^{187,188} from a readily available ketone **339**. The precursor dienyne **342** on treatment with Grubbs' catalyst I or II afforded the RCM product **343** exclusively. The dioxatriquinanes skeleton **344** was achieved by removing the acetonide group from the precursor **342** which in turn could probably bring the two double bonds closer after the initial enyne metathesis to relieve the ring strain and protecting the hydroxyl group as acetate and finally with Grubbs' catalyst I / II under different reaction conditions (Scheme 86).



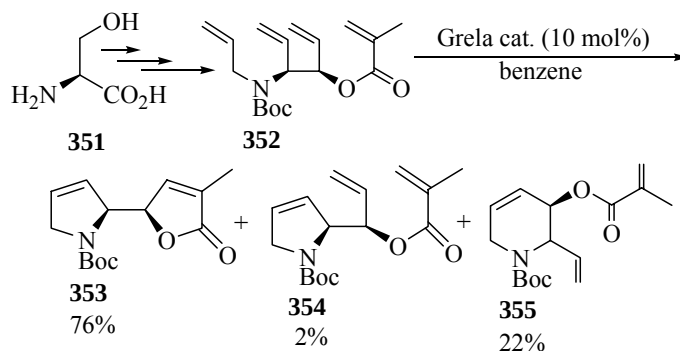
Scheme 86 Synthesis of a novel angularly fused dioxatriquinane by RCM/RCM.

An interesting multiple RCM reaction i.e. quadruple ring-closing metathesis strategy has been developed¹⁸⁹ by Wallace (Scheme 87).



Scheme 87 A multiple RCM sequence to form the stereoselective oxacycles.

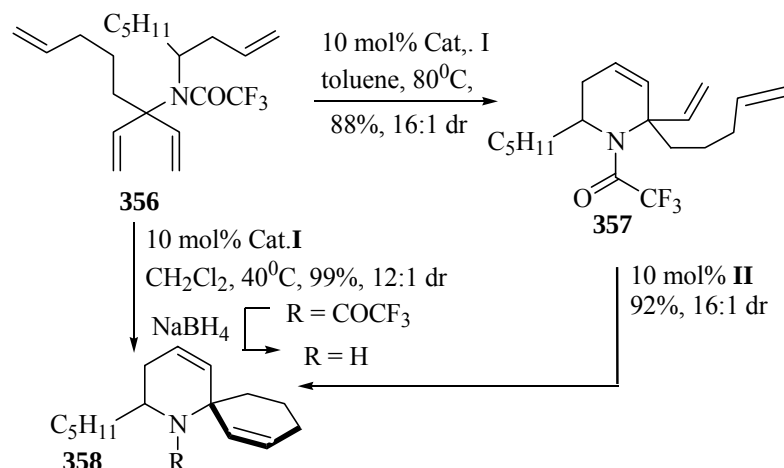
A novel synthesis¹⁹⁰ of enantiopure (+)-*N*-Boc-norpandamarilactone-A, a part of *Pandanus* variety distributed in tropical and subtropical regions used in traditional folk medicine for strengthening the heart and hypoglycemic purpose was reported recently by Honda *et al.* A double ring closing metathesis is the key step where two five membered heterocyclic rings were constructed in one step. The RCM precursor triene **352** was prepared by a sequence of reaction starting from L-serine. Examining a variety of reaction conditions for compound **352**, they have found among several catalysts (Grubbs' catalyst I, Hoveyda catalyst and Grela catalyst) Grela catalyst was proved to be most effective one in 10 mol% which afforded the targeted molecule **353** in 76% yield (Scheme 88). The bis-five-membered product **353** is supposed to be a kinetically controlled product.



Scheme 88 RCM for the triene system.

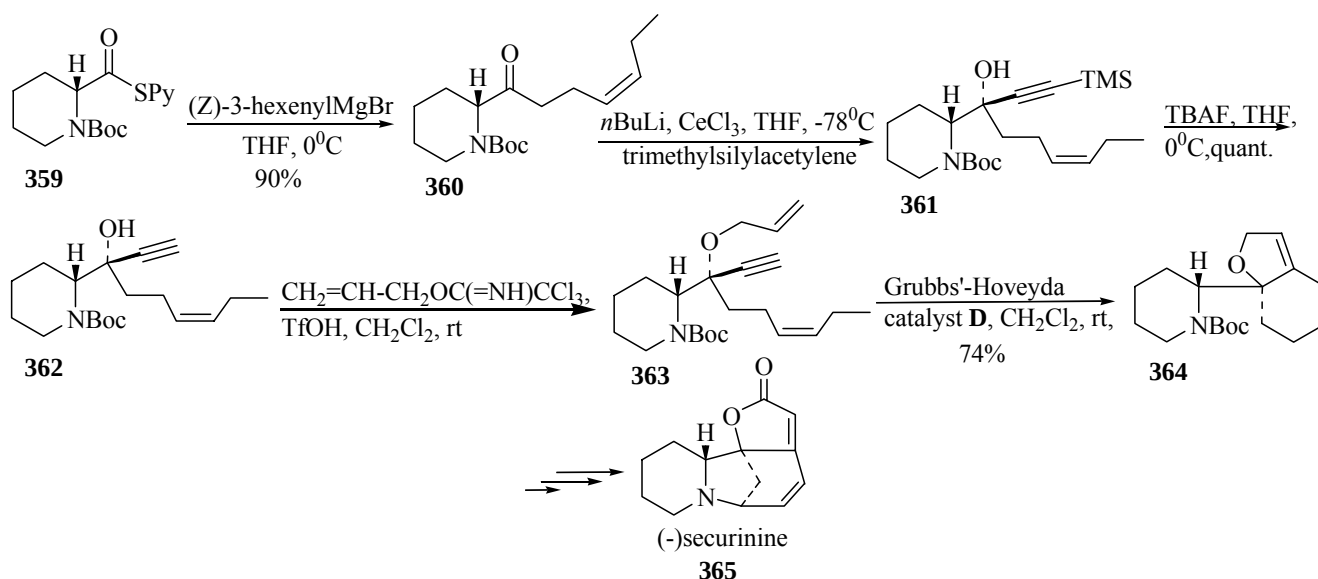
Harrity *et al.* recently reported¹⁹¹ the stereo-controlled synthesis of functionalized spiro-piperidine through a diastereoselective tandem RCM reaction. The tetraene **356** was subjected to the tandem RCM reaction in CH_2Cl_2 and toluene at elevated temperature using Grubbs' catalyst II to form spiro-piperidine in excellent

yield, but with an almost equal mixture of diastereomers. The diastereoselectivity could be improved by subjecting the tetraene substrate to less active Grubbs' catalyst I (10 mol%) in refluxing CH_2Cl_2 to provide the spiropiperidine **358** in high yield and in 12:1 diastereomeric ratio. Diastereoselectivity, therefore strongly depends on the nature of the catalyst used in the reaction medium (Scheme 89).



Scheme 89 Stereocontrolled synthesis of functionalized spiropiperidine by a tandem RCM.

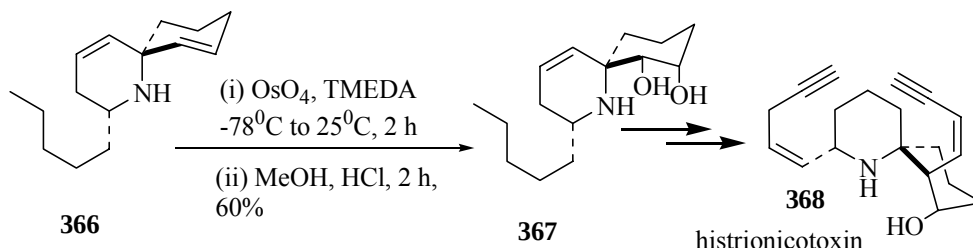
A diastereoselective total synthesis of (-)-securinine, a naturally occurring securinega alkaloid in optically pure form was achieved¹⁹² by ring closing metathesis strategy as one of the key steps from the corresponding dienyne. The dienyne **363** was treated with highly active ruthenium catalyst (Grubbs'-Hoveyda catalyst **D**) in CH_2Cl_2 to furnish the cyclized product **364** and accomplishment of the total synthesis of (-) securinine **365** was completed in a sequence of reactions, oxidation at the allylic position followed by bromination, deprotection with TFA and subsequent cyclization with K_2CO_3 (Scheme 90).



Scheme 90 RCM-RCM is the main step for the total synthesis of (-)-securinine.

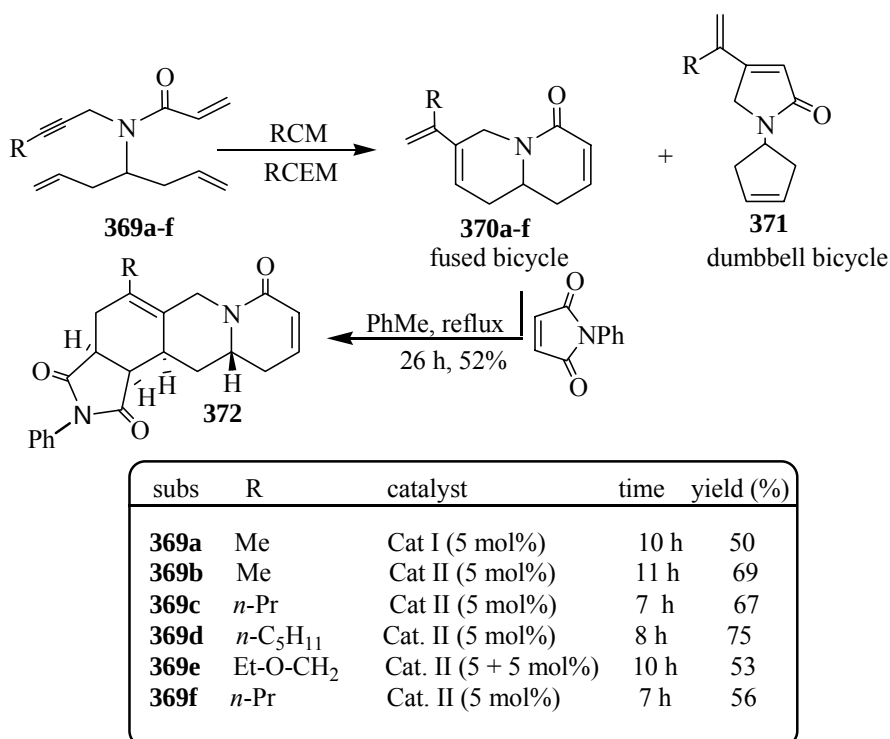
Additionally further functionalization of the spiropiperidine was carried out through a regio-stereoselective dihydroxylation reaction employing Donohue's OsO_4 -TMEDA conditions (Scheme 91). This tandem

RCM-dihydroxylation sequence had successfully set three of the four-stereogenic centres required for elaboration to histrionicotoxin target.



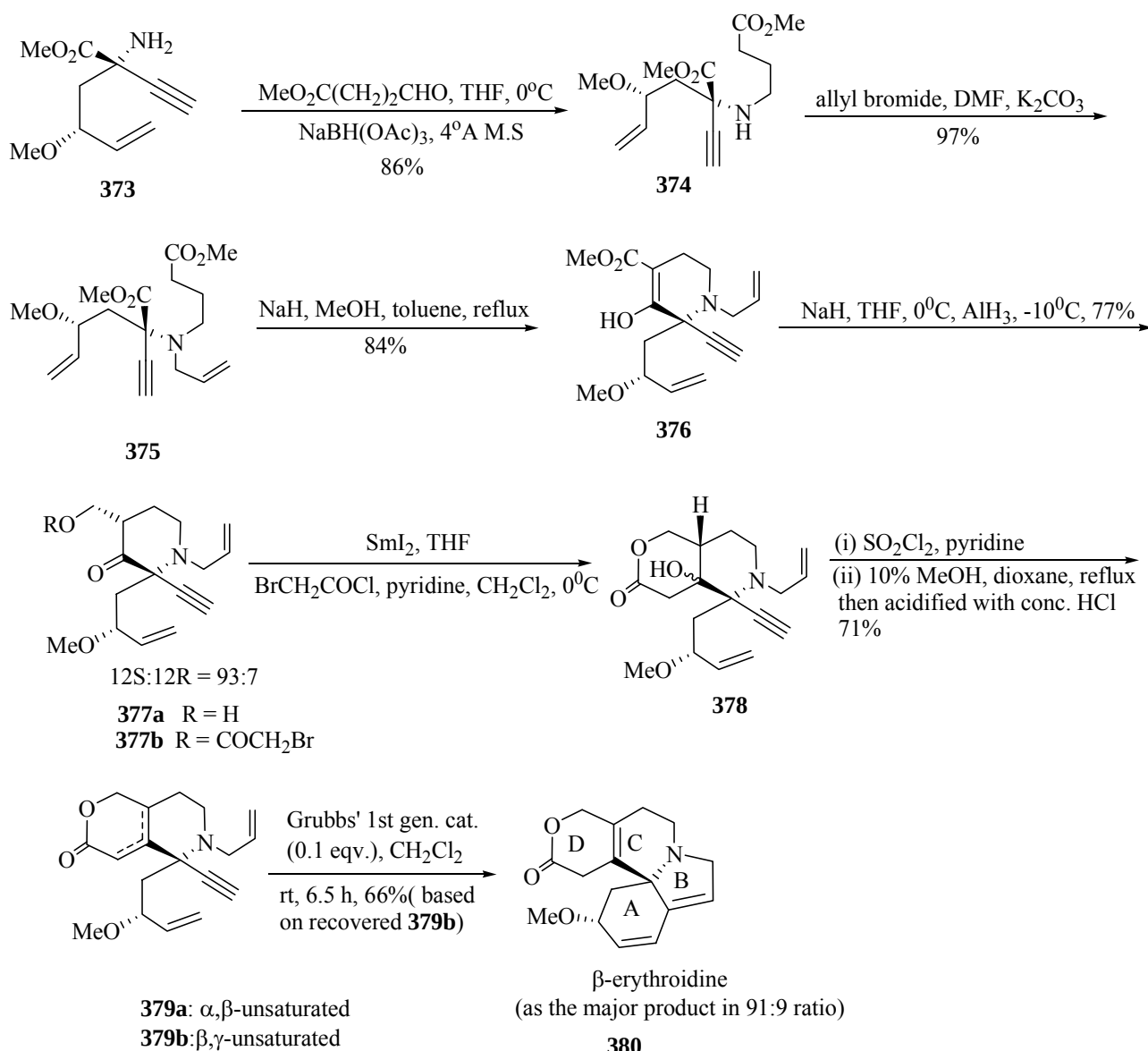
Scheme 91 A tandem RCM-dihydroxylation sequence.

Fused bicyclic lactams having quinolizidine alkaloid skeleton are common structural units of many important compounds displaying a broad range of biological activities.¹⁹³ Recently, Ma and co-workers reported¹⁹⁴ a highly stereoselective synthesis of bicyclic quinolizidine alkaloids and their analogues bearing 1,3-diene moiety *via* tandem ring closing metathesis reaction of *N*-alkenyl-(1, ω)-alkedienyl acrylamides using Grubbs' catalyst I or II. The excellent stereoselectivity of the fused/dumbbell-mode cyclization has been realized by the higher reactivity of the electron rich $\text{C}=\text{C}$ bond or carbon-carbon triple bond combined with the lower reactivity of the electron deficient $\text{C}=\text{C}$ towards metallocarbenes and the thermodynamically more stable nature of the fused-bicyclic compounds versus dumbbell-type bicyclic compounds. The RCM precursors, *N*-containing trienynes **369a-f** were subjected to tandem RCM using 5 mol% of Grubbs' catalyst I or II in refluxing CH_2Cl_2 for 7-11 h to afford the desired fused bicyclic lactams that are suitable substrates for the preparation of polycyclic quinolizidine and other alkaloid derivatives *via* Diels-Alder reaction (Scheme 92).



Scheme 92 RCM, RCM and Diels-Alder reaction for the synthesis of condensed heterocycles.

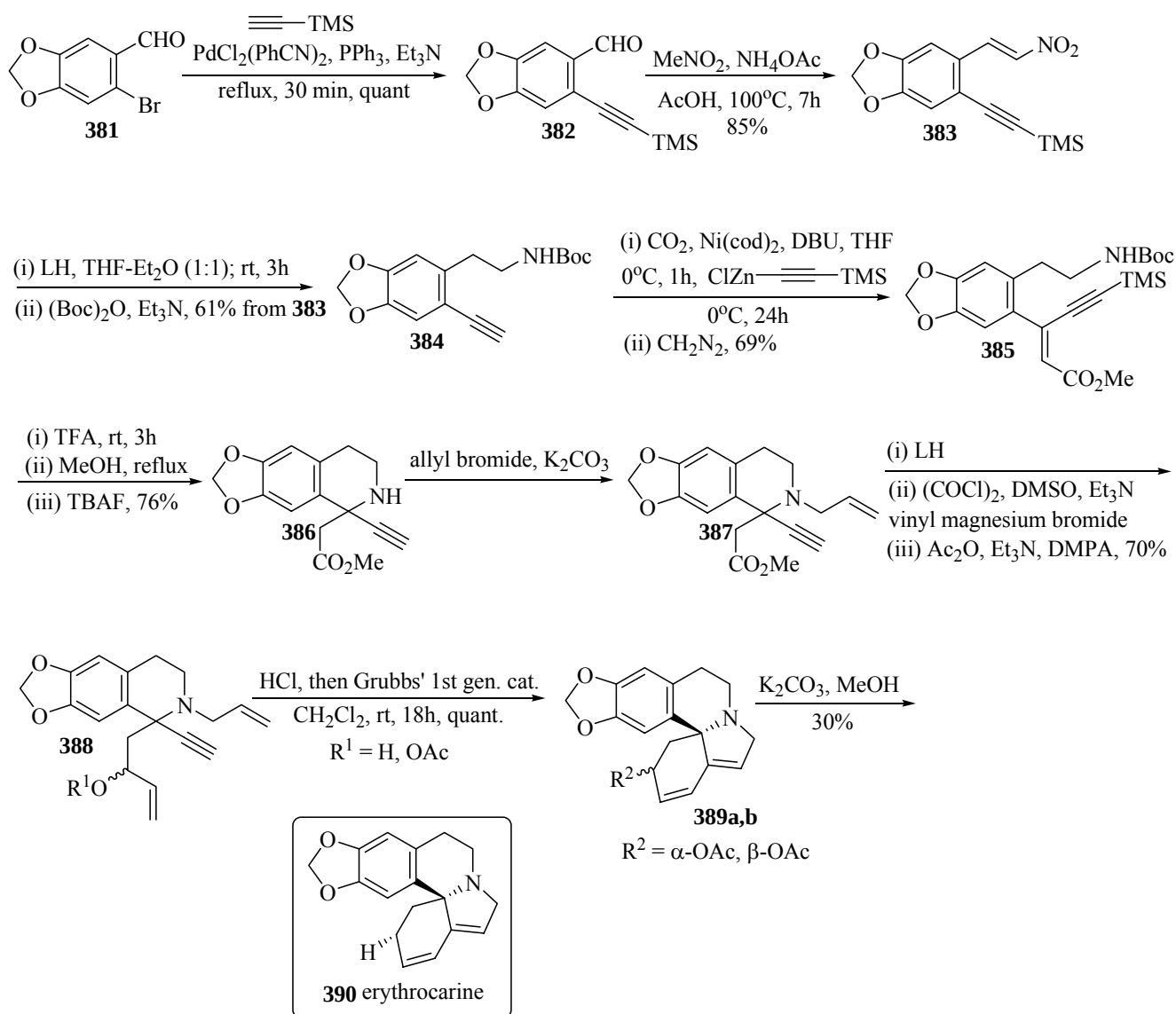
Erythrina alkaloids are well known owing to their interesting biological activity. The first total synthesis¹⁹⁵ of (+)- β -erythroidine, a non-aromatic erythrina alkaloid, in nature occurring for m by employing Lewis acid promoted cyclization of the dienynes **379a,b** as the key step. This work opened up a new avenue for the enantioselective synthesis of erythrina alkaloids (Scheme 93).



Scheme 93 Total synthesis of non-aromatic erythrina alkaloid by RCM.

Mori and co-workers recently described¹⁹⁶ the total synthesis of erythrocarine **390** by using a number of important reaction sequences and the ring-closing metathesis of dienyne as the key step. The reaction of **381** and trimethylsilylacetylene in the presence of palladium catalyst gave the alkyne **382** which was then condensed with nitromethane to afford **383**. Treatment of **383** with LiAlH₄ followed by Boc-protection afforded the corresponding alkyne **384**. The RCM precursors **388** were synthesized from compound **384** by the application of a number of reaction sequences. When a CH₂Cl₂ solution of dienyne hydrochloride was treated with Grubbs' 1st generation catalyst (10 mol%) at rt for 18 h, the corresponding cyclized

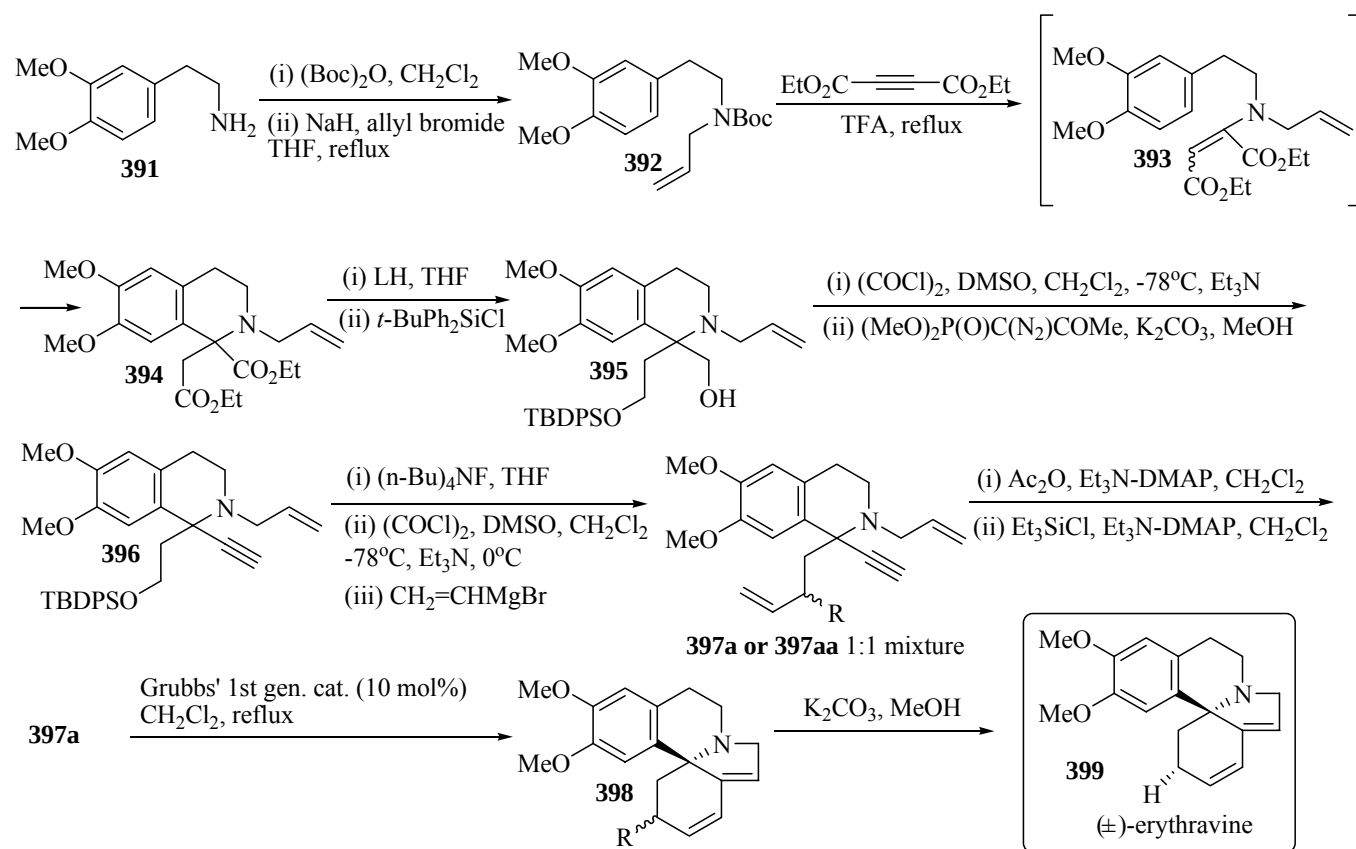
product **389** was obtained in almost quantitative yield. Treatment of **389a** with K_2CO_3 in MeOH gave the corresponding alcohol, erythrocarine **390** (Scheme 94).



Scheme 94 Total synthesis of erythrocarine by metathesis reaction.

The first total synthesis of ($\pm$)-erythravine was achieved¹⁹⁷ in thirteen steps from 3,4-dimethoxyphenethylamine **391** using ring-closing dienyne metathesis as the key step by Hatakeyama et al. 3,4-Dimethoxyphenethylamine **391** was initially converted to its Boc-protected-*N*-allyl derivative **392**, which was then reacted with diethylpropiolate in boiling TFA acid to give the diester **394** via Pictet-Spengler type of reaction. Subsequent reduction of compound **394** with $LiAlH_4$ followed by selective silylation afforded TBDPS-ether **395**. The enyne **396** was synthesized by Swern oxidation of the compound **395**. Upon sequential desilylation, Swern oxidation and Grignard reaction using vinylmagnesium bromide, **396** gave dienyne **397a** and **397aa** as a 1:1 epimeric mixture. For the next ring-closing metathesis reaction, acetate **397a** and TES-ether **397aa** were also prepared each as a 1:1 epimeric mixture from **396**. When the precursor **397a** was treated with Grubbs' catalyst in refluxing CH_2Cl_2 for 8 h, afforded the corresponding tetracyclic compounds **398a** and **398aa** in a ratio of 63:37 in

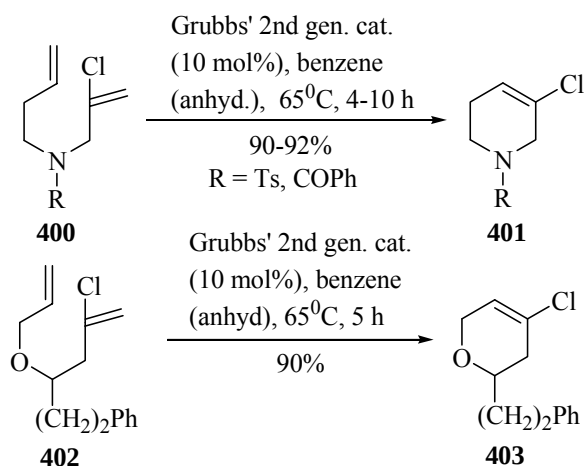
78% yield. (±)-Erythravine **399** was finally obtained from **389a** treatment with K_2CO_3 in methanol (Scheme 95).



Scheme 95 Total synthesis of (±)- erythravine by tandem RCM approach.

6. MISCELLANEOUS

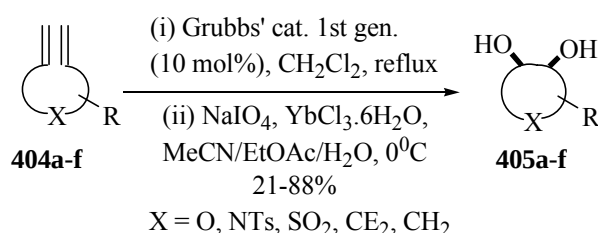
Construction of heterocyclic ring system by ring-closing metathesis has also been extensively explored as an annulation strategy. Weinreb *et al.* reported¹⁹⁸ the synthesis of six-membered heterocyclic system from the corresponding vinyl chlorides by ring-closing metathesis utilizing Grubbs' catalyst II. This protocol also provides five- and seven-membered heterocycles as well as six-membered carbocycles (Scheme 96).



Scheme 96 RCM of the homoallyl and vinyl chloride systems.

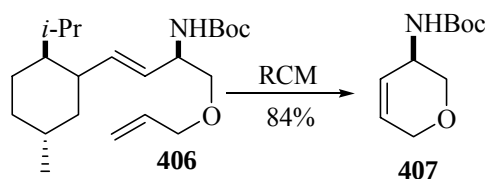
The utility of some ruthenium complexes in catalytic processes has been extended beyond olefin metathesis to other synthetic transformation. One of the most striking example is the one-pot synthesis of

(R)-(-)-muscone reported by Grubbs¹⁹⁹ in 2001 in three steps *viz.* RCM, transfer dehydrogenation and hydrogenation catalyzed by a single ruthenium source. Snapper *et al.*²⁰⁰ as well as Schmidt *et al.*²⁰¹ have also reported the synthesis of cyclic enols by tandem RCM / olefin isomerization. A new process combining a metathesis step utilizing Grubbs' catalyst I and a dihydroxylation step has been developed by Blechert *et al.*²⁰² for the synthesis of a variety of dihydroxylated products. Owing to the high tolerance of functional groups, this protocol has an interesting potential for application in natural product synthesis (Scheme 97). The process also presents an alternative to the pinacol coupling. The combination of two catalytic processes depending on a single ruthenium source, in addition to low catalyst loading makes this reaction particularly useful.



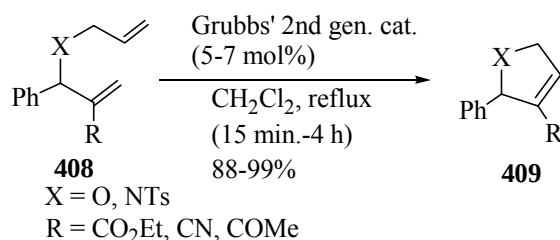
Scheme 97 Cyclic diols by tandem RCM / olefin dihydroxylation.

Spino *et al.* reported²⁰³ the selective tandem Mitsunobu/[3,3] sigmatropic rearrangement of hydrazoic acid that produces enantiopure allylic azide, which provides nitrogen heterocycles by applying ring-closing metathesis. The ring closing metathesis of the precursor **406** was performed by using Grubbs' or Nolan catalyst in refluxing CH₂Cl₂ to give nitrogen and oxygen heterocycles (Scheme 98). This protocol was also successfully utilized for the short and highly selective synthesis of α -amino acids and nitrogen heterocycles. This excellent regioselectivity of the azide rearrangement and the efficient cleavage of the chiral auxiliary by RCM is notable.



Scheme 98 RCM for the formation of oxa-heterocycles.

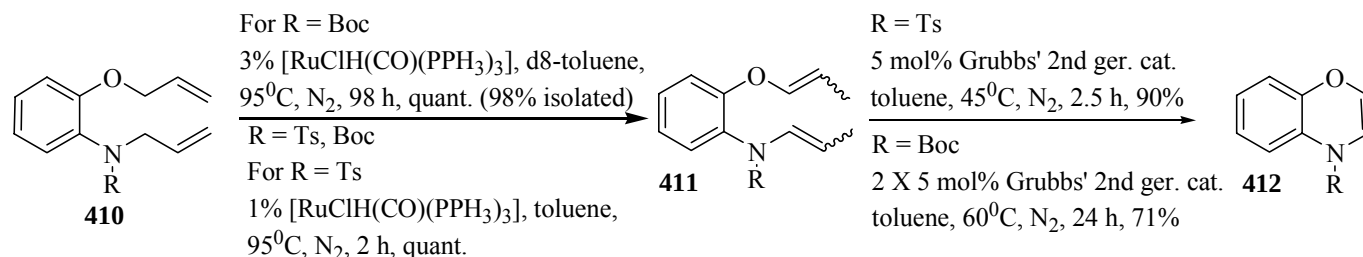
An efficient method for the synthesis of furan and pyrrole skeleton from the Baylis-Hillman adduct by ring closing metathesis was reported²⁰⁴ by Kim *et al.* (Scheme 99).



Scheme 99 Synthesis of furan and pyrrole skeleton via RCM.

Isomerization-RCM strategy has recently been proved to be an excellent method for the formation of small to medium size ring heterocycles. Utilizing this strategy, van Otterlo reported²⁰⁵ the synthesis of

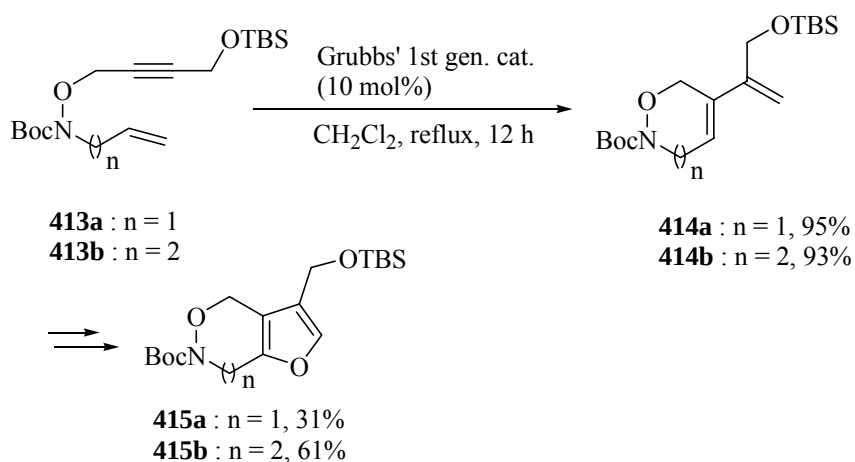
benzo-fused six-membered heterocycles **412** by Grubbs' catalyst II starting from aminophenol. However, benzofused eight-membered heterocycles were obtained from **411** by using Grubbs' catalyst II (5 mol%) (Scheme 100).



Scheme 100 Isomerization-RCM strategy to form the heterocycle **412**.

Isomerization of the diallyl compounds followed by ring closing metathesis reaction afforded the 4*H*-benzo-[1,4]-oxazines in good yields, although ring closing metathesis reaction using Grubbs' catalyst on the substrates containing electron rich vinylic olefins is known to be problematic.

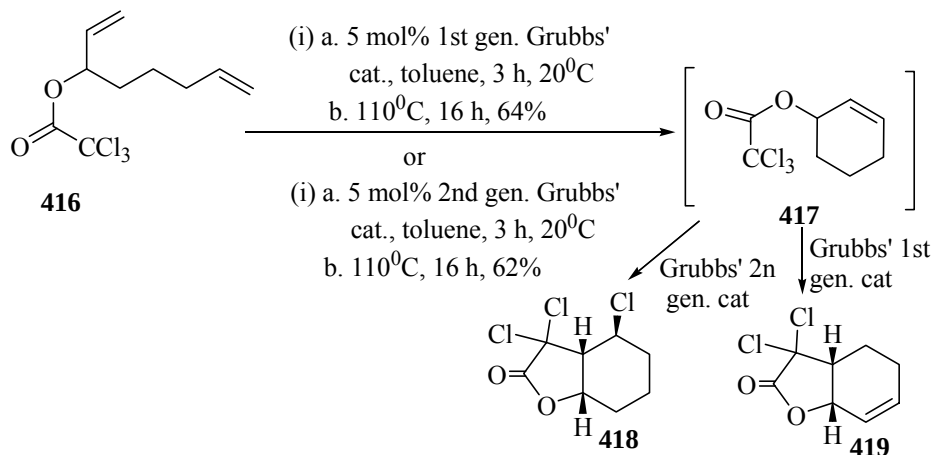
One of the most interesting disclosures concerning the enyne metathesis is the formation of 2,3-di and 2,3,4-trisubstituted furans from 1,2-dioxines.²⁰⁶ The methodology is based on the enyne-RCM/Diels-Alder reaction sequence. The reaction conditions for the transformation of 1,2-dioxines into furans are delineated in Scheme 101. Compounds **413a** and **413b** with the Grubbs' catalyst I in refluxing dichloromethane yielded compounds **414a** and **414b**. Cycloaddition reaction of the dienes **414a** and **414b** with singlet oxygen followed by FeSO₄-catalyzed reaction led to the corresponding substituted furan **415a** and **415b**, respectively (Scheme 101).



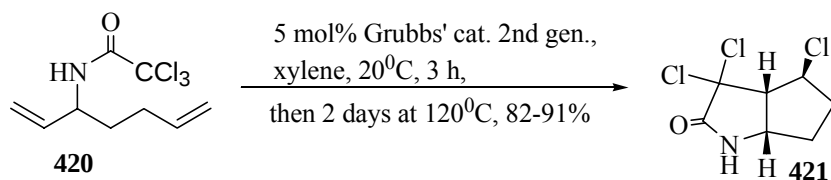
Scheme 101 RCEM for the synthesis of the heterocycles **415**.

Grubbs' carbene complexes, which are easily associated with metathesis chemistry, also proved to be efficient catalyst for the promotion of other intramolecular reactions depending upon the reaction conditions. These non-metathetical activities were mostly due to the *in situ* decomposition of the initial carbene complex to an uncharacterized ruthenium complex.^{59,207-209} Recently, Quayle and co-workers reported^{210,211} that sequential ring closing metathesis (RCM)-Kharasch cyclization^{212,213} could be promoted by the use of Grubbs' catalysts I and II to provide rapid access to bicyclic lactones and lactams

(Scheme 102).

**Scheme 102** Synthesis of trichloromethyl-tethered ester.

Treatment of the substrate **416** with Grubbs' catalyst I (5 mol% in degassed toluene) first at ambient temperature for 3 h then under mild thermolysis at 110°C afforded directly lactone **419** as the major product, however repeating the reaction with 2nd generation Grubbs' catalyst resulted the isolation of a lactone **418** in 62% yield as the major product, indicating that the product distribution is solely dependent upon the catalyst employed in the reaction. This sequential RCM-Kharasch reaction was also found to be effective for the synthesis of bicyclic lactams **421** (Scheme 103).

**Scheme 103** RCM of trichloromethyl containing amide precursor.

7. CONCLUSIONS

The results and examples discussed above demonstrate that olefin metathesis has proven to be an efficient method, especially for the preparation of different ring-sized compounds with varying complexity. RCM catalysts display the scope and activity required for a generally useful synthetic approach to complex molecules. With the advent of well-defined metathesis catalysts 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 reactions are simple, high yielding and truly friendly to the environment. A number of applications of RCM to the synthesis of complex and highly functionalized organic molecules, various regular-sized heterocycles, lactam and lactone containing natural products have been presented. The successful application of the olefin metathesis reaction hinges on the selectivity of the carbon-carbon bond-forming reaction and cross metathesis reaction. Improved catalyst for specific applications, including enantioselective synthesis has been developed and will continue to be developed. Metathesis is presently used by the entire organic community because of its extraordinary potential for the

synthesis of molecular target. Application of this area in organic synthesis will continue to grow, as we can count on the future development of even more active and functional group tolerant metal complexes. The future holds considerable promise for more advances and applications of RCM / RCEM not only in heterocyclic chemistry but in other arenas as well. Metathesis now is at the forefront of green chemistry by providing shorter synthetic routes and more facile access to the natural products and therapeutic agents under more environmentally friendly catalytic conditions. We hope that this review article will be useful to the synthetic chemists and especially to those who work with heterocyclic compounds.

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9. ABBREVIATIONS

RCM, Ring-closing metathesis; RCEM, Ring-closing enyne metathesis; ROM, ring opening metathesis; CH₂Cl₂, Dichloromethane; Bn, Benzyl; Boc, Tertiary-butyloxycarbonyl; PhH, Benzene; Ac₂O, Acetic anhydride; THF, Tetrahydrofuran; DMAP, Dimethylaminopyridine; Pyr, Pyridine; DCC, Dicyclohexylcarbodiimide; Et₃N, Triethylamine; LHMDs, lithium hexamethyldisilazide; KHMDs, Potassium bis(trimethylsilyl)amide; DBU, 1,8-Diazabicyclo[5.4.0]undec-7-ene; TMSCl, Trimethylsilyl chloride; TBDPS, *tert*-Butyl(chloro)diphenylsilane; PCC, Pyridinium chlorochromate; MOM, Methoxymethyl; TsOH, *p*-Toluenesulfonic acid; AcOH, Acetic acid; TFAA, Trifluoroacetic anhydride; LiAlH₄, Lithium aluminium hydride; NaBH₄, Sodium borohydride; NaCNBH₃, Sodium cyanoborohydride; Cp₂TiMe₂, Dicyclopentadienyl dimethyl titanocene; MeCN, Acetonitrile; TFA, Trifluoroacetic acid; Dppp, Diphenyl phosphinopropane; NMO, N-methyl morpholine oxide; CM, Cross metathesis; RRM, ring rearrangement metathesis; dRRM, diastereoselective ring rearrangement metathesis; TCQ, tetrachloroquinone.

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