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Formation of medium-ring heterocycles by diene and enyne metathesis

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Contents

1. Introduction

Several medium-sized heterocyclic rings form parts of the structures of a range of biologically active natural products[1] and medicinally important compounds[2] and, for this and other reasons, a number of methodologies have been developed[3] over the last few years for the synthesis of such ring systems. Because of enthalpic and entropic factors, medium-sized rings are the most difficult to prepare. Most of the classical cyclization strategies are often hampered by entropic factors and transannular interactions.[4] In general, relatively fewer methods based on cyclization or cycloaddition reactions have been used[5] for the preparation of medium-ring heterocyclic compounds from acyclic precursors, although these have been extensively used for the synthesis of common heterocyclic ring systems. The discovery and development of olefin metathesis over the past few years have revolutionized the area of medium-ring synthesis. Although a number of authoritative reviews[6] have been written on the general topic, a separate compilation of medium-ring heterocycle formation by this methodology has still not appeared, to the best of our knowledge. The present review will therefore focus on recent applications of diene and enyne metathesis reactions in the synthesis of medium-ring heterocycles.

2. General aspects of olefin metathesis

The word 'metathesis' describes the interchange of covalent bonds between two molecules. In olefin chemistry, it refers to the redistribution of alkylidene moieties between two alkenes in the presence of a catalytic amount of a metal carbene. Olefin metathesis has been utilized in four closely related types of reactions, viz. (a) ring-opening metathesis polymerization[7] (ROMP), in which a cyclic olefin is the substrate and a polymer is the product; (b) ring-closing metathesis (RCM), in which an acyclic diene is converted into a cyclic olefin; (c) cross-metathesis[8] (CM), in which two different olefins react to form a new product olefin and

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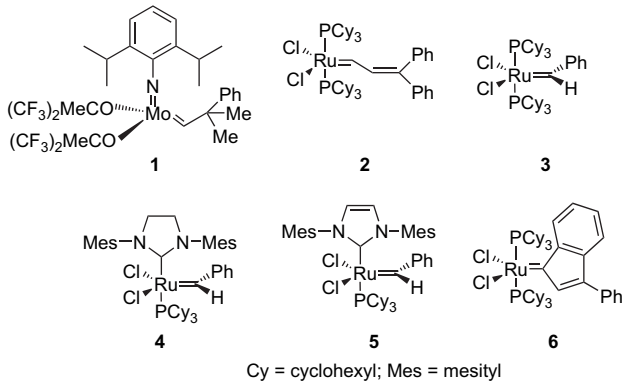


Figure 1.

a by-product as a volatile olefin (usually ethylene) and (d) ring-opening metathesis[9] (ROM), in which a cyclic olefin and an acyclic olefin produce a new acyclic olefin. Another variant of the reaction is the metathesis of an alkene and an alkyne, popularly known as enyne metathesis (EM), of which both the intramolecular and intermolecular versions are known.[10] Of the above few types, ring-closing metathesis (RCM) has received a great deal of attention from the synthetic organic chemical community and, over the last few years, it has developed as a powerful tool for the synthesis of various carbocyclic and heterocyclic ring systems of different sizes. A large number of catalyst systems have been used to initiate olefin metathesis. It was only since the early 1990s' however, when well-defined, single-component catalytic systems were developed by the groups led by Schrock[11] and Grubbs[12] that the reaction became useful in organic synthesis. Schrock's molybdenum catalyst **1** (Fig. 1) and Grubbs' first- and second-generation catalysts **2**–**5** have seen the most applications. These catalysts have been found to be compatible in the presence of many functional groups. In general, the functional-group tolerances of the Grubbs' catalysts **2**–**5** are reported to be higher than that of the Schrock catalyst **1**, but the reactivity of the latter has been claimed to be superior to that of the ruthenium catalysts **2** and **3** in some instances. The molybdenum catalyst **1** also has the ability to form rings in substrates[13] with many steric or electronic demands. An extensive compilation of functional-group compatibilities of the catalysts **1**–**3** is available.[6i] The second-generation catalysts **4**–**5**, the 'phosphine mimics', have opened new opportunities in optimizing the efficiency of RCM, as well as C–C[13a] and C–N[13b] bond formation. Chirally modified catalyst systems have also been developed recently and a few examples of enantioselective olefin metathesis reactions have appeared.[14]

3. Ring-closing metathesis (RCM)

The area of olefin metathesis that has expanded most dramatically in recent years is the catalytic ring-closing metathesis (RCM). Catalysts **1**–**6** have made it possible to cyclize substrates containing diverse functionalities leading to a wide range of carbo- and heterocycles of almost any ring size. The mechanism of the RCM reaction has been extensively studied both experimentally[15] and theoretically.[16] It is now well accepted[17] that, during the reaction, the catalytically active metalacarbene complex such as [M]=CH_2 is

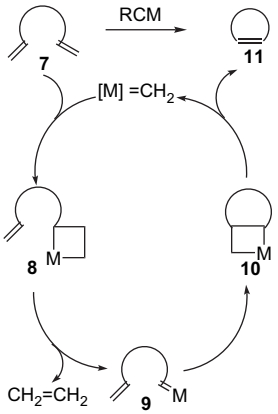


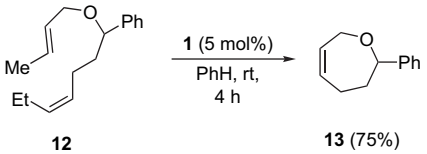
Figure 2.

formed from the diene precursor **7** (Fig. 2) and the overall reaction mechanism involves, effectively, a series of alternating [2+2] cycloadditions. Metallacyclobutane intermediate such as **8** is formed, which opens in a retro [2+2] fashion to form the carbene **9** as intermediate. The latter then undergoes re-cyclization to form the new metalacyclobutane **10**, which analogously opens to the product cycloalkene **11** and the catalyst is regenerated. The mechanism is depicted schematically in Figure 2. The equilibrium is continuously shifted towards the cycloalkene, due to the release of a volatile olefin (usually ethylene). This entropically driven reaction has been utilized for closing many medium and large rings, which are otherwise difficult to access. In the following section, an attempt will be made to briefly review the formation of various medium-ring (7–10) heterocyclic systems through the application of RCM of dienes.

4. Formation of medium-ring oxygen heterocycles by RCM

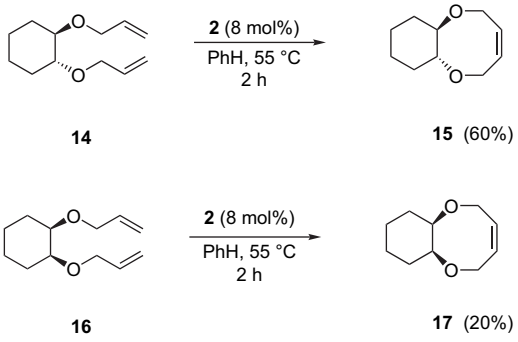
The synthesis of medium-ring oxacycles by RCM methodology tends to work best when some conformational constraints favour ring formation. Some of the structural features that have been helpful include the presence of a ring, a *gem*-dimethyl group or a large group present within the chain connecting the reacting double bonds. The presence of these beneficial groups, however, does not always guarantee the success of the reaction. Similarly, there are also reports, which describe successful medium-ring formation by RCM wherein no such conformationally beneficial factors are present.

Grubbs and Fu first demonstrated[18] that otherwise incompatible allyl ethers could be subjected to an RCM reaction with the Schrock catalyst **1**, leading to the formation of medium-ring cyclic ethers in good yield, e.g., the formation of **13** from **12** (Scheme 1).



Scheme 1.

Grubbs' work has revealed that trans ring fusion is highly beneficial for the synthesis of [6.4.0] systems. Thus, the diene **14** (Scheme 2) provided the bicyclo[6.4.0] system **15** in 60–75% yield, whereas the corresponding cis-system **16** gave[19] a low yield of the cyclized product **17**.



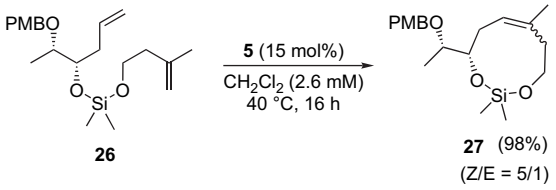
Scheme 2.

Grubbs and Chang also reported[20] that the RCM of silicon-tethered dienes is efficient for the synthesis of five- to eight-membered rings, even in fairly concentrated solutions (Scheme 3). Thus, the silyloxydienes **18** on RCM with either of the catalysts **1** and **3** provided the cyclic compounds **19** in very good yields. It was found that the catalyst **1** was more effective for the cyclization of the sterically more hindered vinylsilyl substrates (**18**, n=0). Subsequent removal of the temporary tether by oxidative ring cleavage produced the corresponding *cis*-olefinic diols **20** in excellent yields.

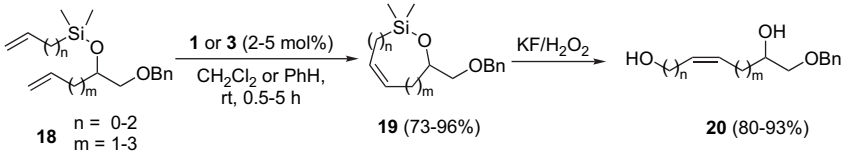
Cossy and Meyer developed[21] an elegant route to substituted tetrahydrofurans from cyclic allylsilanes, which were prepared by RCM of a silicon-tethered diene. Thus, the silyloxydienes **21** (Scheme 4) were converted by RCM with catalyst **3** into the corresponding cyclic allylsilanes **22**, which reacted with a range of aldehydes, ketones or ketals to give the tetrahydrofurans **23** in very good yields.

Silicon-tethered RCM reactions have found diverse applications. In studies directed towards the synthesis of the cytotoxic attenols, a French group observed[22] remarkable diastereoselectivity during the metathesis step. Thus, the epimeric mixture of the diene **24** (Scheme 5) on RCM with the catalyst **1** gave the cyclic ether **25** as the only stereomer.

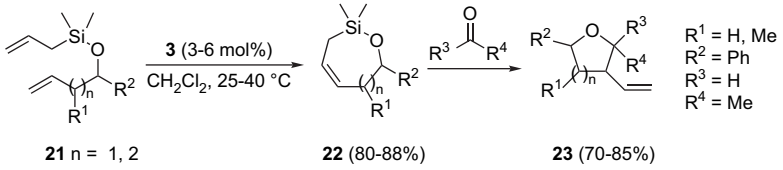
A recent application of a silicon-tethered RCM reaction was reported[23] by Mulzer et al. during their synthesis of epothilones B and D, which are rapidly becoming established as forthcoming anticancer drugs with high cytotoxic activity combined with low multidrug resistance.[24] The key feature of their synthesis is the silicon-tethered RCM reaction of an appropriate diene, e.g., **26** (Scheme 6), to incorporate the C_{12}–C_{13} trisubstituted *Z*-double bond of the advanced intermediate **27**. The isomeric mixture (5:1) could be separated at a later stage of the synthesis. Yields of the RCM turned out to be strongly dependent on the rate of catalyst addition. Quantitative yields were only obtained when the catalyst was added over 16 h. By contrast, addition of the catalyst in one portion reduced the yield to 50%.



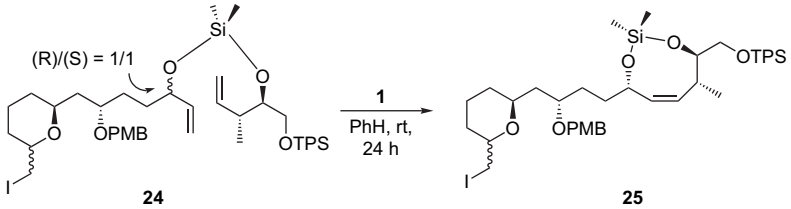
Scheme 6.



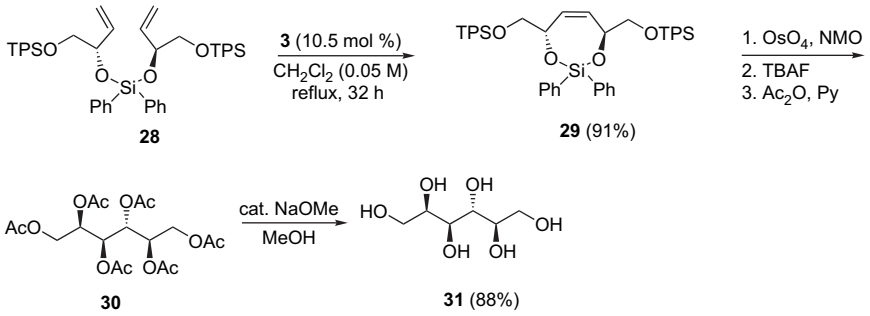
Scheme 3.



Scheme 4.



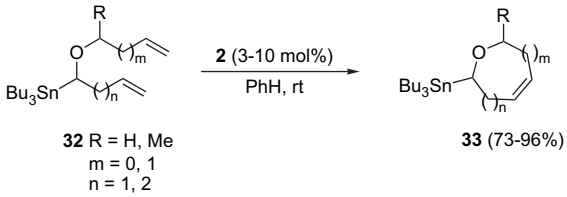
Scheme 5.



Scheme 7.

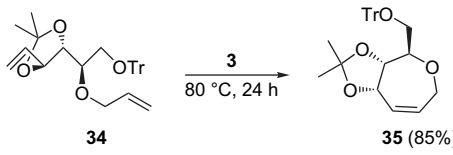
cis-Alkene synthesis via a silicon-aided RCM reaction has been utilized[25] in the synthesis of the carbohydrate, D-altritol (**31**) (Scheme 7). RCM of the diene **28** with the catalyst **3** led to the silacycle **29** in excellent yield. The authors noted that a catalyst loading in two different portions was crucial to this high yield conversion. Compound **29** was converted into the polyol **31** via **30** under conventional conditions. Other applications of silicon-tethered RCM reactions via medium-ring silacycle formation are also known.[26,27]

It was reported[28] that the tributylstannyl group could be used as a large, yet removable, group to affect a favourable conformational bias for the synthesis of an oxocine ring via metathesis from an acyclic diene precursor. RCM of the dienes **32** (Scheme 8) with the catalyst **2** led to the cyclic ethers **33** in good to excellent yields. The α-(alkoxyalkyl)stannane moiety can further undergo transmetallation by lithiodestannylation, and the intermediate carbanion could be trapped by electrophiles to provide the substituted oxocines.



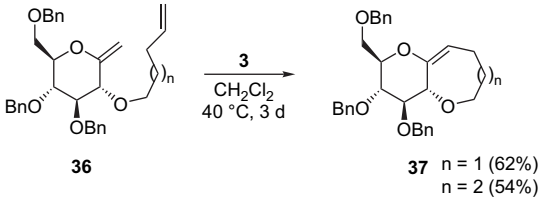
Scheme 8.

van Boom et al. have developed[29] an expeditious route to highly functionalized chiral oxepines. RCM of the linear diene **34** with Grubbs' catalyst **3** afforded the oxepine **35** in high yield (Scheme 9). Possibly, the presence of the acetonide group was beneficial.



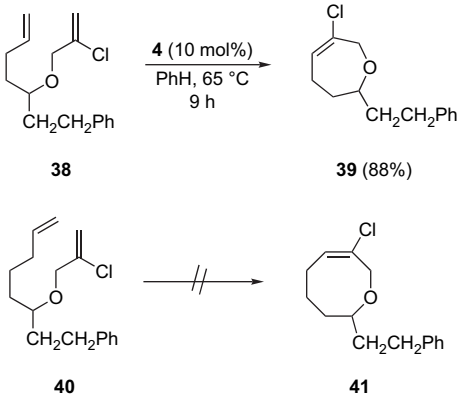
Scheme 9.

Enol ethers are usually not good substrates for an RCM reaction. The methylene glucose derivatives **36**, however, on RCM with Grubbs' catalyst **3**, afforded[30] the corresponding *C*-glycosylidine compounds **37** (Scheme 10).



Scheme 10.

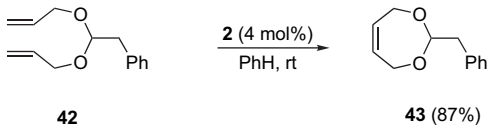
RCM reactions of olefins bearing electronegative substituents have proved to be problematic and are mechanistically less well understood. Weinreb's group reported[31,32] the first example of RCM of vinyl chlorides for the synthesis of a range of carbo- and heterocycles including medium-ring cyclic ethers. RCM of the diene **38** (Scheme 11) with Grubbs' second-generation catalyst **4** under carefully optimized conditions led to the chloro-substituted oxepin derivative **39** in high yield. Surprisingly, all attempts to synthesize the corresponding oxocin derivative **41** from **40** did not meet with success. Similarly, RCM of fluorine-containing olefins has not proved to be successful for medium-ring oxacycle formation.[33]



Scheme 11.

Medium-ring oxacycles, which have been prepared using the RCM reaction are mostly cyclic ethers and lactones. There are also reports of the formation of seven-membered unsaturated acetals, e.g., by the conversion[19b] of **42** into **43** (Scheme 12).

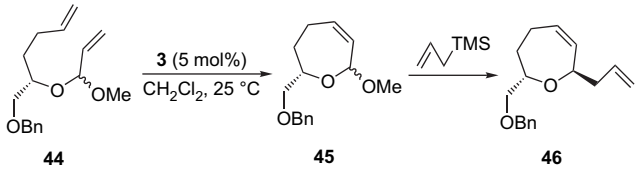
An interesting example[34] is the conversion of the acetal **44** into **45**, which was further elaborated to the required product



42 43 (87%)

Scheme 12.

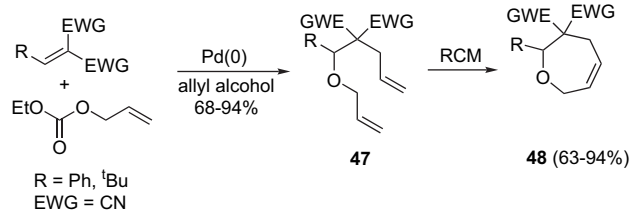
46 (Scheme 13) through an oxycarbenium ion-mediated coupling reaction with allyltrimethylsilane.



44 45 46

Scheme 13.

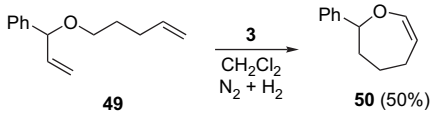
A few important methodologies for the synthesis of diene precursors have been disclosed. Hauske and Xie developed[35] a method involving a tandem palladium-catalyzed alkoxyallylation of activated olefins followed by an RCM reaction for the synthesis of highly functionalized oxepine derivatives e.g., the conversion of **47** into **48** (Scheme 14).



47 48 (63-94%)

Scheme 14.

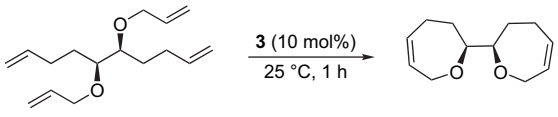
An elegant methodology involving tandem RCM and olefin isomerization in a one-pot manner using a Grubbs' catalyst and a mixture of nitrogen and hydrogen gas has recently been developed[36] for the synthesis of a range of cyclic enol ethers including medium-ring compounds as illustrated by the conversion of **49** into **50** (Scheme 15). Presumably, a ruthenium-hydride (Ru–H) complex is generated in situ, which catalyses both reactions. It is interesting to note that olefin hydrogenation does not take place under low concentrations of hydrogen. The ability of Ru–H species to promote both isomerization and metathesis is well documented.[6b]



49 50 (50%)

Scheme 15.

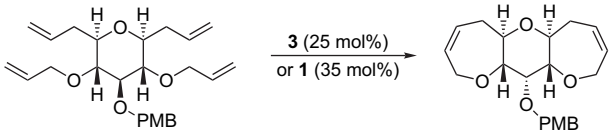
In recent years, the concept of multiple RCM reactions of a suitably prepared polyene has been efficiently utilized[37,38] in a one-pot manner to deliver fused-, bridged- and spiro-cyclic systems of interest including medium-ring heterocycles. Crimmins and Choy disclosed[39] that two-directional RCM (TDRCM) of the bis(*O*-allyl) ether **51** with Grubbs' catalyst **3** afforded the bis-oxepine derivative **52** in moderate yield (Scheme 16).



51 52

Scheme 16.

A novel approach to the synthesis of trans-fused polyoxacyclic frameworks involving double RCM reactions of ethers, enol ethers and alkynyl ethers has been developed[40] by Clark and Hamelin (Scheme 17). The unsaturated substrate **53**, obtained from commercially available tri-*O*-acetyl-D-glucal, was treated with 15–30 mol % of the first-generation Grubbs' catalyst **3** to give the tricyclic ether **54** in very good yield. Interestingly, the formation of the bridged bicyclic ether was not observed. The relative efficacies of the catalysts **1** and **3** were also compared in a number of related substrates. Although these cyclizations required relatively high catalyst loadings and extended reaction times, the use of the more reactive Schrock catalyst **1** led to somewhat lower yields of the products.



53 54 (85-88%)

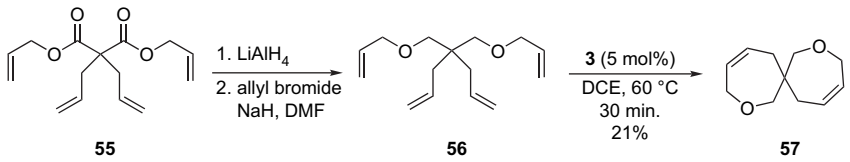
Scheme 17.

Harrity et al. demonstrated[41] the formation of medium-ring spirocyclic ethers from the readily prepared tetraene precursors via a multiple RCM reaction. Thus, reduction of the diester **55** (Scheme 18) and subsequent base-promoted allylation of the resulting 1,3-diol provided the requisite tetraene **56** in excellent overall yield. The latter compound was then subjected to RCM with catalyst **3** in 1,2-dichloroethane (DCE) at 60 °C to furnish the spirocyclic ether **57**, but in low yield (21%).

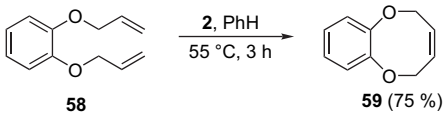
Benzannulated common-ring heterocyclic systems have remained privileged structures, owing to their presence in diverse compounds of natural and non-natural origin. On the other hand, benzo-fused medium-ring heterocyclic systems have not been explored to a great extent until recently, which may, in part, be due to a lack of general methods for their synthesis. With the advent of olefin metathesis, these methods have received considerable attention in recent years. Like other cyclizations that produce medium rings, RCM tends to work best when there are conformational constraints that favour ring formation. That a benzene ring constitutes an excellent conformational constraint is illustrated by the use of RCM in the recent synthesis of several medium-ring oxacycles fused to a benzene ring.

Grubbs et al. first reported[19] the use of RCM in the preparation of benzo-fused medium-ring heterocyclic systems, e.g., the conversion **58**→**59** (Scheme 19).

A simple stereoselective synthesis of *cis*- and *trans*-2,3-disubstituted medium-sized cyclic ethers **64** and **66** (Scheme 20) has been developed,[42] based on the Ireland–Claisen



Scheme 18.

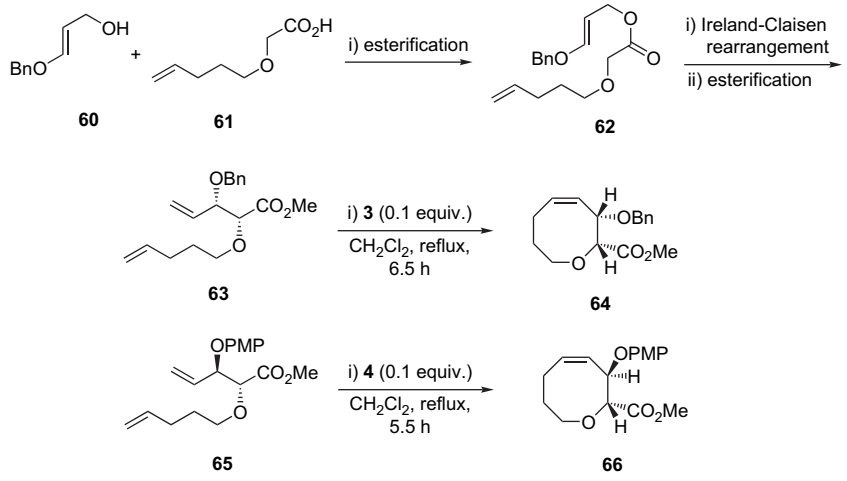


Scheme 19.

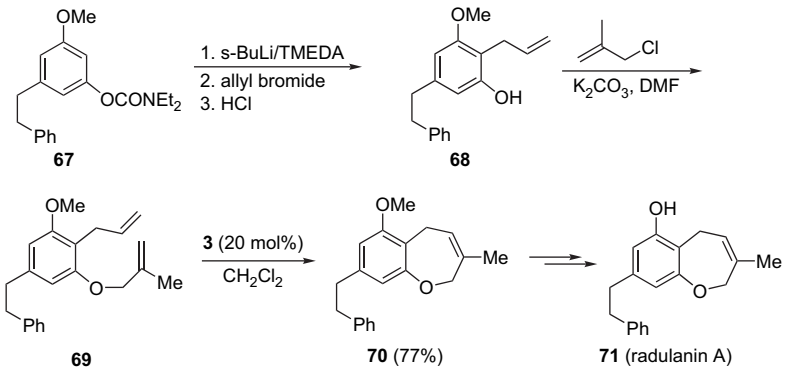
rearrangement and ring-closing olefin metathesis. The glycolate ester **62** was prepared by a condensation reaction of glycolic acid **61** with *E*-3-benzyloxy-2-propenol **60**. Deprotonation of **62** with KHMDS at −78 °C for 5 min followed by treatment with TMSCl and warming to ambient temperature induced an Ireland–Claisen rearrangement and, finally, esterification with diazomethane led to the ester **63** in 79% overall yield. Ring-closing alkene metathesis with the first-generation Grubbs' catalyst **3** provided the eight-membered cyclic ether **64** in 87% yield. Similarly, the diene **65** smoothly underwent a ring-closure reaction with the second-generation Grubbs' catalyst **4** to give the cyclic ether **66** in 53% yield.

Snieckus and Stefinovic combined RCM methodology with their directed *o*-metallation (DOM) protocol for the construction[43] of benzannulated oxygen heterocycles. Thus, directed metallation of the *O*-carbamate derivative **67** (Scheme 21) followed by allylation provided access to the *C*-allyl derivative **68**. Hydrolysis of the *O*-carbamate functionality in the latter compound followed by further O-alkylation of the resulting phenol provided access to the diene **69**. RCM of this diallylated benzene derivative **69** with the catalyst **3** gave the benzoxepine derivative **70** (77%), which was converted into radulanin A (**71**).

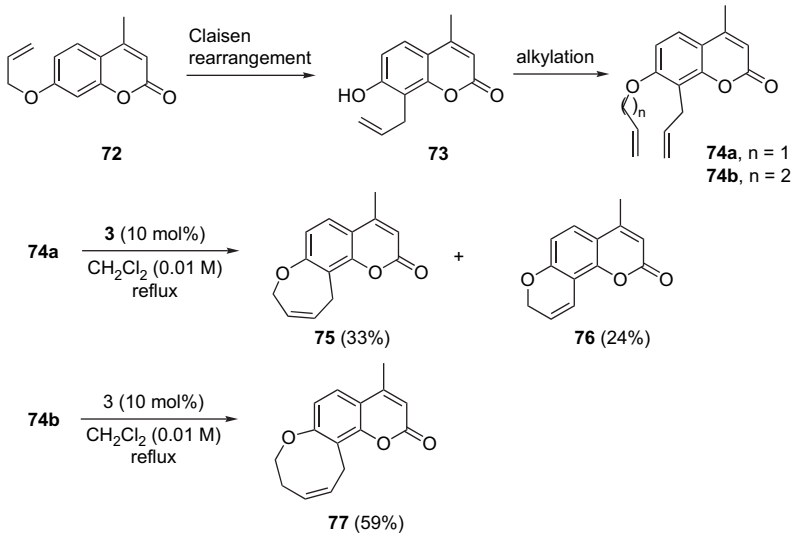
Chattopadhyay et al. combined[44,45] a Claisen rearrangement with RCM for the synthesis of a range of carbocycles and heterocycles of interest. Thus, 8-allyl-7-hydroxy-4-methylcoumarin (**73**), obtained (Scheme 22) by a Claisen rearrangement of 7-allyloxy-4-methylcoumarin (**72**), was alkylated with allyl bromide or butenyl bromide to install the diene precursors **74a**,**b**. Compound **74a** on RCM with Grubbs' catalyst



Scheme 20.



Scheme 21.



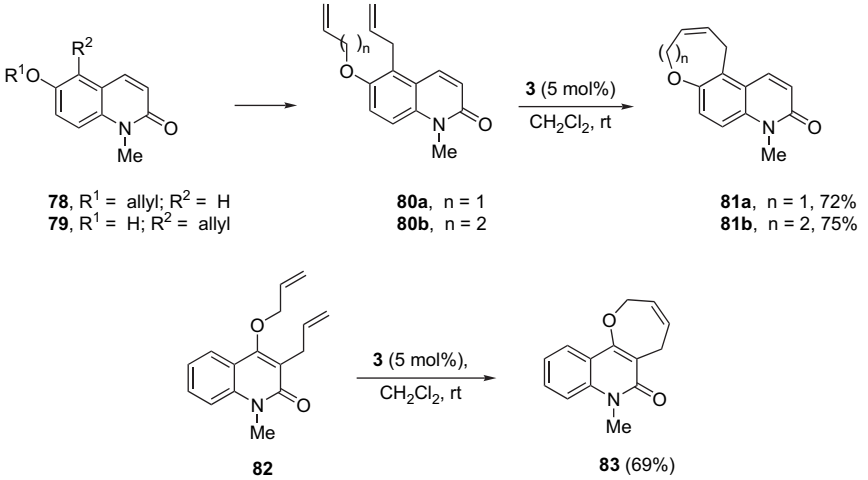
Scheme 22.

3 provided the expected oxepine derivative **75**, along with the pyranocoumarin derivative **76**. The authors invoked a selective in situ isomerization of the *C*-allyl group in **74a** preceding RCM to account for the formation of **76**. On the other hand, RCM of the butenyl ether **74b** provided the oxocin-annulated coumarin derivative **77** as the only product. Several other oxepino- and oxocinocoumarins were analogously prepared.

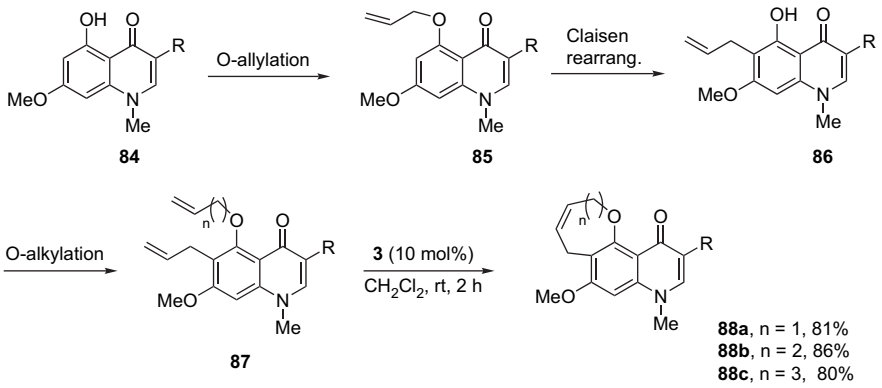
The study was later extended to the preparation of oxepine- and oxocine-annulated 2-quinolones.[46] Thus, Claisen rearrangement of 6-allyloxy-*N*-methyl-2-quinolone (**78**) (Scheme 23) neatly provided the rearranged hydroxyquinolone **79** in good yield. Separate alkylation of the phenol **79** with allyl bromide and 4-bromo-1-butene afforded the allyl ether **80a** and the butenyl ether **80b**, respectively. RCM of each of these dienes separately with catalyst **3** proceeded smoothly to provide the angularly fused oxepinoquinolone **81a** and oxocinoquinolone **81b**, respectively. Following a similar strategy, oxepinoquinolone derivative **83** had also been synthesized from the diene **82**. A similar approach[47] to oxepinoquinolones using tandem applications of the Claisen rearrangement and RCM has also appeared (Scheme 24). Thus, Claisen rearrangement of the *O*-allyl ether **85**, prepared from the hydroxyquinolone **84**, led to the rearranged phenol **86**, which on subsequent alkylation (leading to the dienes **87**) followed by RCM provided the oxepino-, oxocino- and oxoninoquinolones **88a–c** in very good yield.

The combined Claisen rearrangement and RCM methodology leading to oxepine-annulated aromatics has also been adopted[48] by Kotha and Mandal for the synthesis of naphthoxepine derivatives from β-naphthol. Thus, microwave-assisted Claisen rearrangement of 2-allyloxynaphthalene produced the known rearranged phenol **89**, which, on further alkylation with allyl bromide, gave the required oxygen-tethered diene **90**. The latter diene underwent RCM with the catalyst **3** to the desired naphthoxepine **91** in moderate yield (Scheme 25).

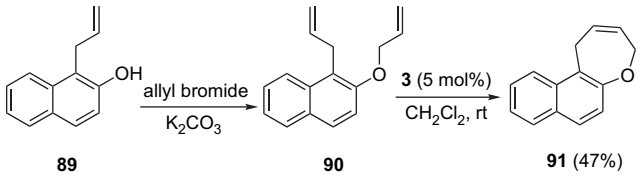
Majumdar et al. have also applied[49] this methodology to access oxepine-annulated 1,8-naphthyridinones e.g., the conversion **92**→**93** (Scheme 26).



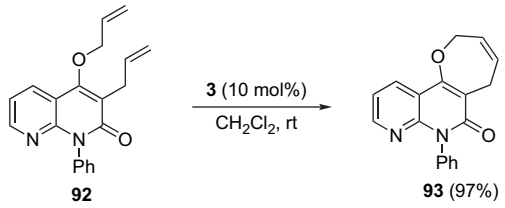
Scheme 23.



Scheme 24.



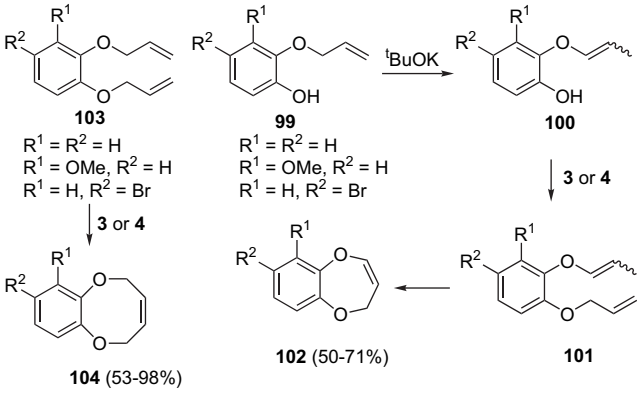
Scheme 25.



Scheme 26.

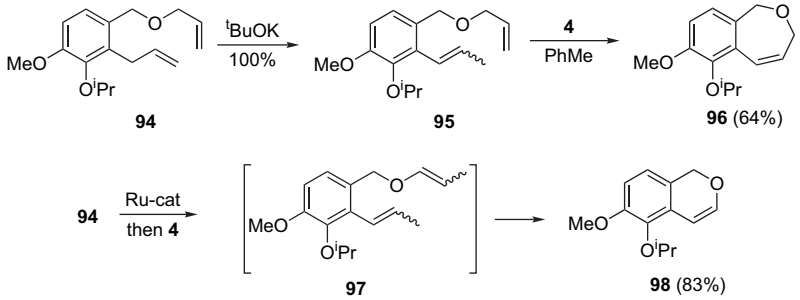
de Koning et al. reported[50] a combined isomerization and RCM reaction protocol to prepare a range of benzannulated six- to eight-membered heterocycles. Thus, stepwise isomerization and RCM of the compound **94** (Scheme 27) led to the medium-ring heterocycle **96** (via **95**) whereas sequential treatment of **94** with the catalyst $RuClH(CO)(PPh_3)_3$ followed by Grubbs' second-generation catalyst **4** in a one-pot manner led to the six-membered heterocycle **98** through a doubly isomerized intermediate **97**. The authors also prepared medium-ring benzannulated azacycles in a similar way. The same group further developed this isomerization-RCM protocol for the synthesis of a range of common-ring oxygen, nitrogen and sulfur heterocycles.[51]

Various benzodioxepin and benzodioxocin derivatives have also been prepared[52] involving an RCM reaction as the key step. Thus, the substituted catechol monoallyl ether derivatives **99** on base-mediated isomerization to the vinyl ethers **100** followed by O-alkylation led to the dienes **101** (Scheme 28). RCM of the latter under a range of conditions provided the benzodioxepin derivatives **102** in varying yields of 50–71%. Similarly, the bis-allyl ether derivatives **103** directly led to the corresponding dioxocins **104** in good to excellent yield. It was found that the catalyst **4** worked better in some instances.



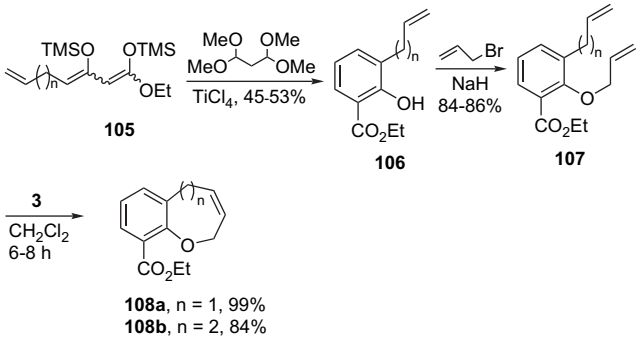
Scheme 28.

Very recently, a new method involving tandem application of [3+3]-cyclization and RCM methodology has been disclosed[53] for the synthesis of benzoxepin and benzoxocin derivatives (Scheme 29). Thus, $TiCl_4$-mediated cyclization of



Scheme 27.

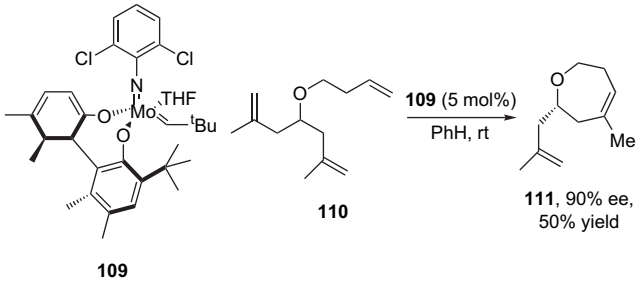
a bis-silyl enol ether **105** with 1,1,3,3,-tetramethoxypropane resulted in the formation of the phenol derivative **106**.



Scheme 29.

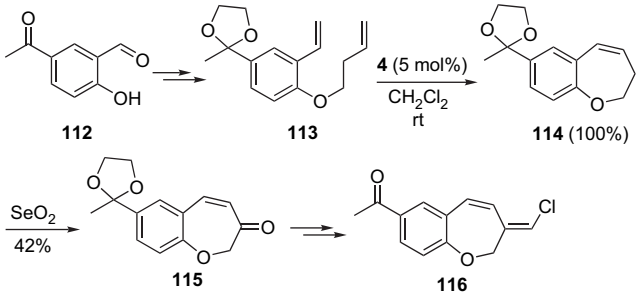
The latter on O-allylation (leading to **107**) followed by RCM with the catalyst **3** afforded the cyclized products **108a**,**b** in excellent yields.

A few examples of asymmetric ring-closing metathesis (ARCM) reactions have recently appeared in the literature. Chiral molybdenum-based catalysts such as **109** have been found to be effective for the enantioselective synthesis of medium-ring oxygen heterocycles. An example[54] is the conversion of **110** into **111** (Scheme 30).



Scheme 30.

Much of the activities related to medium-ring oxacycle formation by the RCM methodology have centred on some notable natural products accommodating these ring systems. Pterulone (**116**, Scheme 31) is a chlorinated fungal metabolite that was synthesized by Grubbs and co-workers.[55] Thus, the substituted salicylaldehyde derivative **112** was elaborated in three steps into the required diene **113**, which underwent a smooth RCM reaction with the second-generation

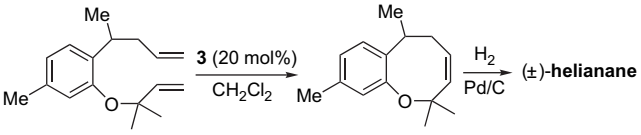


Scheme 31.

Grubbs' catalyst **4** to provide the oxepin derivative **114** quantitatively. The latter was then elaborated via **115** into the natural product, **116**.

The heliannuols are a promising group of phenolic allelochemicals isolated[56] from *Helianthus annuus* that exhibit useful biological activity. The benzoxepin/benzooxocin ring system present within these molecules has lured synthetic activity using metathesis for their preparation. A number of synthetic reports have emerged for the preparation of some members belonging to this family.

Snieckus and Stefinovic first reported[43] that the diallylated benzene derivative **117** (Scheme 32), prepared by their directed-metallation protocol, on ring closure with the catalyst **3** followed by catalytic hydrogenation of **118** provided (±)-helianane.



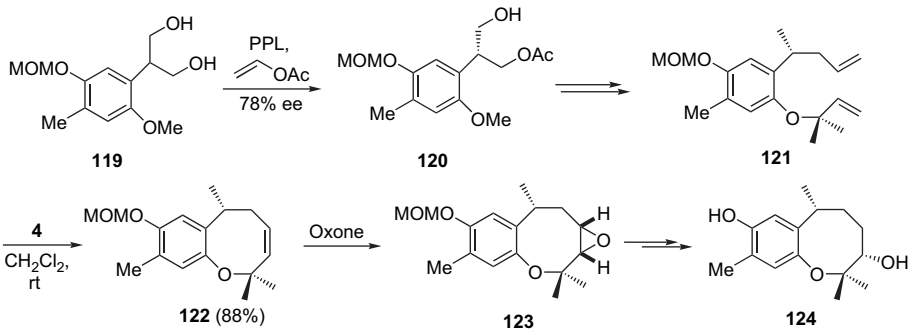
Scheme 32.

Shishido et al. reported[57] the enantioselective total synthesis of (−)-heliannuol A (**124**, Scheme 33), the most active member of the family[58] with an effective concentration as low as 10^{-9} M for the germination inhibition of lettuce and cress. The diene **121** was prepared in a sequence of 10 steps in which the stereogenic centre at C_7 was set by the enzymatic desymmetrization of the prochiral diol **119**. Compound **120** was obtained in 78% ee, which was raised to 100% by recrystallization. Catalyst **4** induced RCM of the diene **121** to provide the oxocin derivative **122** in an impressive yield of 88%. The high yield for this cyclization might be a consequence of conformational constraints induced by both the benzene ring and the geminal dimethyl group.[59] Compound **122** was then elaborated via into the natural product through a selective epoxidation.

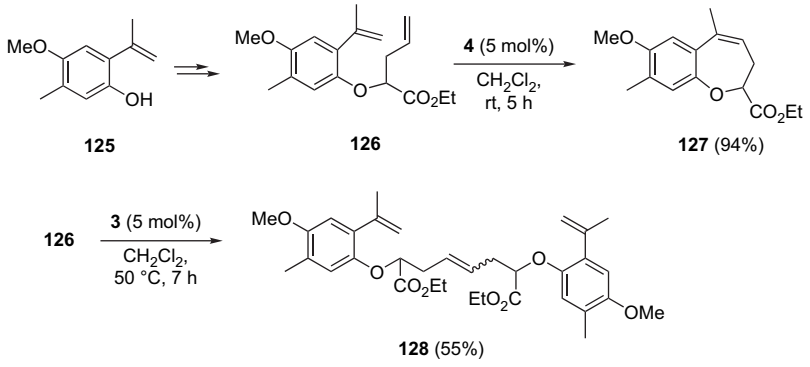
Venkateswaran and Sabui recently reported[60] a synthesis of the allelochemical, heliannuol D, in racemic form. The starting styrenol **125**, obtained from the ring opening of an appropriate coumarin derivative, was converted into the diene precursor **126** (Scheme 34). A successful RCM of the latter with the catalyst **4** (5 mol %) led to the benzoxepine ester **127** in 94% yield. Attempted RCM of the diene **126** with the first-generation catalyst **3** under forcing conditions led to the cross-metathesis product **128**.

Several non-metathetic routes to different heliannuols have also been published.[61]

Many naturally occurring polycyclic ether antibiotics having potent biological activities contain seven- to nine-membered oxacyclic rings as structural elements. In recent years, much of the synthetic challenges in forming these rings have now been overcome by the application of RCM of appropriate dienes. Thus, a number of key studies in this area are based on olefin metathesis.

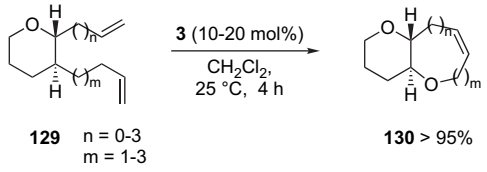


Scheme 33.



Scheme 34.

The synthesis of trans-fused polycyclic ethers has remained considerably challenging. Martin and Delgado have developed[62] a route to trans-fused bicyclic ethers, e.g., the conversion **129**→**130** (Scheme 35).



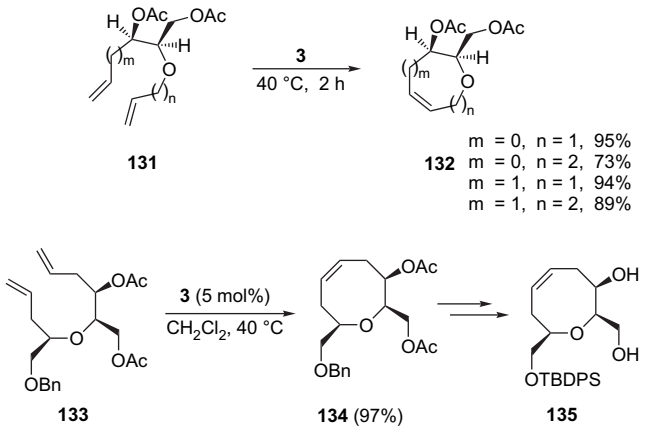
Scheme 35.

Crimmins and Choy published[63] a general enantioselective synthesis of seven-, eight- and nine-membered-ring cyclic ethers by RCM. Thus, exposure of dienes **131** to catalyst **3** readily afforded the oxacycles **132** (Scheme 36). Later, the authors applied[39] this methodology to the RCM of the diacetate **133** to obtain the oxocene derivative **134**, which was converted into an advanced intermediate **135** as a formal synthesis of (+)-laurencin.

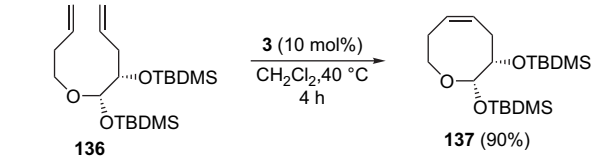
Taylor et al. reported[64] that RCM of the diene **136** with Grubbs' catalyst **3** provided the oxocene derivative **137**, as part of a program directed towards the synthesis of the laureatin natural products (Scheme 37).

The key reaction in Grubbs' enantioselective synthesis[65] of (−)-frontalin (via **139**) was the RCM of the diene **138** (Scheme 38).

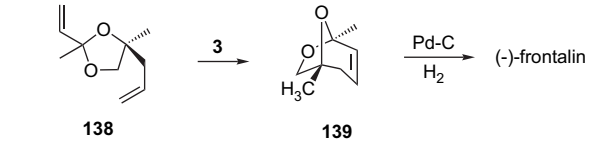
In their synthetic studies towards brevetoxin A, Clark and Kettle developed[66] a general enantioselective synthesis of



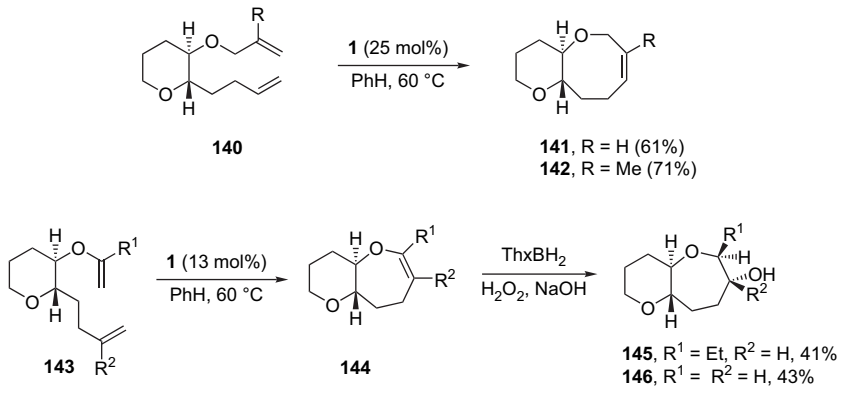
Scheme 36.



Scheme 37.



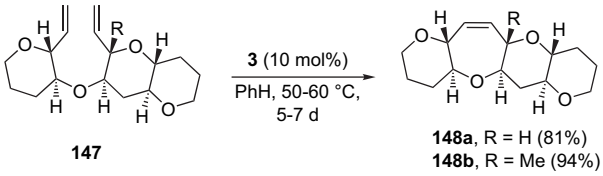
Scheme 38.



Scheme 39.

eight- and nine-membered bicyclic oxygen heterocyclic systems, which involved RCM of an appropriate oxygen-tethered diene (**140**) using Schrock's catalyst **1** to the corresponding oxacycles (**141** and **142**) (Scheme 39). The same group also developed[67] a new strategy for the synthesis of the bicyclic subunits of brevetoxin B. Thus, treatment of the enol ethers **143** with catalyst **1** led to the cyclic enol ether **144**, which on stereoselective hydroboration provided access to the 6,7-bicyclic ethers **145** and **146**.

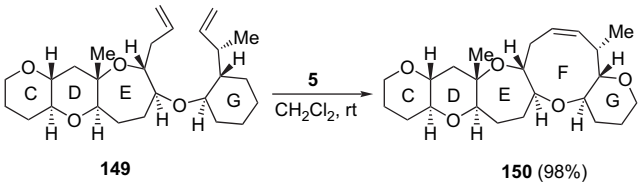
Hirama et al. applied[68] the RCM reaction for the construction of the tetracyclic ether system of ciguatoxin. Thus, the dienes **147** on treatment with Grubbs' catalyst **3** provided the tetracyclic ethers **148** in excellent yield (Scheme 40).



Scheme 40.

The authors (similarly) constructed the pentacyclic framework of the ciguatoxins using a similar protocol.[69] Sasaki et al. also employed[70] RCM methodology for the construction of the FGH ring fragment of ciguatoxin.

Sasaki and Sato described[71] a convergent synthetic route to the CDEFG-ring system **150** of the marine natural products, gambieric acids, having a polycyclic ether skeleton and potent antifungal properties. Thus, they conducted RCM of the diene **149** with the second-generation Grubbs' catalyst **5** to construct the nine-membered F-ring of the desired CDEFG-ring system **150** in 98% yield (Scheme 41).



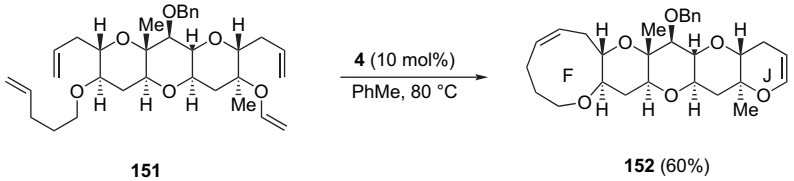
Scheme 41.

Clark et al. reported[72] a rapid two-directional synthesis of the F–J fragment **152** of gambieric acids by iterative double ring-closing metathesis in which the nine-membered F-ring and the six-membered J-ring were created in one step in 60% yield. The precursor **151** (Scheme 42) was derived from D-glucal.

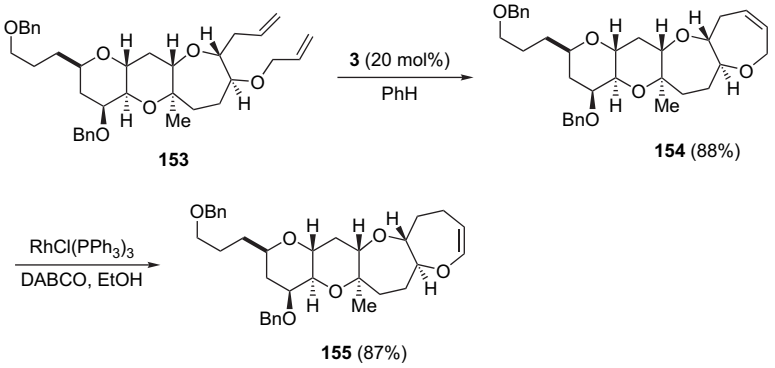
Other examples of polyether construction by RCM of enol ethers are also known.[73,74]

An alternate strategy for the ultimate synthesis of polycyclic enol ethers, adopted for the synthesis of the hemibrevetoxin A–D ring system, was the RCM-isomerization sequence reported[75] by Rainer and co-workers. Thus, RCM of the diene **153** (Scheme 43) with the catalyst **3** led to the cyclic ether **154**, which was isomerized with Wilkinson's catalyst to the enol ether **155**.

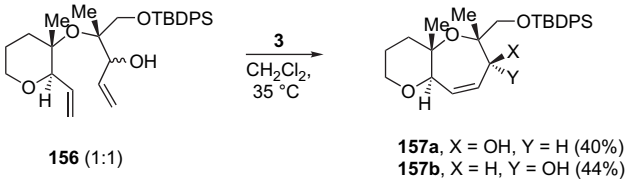
Gymnocins represent a series of cytotoxic marine polycyclic ethers, isolated from the red tide dinoflagellate, *Karenia mikimotoi*, by Satake et al.[76,77] These toxin molecules exhibit potent in vitro cytotoxic activity against P388 murine leukemia cells. Structurally, gymnocin B is characterized by 15 contiguous ether rings and is the largest among the polycyclic ether compounds reported so far.[78] Sasaki and Tsukano reported[79] the construction of the seven-membered O-ring by RCM. Treatment of **156** (Scheme 44) with the Grubbs'



Scheme 42.



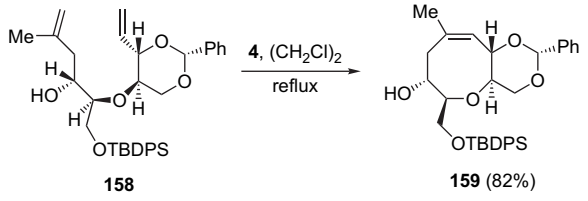
Scheme 43.



Scheme 44.

catalyst **3** produced the seven-membered ethers **157a** (40%) and **157b** (44%). The stereochemistry of each of these products was unambiguously established by NOE experiments. The authors recently completed[80] the total synthesis of gymnocin A and have evaluated its synthetic analogues.

Fujiwara et al. described[81] an efficient synthesis of the IJKLM-ring part of ciguatoxin CTX3C, which displays strong bioactivity and potent neurotoxicity by strong binding to voltage-sensitive sodium channels.[82] Their synthesis also featured RCM as the key step. Thus, ring closure of **158** (Scheme 45) in refluxing 1,2-dichloroethane by Grubbs' second-generation ruthenium catalyst **4** afforded the cyclic olefin **159** in 82% yield. The latter was then elaborated into the required part of the natural product.



Scheme 45.

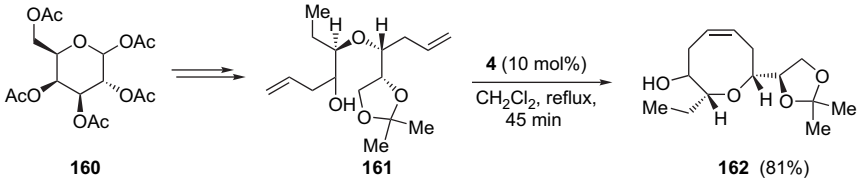
A total synthesis of CTX3C has been reported[83] by Hirama et al., in which the penultimate step involved RCM-mediated construction of the central eight-membered O-ring.

Fujiwara et al. have reported[84] a synthesis of the naturally occurring[85] (+)-laurencin from β-D-galactose pentaacetate (**160**). RCM of the derived diene **161** (Scheme 46) led to the oxocene derivative **162**, which was then elaborated into (+)-laurencin in nine steps.

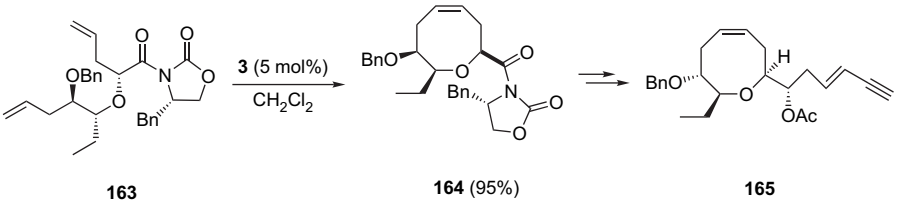
Crimmins et al. discovered that α,ω-dienes having vicinal stereogenic centres bearing oxygen atoms underwent cyclization via RCM with the facility to produce α,α′-*cis* and α,α′-*trans*-disubstituted eight- and nine-membered cyclic ethers. The authors ascribed the success of the reaction to the favourable *gauche* effect of 1,2-dioxygen substitution that predisposed the pendant olefinic side chains in a favourable conformation for effective ring closure. The required 1,2-dioxy intermediates were prepared by enantioselective aldol and alkylation reactions. Thus, a key step in a synthesis of (+)-laurencin involved the RCM of the diene **163** using catalyst **3** to provide the α,α′-*cis*-oxocene **164** (Scheme 47) in excellent yield.[86] The latter was converted into (+)-laurencin in 10 subsequent steps.

Crimmins and Tabet in their studies towards the total synthesis of the natural product, prelauretin (**168**) (Scheme 48),[87] exploited the beneficial *gauche* effect during an RCM reaction. Thus, treatment of **166**, prepared using a diastereoselective aldol reaction, with Grubbs' catalyst **3** gave **167** with no detectable dimerization. The latter was then converted into the natural product.

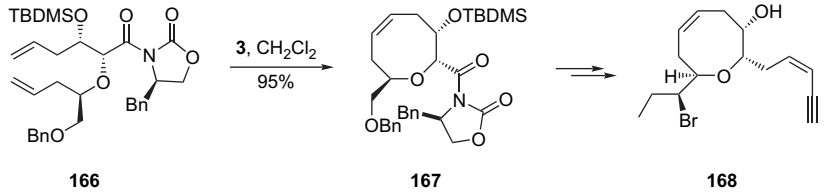
Further exploitation of the beneficial role of the *gauche* effect induced by vicinal dihydroxy groups leading to the formation of nine-membered cyclic ethers has been reported by Crimmins et al. during the synthesis of isolaurallene (**171**) (Scheme 49).[88] With this aim, the diene **169** was subjected to cyclization with Grubbs' catalyst **3** leading to the oxacycle **170**. It was argued that the diene **169** underwent such facile closure because of two synergistic *gauche* effects



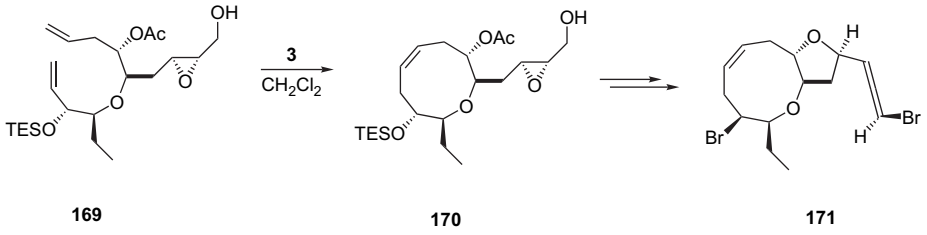
Scheme 46.



Scheme 47.



Scheme 48.



Scheme 49.

at C_6–C_7 and C_{12}–C_{13}. Compound **170** was then elaborated to (−)-isolaurallene (**171**).

The same group also applied a similar RCM-based strategy for the synthesis of (+)-obtusenyne.[89]

During the total synthesis of the structurally novel natural product, mycoepoxydiene (**174**, Scheme 50), an RCM approach was employed[90] for the construction of the oxygen-bridged eight-membered bicyclic skeleton. Thus, RCM of the diene **172** with the catalyst **3** furnished the cyclic product **173** in high yield. The latter was elaborated into the natural product.

Eleutherobin (Fig. 3), a potent cytotoxic compound[91] with an IC_{50} value of 10.7 nM, contains a central nine-membered unsaturated heterocyclic ring. This has generated metathetic activity to construct the challenging oxa-bridged bicyclic skeleton.

Kaliappan and Kumar reported[92] that the glucose-derived diene **176**, prepared from **175** (Scheme 51), when treated with

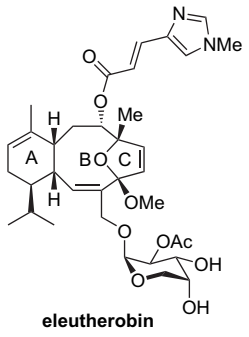
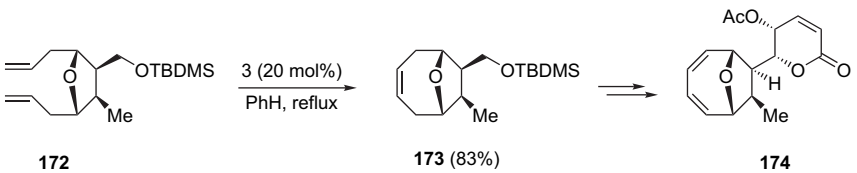
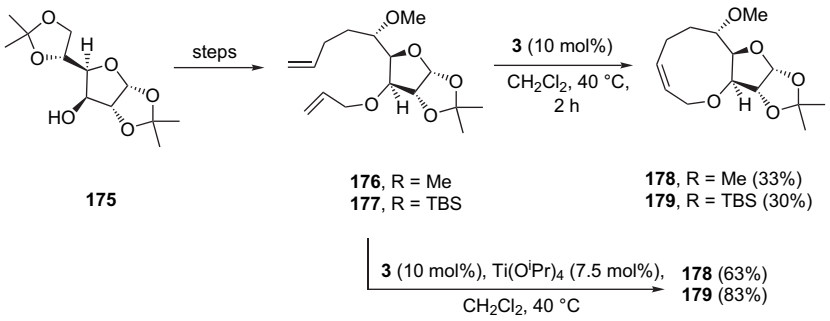


Figure 3.

the catalyst **3** under high-dilution conditions (0.003 M, 10% cat.), only 33% of the desired cyclized product **178** was obtained, the remainder being unreacted starting material and, presumably, some cross-metathesis product. The observation of a similar result with the TBS ether **177** suggested that the low yield could be attributed to coordination of the metal centre with the oxygen of the furanose ring. In order to destabilize this chelate structure, the RCM reaction of



Scheme 50.

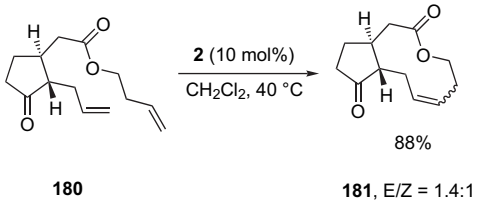


Scheme 51.

the dienes **176** and **177** was carried out with a catalytic amount of **3** in the presence of a substoichiometric amount of $Ti(O^iPr)_4$. This modified protocol successfully led to the formation of the desired RCM products **178** and **179**, respectively, in high yields.

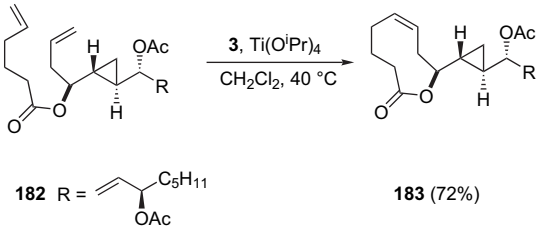
The formation of medium-size lactones by RCM constitutes a considerable challenge, since the inherent ring strain predisposes cycloalkenes containing 8–11 atoms towards ring-opening metathesis or ring-opening metathesis polymerization.

The first construction of a 10-membered lactone using an RCM was reported by Fürstner and Müller in 1997 in their synthesis of the jasmine ketolactone (*Z*)-**181**, a minor component of the essential oil of jasmine.[93] Heating a dilute solution of **180** (Scheme 52) in the presence of **2** resulted in the formation of **181** as a mixture (1.4:1) of *E*/*Z*-isomers in 88% combined yield. Chromatographic separation provided access to the natural product (*Z*)-**181**.



Scheme 52.

A rare example of the formation of a nine-membered lactone unit by RCM was reported by Takemoto in a synthesis of the acetyl derivative of halicholactone (**183**) (Scheme 53).[94,95] After considerable experimentation, it was found that the diene **182** underwent efficient RCM at high dilution under the Fürstner protocol to give the desired *Z*-isomer **183** as the major product, together with 11% of the corresponding dimer.



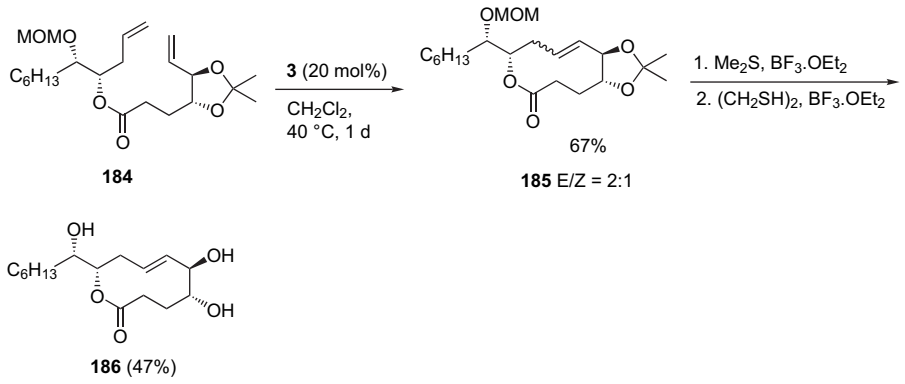
Scheme 53.

Marco et al. reported[96] a total synthesis of microcarpalide (**186**, Scheme 54), a naturally occurring nonenolide with cytotoxic and antimicrofilament activity. This study also featured RCM as the key ring-forming reaction. Thus, cyclization of the diene **184**, prepared from (*S*,*S*)-tartaric acid and (*R*)-glycidol, with the catalyst **3** led to a mixture (*E*/*Z*=2:1) of the macrocyclic lactones **185**, from which the required *E* isomer was separated. On the other hand, treatment of **184** with the second-generation catalyst **4** furnished almost exclusively the thermodynamically more stable (*Z*)-**185**. This observation is in agreement with those of Grubbs, who found that the *E*/*Z*-ratio in ring closures using **4** is not kinetically controlled, but is rather the result of an equilibration of the products.[97] The synthesis of **186** was then completed by sequential deprotection of **185**.

Since the nonenolides **187**–**189** (Fig. 4) all contained a carbon–carbon double bond, the RCM reaction, in principle, could provide a convergent approach to these targets. This has indeed been corroborated by the experimental results.

Grubbs' work[97] on the synthesis of herbarumin I revealed several salient features of using RCM in ester-tethered dienes. The diene **190** (Scheme 55) was prepared from D-ribose using conventional transformations. The diol protecting group was chosen as the isopropylidine group with the expectation that it would help to stabilize a conformation of **190** that would be favourable for ring closure. Semiempirical calculations on **191** revealed that the *Z*-isomer is more stable than the *E*-isomer (3.5 kcal mol^{-1}), thereby indicating that, conducting its RCM (or that of any other appropriate diene) under the conditions of thermodynamic control, would be expected to be counterproductive for obtaining the *E*-alkene present in the natural product. This, in turn, suggested that an RCM catalyst known to equilibrate the initial products should not be employed. Gratifyingly, the results obtained using two different RCM catalysts were fully consistent with this hypothesis. Thus, cyclization of **190** with the second-generation catalyst **5**, which was known to provide mixtures, enriched with the thermodynamically favoured products, led to the selective formation of (*Z*)-**191**. In contrast, exposure of **190** to catalytic amounts of the ruthenium indenylidene complex **6** afforded the desired lactone (*E*)-**191** as the major product, together with a small amount of the *Z*-isomer.

Methyllycaconitine is the principle toxin in *Delphinium brownii* and is found in at least 30 *Delphinium* species as well as in *Consolida ambigua* and *Inaularoyaleana*.[98]



Scheme 54.

Methyllycaconitine displays specific reversible, competitive antagonistic activity towards α-bungarotoxin-sensitive *n*AChRs.[99] A total synthesis of methyllycaconitine has not been reported to date, but several semisyntheses of methyllycaconitine from its parent alkaloid, lycoctonine, have been reported by Blagbrough and co-workers[100] and others.[101] Attention to the synthesis of tricyclic analogues of methyllycaconitine has mainly concentrated on the assembly of AEF analogues. McLeod and co-workers reported[102] the syntheses of ABE tricyclic analogues of the alkaloid, methyllycaconitine, using Grubbs' RCM to construct the seven-membered B-rings present in **195** and **197** (Scheme 56) in excellent yield. Thus, the allyl ether **194**, derived from the alcohol **192**, was subjected to RCM with Grubbs' catalyst **3** at room temperature for 22 h to afford the seven-membered ether **195** in excellent yield. Similar treatment of the epimeric alcohol **193** afforded the tricyclic ether **197** in 96% yield through the diene **196**.

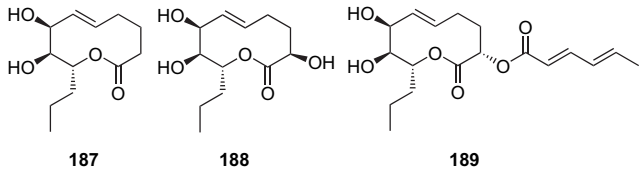
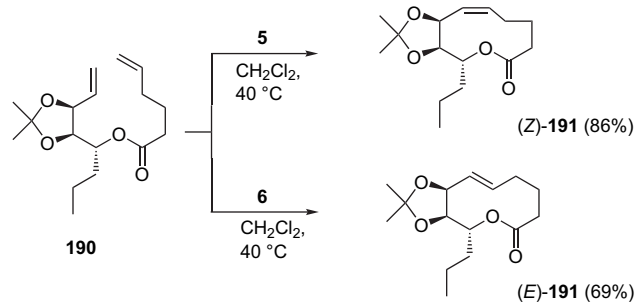


Figure 4.

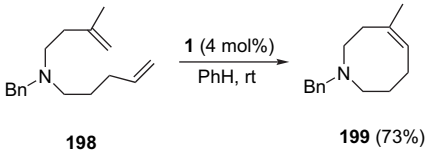


Scheme 55.

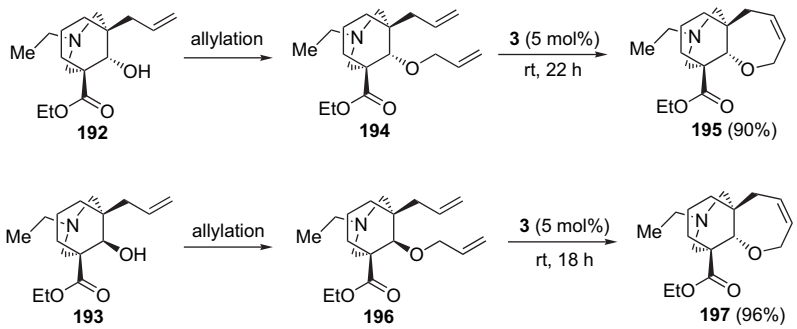
5. Formation of medium-ring nitrogen heterocycles by RCM

Various nitrogen heterocyclic systems accommodating common to large rings have been conveniently prepared involving RCM methodology over the last few years. These studies have revealed several general features of RCM of *N*-tethered dienes, which are briefly reviewed with reference to medium-ring azacycle formation.

Grubbs and Fu first reported[18] that the tertiary amine **198** (Scheme 57) could be converted into the azepine derivative **199** on prolonged exposure to Schrock's molybdenum catalyst **1**.

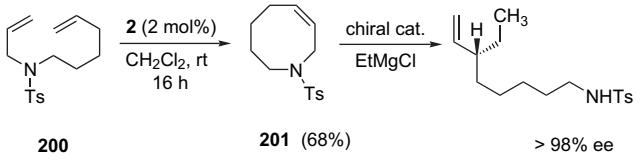


Scheme 57.



Scheme 56.

Hoveyda's group later reported[103] that the presence of an *N*-tosyl group accelerates the cyclization, e.g., the diene **200** gave the eight-membered cyclic product **201** (Scheme 58). The authors developed an asymmetric ethylmagnesation reaction to prepare acyclic unsaturated amides from the cyclic product **201**.

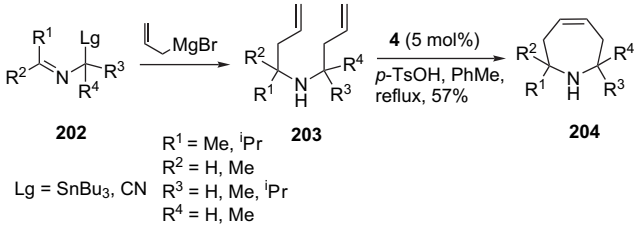


200 **201** (68%) > 98% ee

Scheme 58.

Similarly, it has been realized that the presence of other electron-withdrawing groups on nitrogen considerably accelerates the RCM of *N*-tethered dienes.

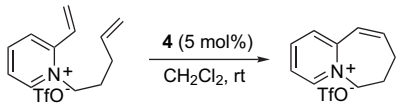
Protonated amines also undergo effective RCM reactions. Pearson et al. reported[104] a synthesis of 2,3,6,7-tetrahydroazepines **204** (Scheme 59) employing RCM as the key step. Their strategy involved the double allylation of an imine (**202**) containing a leaving group such as (2-azaallyl)stannanes or (2-azaallyl)nitriles. The dienes *N*,*N*-bis(3-butenyl)-amines (**203**), thus prepared, were then subjected to RCM with catalyst **4** in the presence of an equivalent amount of tosic acid to afford the azepine derivatives in moderate to excellent yield (56–98%).



Scheme 59.

Mendiola et al. described[105] a straightforward strategy for the synthesis of a novel series of azepine derivatives utilizing an RCM reaction as the key ring-forming step. Thus, the *N*-tosylpyrrolidinone derivative **205** (Scheme 60) on reduction to **206** followed by a one-pot Wittig olefination/N-allylation process provided the required diene **207**. The latter, when subjected to RCM in refluxing dichloromethane in the presence of 10 mol % of **4**, provided the azepine derivative **208** in moderate to excellent yield. This methodology allowed the incorporation of a variety of substituent types at the 4-position of the resulting azepine ring system.

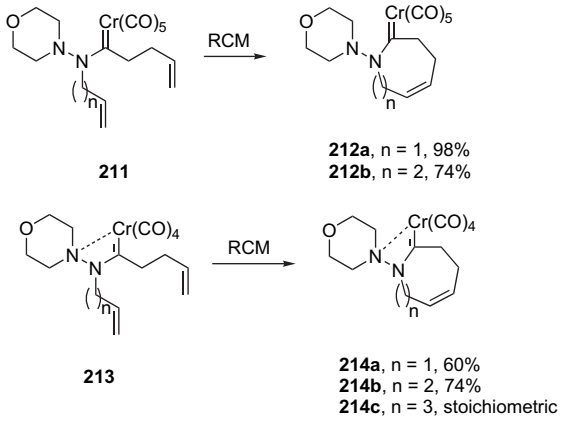
Vaquero et al. described[106] the first example of an RCM reaction on cationic heteroaromatic systems. Dihydroquinolizinium cations and a variety of related cationic systems were synthesized in an efficient approach from *N*-alkenyl azinium salts using Grubbs' catalyst **4**, e.g., the conversion **209**→**210** (Scheme 61).



209 **210** (88%)

Scheme 61.

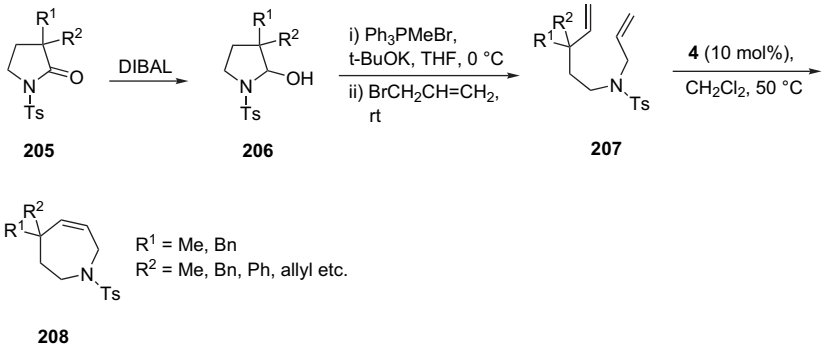
RCM reactions of Fischer hydrazine complexes of the type **211** proved[107] to be efficient for the synthesis of seven- or eight-membered heterocyclic rings **212a**,**b** (Scheme 62). No nine-membered cycles could, however, be formed. In an attempt to solve the problem, the corresponding tetracarbonyl chelate complexes **213** (n=1–3) were prepared with the expectation that the chelate would impose conformational restrictions on the diene favouring ring closure. This, indeed, proved to be true, but the reaction required a stoichiometric amount of Grubbs' catalyst (unspecified)



211 **212a**, n = 1, 98%
212b, n = 2, 74%

213 **214a**, n = 1, 60%
214b, n = 2, 74%
214c, n = 3, stoichiometric

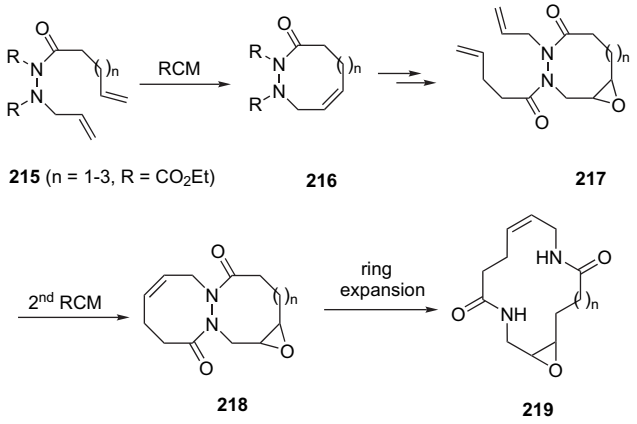
Scheme 62.



Scheme 60.

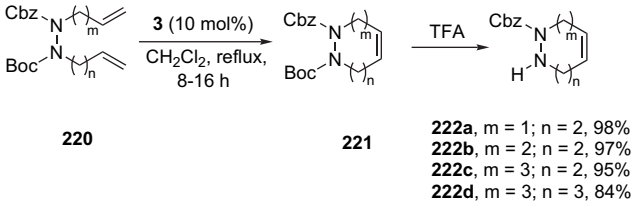
leading to **214a–c**. Tandem applications involving the utility of the ring-closed Fischer complexes thus prepared are expected to emerge.

A unique strategy[108] based on consecutive RCM for the formation of a 14-membered macrocyclic enamide has been developed by Lee and Kim. This strategy depends on the well-known stereodynamic and conformational behaviour of *N*-substituted diacylhydrazines, which promotes an effective ring-closing metathesis of hydrazine-derived dienes to form eight- to fourteen-membered rings. Thus, *N*-substituted diacylhydrazines **215** (Scheme 63) were subjected to a first RCM to produce the eight- to ten-membered rings **216**. Subsequent installation of the *N*-tethered diene unit in the latter followed by stepwise RCM of **217** and ring expansion of the resulting **218** via N–N bond cleavage provided unique access to the macrocyclic bis-lactams **219**.



Scheme 63.

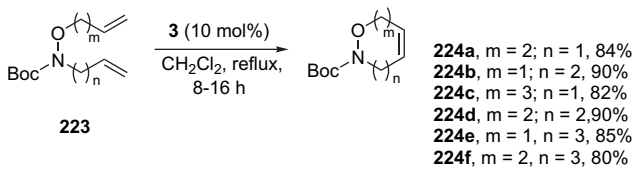
Similar applications of N–N and N–O bond tethered diene metathesis have also appeared. Thus, RCM of the dienes **220** (Scheme 64) tethered by an N–N bond with the catalyst **3** produced seven- to ten-membered cyclic 1,2-diaza compounds **221**. Lower substrate concentrations (0.005–0.008 M) were required for the efficient formation of the medium-ring compounds. Because the ^{1}H and ^{13}C NMR spectra of the cyclic hydrazine compounds were broad and complicated, the corresponding Boc-deprotected compounds **222a–d** were prepared[109] for better characterization.



Scheme 64.

The same group also reported[110] the synthesis of six- to ten-membered cyclic oxazines from the RCM of dienes tethered by an N–O bond, e.g., the conversions **223**→**224a–f** (Scheme 65).

Grigg et al. utilized[111] sequential palladium-catalyzed cyclization-anion capture reactions to prepare the diene precursor



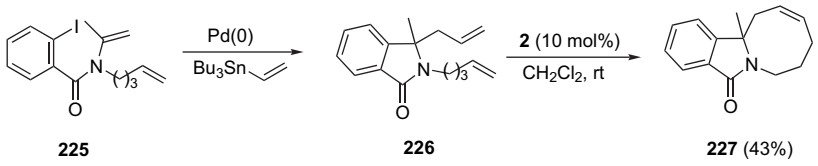
Scheme 65.

226 from the aromatic iodide **225** (Scheme 66) for the RCM reaction leading to **227**. The methodology has been extended for the synthesis of fused azacyclic systems.

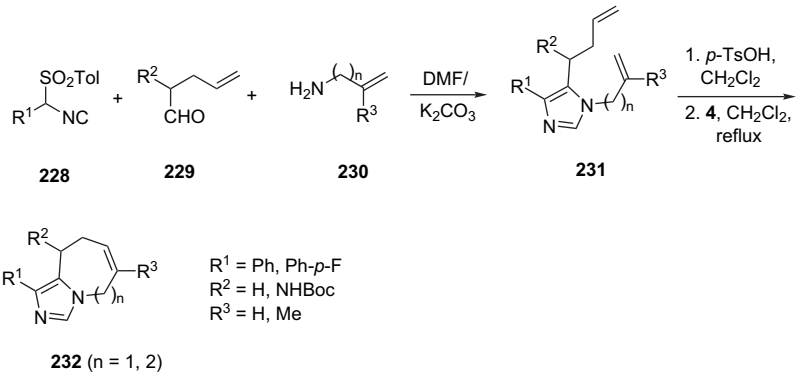
Gracias et al. reported[112] an efficient methodology for the synthesis of fused bicyclic imidazole rings **232** (Scheme 67) employing the van Leusen three-component reaction and an RCM reaction in a sequential fashion from simple starting materials. Condensation of isocyanide **228**, aldehyde **229** and allyl- or homoallylamine **230** components in the presence of DMF and potassium carbonate afforded the van Leusen imidazole products **231** in moderate to good yields (51–92%). The latter products were then pretreated with 1 equiv of *p*-TsOH before subjecting then to RCM. In some cases, however, the amine derivative underwent RCM reaction as such with the second-generation Grubbs' catalyst **4** in refluxing dichloromethane to give products in moderate to very good yields.

Some interesting observations have been made during a study[113] involving tandem applications of isomerization and RCM reactions for the synthesis of six-, seven- and eight-membered benzo- and pyrido-fused *N*,*N*-, *N*,*O*- and *N*,*S*-heterocycles. Thus, RCM of the *O*,*N*-tethered dienes **233** (Scheme 68) with catalyst **4** led to the formation of the corresponding heterocycles **234a**,**b**. Analogously, the *N*,*N*-heterocycles **238a**,**b** were prepared from the RCM of the dienes **237**. On the contrary, RCM of the *S*,*N*-tethered diene **240** with the catalyst **4** failed under a range of conditions. Oxidation of the sulfide **240** to the sulfone **241** followed by RCM proceeded with high efficiency to provide the eight-membered heterocycle **242**. The authors then studied isomerization-RCM sequences on the variety of the dienes prepared. Thus, double isomerization of **233** with the catalyst $RuClH(CO)(PPh_3)_3$ followed by RCM of the resulting intermediate **235** smoothly led to the heterocycles **236** in 70–91% yields. With the *N*,*N*-tethered diene **237** (R=Ts), double isomerization proceeded well to give the isomerized diene **239**, but the latter failed to undergo RCM. Changing the protecting group to an *N*-Boc moiety in **237** also did not alter the course of the reaction. The sulfone-tethered diene **241**, however, underwent selective isomerization of the *N*-allyl moiety to the corresponding *N*-vinyl derivative **243**. The latter, on RCM with the catalyst **4**, provided the ring-closed product **244** (41%) along with unchanged starting material (59%).

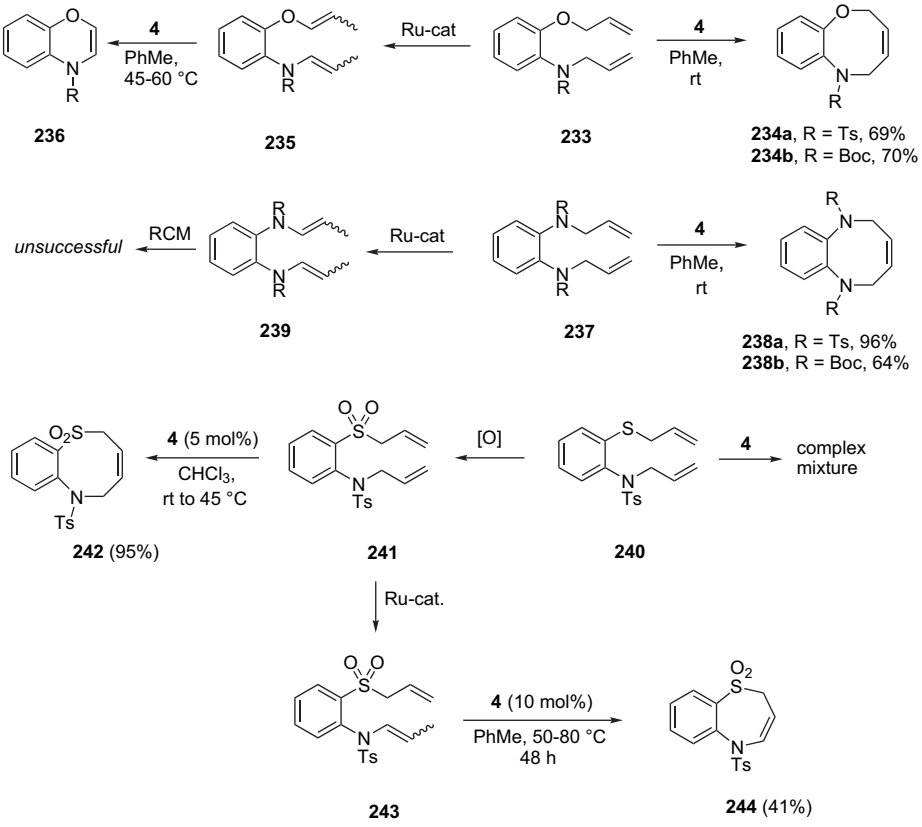
A new entry into unsaturated nine-membered lactams of potential use as external reverse-turn inducers, reported[114] by Banfi et al., employed a sequential Ugi multicomponent reaction (U-*n*CR) and RCM as the key steps. Thus, an U-4CR between an unsaturated imine, a carboxylic acid and an allyl-substituted racemic isocyanide led to the formation of the dienes **245** (Scheme 69) in good to excellent yields.



Scheme 66.



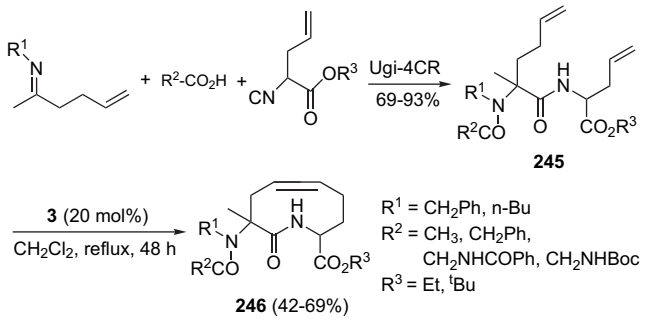
Scheme 67.



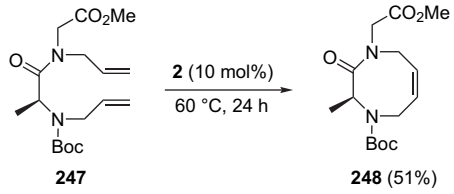
Scheme 68.

The Ugi-adducts on RCM with the catalyst **3** were transformed into the nine-membered lactams **246** in yields that could be considered quite good for the closure of a mesocyclic ring. It is worth noting that the similar cyclization of secondary amides to afford eight-membered rings by RCM is reported to be unfeasible.[115] The authors argued on the basis of computer-aided analysis that probably the *anti* amide bond conformations in hexahydroazoninones favour such cyclizations.

In studies directed towards the synthesis of conformationally constrained peptides, Grubbs et al. reported[19a] that the RCM of the bis-(*N*-allyl)dipeptide derivative **247** gave the cyclic peptide **248** in moderate yield (Scheme 70).

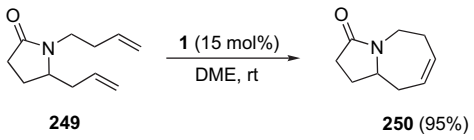


Scheme 69.



Scheme 70.

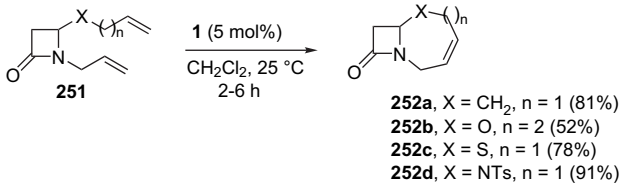
Martin et al. synthesized[116] the bicyclic lactam **250** (Scheme 71) from the RCM of the α,ω-diene **249** using Schrock's catalyst **1** using dimethoxyethane (DME) as solvent.



Scheme 71.

Similarly, Westermann and Diedrichs reported[117] the formation of optically pure bicyclic lactams from enantiomerically pure dienes using Grubbs' catalyst **3**.

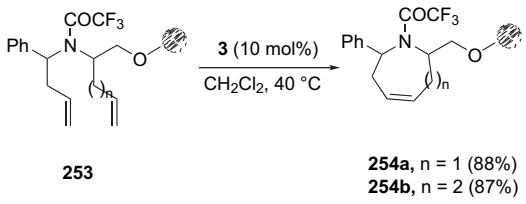
Medium-ring annulated β-lactams were conveniently prepared[118–120] using the RCM reaction by Barrett et al. Thus, the dienes **251** underwent smooth ring closure with the Schrock catalyst **1** to afford a range of bicyclic lactams **252a–d** in good to excellent yields (Scheme 72). It is interesting to note that the *N*- and *S*-tethered dienes gave higher yields than the corresponding *O*-tethered diene.



Scheme 72.

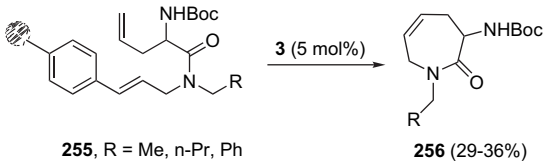
Similarly, bicyclic lactams, including β-lactams, were also prepared[121] by Holmes et al. involving the RCM reaction.

Performing the RCM reaction on solid supports has interesting chemical features. Blechert et al. reported[122] that the solid-supported dienes **253** underwent smooth RCM with Grubbs' catalyst **3** to provide the azacycles **254a**,**b** in excellent yields (Scheme 73).



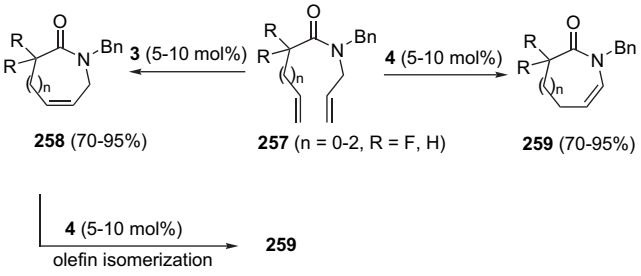
Scheme 73.

A clever application of the RCM on a solid support for the synthesis of a target structure as well as cleavage of the solid support in one step has been reported.[123] Thus, RCM of the solid-supported dienes **255** gave the β-turn mimetic **256** belonging to the class of Friedinger's lactam (Scheme 74). The final products were, however, obtained in poor yields.



Scheme 74.

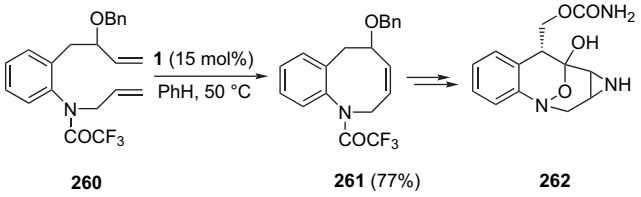
A tandem RCM-isomerization protocol for the synthesis of unsaturated lactams has been disclosed[124] recently. Careful selection of the metathesis catalyst, solvent and reaction conditions allowed efficient and regioselective synthesis of isomeric fluorinated and nonfluorinated lactam derivatives **258** and **259** (Scheme 75) from the precursor amides **257** through an RCM reaction or a tandem RCM-isomerization protocol, respectively. The presence of the *gem*-difluoro moiety in the starting material exerts a pivotal effect by directing the isomerization step, making the overall tandem transformation a regioselective process.



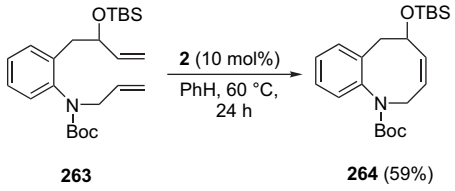
Scheme 75.

Azacyclic frameworks of several important natural products and medicinally important compounds have been conveniently constructed employing the RCM methodology. RCM has been used in several instances[125–127] to prepare azacyclic eight-membered rings that were then elaborated into bicyclic ring systems via a subsequent transannular reaction. A model study directed towards the total synthesis of the unusual antitumor antibiotic, FR-900482 (**262**), utilized[125] RCM of the diene **260** (Scheme 76) with Schrock's catalyst **1** to afford the benzoazocine derivative **261**.

Grubbs employed[19a] RCM on the similar type of intermediate **263** using catalyst **2** to access the benzoazocine derivative **264** (Scheme 77).



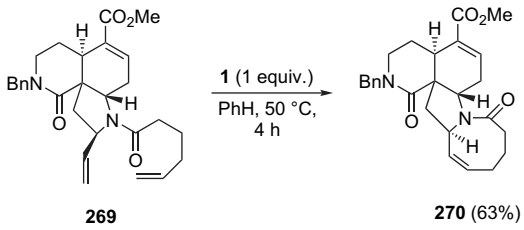
Scheme 76.



Scheme 77.

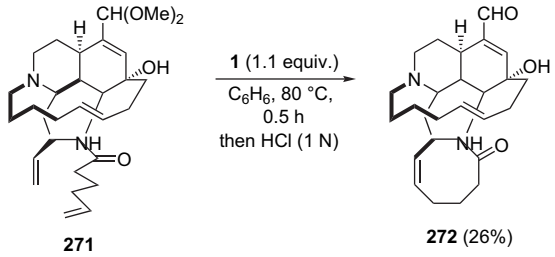
In Martin's approach[128] towards the synthesis of FR-900482, commercially available 4-hydroxy-3-methoxy-5-nitrobenzaldehyde (Scheme 78) was first converted into enantiomerically pure **265** in a sequence of 11 steps, which featured enzymatic desymmetrization of a prochiral diol as the key step. The latter was then elaborated into the RCM substrate **266** in five steps. The crucial RCM reaction proceeded well in refluxing benzene in the presence of Grubbs' catalyst **3** and the benzoazocine **267** was isolated in a gratifying yield of 78%. The authors attributed the efficiency of this cyclization to the conformational constraints imposed by the benzene ring and the amide nitrogen atom in the chain linking the two double bonds in **266**. The latter was converted into an advanced precursor **268**, which has been previously converted into the natural product.[129]

Martin et al. have reported one of the earliest examples of the use of RCM to access medium rings. They employed Schrock's catalyst **1** in the ring-closing reaction of the tricyclic amide **269** to give the tetracyclic azocine derivative **270** (Scheme 79), an advanced precursor in the synthesis of manzamine A.[130a] The required transformation, however, needed an equivalent of the catalyst. Pandit et al. also reported an RCM strategy for the synthesis of the tetracyclic ring system of manzamines.[130b]



Scheme 79.

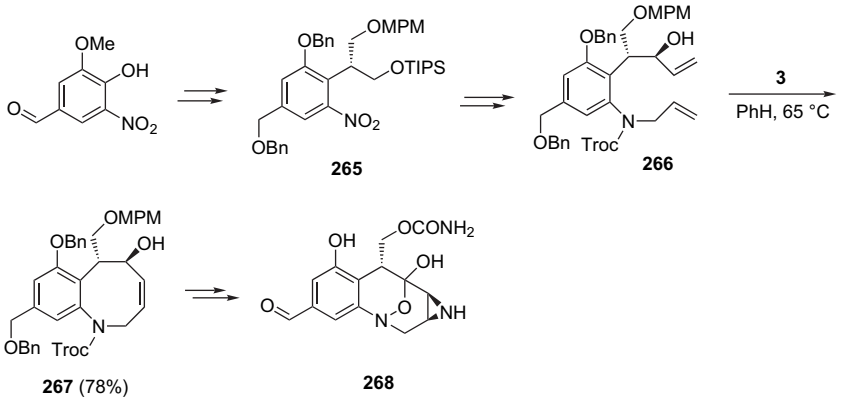
Martin's group later reported[131] that the RCM of the tetracyclic amide **271** (Scheme 80) gave the pentacyclic amide **272** with 1.1 equiv of the catalyst **1**. The desired product was obtained in low yield (26%), even with an equivalent of the catalyst, possibly because of the tertiary amino group. The product thus obtained was elaborated into the natural product, ircinal A.



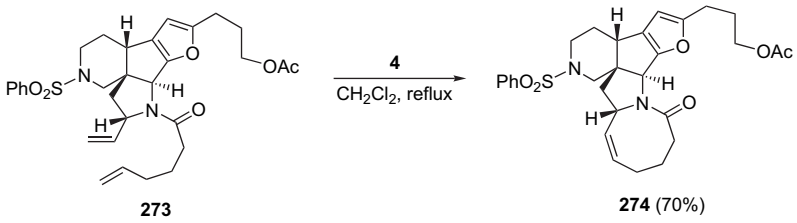
Scheme 80.

Nishida et al. reported the synthesis of an enantiomer of the unusual marine natural product, nakadomarin A, that is, believed to belong to the manzamine family. Their approach exploited RCM reactions to construct the eight- and the fifteen-membered azacycles present in this natural product.[132] The authors observed that cyclization of the advanced intermediate **273** (Scheme 81) proceeded best with the second-generation Grubbs' catalyst **4** to deliver the lactam **274** in good yield. On the other hand, attempted cyclization of **273** using the alkylidene catalyst **3** met with limited success.

In studies directed towards the synthesis of the natural product, australine, White et al. reported[133] that the RCM of the diene **275** with Grubbs' catalyst **3** gave a very high yield of

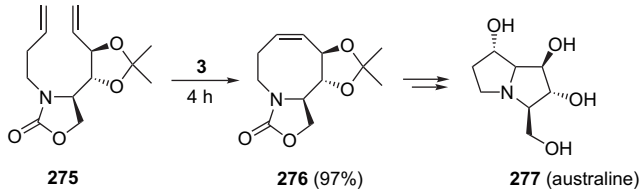


Scheme 78.



Scheme 81.

the bicyclic azacyclooctene **276**, which was eventually elaborated into the natural product **277** (Scheme 82).



Scheme 82.

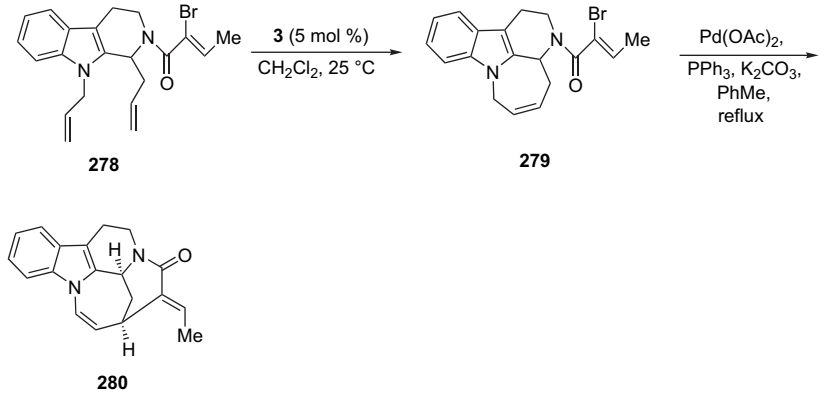
Trost and Oslob also utilized[134] the RCM reaction to construct the heterocyclic core of the natural product, (−)-anatoxin A.

In studies directed towards developing new stereocontrolled routes to the geissoschizine and akagerine family of natural products, Rawal and Birman reported[135] the RCM of the diene **278** to give the tetracyclic **279** (Scheme 83). Intramolecular Heck reaction of the latter produced the pentacycle **280**.

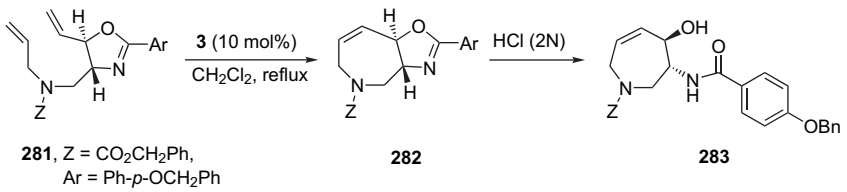
In order to construct a seven-membered nitrogen heterocycle carrying a 1,2-amino alcohol by an RCM cyclization, Cook et al. used[136a] an oxazoline ring as a constraint. The substrate **281** (Scheme 84) was prepared from D-serine utilizing a palladium-catalyzed equilibration of vinyloxazolines to control the stereochemistry of the vicinal amino alcohol. As deduced from force-field calculations, the torsional angle of the side chain in **281** is about 95°, which is easily accommodated by the bicyclic structure **282**. Accordingly, the RCM reaction with the catalyst **3** in refluxing dichloromethane furnished the heterocycle **282** in 77% yield. The latter was then hydrolyzed to form the advanced intermediate **283** for the ultimate synthesis of the potent protein kinase C inhibitor, balanol. Furstner and Thiel also reported[136b] an elegant route to balanol involving RCM as the key step.

Jenkins et al. described[137] a new RCM route to seven-membered aza-heteroannulated sugars having potential biological applications. Thus, the known carbohydrate derivative **284** (Scheme 85) underwent a diastereoselective reductive amination to provide the allylamine derivative **285** in high yield, which was converted into the corresponding *N*-trifluoroacetyl derivative **286**. The latter, on treatment with the catalyst **3**, smoothly transformed into the azepane derivative **287**, which was sequentially deprotected to the amino diol **289** through the amine **288**.

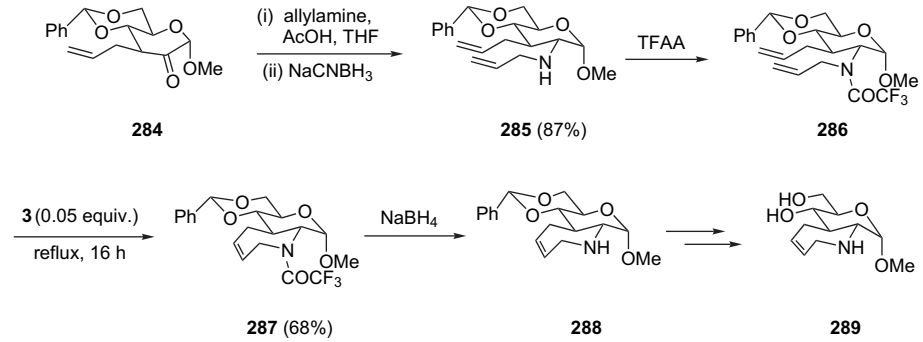
RCM has found extensive applications in the synthesis of common-ring azasugars[138] and other examples of the formation of medium-ring azasugars such as **290** (Fig. 5) by an RCM reaction are also known.[139]



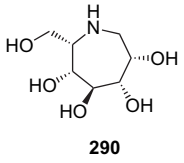
Scheme 83.



Scheme 84.



Scheme 85.



290

Figure 5.

The apogalanthamine analogues (Fig. 6) represent an intriguing class of natural products belonging to the *Amaryllidaceae alkaloid* family[140] featuring a rare 5,6,7,8-tetrahydrobenzo[*c*,*e*]azocine skeleton incorporating a biaryl unit. Buflavine (**291**) (Fig. 6) is a typical member of this family, exhibiting interesting biological activities such as α-adrenolytic and anti-serotonin activities.[141]

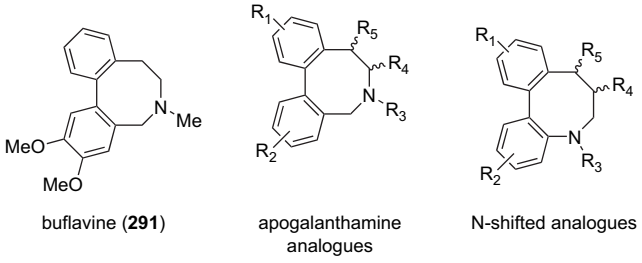
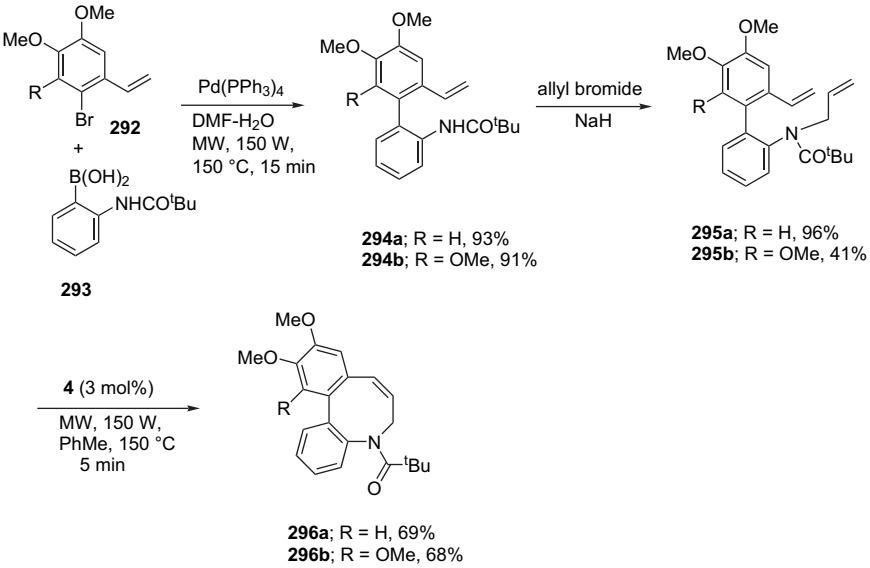


Figure 6.

Eycken et al. reported[142] the synthesis of *N*-shifted buflavine analogues (Fig. 6). Their approach involved RCM of the biaryl derivatives **295a**,**b** (Scheme 86) as the key step. The authors developed a microwave-assisted Suzuki–Miyaura cross-coupling protocol for the synthesis of the biaryls **294a**,**b** from the corresponding aryl bromide **292** and the aryl boronic acid **293**. The RCM of the dienes **295a**,**b**, prepared by N-allylation of the carbamates **294a**,**b**, proceeded with difficulty under a range of conditions in varying yields of 17–69%. Microwave-assisted RCM reaction with the catalyst **4**, however, ultimately led to the products **296a**,**b** in moderate to good yields.

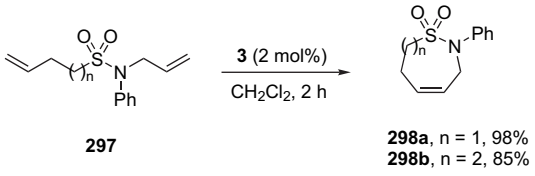
6. Formation of medium-ring sulfur heterocycles by RCM

Although many examples of the synthesis of oxygen- and nitrogen-containing cyclic molecules by RCM are known, the application of RCM to the synthesis of sulfur-containing medium-ring heterocycles remains very limited. Thus, both



Scheme 86.

the catalysts **2** and **3** were shown to be either unreactive or of low reactivity towards the RCM of α,ψ-dienes containing a sulfide moiety,[143] possibly due to poisoning of the ruthenium catalyst by the sulfide functionality. RCM of substrates containing a sulfonamide group has been well documented,[144] an application to medium-ring synthesis being the conversion of **297** into **298a**,**b** (Scheme 87).



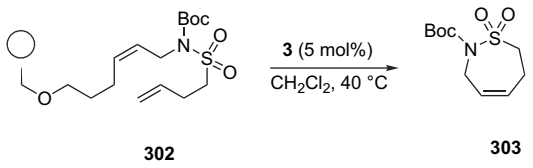
Scheme 87.

Brown et al. reported a cyclorelease RCM strategy towards cyclic sulfonamides[145] using solid-phase synthetic methods. The crucial metathesis reaction as well as release of the solid support in a single step was utilized to form a Boc-protected seven-membered cyclic sulfonamide (**301**) from the double-armed and single-armed polystyrene-bound precursors **299** and **300**, respectively (Scheme 88). This cyclorelease protocol, however, met with somewhat limited success, due to problems of catalyst deactivation as a direct result of becoming bound to the resin following the metathesis event.

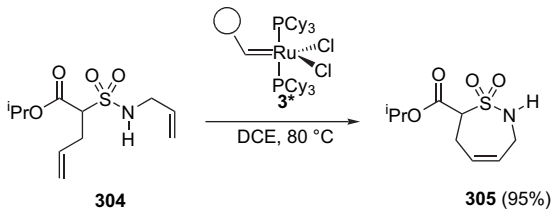
The authors extended this methodology to generate a small library of unsubstituted and *N*-substituted cyclic sulfonamides, an example being the conversion **302**→**303** (Scheme 89).

Similarly, Termin and Long reported[146] the synthesis of seven-membered cyclic sulfonamides **305** (Scheme 90) using RCM on a solid support. RCM of the diene **304** was carried out with catalyst **3** and its polystyrene-bound variant[147] **3*** in refluxing dichloroethane, using 1-hexene as a cofactor. The authors noted that the catalysts **3** and **3*** are comparable in efficiency, the former being more advantageous due to the ease of product purification. The only drawback to this approach was the catalyst behaviour upon re-use. Catalyst **3*** proved to be much less effective for re-use than previously reported[147] in terms of the chemical yield.

Snieckus and Lane reported a combined *ortho*-metallation/RCM methodology[148] for the preparation of benzannulated cyclic sulfonamides. The cyclization precursors **306a**,**b**, prepared via directed *ortho*-metallation followed by allylation, underwent a high-yielding cyclization with the catalyst **3** to

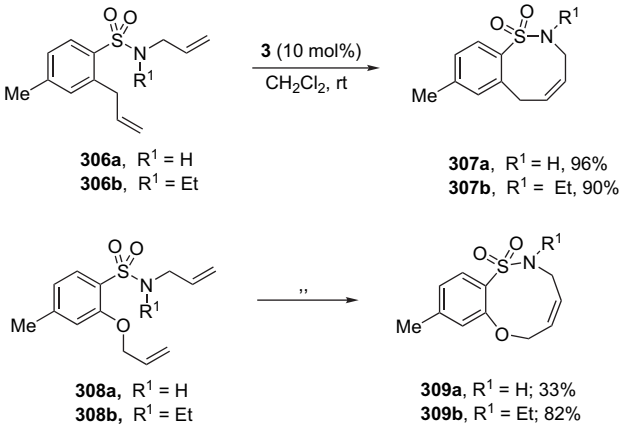


Scheme 89.



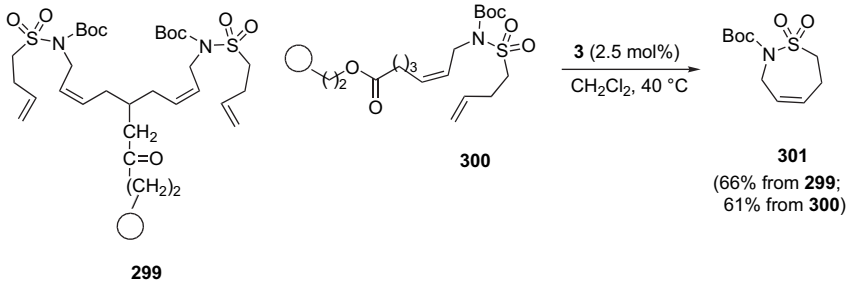
Scheme 90.

provide the benzannulated sulfonamides **307a**,**b** (Scheme 91). Nitrogen substitution had little effect on the RCM efficiency. Oxygenated sulfonamides were also synthesized in modest to good yields. The metathesis of unsubstituted sulfonamide **308a** yielded only 33% of the corresponding nine-membered product **309a**, while RCM of the corresponding *N*-ethyl derivative **308b** afforded the bicyclic sulfonamide **309b** in high yield. Attempts to cyclize sulfonamides with disubstituted olefins gave only products arising from cross-metathesis of the monosubstituted alkenes.



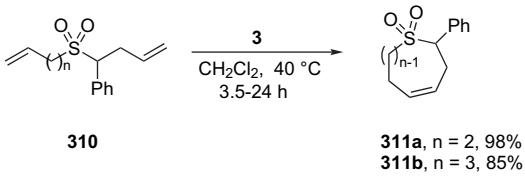
Scheme 91.

RCM of sulfone derivatives has also been reported[149] including the synthesis of medium-ring sulfones. Yao carried



Scheme 88.

out[150] a systematic study of RCM of sulfone derivatives **310**. A number of structurally diverse cyclic sulfones were prepared including medium-ring cyclic sulfones **311a**,**b** (Scheme 92).



310 **311a**, n = 2, 98%
311b, n = 3, 85%

Scheme 92.

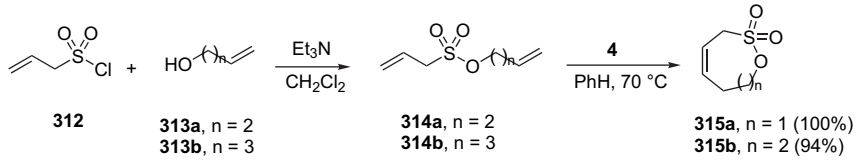
The RCM of vinylic and allylic sulfonates has provided access to synthetically useful cyclic sulfonates (sultones). Sultones of varying sizes have been generated utilizing both Grubbs' catalysts **3** and **4**, although catalyst **4** has proved to be more effective. Metz et al.[151] and Cossy et al.[152] independently synthesized sultones using catalyst **4**. The required *S*-*O*-tethered dienes were prepared from the condensation of allylsulfonyl chloride **312** with olefinic alcohols **313a**,**b** (Scheme 93). The dienes **314a**,**b** underwent near-quantitative transformation to the corresponding sultones **315a**,**b**. These studies revealed a general trend that the formation of medium-sized rings with β,γ-unsaturated substrates is more facile than their α,β-unsaturated analogues.

RCM strategies proved to be successful to generate symmetric and unsymmetric cyclic sulfamides[153,154] related to the potent HIV protease inhibitor,[155] DMP-323.

Thus, RCM of the sulfamide-tethered diene **316** with 5 mol % of the catalyst **6** provided the cyclic sulfamide **317** in 69% yield (Scheme 94). The latter on subsequent dihydroxylation produced the required cyclic sulfamide diol **318** in 99% yield. Unsymmetrical sulfamides were also generated with high efficiency.

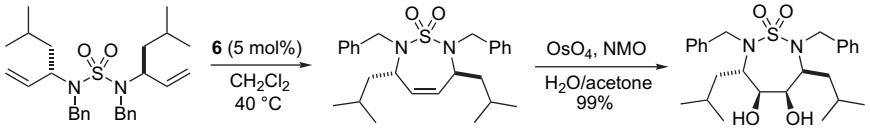
Bates et al.[156] described a new protocol for the synthesis of thiazocine-2-acetic acid derivatives, which involved conjugate addition of allyl mercaptan to an acrylate containing a tethered olefinic site followed by RCM (Scheme 95). The resulting sulfanyl derivatives such as **320** were found to be unreactive towards RCM, whereas the corresponding sulfoxide (**321**) and sulfone (**323**) analogues provided the required thiazocines **322** and **324**, respectively, in fair to excellent yields.

The lack of reactivity of **320** was possibly not due to coordination of the Ru-catalyst with the ester carbonyl as revealed



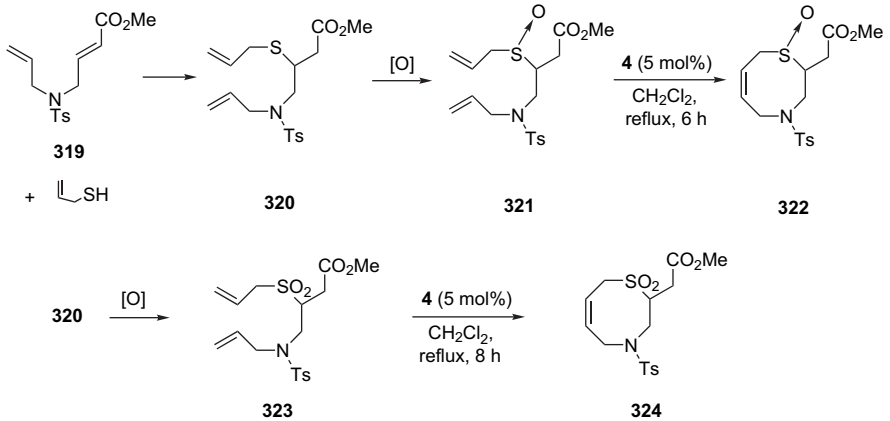
312 **313a**, n = 2
313b, n = 3
314a, n = 2
314b, n = 3
315a, n = 1 (100%)
315b, n = 2 (94%)

Scheme 93.



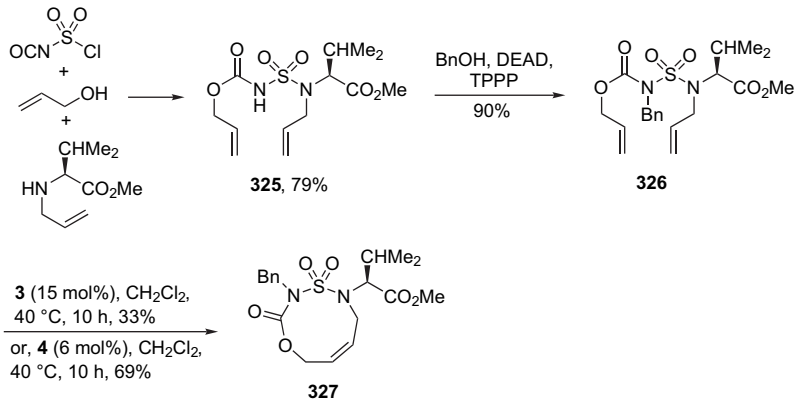
316 **317** (69%) **318**

Scheme 94.



319 **320** **321** **322**
323 **324**

Scheme 95.

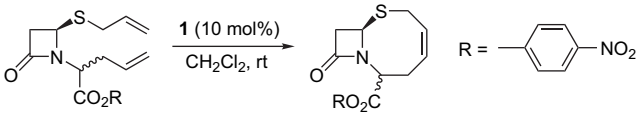


Scheme 96.

by the fact that the addition of $Ti(O^iPr)_4$ did not alter the fate of the reaction. The problem is more likely to be due to inactivation of the catalyst by coordination of the Ru to S. Coordination/inactivation could occur intermolecularly, prior to interaction of the Ru with the olefinic sites, or intramolecularly.

Hanson et al. described[157] a new synthetic route to a diverse set of cyclic sulfamoyl carbamates and ureas. This route involved a three-component coupling, Mitsunobu alkylation and ring-closing metathesis as the key steps. Thus, initial three-component coupling between allyl alcohol, chlorosulfonyl isocyanate and *N*-allyl-(L)-valine methyl ester generated the corresponding sulfamoyl carbamate **325** (Scheme 96). The latter under Mitsunobu reaction conditions for N-alkylation provided the *N*-benzylsulfamoyl carbamate **326** in excellent yield. Compound **326** was then subjected to RCM with catalyst **3** to provide the nine-membered cyclic sulfamoyl carbamate **327** in only 33% yield. An improved result (69%) was, however, obtained employing the second-generation Grubbs' catalyst **4**.

Barrett et al. reported the synthesis[158] of a variety of β-lactam carboxylic esters by tandem Ireland–Claisen rearrangement/catalytic RCM reactions. A notable advantage of the molybdenum-based catalyst **1** (vs Ru complexes) was demonstrated in the context of this investigation. Thus, the sulfur-containing diene **328** (Scheme 97) was readily converted into the desired cyclic product **329**. In contrast, with the Ru-catalyst **3** (20 mol %), only 5% product formed, indicating decomposition of the catalyst.



Scheme 97.

7. Formation of medium-ring heterocycles by ring-closing enyne metathesis (RCEYM)

Enyne metathesis may be defined as the re-organization of covalent bonds between an alkene and alkyne to develop a 1,3-diene unit. Two possible pathways for ring-closing enyne metathesis (RCEYM) with ruthenium carbene catalysts are illustrated in Figure 7.[159–161] In pathway A, ruthenium carbene has been shown to react initially with the alkene part of the enyne **330** leading to **331**, and then a sequential intramolecular [2+2] cycloaddition and retro-cycloaddition have been proposed to lead to the 1,3-diene unit **340** through the intermediates **334** and **337**, whereas, in pathways B_1 and B_2, ruthenium carbene is supposed to

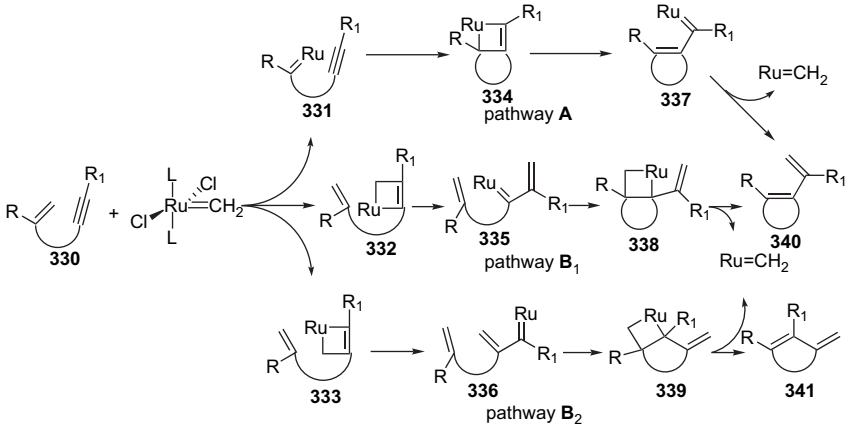
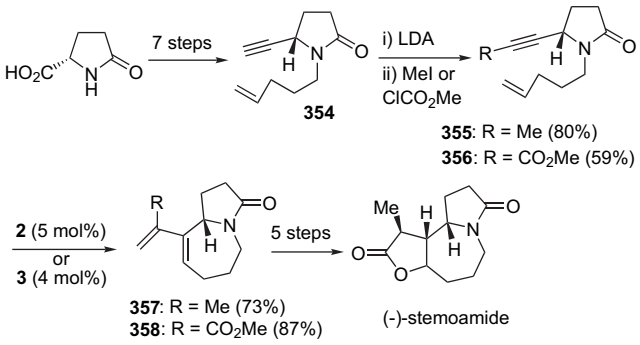


Figure 7.

react with alkyne moiety in two possible modes to generate ruthenacyclobutene regioisomers **332** and **333**, which have been converted into two different 1,3-dienes **340** (via **335** and **338**) and **341** (via **336** and **339**), respectively, following a similar type of retrocycloaddition and cycloaddition reaction sequences.

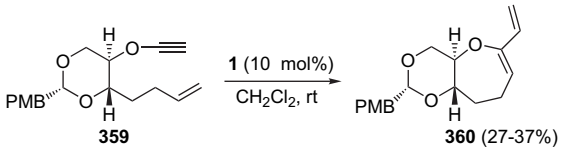
Intramolecular diene metathesis is an entropically favourable reaction, as cycloalkene and ethylene are generated from the starting diene on RCM, whereas, no such inherent driving force is present during the intramolecular ring-closing enyne metathesis reaction. Thus, medium-ring formation is very difficult via enyne metathesis. In most of the cases, it requires a prolonged reaction time and a high catalyst loading. It was reported that the construction of seven-membered rings needed longer reaction times and the products were formed in varying yields.[162–166] The formation of eight- and nine-membered rings is very difficult, as, in these cases, the dimerization product is found to be a competitor of the cyclized product.[167] Moderate yields of the eight- and nine-membered products were, however, reported[167] when two heteroatoms or quaternary centres were present as the enyne tether. Some examples regarding the synthesis of seven (**343a–c** from **342a–c**; **345a**,**b** from **344a**,**b**)-, eight (**347a**,**b** from **346a**,**b**; **349a**,**b** from **348a**,**b**; **351** from **350**)- and nine-membered (**353** from **352**) oxacycles or azacycles via RCEYM are depicted in Scheme 98.

Using RCEYM as the key step, Kinoshita and Mori were the first to demonstrate[168,169] the total synthesis of the natural product, (−)-stemoamide (an insecticidal alkaloid). Thus, treatment of enyne **355** (Scheme 99) with catalyst **2** (5 mol %) afforded the diene **357** (73%), whereas the ester-substituted enyne **356** on RCEYM with catalyst **3** (4 mol %) produced **358** in 87% yield. Interestingly, in both cases, the two newly generated double bonds were not in conjugation, due to steric effects, as demonstrated by NMR chemical shifts. The diene **358** was then elaborated into (−)-stemoamide in five steps.[169]

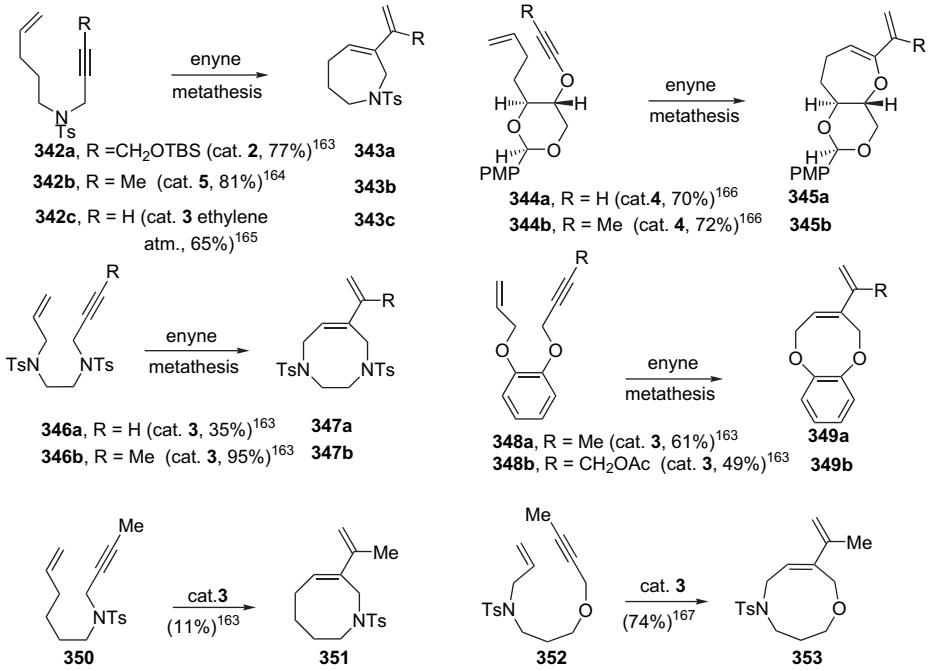


Scheme 99.

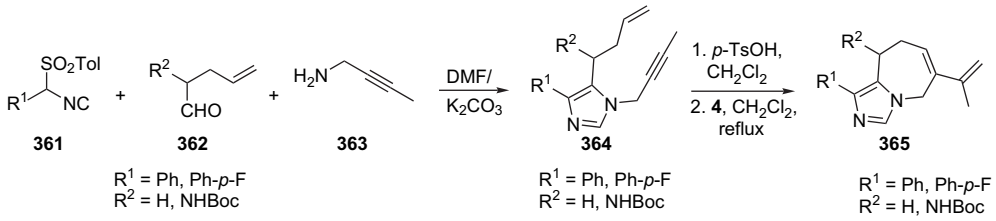
Clark et al. developed[170] the enyne metathesis protocol for the synthesis of alkenyl-substituted seven-membered cyclic enol ethers. A new strategy for the construction of trans-fused bicyclic ethers corresponding to the subunit of brevetoxin B has also been reported[171] by the same group. They had shown that RCEYM of enyne **359** with Schrock's Mo catalyst **1** furnished **360** (Scheme 100) in 27–37% yield. Their further investigations revealed that, for this particular case, the second-generation Grubbs' catalyst was superior to the first-generation catalyst.[167]



Scheme 100.



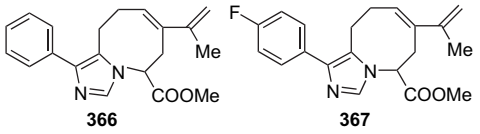
Scheme 98.



Scheme 101.

Gracias et al. introduced[172] a facile synthesis of fused imidazoazepine derivatives **365** (Scheme 101), which involved a van Leusen three-component reaction and an intramolecular enyne metathesis reaction as the key steps. Thus, a condensation involving the isocyanides **361**, aldehydes **362** and the alkynylamine **363** led to the required substrates **364** in excellent yield. The latter, on subsequent cyclization with the second-generation Grubbs' catalyst **4** in refluxing CH_2Cl_2, produced the cyclized products **365** also in very good yield.

The same workers also reported the synthesis of **366** and **367** (Scheme 102) using a different amine component, but following a similar strategy and reaction conditions.

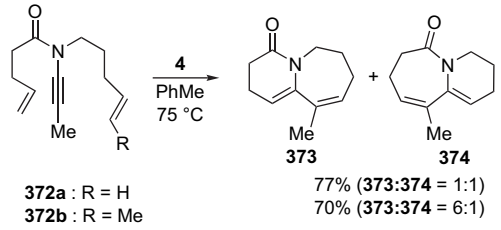


Scheme 102.

The efficacy of the RCEYM reaction has been increased further by combining various processes with regard to further transformation of the initial diene product. In recent years, the scope of these transformations has been explored in the field of complex polycycle construction and natural product synthesis.[173] The application of tandem enyne metathesis in carbocycle construction was reported by Grubbs and co-workers as early as in 1994.[174,175] Over the years, the concept has found many applications in heterocyclic synthesis.

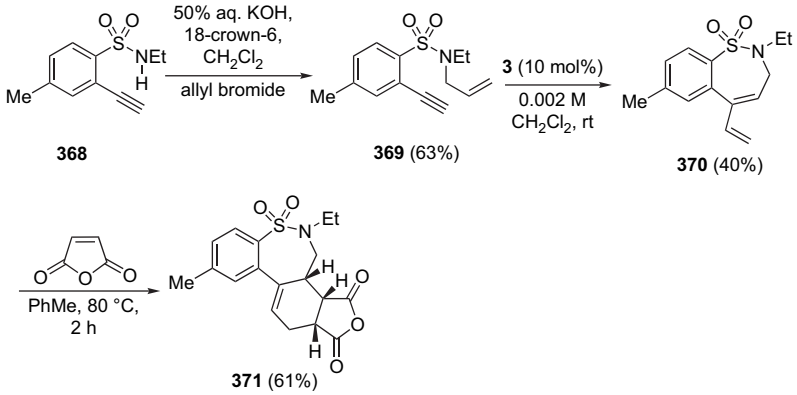
Benzannulated seven-membered cyclic sulfonamides were synthesized[148] by Snieckus et al. via enyne metathesis to generate the diene **370** (Scheme 103), a suitable precursor for a subsequent Diels–Alder reaction. Thus, allylation of the acetylenic sulfonamide **368** under conventional conditions led to the enyne sulfonamide **369**, which on RCEYM employing 10 mol % of the catalyst **3** in high dilution was converted into the diene sulfonamide **370** in modest yields. Diels–Alder reaction of the latter with maleic anhydride as dienophile led smoothly to the polycyclic sulfonamide **371** in 61% yield.

Huang et al. reported[176] an interesting observation during the tandem metathesis of diene-ynamides **372a**,**b** (Scheme 104). Thus, metathesis of diene-ynamide **372a** with Grubbs' second-generation catalyst **4** afforded a 1:1 mixture of **373** and **374**. On the other hand, the ratio became 6:1 when the starting material was the substituted dienyne **372b**. In these transformations, the first ring-closing enyne metathesis is followed by a second ring-closing diene metathesis. Steric factors arising due to methyl substitution at one of the olefinic tethers seem to have controlled the initial direction of RCEYM, as reflected by the product geometry.

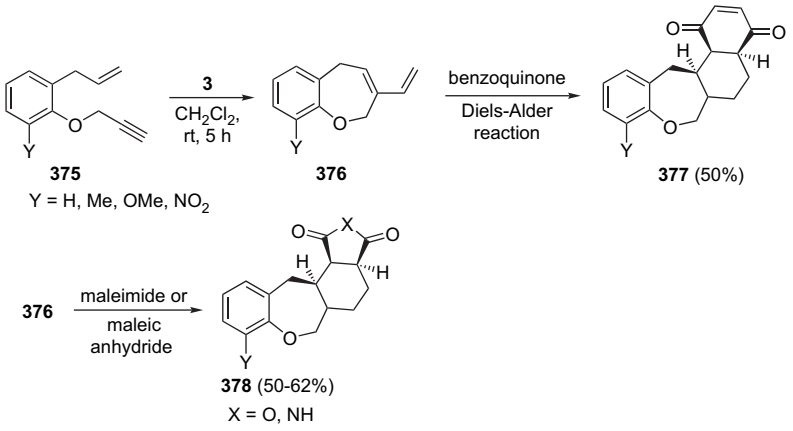


Scheme 104.

Moreno-Manas et al. reported[177] the synthesis of tri- and tetracyclic benzoxepine derivatives (**377** and **378**) (Scheme 105) by a one-pot enyne metathesis/Diels–Alder reaction



Scheme 103.

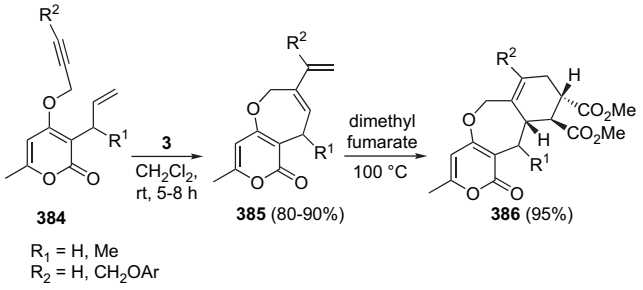


Scheme 105.

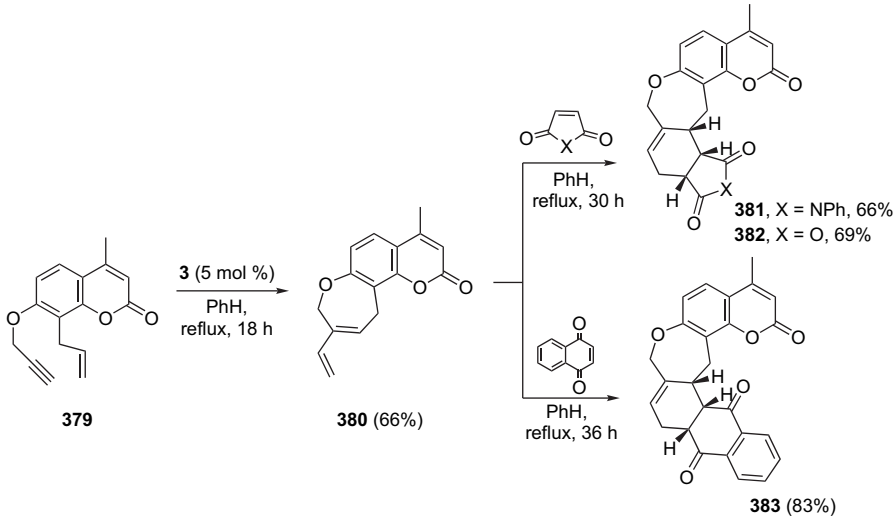
starting from differently substituted 2-allyl-1-propargyloxybenzenes **375**. Enyne metathesis on **375** with Grubbs' catalyst **3** in dichloromethane at room temperature for 5 h afforded the corresponding vinyloxepines **376**. The resulting dienes underwent Diels–Alder reactions with a range of dienophiles to afford the corresponding **377** and **378**. The stereochemistry of these products was unambiguously determined from extensive NMR experiments.

Various coumarin derivatives are known[178] to display important photophysical and biological activities. In a recent study, Chattopadhyay et al. described[179] the synthesis of several 6,6,7,6,5- and 6,6,7,6,6,6-ring fused, hitherto unknown, coumarin derivatives utilizing tandem applications of three-atom-economic processes, viz. Claisen rearrangement, RCEYM and Diels–Alder reaction. Thus, RCEYM of enyne **379** (Scheme 106), derived from an appropriate coumarin derivative employing Claisen rearrangement as the key step, with Grubbs' catalyst **3** afforded the 6,6,7-fused diene **380**. The latter was then subjected to a Diels–Alder reaction separately with *N*-phenylmaleimide and maleic anhydride in refluxing benzene to provide 6,6,7,6,5-ring fused coumarin derivatives **381** and **382**, respectively. Similarly, the 6,6,7,6,6,6-ring fused coumarin derivative **383** was obtained when naphthaquinone was used as the dienophile. Similar types of other linearly and angularly architectured polycyclic coumarin derivatives have also been synthesized.

Majumdar et al. have recently synthesized[180] tricyclic oxepine-annulated pyrone derivatives by the tandem Claisen rearrangement and RCEYM protocol. When a dichloromethane solution of the enyne **384** (Scheme 107) and catalyst **3** were stirred at room temperature for 5–8 h, the corresponding oxepine derivative **385** was obtained in 80–90% yield. The Diels–Alder reaction of these cyclized products with



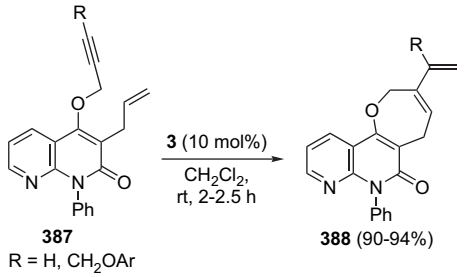
Scheme 107.



Scheme 106.

dimethyl fumarate proceeded smoothly to afford the tricyclic compounds **386** in excellent yield.

The importance of naphthyridine derivatives is due to their exceptionally broad spectrum of biological activities. Substituted 1,8-naphthyridine derivatives are used for the diagnostic therapy of human diseases including AIDS and for combating *exo*- and *endo*-parasites in agriculture.[181] Majumdar et al. have recently reported[49] the utility of the tandem Claisen rearrangement and ring-closing enyne metathesis methodology for the synthesis of oxepine-annulated naphthyridine derivatives. When a dichloromethane solution of the enyne **387** (Scheme 108) and the catalyst **3** was stirred at room temperature for 2–2.5 h, the ring-closed product **388** was obtained in almost quantitative yield.



387
R = H, CH_2OAr

388 (90-94%)

Scheme 108.

8. Conclusions

In conclusion, the examples mentioned above illustrate the broad applicability of the ring-closing diene and enyne metathesis reactions for the synthesis of medium-sized heterocycles of various importances. It is clear that these reactions have already found a unique position in organic chemistry in view of their ability to form rings of almost any size. For medium-sized rings, it is beneficial to use conformational constraints such as cyclic tethers, bulky substituents or stereoelectronic effects. Tandem reactions involving RCM are becoming more popular, as such processes enable the rapid construction of complex skeletal architectures. Improved catalysts for specific applications, including enantioselective synthesis, continue to be discovered. Future applications are expected to emerge along these general directions.

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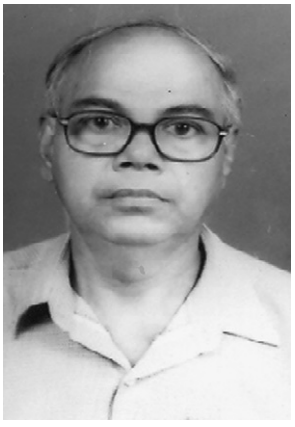

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