

Factors influencing ring closure through olefin metathesis – A perspective

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Abstract. Success of ring closure reactions of substrates having two terminal alkenes through olefin metathesis depends on a number of factors such as catalysts, nature and size of the rings to be formed and the substituents/functional groups present on the alkenes as well as at the allylic position. This article presents an overview of these influencing factors with illustrative examples.

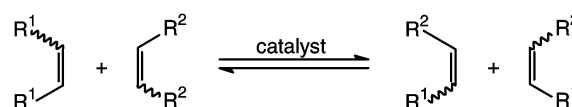
Keywords. Olefin metathesis; molybdenum and ruthenium alkylidines; ring closure; carbocycles; heterocycles.

1. Introduction

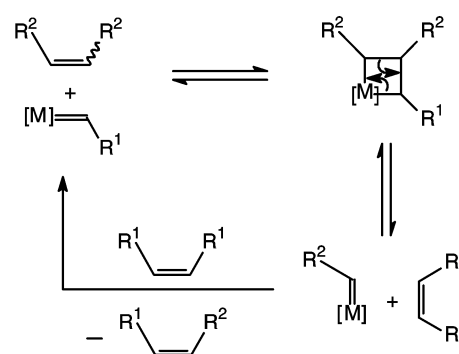
Construction of rings is one of the fundamental processes in organic synthesis. Of the various strategies available, cyclization is the most straightforward way of obtaining rings. Commonly employed cyclization methods involve reactions of cationic, anionic or radical species. Common rings such as 5–7 membered ones are easily available by these methods. However, formation of medium or large rings by these methods either proceeds with low yields or does not proceed at all due to unfavourable enthalpic and entropic factors. In recent years, olefin metathesis has emerged as a powerful tool for carbon–carbon bond formation and has enabled the synthesis of rings of different sizes.

Mutual exchange of alkylidene groups between two substituted alkenes in the presence of a transition metal catalyst (scheme 1) is termed as olefin metathesis. It is now well established that metathesis proceeds through a [2 + 2] cycloaddition between an alkene and a metal carbene complex followed by cycloreversion as proposed by Herisson and Chauvin (scheme 2).¹ The intramolecular olefin metathesis of an *a,w*-diolefin leading to cycloalkenes is known as ring-closing metathesis (RCM) (scheme 3). The driving force for this reaction is the release of highly volatile ethylene. The efficiency of RCM depends

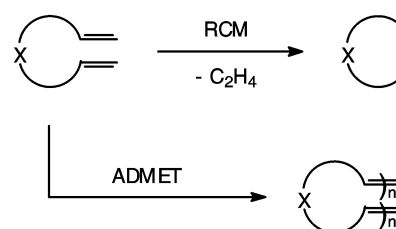
on to what extent the competing acyclic diene metathesis polymerization (ADMET) (scheme 3) can be



Scheme 1.



Scheme 2.



Scheme 3.

*For correspondence

overcome. Concentration of the substrate helps to reduce ADMET to some extent. However, the success of a ring-closure reaction through olefin metathesis is influenced to a great extent by a number of factors. These include (1) efficiency of the catalyst, (2) nature of the resulting rings, (3) size of the rings to be formed and (4) functional groups/substituents present in the substrate. The past several years have witnessed an explosive growth of the applications of olefin metathesis. A number of excellent accounts² focusing mainly on the application have been published. The prime objective of this account is to focus on the factors that influence RCM with illustrative examples.

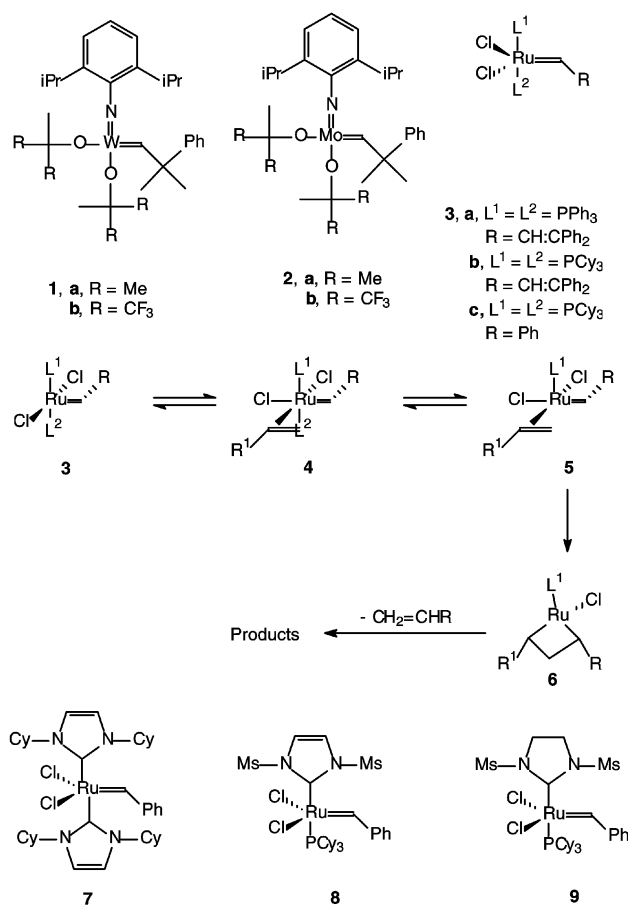
2. Influence of catalyst on RCM

The classical olefin metathesis catalysts composed of transition metal salts and their complexes with main group alkylating agents (such as WCl_6/Bu_4Sn , MoO_3/SiO_2 , $Re_2O_7/N_2O_3Cl_2$) were inefficient for RCM. An efficient RCM catalyst³ should be a good initiator of metathesis, should react exclusively or at least preferentially with olefins over the other polar groups present in the olefinic substrate and should be stable to air and moisture. The mechanism of olefin metathesis proposed by Herisson and Chauvin (scheme 2) guided the design and development of active catalysts. According to this mechanism, stabilized alkylidene-transition metal complexes should be efficient initiators. In fact, Fu and Grubbs⁴ first demonstrated that tungsten and molybdenum alkylidene complexes **1a,b** and **2a,b**, developed by Schrock for polymerization initiator, can induce RCM for the formation of 5–7 membered rings. However, W and Mo have a strong tendency to react with polar groups such as hydroxyls, aldehydes, carboxylic acids etc in addition to olefins. Thus, W and Mo catalysts are highly oxophilic and have poor functional group tolerance. Compared to W and Mo, Ru reacts preferentially with olefins over the polar groups. A systemic investigation by Grubbs and coworkers⁵ led to the discovery of ruthenium carbene complexes of the general formula **3** as active catalysts for RCM.

The initiating ability of the catalyst **3** depends on the substituent 'R', while the activity of the catalyst **3** is dependent on the type of ligands L^1 and L^2 . An understanding of the detail steps involved during metathesis enables to understand how the ligands L^1 and L^2 influence the reactivity of the catalyst. Based on the reactivity trend of a number of catalysts, Grubbs proposed a three-step sequence for metathe-

sis (scheme 4): (i) olefin coordination to the metal centre to form the species **4**, (ii) dissociation of one of the ligands (L^2) to form **5**, and (iii) formation of the metalocyclobutane **6** followed by cycloreversion to the product.

For productive metathesis, the dominant pathway is the dissociation of one of the ligands. Thus, any variation of the ligands or substituent R that assist ligand dissociation make **3** an active catalyst. A bulkier and more strongly electron-donating ligand helps in dissociation of the other ligand as well as stabilize the reactive intermediate **5**. For example, a ligand more basic and bulkier than PPh_3 increases the stability and reactivity of a catalyst. Thus, **3b** is a more active RCM catalyst than the catalyst **3a**. The catalyst **3c** has significantly improved activity over the catalyst **3b** due to its high rate of initiation. The bulk of the Ph group probably assists ligand (phosphine) dissociation. The catalyst **7** having more basic and bulkier N-heterocyclic carbene (NHC) than PCy_3 , would be expected to be more active than the catalyst **3c**, but however does not show any improved activity. However, catalysts **8** and **9** having

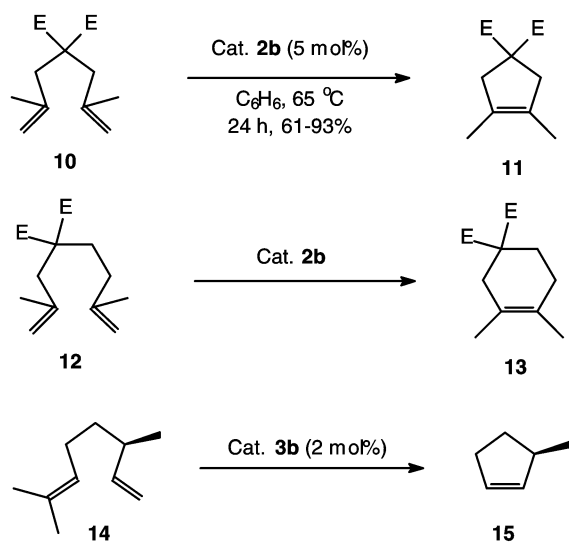


Scheme 4.

NHC and PCy_3 as the ligands (L^1 and L^2 in **3**) show enhanced metathesis activity. The more strongly electron-donating NHC ligand enhances the dissociation of the more labile phosphine and more efficiently stabilizes the electron-deficient intermediate **5** (scheme 4). This accounts for the increased reactivity of the catalysts **8** and **9**. The reactivities of **8** and **9** are superior to that of the catalyst **3c** and are comparable to the reactivity of the Schrock catalyst **2b** but with greater functional group tolerance. However, easy accessibility and low cost of the catalyst **3c** make it the most popular catalyst and it has been widely used for various synthetic purposes. The following examples illustrate how RCM of diolefins is influenced by these catalysts.

The dienes **10** and **12** undergo ring closure very efficiently⁶ using the Mo catalyst **2b** to give the tetra-substituted cyclopentene **11** and cyclohexene derivative **13** in 93% and 61% yields respectively (scheme 5). However, RCM of the dienes **10** and **12** does not proceed at all with Grubbs' catalyst **3c**. Similarly, the diene **14** undergoes ring closure⁷ with 2 mol% of the Mo catalyst **2b** to give the cyclopentene **15** quantitatively, while the same cyclization with Ru catalyst **3c** proceeds with lower yield.^{2b} These examples illustrate the efficiency of the Mo catalyst to induce metathesis of substituted olefins.

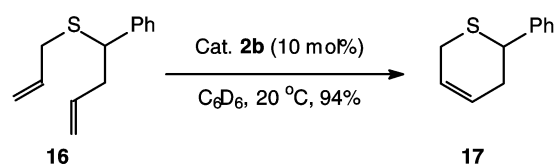
RCM of the sulphur containing diene **16** proceeds⁸ smoothly in the presence of the catalyst **2b** but fails in the presence of the Ru carbene **3c** (scheme 6). The difference in reactivities of the Mo and Ru carbenes for effecting the cyclisation of **16** has been



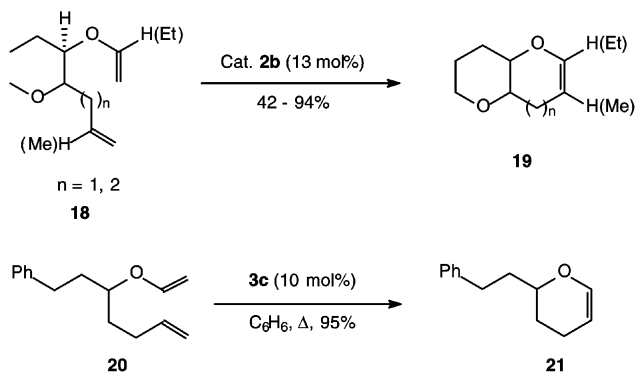
Scheme 5.

explained by ‘mismatch’ of the ‘hard’ Mo^{vi} centre with ‘soft’ sulphur or phosphine functionalities. For RCM of dienes with vinyl ether as one of the alkene units, Mo catalyst **2b** is required. Thus, dienes **18** undergo smooth ring closure⁹ with the Mo carbene **2b** to produce the cyclic vinyl ethers **19** in good to excellent yields (scheme 7). On the contrary, the Ru catalyst **3c** proved to be totally ineffective for the cyclization of enol ethers. This failure of the Ru-catalyst has been attributed to the formation of the inert carbenes from rapid reaction of the vinyl ethers with Ru catalysts. However, Sturino and Wong¹⁰ have demonstrated that vinyl ethers can also be cyclised with Grubbs' catalyst **3c** as illustrated by conversion of **20** to **21** (scheme 7).

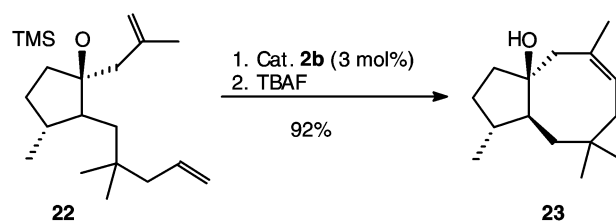
The superiority of the catalyst **2b** is further demonstrated¹¹ by smooth ring closure of the diene **22** to form the strained medium-sized ring **23** (scheme 8). Ring closure fails completely with the Ru catalyst **3c**.



Scheme 6.



Scheme 7.



Scheme 8.

Comparison of the reactivity of the Mo catalyst **2b** with those of the Ru catalysts **3c** and **8** shows that the Ru catalyst **8** has reactivity comparable with the Mo catalyst **2b**, while the Ru catalyst **3c** is much less reactive than **2b** and **8**. RCM of the diene **24** was complete¹² in 1 h with Schrock's catalyst to afford **25** in 92% yield (scheme 9). With the Ru catalyst **3c**, cyclization required longer reaction time and high concentration of the catalyst to give **25** in poor yield (32%). However, with the Ru complex **8**, the reaction was complete in 2 h with 89% yield of the cyclised product.

Owing to its steric crowding, the Ru catalyst **3b** is able to cyclise only one diastereoisomer in the diene mixture **26** to afford the cyclohexene derivative **27** while the Mo catalyst **2b** indiscriminately cyclises both the diastereoisomers of **26** to afford a mixture of the products **27** and **28** (scheme 10).¹³

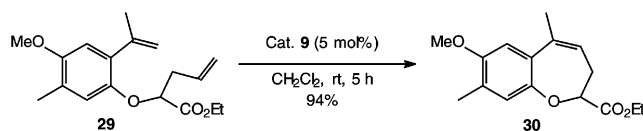
The greater reactivity of the Ru catalyst **9** over the Ru catalyst **3c** towards RCM can be demonstrated by the recently reported¹⁴ total synthesis of helianuol D using RCM as the key step (scheme 11). Attempted RCM of the diene **29** using Grubbs' catalyst **3c** at room temperature fails to form the oxepene **30**. At elevated temperature (50°C) only dimerisation is observed. However, RCM of the diene **29** proceeds smoothly at room temperature (RT) with catalyst **9** to produce the desired oxepene **30** in 94% yield.

Recently, we also observed¹⁵ that RCM of the diene **31** with Ru-catalyst **3c** at RT fails to produce any cyclised product **32** but at elevated temperature only

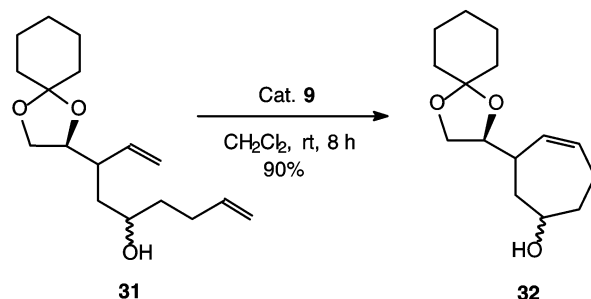
a dimer is formed. With the catalyst **9**, RCM of the diene **31** is smooth at RT and in 8 h produces the cycloheptenol **32** in greater than 90% yield (scheme 12).

Unsaturated esters are not considered as good substrates for RCM. In spite of this, RCM of the diene **33** with the catalyst **3b** affords the cyclic product **34** (scheme 13)¹⁶ in very good yield when carried out at elevated temperature. *a,b*-Unsaturated ketones have not generally been used in RCM, possibly due to the electron-deficient character of the double bond which reduces the metathesis efficiency. However, Paquette and coworkers have recently shown that with the catalyst **9**, RCM of the dienone **35** proceeds¹⁷ smoothly to produce the cyclooctenone derivative **36** in 90% yield (scheme 13).

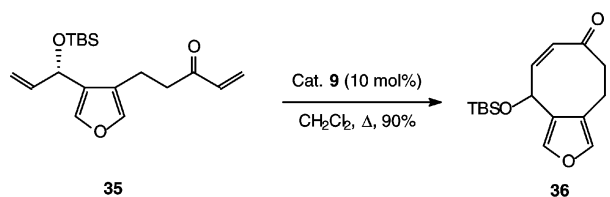
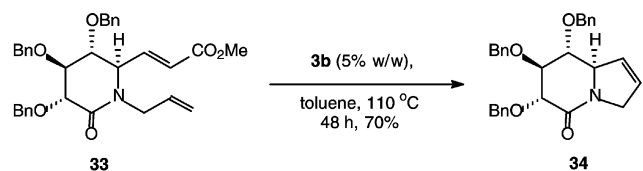
Remarkable catalytic specificity has been observed¹⁸ during RCM of the enantiopure triene **37**. While the Ru catalyst **3c** affords the *anti* product **38**,



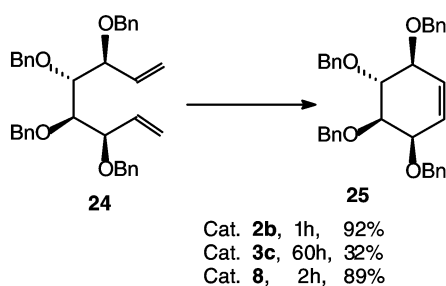
Scheme 11.



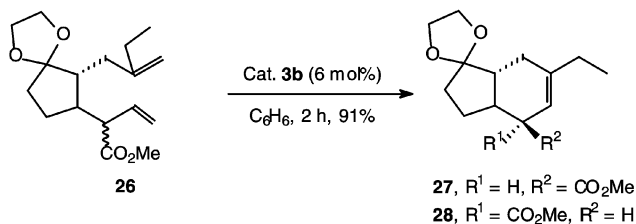
Scheme 12.



Scheme 13.



Scheme 9.

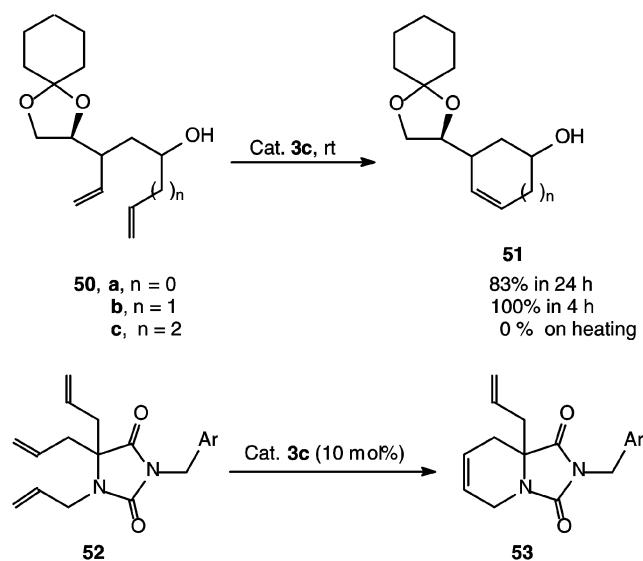


Scheme 10.

4. Size of the ring to be formed

Reactivity in RCM of dienes is influenced to a great extent by the size of the rings to be formed. This is illustrated by the cyclization of the dienes **50a–c**. The diene **50a** undergoes smooth ring closure in 24h at RT to form the cyclopentenol **51a** with Grubbs' catalyst **3c** in 83% yield. Under similar conditions, the diene **50b** produces the cyclohexenol **51b** quantitatively in only 4 h (scheme 17). However, the diene **50c** fails to produce the cycloheptenol **51c** even on prolonged reaction at RT as well as at elevated temperatures. Thus, as ring size increases it becomes difficult to construct rings through cyclization.

Reactivity in cyclization reaction is influenced by the activation energy in the transition state and the probability of end-to-end encounters (entropy). The activation energy is thought to reflect the strain energy of the ring to be formed and is markedly dependent on ring size, as shown by strain energy data



Scheme 17.

Table 1. Strain energy of various rings.

Ring size	Strain energy (kcal mol ⁻¹)
5	6.5
6	0.0
7	6.3
8	9.6
9	12.6
10	12.0
11	11.0

(table 1).²⁴ From these data it is clear why the 6-membered ring **50b** is easily formed. Although 5- and 7-membered rings have comparable strain energies (higher than 6-membered), it is the entropic factor that prohibits cyclisation of **50c** to form the seven-membered ring **51c**.

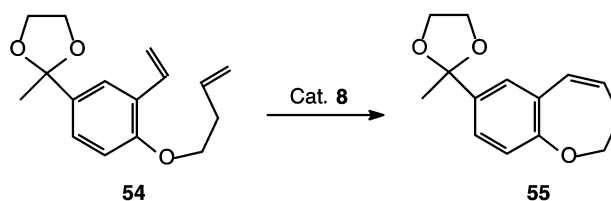
Formation of medium size rings through RCM requires several features to be installed in the substrate and provide some sort of conformational constraint. This conformationally predisposes the dienes for ring closure. These constraints are achieved either by using a pre-existing ring, i.e. cyclic conformational constraint, or acyclic conformational constraint.

4.1 Pre-existing ring as cyclic conformational constraint

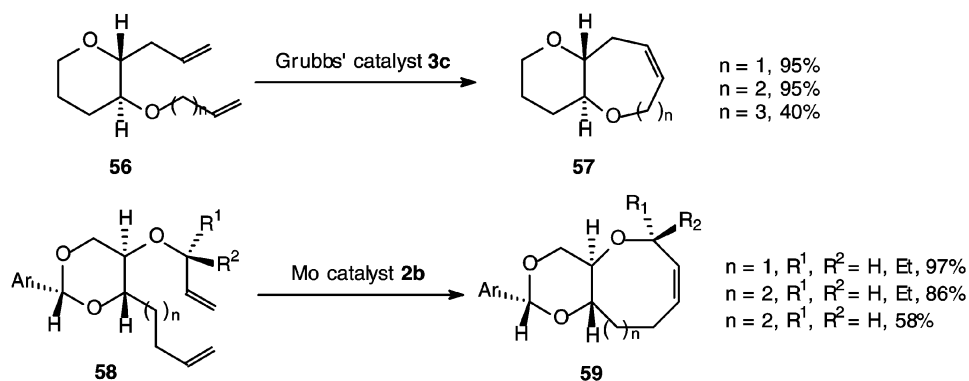
There are several reports where aromatic rings have been used for cyclic conformational constraint. For example, RCM of the diene **28** using Grubbs' catalyst **9** produces seven-membered cyclic ether **29** in excellent yield. Similarly, the diene **54** is ring closed using the catalyst **8** to form the oxepene **55** (scheme 18).²⁵

Cyclic ethers also provide very good conformational constraint. For example, the dienes **56** easily cyclise with Grubbs' catalyst **3c** to form seven- to nine-membered cyclic ethers **57** in excellent yields.²⁶ Ring closure of the dienes **58** is achieved with the Mo catalyst **2b** to form eight- and nine-membered cyclic ethers **59** (scheme 19).

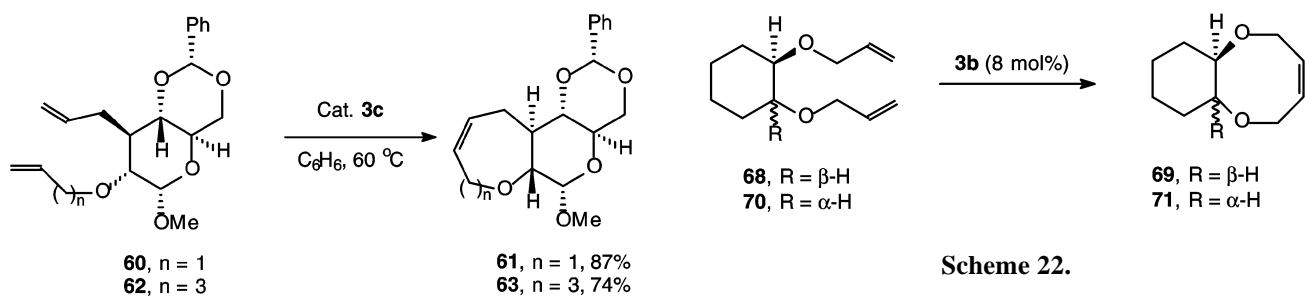
Derivatives of sugars provide excellent conformational constraint. For example, cyclization²⁷ of dienes **60** and **62** can be achieved with Grubbs' catalyst **3c** to form seven and nine-membered cyclic ethers **61** and **63** respectively, in excellent yields (scheme 20). Pre-existing carbocycles also facilitate formation of cycloheptenes²⁸ through RCM. In an approach toward the synthesis of guanacastepenes, Mehta and coworkers^{28a} demonstrated that seven-membered rings could be constructed in very high yields on pre-existing five-membered carbocycle **64** to afford the hydroazulene derivative **65** (scheme 21). Similarly,



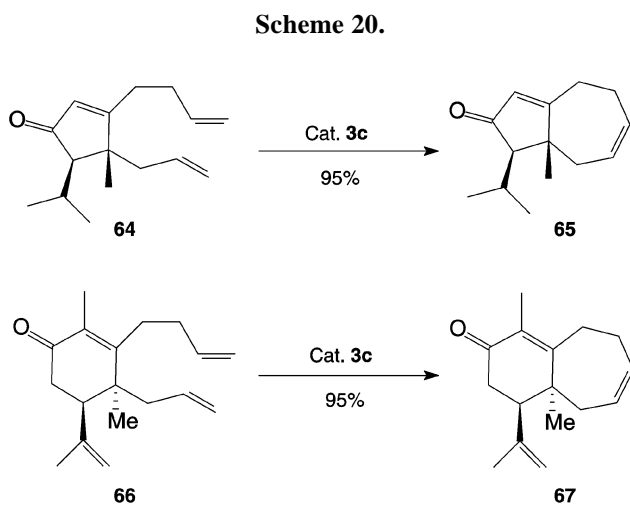
Scheme 18.



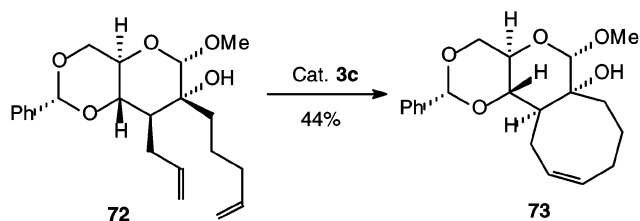
Scheme 19.



Scheme 22.



Scheme 21.



Scheme 23.

seven-membered carbocycle **67** can be constructed in excellent yield on a six-membered carbocycle **66**^{28b} (scheme 21).

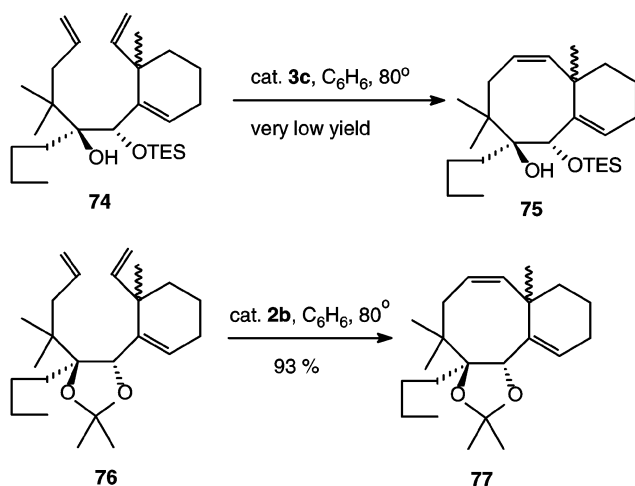
Stereochemistry at the ring fusion of the bicycles to be formed has profound influence on the rate of RCM reaction. Grubbs *et al.*²⁹ demonstrated that *trans* ring fusion facilitates the synthesis of the [6·4·0] system. Thus, the *trans*-diene **68** produces 60–75% of the cyclised product **69** whereas the corresponding *cis*-diene **70** affords only 20–33% of the cyclic ether **71** (scheme 22).

Synthesis of eight-membered carbocyclic rings is of considerable importance because of the presence of this ring in many biologically active natural products. A large number of methodologies other than cyclization for the synthesis of eight-membered rings have been developed. Olefin metathesis offers an excellent route for achieving synthesis of 8-membered rings. Facile construction of 8-membered rings has been possible only when the alkene units are present on a pre-existing ring. For example, the diene **72** undergoes smooth ring closure when treated with Grubbs' catalyst **3c** to form the cyclooctene derivative **73** in good yield (scheme 23).³⁰

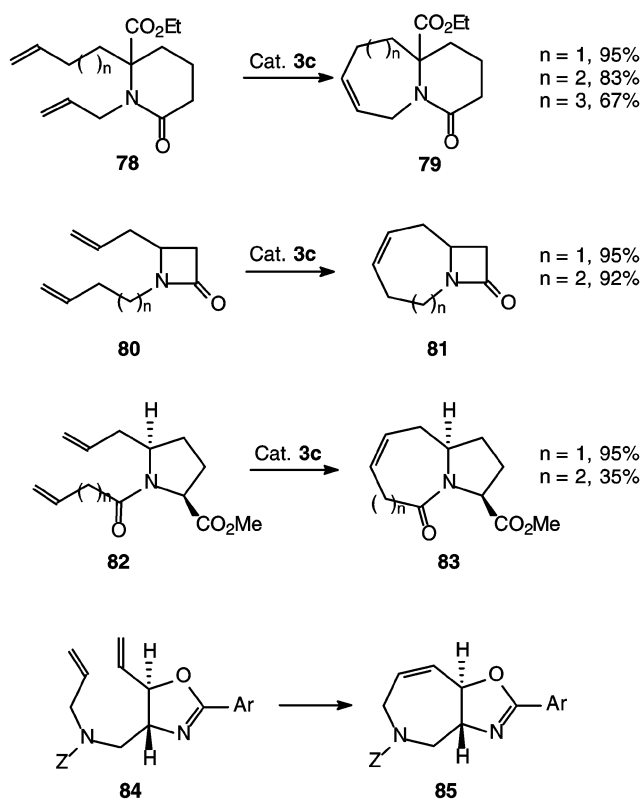
The importance of a pre-existing ring for the formation of 8-membered ring has been nicely demonstrated by Prunet *et al.*³¹ The diene **74** produces the cyclised product **75** in very poor yield. However, when the two vicinal hydroxyl groups on the chain

bearing the alkene units are protected as a cyclic acetal, the resulting dioxolane ring in **76** provides the necessary conformational constraint that facilitates RCM to form the cyclooctene derivative **77** in excellent yield (scheme 24).

Lactams,³² pyrrolidines³³ and oxazolines³⁴ also provide excellent conformational constraints. Seven,



Scheme 24.



Scheme 25.

eight and nine-membered rings can be easily annulated on them through RCM of vicinal chains containing terminal alkene units to lead to bicyclic systems (scheme 25).

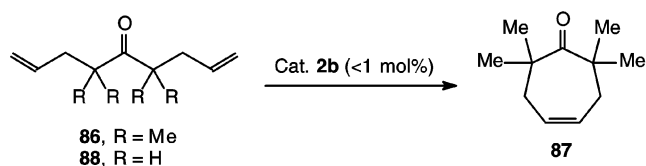
4.2 Acyclic conformational constraint

The Thorpe–Ingold effect of the geminal substituents provides conformational constraint to acyclic *a,w*-dienes and facilitates RCM. This is nicely demonstrated³⁵ by smooth ring closure of the diene **86** with the Mo catalyst **2b** to form the cycloheptenone **87** (scheme 26). In contrast, the diene **88** devoid of geminal substituents fails to produce any cyclised product under identical condition.

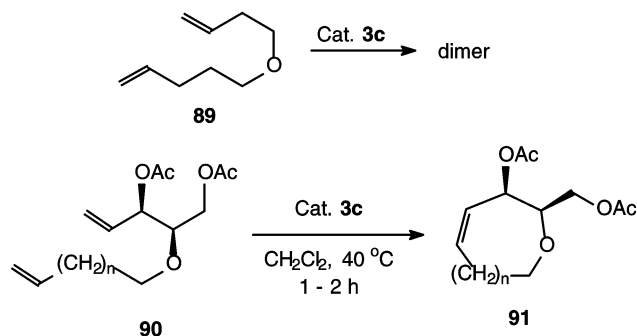
Vicinal stereocentres present on acyclic dienes can lead to conformations where olefinic chains are positioned *gauch* and help in ring closure. A comparison of the reactivity of dienes **89** and **90** towards RCM with the catalyst **3c** is illustrative.³⁶ The ether **89** without any substituent on the chain when treated with the catalyst **3c** gives only the dimer whereas the diene **90** cyclises under identical condition to afford the cyclic ethers **91** in excellent yields (scheme 27).

This concept has been exploited for the synthesis of the key intermediates **93** and **95** in the total synthesis of the natural product laurencin through RCM of the dienes **92** and **94** respectively (scheme 28).³⁷

The nine-membered oxacycle **97** is formed by RCM of the diene **96** in excellent yield (scheme 29).



Scheme 26.



Scheme 27.

The facile formation of **97** from **96** is probably the outcome of two synergistic *gauch* effects provided by a pair of vicinal substituents on the diene.³⁸

Sometimes the steric effect present in the compound acts as an acyclic conformational constraint. The diene **98** when treated with the catalyst **3b** undergoes RCM to form the aza cyclooctene **99** in very good yield (scheme 30).³⁹ The tosyl group, due to its steric bulk, restricts the conformational flexibility of the terminal alkene units and facilitates ring closure.

The steric effect of a bulky substituent on acyclic diene can restrict the conformational freedom, forcing the alkenes to undergo ring closure during RCM, as has been demonstrated by Linderman.⁴⁰ The diene **100a** with a tributyl stannyl group on the diene undergoes smooth ring closure with Grubbs' catalyst **3c** to form the oxocane **101** (scheme 31). When the tributyl stannyl group is replaced by a *t*-Bu group, the diene **100b** undergoes polymerisation under similar conditions. This has been attributed to the larger size of the tributyl stannyl group as compared

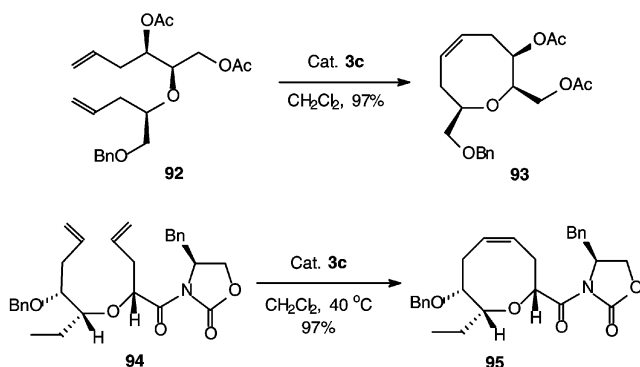
to the *t*-Bu group. Another reason for enhanced reactivity of the diene **100a** is possibly the result of a unique stereoelectronic effect due to the interaction between Sn and O atoms or the Sn and Ru carbene complex.

4.3 Synthesis of macrocycles

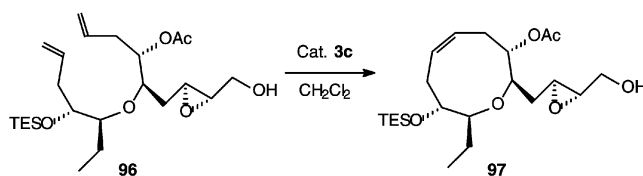
The majority of investigations leading to macrocyclization are aimed at the synthesis of macrocyclic lactones as a number of naturally occurring macrocyclic lactones exhibit significant biological activity. Unlike formation of medium rings by RCM, a suitably biased conformation is generally not required for macrocyclization. However, to reduce the rate of the key competing reaction, oligomerization, during macrocycle formation, a low concentration of the diene with higher temperature and higher catalyst loading is necessary. Thus, cyclization of the highly flexible diene **102** with the catalyst **3b** under slow addition affords the 16-membered lactone **103** (scheme 32).^{41a}

For efficient synthesis of macrocyclic lactones, a well-balanced interaction of Lewis-basic heteroatoms of the diene substrate with the emerging Lewis-acidic carbene intermediates is important. In the absence of any heteroatoms that lead to such interaction, macrocyclization fails as illustrated by failure of the diene **104** to undergo cyclisation^{41b} with 4 mol% of the catalyst **3b** under high dilution.

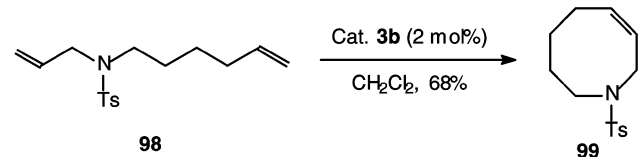
If such interaction becomes too strong as in the case of the diene **105**, the activity of the metal car-



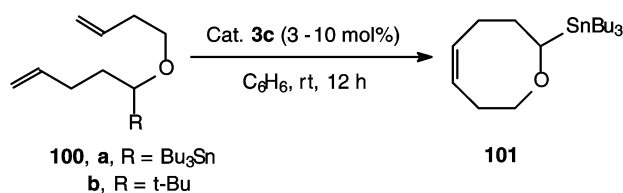
Scheme 28.



Scheme 29.



Scheme 30.



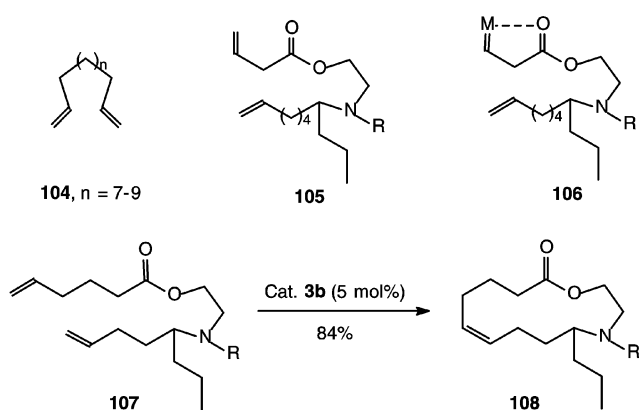
Scheme 31.



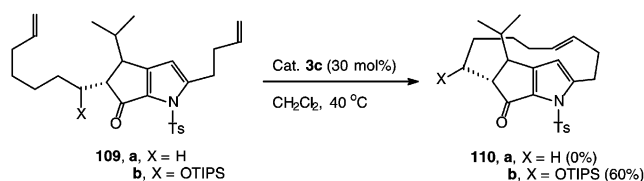
Scheme 32.

bene decreases due to chelation as shown in structure **106** and RCM does not take place.^{41b} The diene **107**, where such chelation is weak or absent, undergoes smooth ring closure to form the macrocycle **108** (scheme 33).^{41b}

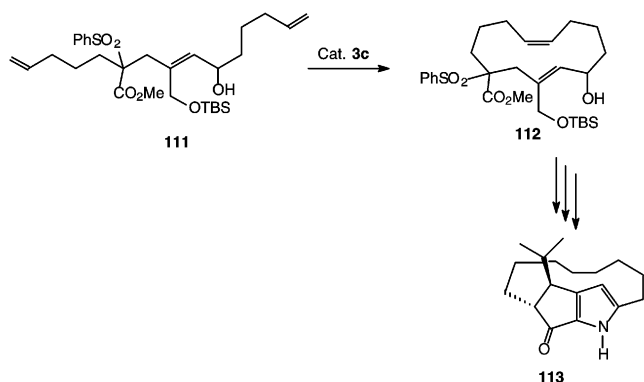
Formation of highly strained macrocycles, however, requires preexisting conformational constraints. In an attempt to construct the macrocyclic ring present in roseophilin, attempted RCM of the diene **109a** fails to produce the macrocycle **110a** even under high dilution. However, a triisopropylsiloxy group on the chain as a conformational control element as in the diene **109b**, forces the alkene side chains to come into closer proximity and cyclization occurs smoothly (scheme 34).⁴²



Scheme 33.



Scheme 34.



Scheme 35.

In contrast, the triene **111** lacking the ketopyrrole unit is free of strain as present in the diene **109a**. No additional conformational control element is required for its cyclisation. Thus it can be smoothly cyclised⁴³ with the catalyst **3c** to form the appropriately functionalised thirteen-membered ring **112** present in roseophilin. The ketopyrrole unit is then constructed (scheme 35) on this macrocycle for elaboration to roseophilin.

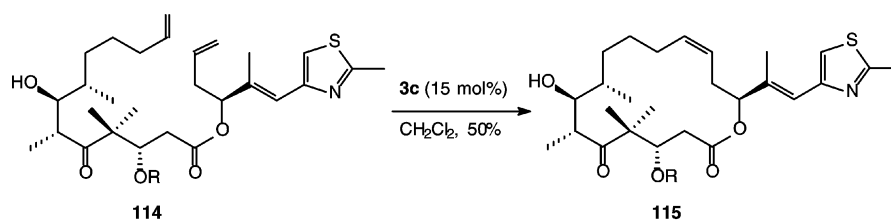
The efficiency of RCM in forming macrocycle has been demonstrated by the construction of the 16-membered macrocyclic lactones by several research groups in approaches to the anticancer compound, epothilone. For example, RCM of the diene **114** is accomplished in dilute CH_2Cl_2 solution with the catalyst **3c** (scheme 36).⁴⁴

Conformational preorganization facilitates macrocycle formation by RCM as has been nicely demonstrated by Iqbal and co-workers⁴⁵ in their studies involving *b*-turn mimics. The tripeptide **116** preorganises itself leading to a *b*-turn. Thus, the diene **116** when subjected to RCM in the presence of catalyst **3c** undergoes smooth ring closure to form the cyclic peptide **117** in very good yield (scheme 37).

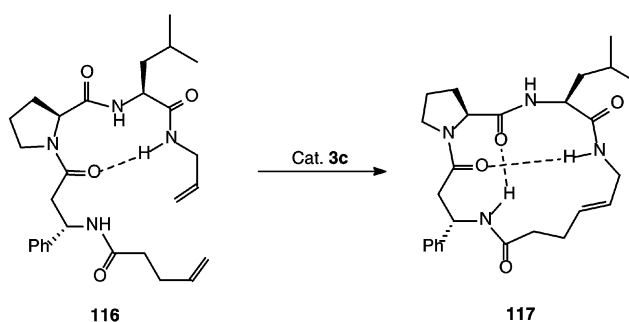
5. Effect of allylic substituents on RCM

Substituent at the allylic position of a substrate greatly influences RCM reactivity. An alkyl substitution at the allylic position retards the reaction of the alkene with metal carbene. Ulman and Grubbs⁴⁶ reported that *t*-butylethylene, containing a fully substituted allylic centre, is inert to reaction with the catalyst **3c**. In contrast, a hydroxyl group at the allylic position has an accelerating effect on RCM. A systematic investigation by Hoye and Zhao⁴⁷ (scheme 38) nicely demonstrates the effect of alkyl and hydroxyl substitution on RCM of the dienes **118a–e**. One of the alkene units in these substrates is trisubstituted so that metathesis is initiated at the terminal alkene.

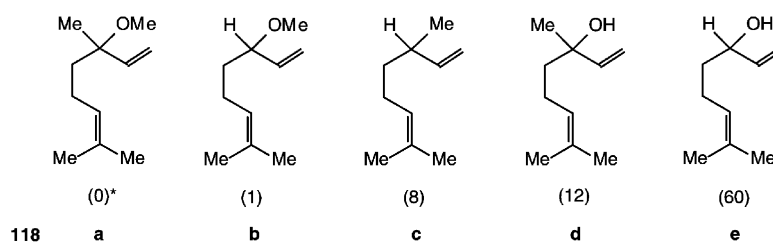
It is observed that on going from **118a** to **118e**, RCM reactivity increases. The diene **118a** in which the allylic carbon is fully substituted is almost inert to ring closure while the diene **118d** having a tertiary hydroxyl group at the allylic position has a significant activating effect on the reaction rate. The diene **118e** having a secondary hydroxyl group being less sterically crowded than **118d** is found to be most reactive, illustrating the activating effect of the hydroxyl group on RCM. This effect of the hydroxyl group may possibly arise through preassociation of



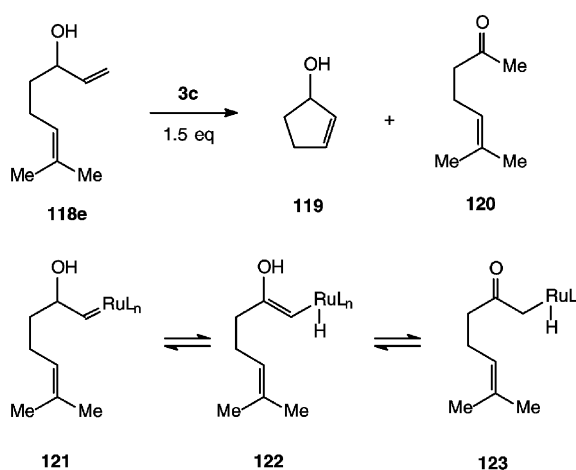
Scheme 36.



Scheme 37.



*Numbers in parentheses show approximate relative reactivities

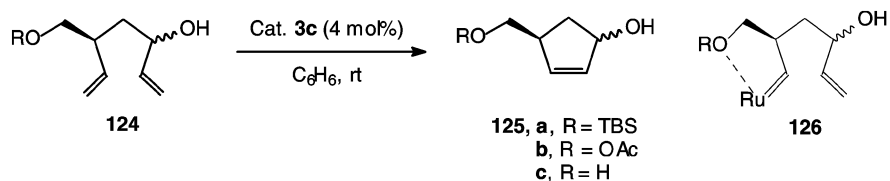


Scheme 38.

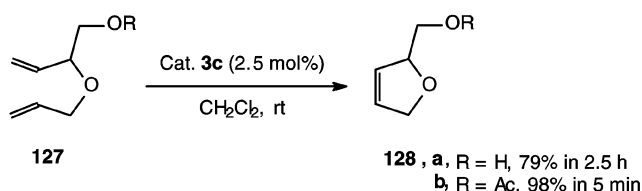
the diene with the catalyst by forming one of the species: $(\text{RO})\text{Cl}(\text{Cy}_3\text{P})_2\text{Ru}=\text{CHPh}$, $\text{Cl}_2(\text{Cy}_3\text{P})(\text{ROH})\text{Ru}=\text{CHPh}$ or $[\text{Cl}_2(\text{Cy}_3\text{P})(\text{RO})\text{Ru}=\text{CHPh}][\text{Cy}_3\text{PH}]^+$. Hydrogen bonding between the hydroxyl group and

one of the chloride ligands may also favour reaction between the alkene and carbene centre.

In spite of the large activating effect of allylic hydroxyl group, a competing reaction during RCM of



Scheme 39.



Scheme 40.

the diene **118e** leads to the formation of the methyl ketone **120** in addition to the RCM product **119** in 1 : 1.5 ratio. Tautomerisation of the initially formed carbene **121** to the enyl ruthenium hydride species **122** followed by reductive elimination to the oxo-alkyl ruthenium **123** (scheme 38) has been suggested as the reason for formation of the methyl ketone. Similar observation on RCM of the diene containing secondary allylic hydroxyl group has been reported by others¹⁷ also.

In contrast to the above observation, we recently observed⁴⁸ that RCM of the dienes **124a,b** having a secondary hydroxyl group at the allylic position, occurs smoothly with the catalyst **3c** to produce only the cyclopentenols **125a,b** in 93% and 79% yields respectively, while the diene **124c** produces only oligomers.

It is noteworthy that the dienes **124a,b** and **c** contain a hydroxyl group at one of the allylic carbons and an alkyl group at the other allylic carbon, both of which deter RCM (scheme 39). The dramatic increase in reactivity of the dienes **124a** and **124b** may be attributed to the stabilization of the initially formed Ru-carbene **126** by the oxygen atom present in the allylic alkyl substituent. This stabilization probably directs metathesis initiation at the alkene nearest to the alkoxy group and thus overrides the competitive fragmentation due to the allylic secondary hydroxyl group. The bulkier alkoxy or acetoxy groups in **124a** and **124b** respectively facilitate dissociation of the oxygen atom from the stabilized Ru-carbene **126** required for subsequent reaction with the second alkene unit. This also explains the lack of RCM reactivity of the dienol **124c**.

Significant rate acceleration in RCM of diene **127** having an acetoxy group (scheme 40) over that of the diene **127** with a hydroxyl group has been observed by Sarkar and co-workers.⁴⁹ Thus, RCM of the diene **127a** with the catalyst **3c** takes 2.5 h to produce the cyclopentene **128a** while RCM of the diene **127b** with the catalyst **3c** is complete within 5 min.

6. Conclusion

Key features that determine the success of ring closure reactions through olefin metathesis have been summarized with illustrative examples. The catalyst plays a major role in the success of a ring closure reaction. Ring closure of substrates containing highly substituted olefin requires the use of Schrock's catalyst **2b** or Grubbs' catalyst **9**. Six-membered rings are the most easily accessible compared to five- and seven-membered rings. For synthesis of medium-sized rings, pre-organization of the substrates is essential. Macrocyclization requires lower substrate concentration with high catalyst loading. Preorganization of the substrates is not always required. Allylic substituents also play an important role. Thus this account provides some guidelines for designing synthesis of cyclic structures.

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