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# Recent Advances in Olefin Metathesis and Its Application in Organic Synthesis

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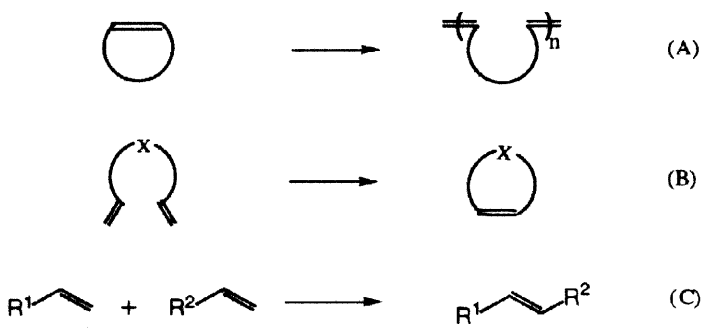
## 1. Introduction

Olefin metathesis is a unique carbon skeleton redistribution in which unsaturated carbon-carbon bonds are rearranged in the presence of metal carbene complexes.[1] With the advent of efficient catalysts, this reaction has emerged as a powerful tool for the formation of C-C bonds in chemistry. The number of applications of this reaction has dramatically increased in the past few years. Of particular significance, this type metathesis utilizes no additional reagents beyond a catalytic amount of metal carbene and the only other product from the reaction is, in most cases, a volatile olefin such as ethylene. The broad applicability of olefin metathesis has attracted attention from both academic and industrial scientists.

Olefin metathesis can be utilized in three closely related type of reactions (Scheme 1): (A), ring-opening metathesis polymerization (ROMP); (B), ring-closing metathesis (RCM); and type (C), acyclic cross metathesis which when carried out on diolefins results in polymers (ADMET). It is now generally accepted that the mechanism of both cyclic and acyclic olefin metatheses proceeds through a series of metallacyclobutanes and carbene complexes.[2] Although the relative stability of the carbenes and metallacyclobutanes can change with reaction conditions, catalyst composition and alkene substitutions, the mechanism of olefin metathesis appears to be the same for all catalysts.

**Scheme 1**



Until recently, olefin metathesis was applied almost exclusively in ring-opening metathesis polymerization reactions (type A). ROMP is thermodynamically favored for strained ring systems such as 3-, 4-, 8- and larger-membered compounds. When bridging groups are present, e.g. when the compound is bicyclic, ΔG of polymerization for the particular ring will tend to be more negative as a result of increased strain energy in the monomer. In many cases, the ROMP of strained cyclic olefins initiated by metal carbene complexes shows the characteristic features of a living polymerization and therefore block copolymers can be made by sequential addition of different monomers.[3]

Recently ring-closing olefin metathesis (RCM, type B) has received a great deal of attention for the synthesis of medium or large sized rings from acyclic diene precursors. This intensive study is primarily due to the development of well-defined metathesis catalysts which are tolerant to many functional groups as well as reactive towards a diverse range of substrates. Acyclic dienes may also be polymerized and whether a polymer or a cyclic compound is formed from any given diene is most often determined by thermodynamic rather than kinetic factors.

Intermolecular olefin metathesis between two alkenes is the third reaction type (C). There are two issues that must be addressed in order for acyclic olefin metathesis to become generally useful in organic synthesis. The first requirement is to obtain high yields of the productive alkenes from cross metathesis while reducing formation of undesired self metathesis products. The second is to control the *cis/trans* olefin geometry in the newly formed double bond. The successful application of acyclic metathesis hinges on both the regio- and stereoselectivity of these reactions.

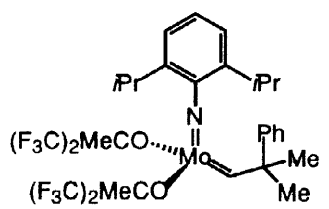
In this review, important recent advances related to ring-closing metathesis (RCM) and cross-metathesis reactions will be discussed based on reports published up until the middle of 1997. Only those applications involving the synthesis of small organic molecules will be reviewed.

## 2. Well-Defined Catalyst Systems.

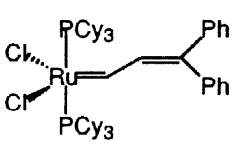
The number of catalyst systems that initiate olefin metathesis is very large.[1c] However, most early work in olefin metathesis was done using ill-defined multicomponent catalyst systems.[4] It is only in recent years that well-defined single component metal carbene complexes have been prepared and utilized in olefin metathesis.

Although a number of titanium and tungsten catalysts have been developed for metathesis and related reactions, the well-defined molybdenum complex **1** and ruthenium systems **2-3** (Scheme 2) have seen the most applications. Unlike the earlier olefin metathesis catalysts these highly active, long-lived catalyst systems do not require Lewis acidic co-catalysts or promoters.

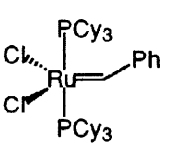
**Scheme 2.**




1




2

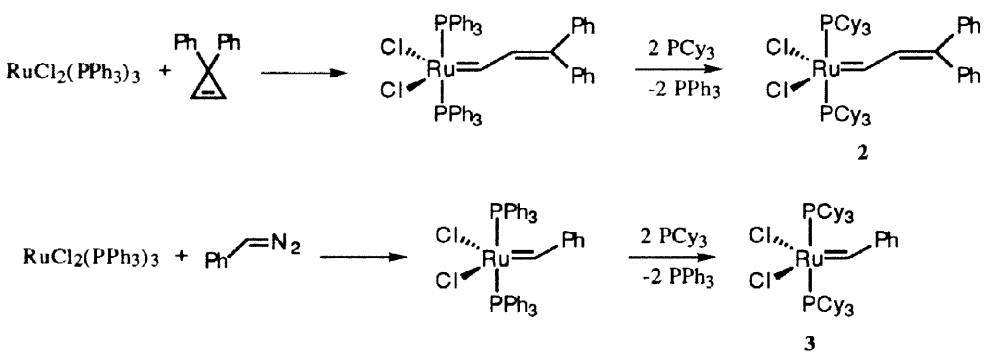



3

One of the most important catalyst systems developed by Schrock and co-workers is the alkoxy imido molybdenum complex represented by **1**.[5] One of the major advantages of this system is its high reactivity towards a broad range of substrates with many steric or electronic variations. The alkoxides in the [Mo] system can be readily altered to adjust their activities. Critical drawbacks of this Mo-based carbene complex are, however, its moderate to poor functional group tolerance, high sensitivity to air, moisture or even to trace impurities present in solvents, thermal instability on storage and expense of preparation.

Much work on the development of well-defined metal carbenes that initiate olefin metathesis has been done by one of the coauthors and co-workers. The ruthenium vinylidene complex **2** can be easily prepared by reaction of $RuCl_2(PPh_3)_3$ with 3,3-diphenylcyclopropene followed by ligand exchange with $PCy_3$ (Scheme 3).[6] Polymer-supported[7] and water soluble[8] versions of **2** have recently been described. Another closely related Ru-benzylidene carbene complex **3** was prepared using phenyldiazomethane instead of cyclopropene.[9]

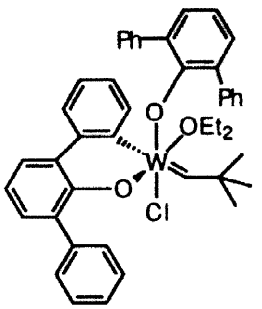
**Scheme 3.**



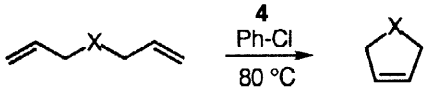

These Ru-carbene systems have drawn a lot of attention, not only because they exhibit high reactivity in a variety of ROMP, RCM and cross-metathesis processes under mild conditions, but also because of their remarkable tolerance towards many different organic functional groups.[10] Catalytic activity is not reduced significantly in the presence of air, moisture or minor impurities in solvents. They can be conveniently stored even under an air atmosphere without severe decomposition for several weeks. Although the Ru-carbene system often exhibits relatively lower propagation rates,[11] especially with sterically bulky substrates when compared to the Mo-catalyst system, their availability and ease of use have resulted in the catalyst of choice for all except the most difficult substrates.

In addition to the Mo- or Ru-based complexes discussed above, a few other transition metal complexes have been investigated for application in these olefin metathesis reactions. Basset and co-workers have prepared a cyclometallated aryloxy tungsten carbene complex **4** by C-H bond activation of an arene substituent (Scheme 4).[12] This stable, sterically crowded complex system has a $d^0$ metal center and has been shown to be an active catalyst system in various olefin metathesis reactions including ROMP, RCM and cross-metathesis.[13] As shown in Scheme 4, at high temperature, some diallyl compounds containing heteroatoms (O, S, Si or P) were cyclized in the presence of the catalyst **4**. Efficiency of the cyclization, however, varied depending on the steric demand of the substrates.[14]

**Scheme 4.**



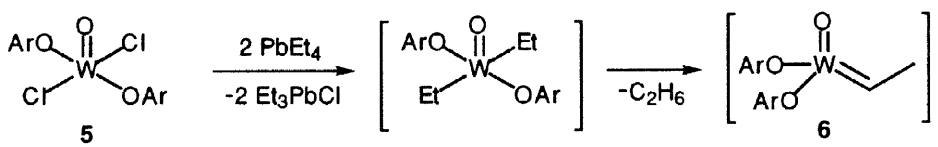

4




| | |
|---|---|
| X = S | **4** (0.4 mol%), 60 min, 100% |
| O | **4** (2.5 mol%), 120 min,100% |
| P-Ph | **4** (5 mol%), 300 min, 100% |
| $Si(Ph)_2$ | **4** (1 mol%), 60 min, 8% |

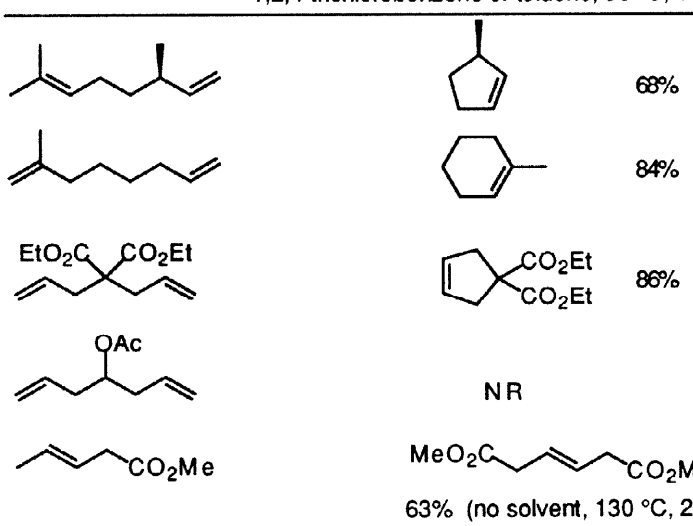
Another tungsten based complex system has been prepared and its viability as a metathesis catalyst has been examined by Nugent and co-workers (Scheme 5).[15,16] Oxo-tungsten complex **5** itself does not perform any metathesis reaction, but when activated by 2 equiv. of tetraethyllead, it becomes an active metathesis catalyst. This promoter is presumed to replace the two chloride ligands in **5** with ethyl groups, ultimately leading to the catalytically active ethylidene complex **6** via α-hydride elimination.

**Scheme 5.**




5 6

Reaction Conditions: **5** (2 mol%), $PbEt_4$ (4 mol%), 1,2,4-trichlorobenzene or toluene, 90 °C, 1 h



Like the Basset system **4**, high temperature is necessary to effect metathesis reactions with the precursor **5** and 2 equiv of $PbEt_4$.[17] Although complex **5** readily performs RCM to yield carbocycles under these conditions, the catalyst lacks the functional group compatibility which characterizes catalysts **1**, and even more **2**-**3**.[18]

Although many different metal carbene systems have been prepared and investigated as olefin metathesis catalysts,[19] most significant examples of metathesis reported in the 1990s have utilized either the Mo-complex **1** or the Ru-based system **2** and **3**. This review focuses mainly on reactions utilizing these metathesis catalysts.

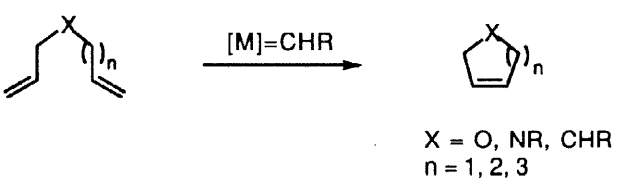
## 3. Ring-Closing Metathesis

Although the first example was reported in 1980 by Tsuji,[20] catalytic ring-closing metathesis (RCM) has only recently emerged as an effective strategy in organic synthesis and has been extensively employed in the preparation of a wide variety of complex molecules with multiple functionalities. This section discusses the most recent advances (up to the mid 1997) in the RCM and its application in organic synthesis mainly published after the previous reviews.[21]

### 3.1. Medium Sized (5-8) Ring Formation

The modern use of olefin metathesis can be tracked to the series of papers[22] that demonstrated the high yielding closure of diolefins to provide 5, 6 and 7 membered rings with a diverse functionality and double bond substitution (Scheme 6).

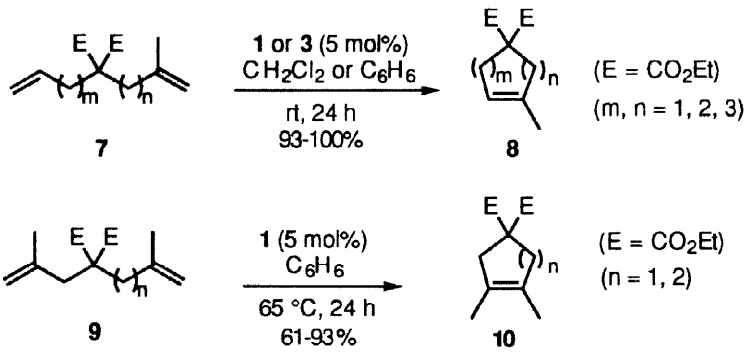
**Scheme 6.**




X = O, NR, CHR
n = 1, 2, 3

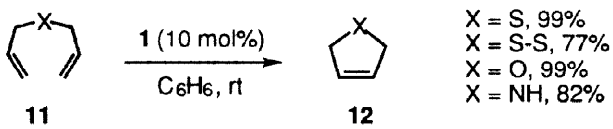
Systematic studies on the RCM of dienes containing various *gem*-disubstituted olefins to yield tri- or tetrasubstituted cyclic alkenes have recently been disclosed (Scheme 7).[23] Cyclization of mono *gem*-substituted dienes **7** afforded trisubstituted cyclic olefins **8** in excellent yield with both Mo-catalyst **1** and Ru-catalyst **3**. However, no 8-membered cyclic olefins (m+n=5) were formed with either catalyst mainly because dimer formation was found to be predominant even under high dilution conditions. Tetrasubstituted cyclic olefins **10** were efficiently obtained from the corresponding substituted dienes **9** only with the Mo-catalyst **1**. Differences in reactivity and functional group tolerance between the Mo-catalyst **1** and the Ru-complex **3** were observed in attempts of RCM with dienes having different steric and electronic properties.

**Scheme 7.**



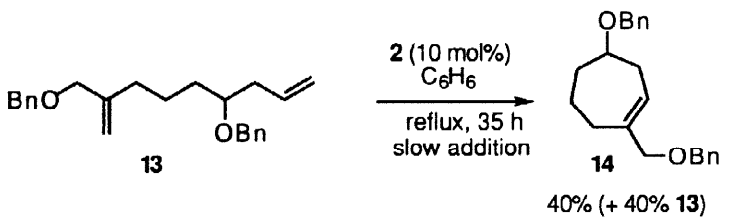

The scope and limitations of RCM have been examined with respect to substrates containing second-row heteroatoms, including sulfide or disulfide containing dienes (Scheme 8).[24] Monosulfide containing dienes **11** (X = S) were cyclized in excellent yields with catalyst **1**. However, the yields for the formation of the disulfide cyclic olefins **12** (X = S-S) were strongly influenced by the substitution pattern around the double bonds. For example, no tetrasubstituted disulfide cyclic olefin was formed. It was observed that the Ru-carbene **2** which is more tolerant of allylic oxygen functions than the Mo-carbene **1** is less effective for the ring closure of diallylic sulfides.[25]

**Scheme 8.**




RCM was utilized for the formation of 1,4-difunctionalized cycloheptenes for eventual use in an enediyne system synthesis (Scheme 9).[26] While the Mo-catalyst **1** rendered only intermolecular dimer, the Ru-carbene **2** was able to convert diene **13** to cycloheptene **14**. The cyclization yield was increased by slow addition of the catalyst and the substrate.

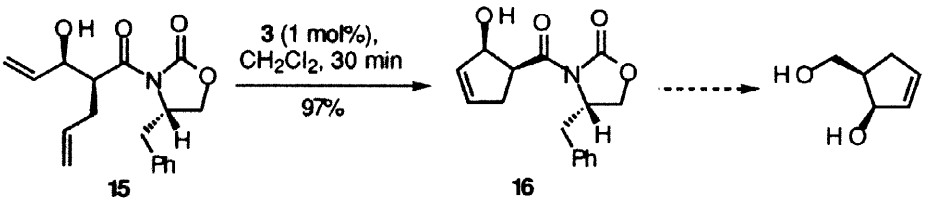
**Scheme 9.**




A highly convergent approach has been disclosed for the synthesis of carbocyclic nucleosides utilizing RCM as a crucial step (Scheme 10). The key ring closing metathesis reaction was accomplished in 97%

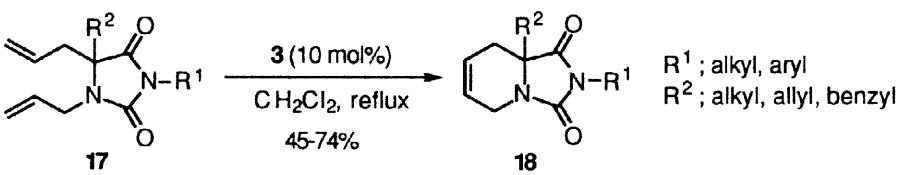
yield by exposure of a $CH_2Cl_2$ solution of diene **15** to 1% of the Ru-catalyst **3** to afford cyclopentenol **16**.[27,18]

**Scheme 10.**



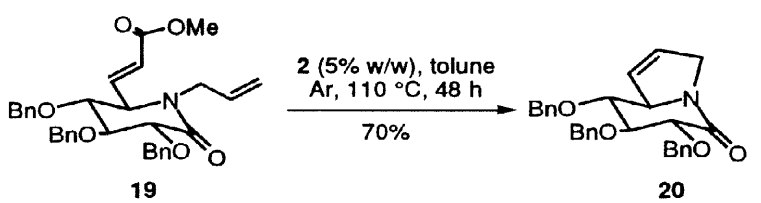

As shown in Scheme 11, bicyclic diaza compounds **18** were prepared through the RCM of diallyl substituted hydantoins **17** which are readily made from amino acids and ureas.[28] Greater than 95% conversion was observed in all reactions using 10 mol% of catalyst **3** in refluxing methylene chloride. Interestingly, in the case of $R^2$ = allyl, no spirocyclic product was observed.

**Scheme 11.**




RCM has been employed as a key step in the synthesis of a natural product castanospermine, a member of a large family of polyhydroxylated alkaloids (Scheme 12).[29] Cyclization of diene **19** with catalyst **2** afforded the bicyclic lactam **20** in 70% yield in refluxing toluene. It is a novel approach using a substrate where one of olefinic groups is an $\alpha,\beta$-unsaturated ester.[30] This is a surprising result since unsaturated esters are not considered good substrates for RCM and reactions are normally not efficient at such high temperatures.

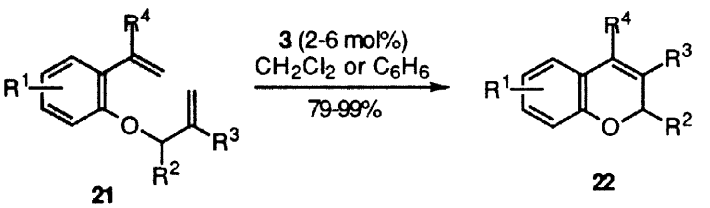
**Scheme 12.**




An efficient and practical method for the preparation of chromenes (2*H*-benzopyran derivatives) **22** has been described (Scheme 13).[31] The styrenyl allyl ether dienes **21** were easily prepared from salicylaldehydes in one pot and the cyclization reactions proceeded in excellent yields. A variety of electronically or sterically

different substituents were introduced at the varying positions on the chromene framework. Of particular interest is the tolerance of **3** to both the aryl amine and nitro substituents.

**Scheme 13.**

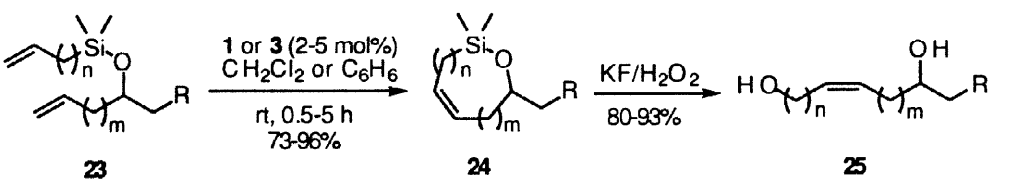



**21** **22**

$R^1$ = Br, Cl, OMe, $NO_2$, $Et_2N$, Alkyl

RCM of temporarily connected dienes and subsequent removal of the tether can afford acyclic alkenes with various functionality. One example has been reported in which silicon was used as the connecting atom between two olefins (Scheme 14).[32] While RCM of allyl- or 3-butenylsilyloxy dienes **23** (n ≥1) proceeded quantitatively with the Ru-catalyst **3**, the Mo-complex **1** was more effective for the cyclization of the more sterically hindered vinylsilyl substrates (n = 0). It is noteworthy that formation of 8-membered rings (m=2, n=1) through RCM is also very efficient for silicon tethered alkenes, even in fairly concentrated solutions (0.15 M, 5 mol% **3**, 91% yield). Subsequent oxidative ring cleavage of the cyclic silyloxyalkenes **24** produced the corresponding *cis*-olefinic dihydroxy compounds **25** in excellent yields.

**Scheme 14.**

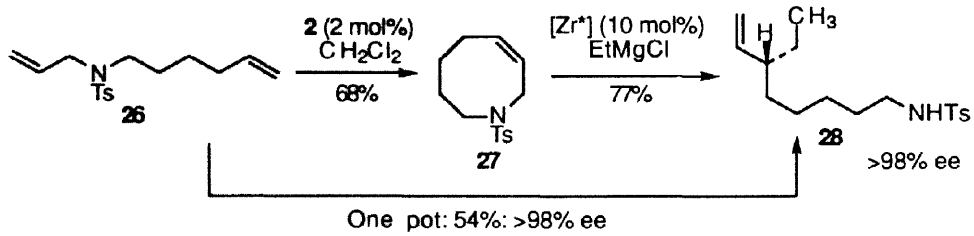



**23** **24** **25**

(m = 1-3, n = 0-2)

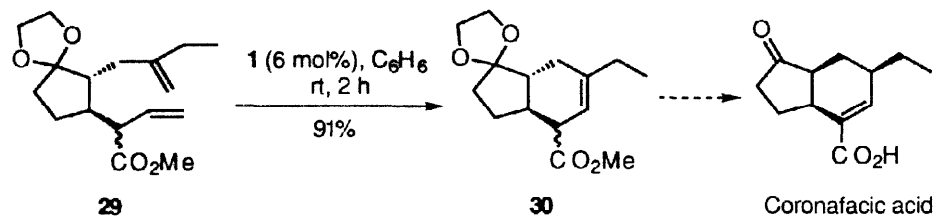
In combination with an asymmetric ethylmagnesation of medium-sized heterocycles, the Hoveyda group has illustrated an efficient procedure involving RCM to afford unsaturated alcohols or amides (Scheme 15).[33] It is particularly noteworthy that reaction of the tosylamide diene **26** with the Ru-catalyst **2** underwent a facile cyclization to generate a 8-membered ring **27** in 68% yield. This result is presumably attributed to the presence of the sterically demanding tosyl group, which restricts the conformation of the diene leading to a more facile cyclization.[34] Subsequent exposure of cycloolefin **27** to catalytic ethylmagnesation conditions delivers the unsaturated amide **28** in >98% ee. Tandem metathesis/carbomagnesation can be carried out in the same reaction vessel giving a similar overall yield.

**Scheme 15.**



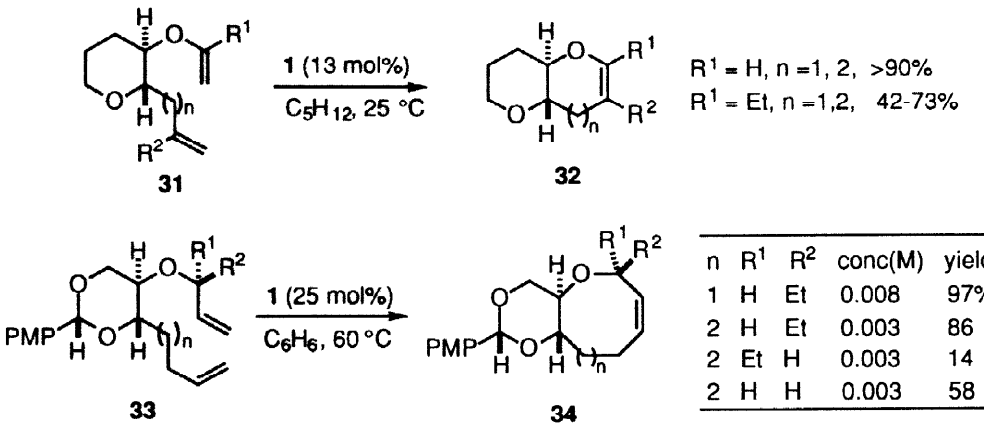

RCM of monocyclic dienes containing a *gem*-disubstituted olefin was utilized to obtain a trisubstituted cyclic olefin in a synthesis of coronafacic acid (Scheme 16).[35] Because the first attempt at cyclization with the corresponding keto ester of **29** was unsatisfactory,[36] the ketone was converted to a ketal group. While the mixture of diastereomers **29** was cyclized cleanly with the Mo-catalyst **1** to the trisubstituted bicyclic olefin **30**, the same reaction with the Ru-catalyst **2** was very slow even at elevated temperature and yielded one diastereomer. Presumably this is due to fact that the increased steric sensitivity of catalyst **2** allows it to cyclize only one diastereomer of **29**.

**Scheme 16.**




Since cyclic ether components are abundant in natural products, numerous approaches have been disclosed for the synthesis of these cyclic structures. Early work by Grubbs and co-workers demonstrated that such systems could be prepared by combined olefination of an ester followed by cyclization.[37] The Mo catalyst **1** must be used in the formation of vinylethers since the carbenes formed by the rapid reaction of vinyl ethers with **2-3** are unreactive for further metathesis reactions. Recently, direct conversion of olefinic esters to cyclic enol ethers was also illustrated using stoichiometric Tebbe-type reagents.[38] As illustrated in Scheme 17, treatment of enol-ether precursors such as **31** with the Mo-catalyst **1** affords the bicyclic products **32** in good yields.[39] However, tetrasubstituted bicyclic enol ethers were not formed under these conditions. Fused bicyclic allyl ethers such as **34** were also obtained by cyclization of the allyl ether precursors **33** with catalyst **1** under high dilution conditions.[40] Again, the efficiency of the reaction was significantly influenced by the conformation of the substrate and the difference of the cyclization yields between two diastereomers is especially noteworthy. This approach to cyclic ether synthesis could be potentially useful in an iterative sense, permitting sequential ring construction to yield multiply fused ring systems frequently found in natural products such as brevetoxins.

**Scheme 17.**

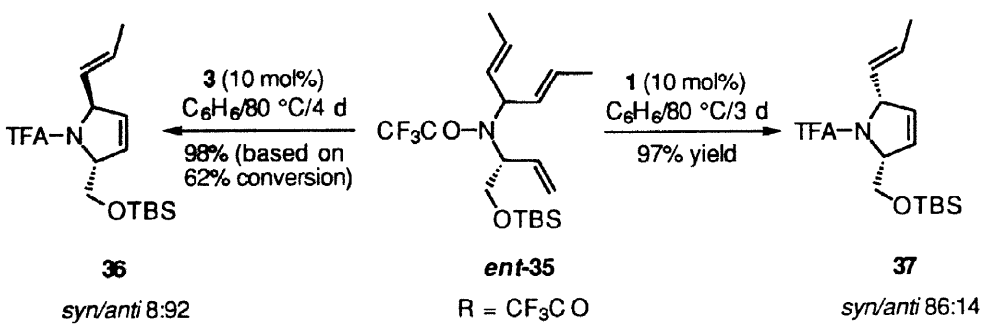



| n | $R^1$ | $R^2$ | conc(M) | yield |
|---|---|---|---|---|
| 1 | H | Et | 0.008 | 97% |
| 2 | H | Et | 0.003 | 86 |
| 2 | Et | H | 0.003 | 14 |
| 2 | H | H | 0.003 | 58 |

## 3.2. Stereoselective RCM

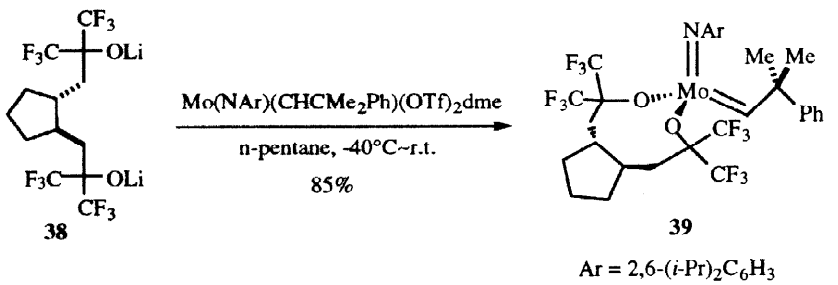
Diastereoselective ring-closing metathesis reactions have been recently described in which an existing chiral center controls the direction of cyclization of prochiral dienes.[41] This strategy requires that initial metathesis occurs at the double bond of the chiral center and that the olefins of the prochiral center do not react with each other. This is possible by a modification of the prochiral olefins from terminal to internal position so that the likelihood of ring closure between the sterically crowded double bonds at the prochiral center is minimized. It was found that cyclization of enantiopure **35** did indeed proceed with a significant diastereoselectivity (Scheme 18).[42] Ru-catalyst **3** provided the *anti*-product **36** with remarkably high d.e., whereas the *syn*-product **37** was preferentially obtained with the Mo-carbene **1**. Even though no general explanation was suggested, this surprising "catalyst-specificity" may be attributed to the different spatial arrangement of the respective ligands in each complex during the cyclization. This observation demonstrates the complementality of the catalyst and suggests that new systems may yield further control of stereochemistry.

**Scheme 18.**



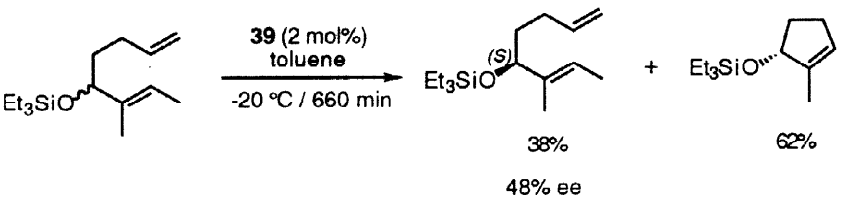

A chiral Mo-carbene catalyst **39** suitable for olefin metathesis was prepared by the reaction of the dilithium salt of a novel chiral diol **38** with the Mo-alkylidene bis(triflate) precursor in high yield (Scheme 19).[43] Complex **39** may be stored under $N_2$ at low temperature (-10 °C) for several months and its solution in frozen benzene is stable over 1 week.

**Scheme 19.**




The chiral Mo-carbene **39** showed excellent catalytic activity both in ring-opening metathesis polymerization (ROMP) and in ring-closing metathesis (RCM) processes under the standard conditions. More significantly, asymmetric RCM (kinetic resolution) was for the first time accomplished by using this chiral catalyst (Scheme 20).[44]

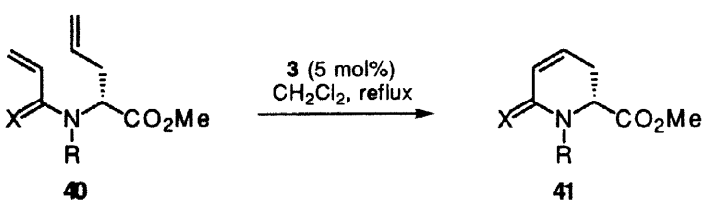
**Scheme 20.**




### 3.3. Application to Peptide Chemistry

Due to the high activity and functional group tolerance of the metathesis catalysts **1**-**3**, RCM has recently extended its utility to the area of peptide chemistry. Highly functionalized 6- and 7-membered amino esters or acrylic amides **41** were prepared from enantiopure amino acid-derived dienes **40** with the Ru-catalyst **3** (Scheme 21).[45]

**Scheme 21.**

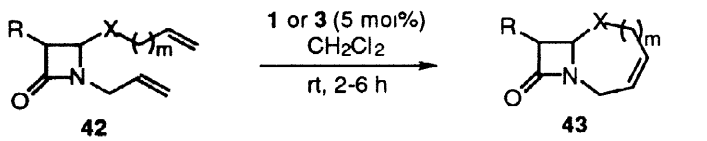



| | | | |
|---|---|---|---|
| X = O; R = H, | 20% | X = $H_2$; R = PMB, | 54% |
| R = PMB, | 93% | R = $CH_2$Fer, | 18% |
| R = $CH_2$Fer, | 89% | R = Boc, | 93% |
| | | R = H, | 0% |

(PMB = *p*-MeO-$C_6H_4CH_2$, Fer = Ferrocenyl-)

Olefin metathesis has shown to be an effective process for the functionalization of monocyclic β-lactams[46] and for the preparation of bicyclic β-lactams **43** via the ring closure of monocyclic diene precursors **42** (Scheme 22).[47]

**Scheme 22.**

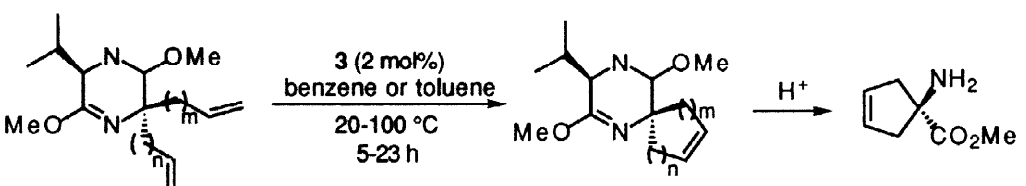



**42** **43**

| | |
|---|---|
| m = 0, X = $CH_2$; | 81% (**3**) |
| m = 1-3, X = O; | 12-84% (**1**) |
| m = 1, X = S; | 78% (**1**) |
| m = 1, X = N-Ts; | 91% (**1**) |

Stereoselective synthesis of rigidified α-amino acids where the α-carbon of the amino acid is incorporated in a 5-, 6- or 7-membered ring has been described as shown in Scheme 23.[48] RCM of the geminal diolefins in **44** was efficiently performed by the Ru- catalyst **3** (2 mol%) in an aromatic solvent. The cyclization appears to be sensitive to the steric interactions between the catalyst and the isopropyl group of the substrates. Spiro bis-lactam ethers **45** were then hydrolyzed under mildly acidic conditions to furnish the cyclic amino ester **46**. In addition, cyclization of substrates containing an α-functional group (for instance, hydroxy-) has been shown to proceed in good yields.[49]

**Scheme 23.**

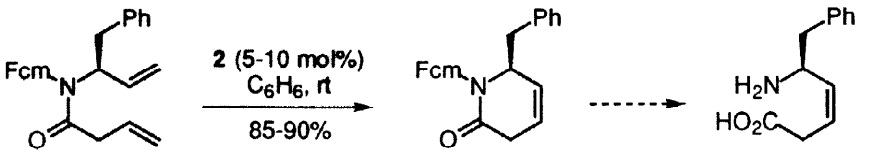



**44** **45** **46**

m, n = 1, 2; 53 - 99%
m + n = 5; <5%

RCM of a dienic amide **47** with the Ru-catalyst **2** led to a dehydro lactam **48**, a direct precursor of the *Z*-ethylenic dipeptide isostere **49** (Scheme 24).[50] It is interesting that the ferrocenylmethyl (Fcm) group was selected for nitrogen protection of the amide bond in the substrate **47** because apparently the steric bulk leads to the formation of the favorable conformation for closure.

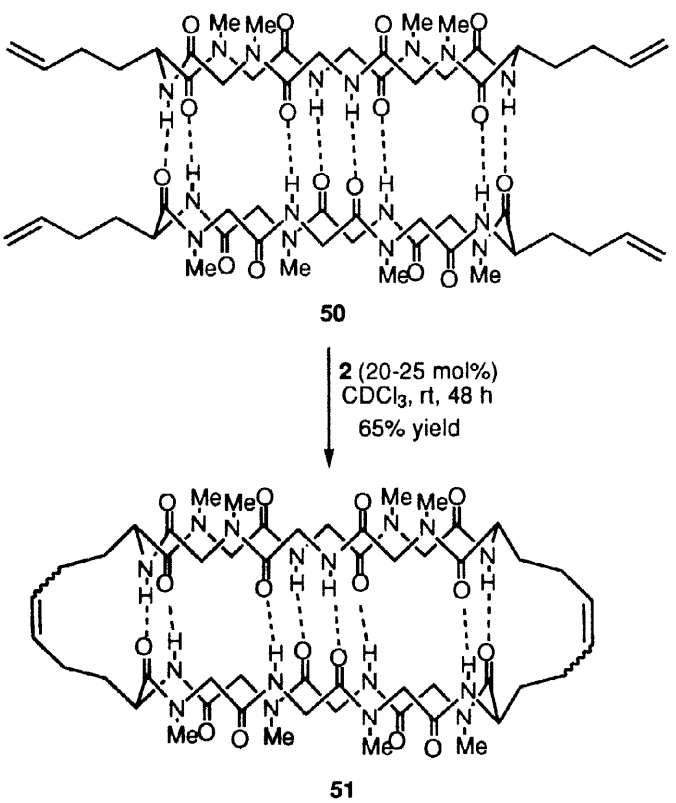
**Scheme 24.**




47 48 49

The wide range of functional group tolerance shown by the Ru-carbenes **2-3** has enabled researchers to apply RCM methodology to the synthesis of biologically relevant macrocyclic peptides which contain many polar functional groups and acidic protons. Ghadiri and a co-worker have shown that the 8-residue cyclic peptide *cyclo*[-(L-Phe-D-$^{Me}$NAla-L-Hag-D-$^{Me}$NAla)$_2$], containing two *L*-homoallylglycine residues, self assembles to form two interconverting hydrogen-bonded diastereomeric ensembles, one of which is represented as **50** in Scheme 25.[51] It contains two pairs of double bonds in sufficiently close proximity that each pair undergoes RCM in the presence of **2** to give tricyclic cylindrical product **51** (38-membered ring) with a mixture of three (*cc*, *ct* and *tt*) isomers. This covalent capture strategy may be useful in stabilizing kinetically labile α-helical and β-sheet peptide secondary structures.

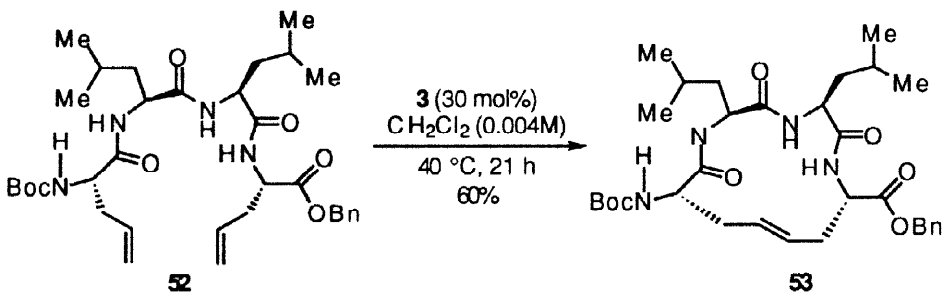
**Scheme 25.**




50 51

Another notable example is the facile synthesis of a cyclic β-turn analogs by RCM, where the naturally occurring disulfide bridge is replaced with a carbon-carbon double bond. Initially it was believed that the Pro-Aib sequence was required to restrict the conformation of the peptide backbone and subsequently allow facile macrocyclization.[52] In a later study, RCM of additional peptides having no such a conformational restriction in the backbone was examined in order to explore the scope of this chemistry (Scheme 26).[53] Reaction of tetrapeptide **52**, in which both the Pro and Aib residues are replaced with leucines, with the catalyst **3** afforded the 14-membered cyclic tetrapeptide **53** in modest yield. This suggests that although interactions increasing rigidity of the system helps to favor cyclization, it is not a strict requirement for the synthesis of many peptide macrocycles by RCM.

**Scheme 26.**

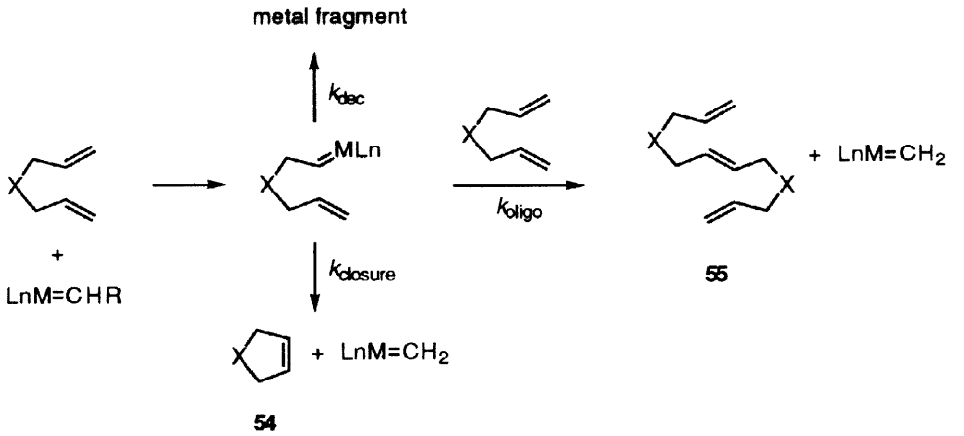



### 3.4. Macrocyclization Using RCM

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

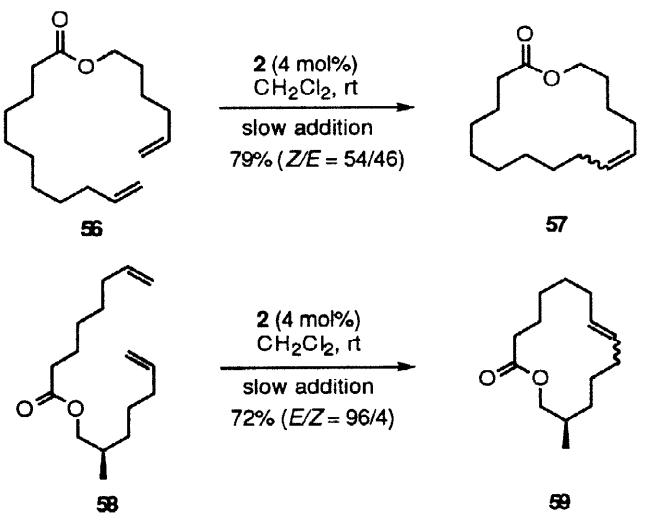
The key competing reactions are shown below (Scheme 27). The ratio of cyclic products **54** to oligomers **55** is determined by the ratio of $k_{closure} / k_{oligo}$[diolefin]. As the rate of closure decreases due to ring size and conformational effects, the competing reactions interfere with the desired reaction. The rate of oligomerization can be decreased by lowering the concentration of the diene or using slow addition of the substrate. Higher temperatures also favor ring closure. However, both of these factors, low concentrations and high temperature, which favor closure also allow catalyst decomposition to start to compete with the desired reaction. As a result, closure of larger rings usually requires higher catalyst loading.

**Scheme 27.**



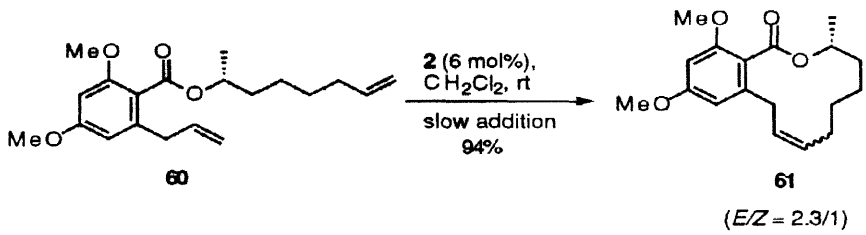

Scheme 28 illustrates macrocyclization of acyclic dienes using RCM. Cyclization of highly flexible α,ω-diene **56** (with **2**) under the slow addition conditions afforded the 16-membered lactone **57** which is an olefinic precursor of exaltolide, a valuable perfumery ingredient.[54] It is surprising that RCM of diene **58** containing a methyl remote to the terminal olefin provided the 14-membered lactone **59** with a remarkably high stereoselectivity (96:4, *E*/*Z*). This result is in stark contrast to the almost statistical ratio obtained in the cyclization of **56** and suggests that the stereochemistry is kinetically controlled.

**Scheme 28.**



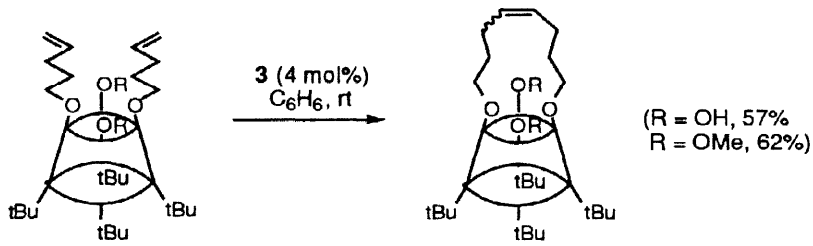

A 12-membered bicyclic macrolide **61** was synthesized via a RCM reaction (Scheme 29).[55] Cyclization was cleanly achieved by slowly combining two solutions of the diene **60** and the Ru-catalyst **2** *via* dropping funnels. The reaction was essentially quantitative affording the 12-membered product as a mixture of *E* and *Z* isomers.

**Scheme 29.**



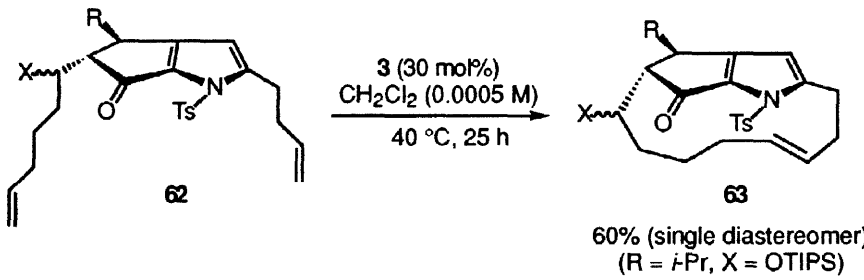

Bridged calix[4]arene derivatives were efficiently prepared by RCM as shown in Scheme 30.[56] Similar yields of cyclic compounds were obtained for dienes with free hydroxyl or dimethyl ethers.

**Scheme 30.**




The tricyclic core of roseophilin has been prepared using RCM as a key step (Scheme 31).[57] Cyclization was shown to proceed, as seen in many examples of conformationally unrestricted acyclic olefins, only with appropriate structural restraints. While metathesis of **62** (X = H) with **3** afforded only macrocyclic dimer as a major product even under the extremely dilute concentrations, cyclization of the diene **62** (X = OTIPS) containing a bulky restraint group on the hexenyl moiety provided the desired *ansa*-bridged silylether product **63** in good yield.

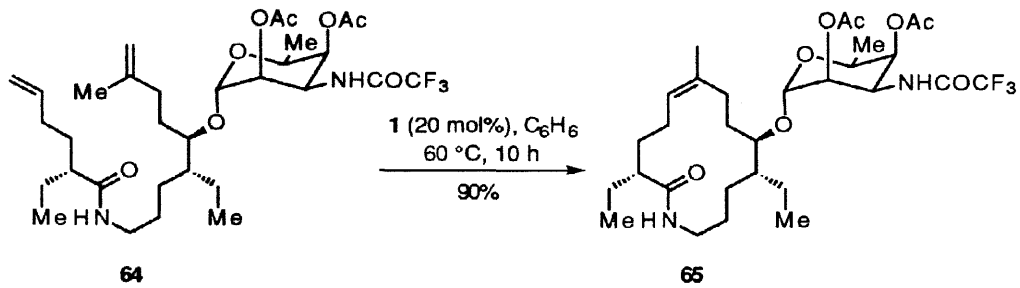
**Scheme 31.**




Hoveyda and co-workers have completed the direct synthesis of the antifungal agent Sch 38516 through the RCM of a fully functionalized acyclic precursor in contrast to their previous report.[58] Mo-catalyzed ring closing metathesis of diene **64** led to the 14-membered trisubstituted olefin **65** in excellent yield (Scheme 32).[59]

Since the Ru catalysts are more sensitive to bond substitution than the Mo catalyst, the [Mo] system appears to be more generally useful for the closure of macrocyclic trisubstituted double bonds (see above for an exception).

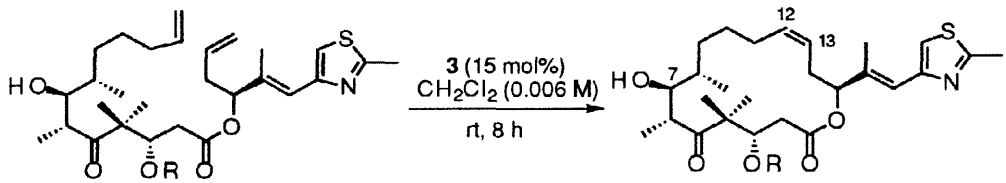
**Scheme 32.**




64 65

The power of olefin metathesis in forming macrocycles has culminated in the synthesis of biologically active epothilone A and its derivatives by several research groups. Nicolaou and co-workers first reported a RCM based approach to the macrocyclic skeleton of the epothilones (Scheme 33).[60,61] The olefin metathesis reaction of acyclic diene **66** having an unprotected hydroxyl group at C7 was effected by the Ru-catalyst **3** in dilute $CH_2Cl_2$ solution to afford the 16-membered macrocyclic *Z*-olefin **67** in 50% yield together with its separable *E*-isomer (35%). It is interesting that the flexibility in the synthesis of the isomeric macrolides by RCM was claimed to potentially allow the generation of a diverse epothilone library for further biological investigations. The same group has reported a similar approach to the same compounds based on solid-phase RCM (*vide infra*).

**Scheme 33.**



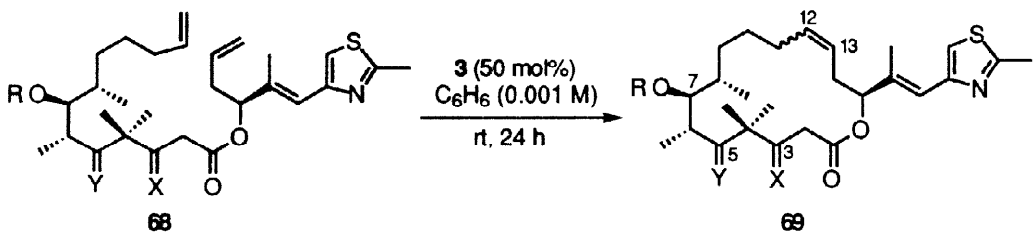

66 67

(50% + 35% *E*-isomer)

Another approach to the synthesis of epothilone A was reported by Schinzer *et al.* in which RCM was also used as a key step for the cyclization.[62] Almost the same strategy was employed as in the Nicolaou synthesis; site of the olefin formation by RCM was chosen to be the $\Delta^{12,13}$-double bond. The C-7 hydroxyl group, in this case, was protected with *t*-butyldimethylsilyl (TBS) and RCM of the diene precursor with **3** gave the cyclic epothilone A intermediate in 94% yield as a 1:1 mixture of diastereomers. Macrocyclic olefin metathesis was also efficiently utilized in a separate report for the construction of a basic skeleton of epothilone A.[63]

Recently, remote side chain effects in macrolide formation by RCM were extensively investigated by the Danishefsky group in the synthesis of epothilone A and its derivatives (Scheme 34).[64] Cyclization of the acyclic dienes **68** with the Ru-catalyst **3** afforded the 16-membered macrolactones **69** having an *E* C12-C13 double bond as the major isomer in most cases. With all protecting groups identical, the proportion of *E* product increases up to 9:1 upon changing from the 3*S* to 3*R* series. Similarly, keeping the C-3 and C-7 groups constant but varying C-5 affords more of the *Z* olefin product.

**Scheme 34.**

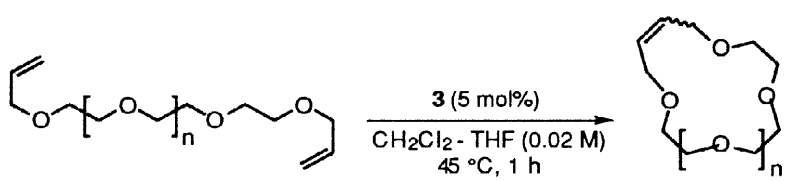



**68** **69**

| | |
|---|---|
| X = α-OH, Y = α-OTPS, R = TBS | 86% (*Z*/*E* = 1/3) |
| X = α-OTES, Y = α-OTPS, R = TBS | 80% (*Z*/*E* = 1/5) |
| X = α-OTBS, Y = O, R = TBS | 86% (*Z*/*E* = 1.7/1) |
| X = α-OH, Y = O, R = H | 65% (*Z*/*E* = 1/2) |
| X = β-OH, Y = α-OTPS, R = TBS | 81% (*Z*/*E* = 1/9) |
| X = β-OH, Y = O, R = TBS | 88% (*Z*/*E* = 1/2) |

An important advance has been disclosed regarding the control of stereoselectivity in RCM based macrocyclization. Template directed RCM of linear oligooxy ethylenic dienes devoid of other conformational constraints has demonstrated that an appropriate metal-ion template significantly promotes not only product yields but, more importantly, stereoselectivity of the cyclic products is greatly changed (Scheme 35).[65]

**Scheme 35.**




**70** **71**

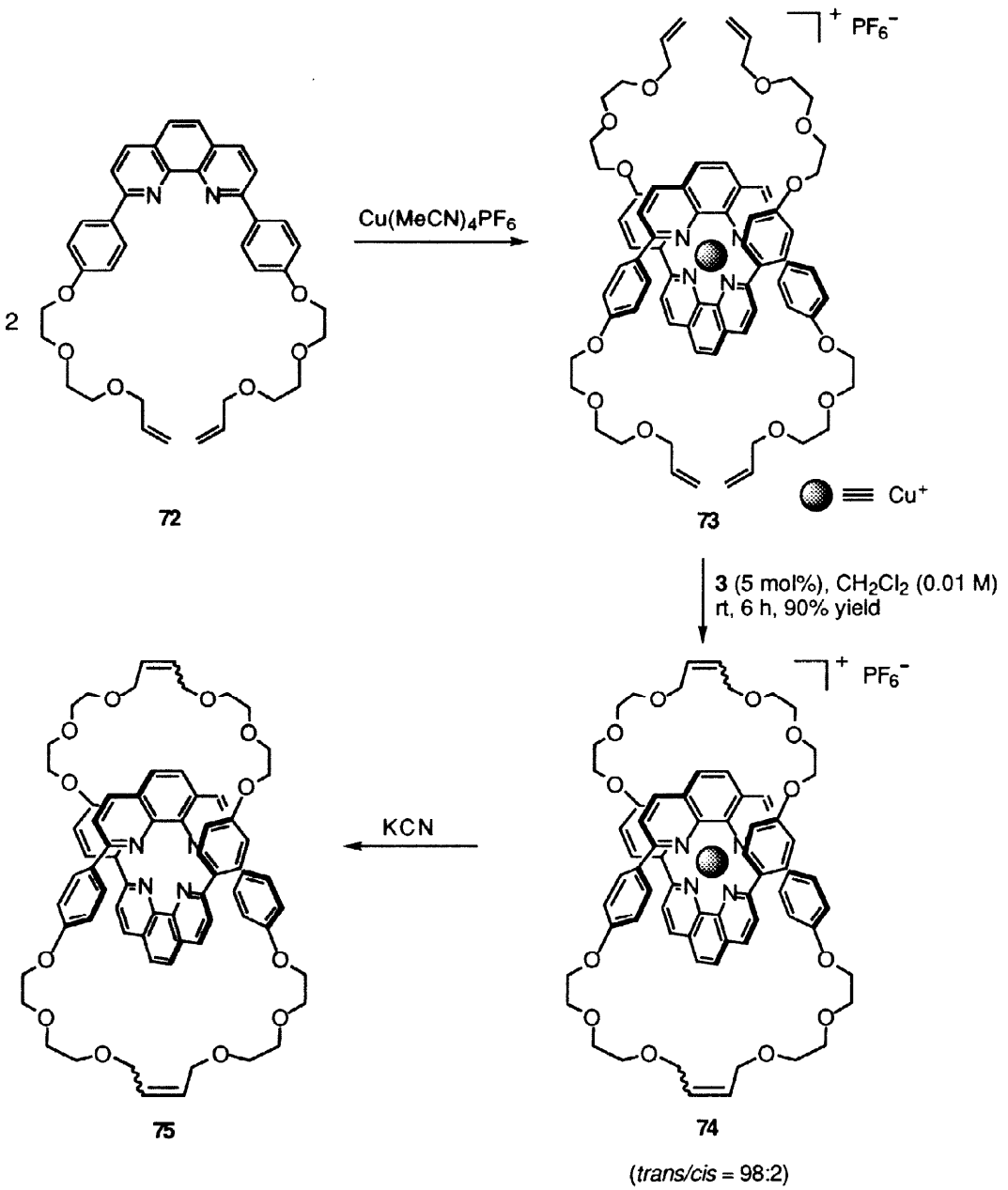
| | |
|---|---|
| n = 1, no template; | 39% (38:62 Z/E) |
| n = 1, $LiClO_4$ (5 equiv); | >95% (100:0 Z/E) |

It is presumed that preorganization of polyether olefin around a complementary metal ion provides a favorable conformation to enhance the rate of cyclization and stereocontrol. Among the many metal ion templates tested, $LiClO_4$ effected a quantitative conversion of an acyclic diene **70** to the *cis* ring-closed crown ether **71**.[66]

Catenanes, interlocked molecular rings, have been shown to be synthesized by the combination of three-dimensional template effects and RCM reaction (Scheme 36).[67] Complex **73**, obtained by complexation of the 2

equiv of the bidentate diene **72** with a copper complex, was cleanly cyclized to form a 32-membered catenate complex **74** in remarkably high yield and subsequent demetallation gave the catenane **75**. For all [*n*] catenates synthesized by this strategy, the energetically favored *trans* configuration at the double bond predominates.

**Scheme 36.**

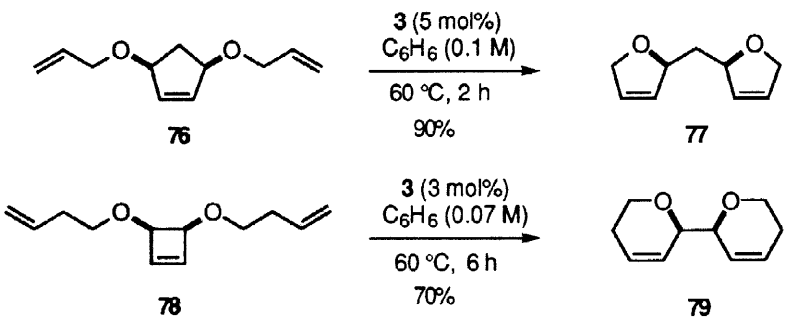



### 3.5. Tandem Reactions

In addition to the ring-closing metathesis (RCM) of acyclic dienes, Mo- and Ru-carbene complexes **1**-**3** also promote the ring opening metathesis of strained cyclic olefins. A new strategy for the formation of bicyclic ring systems has been developed in which intramolecular ring-opening/ring-closing metathesis of cyclic olefins

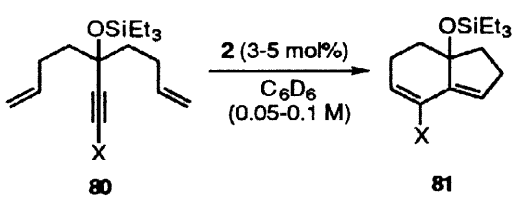
containing two alkenyl side chains is performed in a tandem manner.[68] As shown in Scheme 37, treatment of bis(alkenyl) ethers of several cycloolefin diols such as **76** or **78** with complex **3** afforded the respective bicyclic products **77** and **79** in good to excellent yields. This family of reactions allows for the rapid synthesis of complex molecules from simple substrates. Competing intermolecular metathesis has been frequently observed with less strained ring systems such as 6-8 membered cycloolefins. This undesirable pathway, however, was circumvented by conducting these reactions at low concentrations or by using disubstituted acyclic olefin side chains. Among the two possible sites, initial metathesis at the mono-substituted acyclic olefin was postulated to predominate over the other possibility, initial metathesis at the disubstituted ring olefin.

**Scheme 37.**




The formation of fused bicyclic [*n,m,0*] ring systems was previously developed *via* Ru-carbene catalyzed double RCM of acyclic dienynes, in which the acetylene positioned between the two olefins acts as an olefin metathesis relay.[69] This strategy provides functionalized fused bicyclics containing five-, six-, and seven-membered rings in a highly selective manner. In the proposed mechanism of the dieneyne RCM, the acetylenic substituent is transformed into a vinylic pendent which could subsequently be manipulated into more diverse functionality. To this end, the effects of various acetylenic substituents on the RCM of dienynes **80** were examined (Scheme 38).[70] With alkyl substitution, steric effects are important and reaction rates follow the expected trend (X = H > Me > *i*-Pr ≈ Ph ≈ $CO_2Me$). With the bulky *t*-Bu substituent, no cyclization product **81** was observed. Also substrates containing heteroatoms directly attached to the acetylene were not cyclized by the Ru-catalyst **2**.

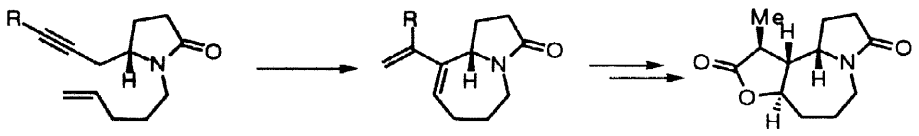
**Scheme 38.**




| | |
|---|---|
| X = H, | >95% (rt, 15 min) |
| Me, | 95% (rt, 8 h) |
| Ph, | 96% (60 °C, 3 h) |
| $CO_2Me$, | 82% (60 °C, 4 h) |
| *t*-Bu, TMS, $SnBu_3$, Cl, Br, I; | NR |

Intramolecular enyne metathesis has been applied in the total synthesis of a natural product, stemoamide (Scheme 39).[71] Cyclic eneynes **82** were smoothly converted to the 5,7-fused compounds **83** in the presence of Ru-carbene catalysts **2** or **3**.

**Scheme 39.**

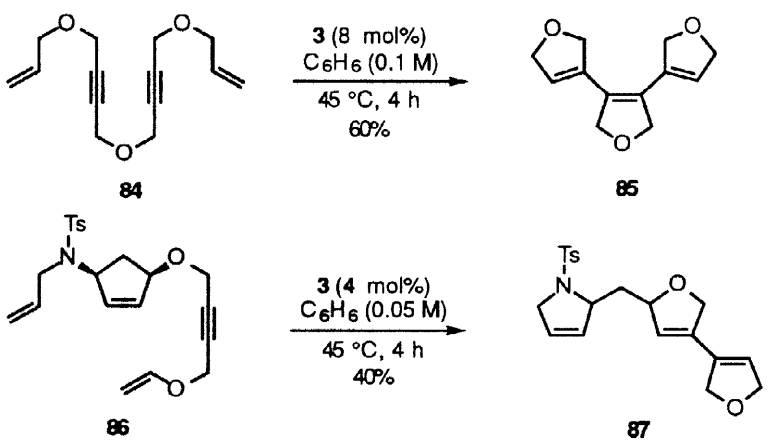



**82** **83** (-)-Stemoamide

R = Me: **2** (5 mol%); $C_6H_6$; 50 °C; 11 h; 73%
R = $CO_2Me$: **3** (4 mol%); $CH_2Cl_2$; rt; 5 h; 87%

In principle, the tandem reactions can be extended to "multi-cyclization" by attaching additional metathesis relays such as acetylenes or cyclic olefins. Recently this has been realized; one step tricyclization was accomplished by the metathesis of dienediynes (Scheme 40).[72] Depending on the dienediynes utilized, both fused and nonfused tricyclic triene systems were produced in the presence of the Ru-catalyst **3**. A substrate with a cyclic olefin relay such as **86** leads to a nonconjugated diene moiety in the triene product **87**.

**Scheme 40.**



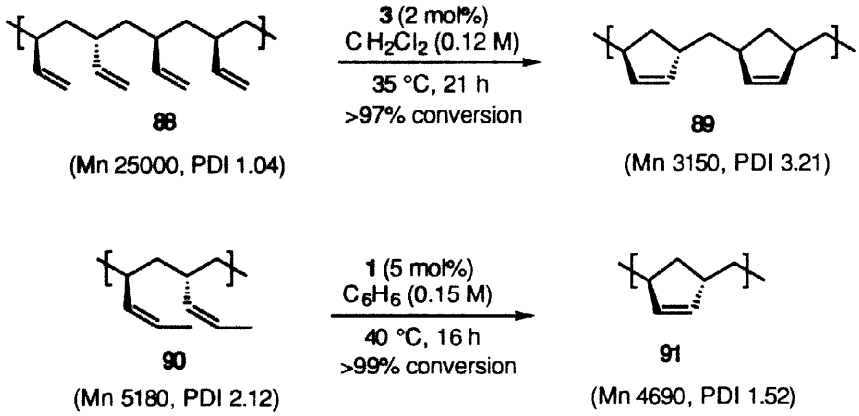

**84** **85**

**86** **87**

RCM of simple α,ω-dienes has been extended to polymeric substrates containing suitably-spaced olefins (Scheme 41).[73] Atactic 1,2-polybutadiene **88** was treated with the Ru-carbene catalyst **3** to cleanly afford the cyclopolymer product **89**. The lower molecular weight ($M_n$) and broader polydispersity (PDI) of the polycyclopentene **89** compared to the starting material **88** suggests that metathetical degradation of the infrequent 1,4-vinyl units of the polymer backbone occurs during the ring-closing process. The reaction proceeds to 90% conversion in the first 30 min and then continues much more slowly to 97% conversion in over 3 h. Reaction of the Mo-alkylidene complex **1** with syndiotactic 1,2-poly(Z-pentadiene) **90** yielded the trans-diisotactic cyclopolymer **91** in a quantitative yield. As a dramatic illustration of the reversibility of RCM, the kinetic

profiles suggest that the catalyst randomly closes adjacent olefins until only isolated olefins remain and then the catalyst migrates up and down the chain until all olefins are cyclized.

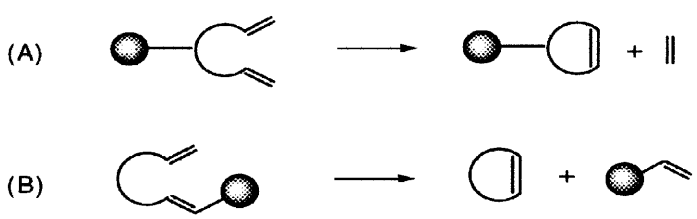
**Scheme 41.**




### 3.6. RCM of Solid Supported Substrates

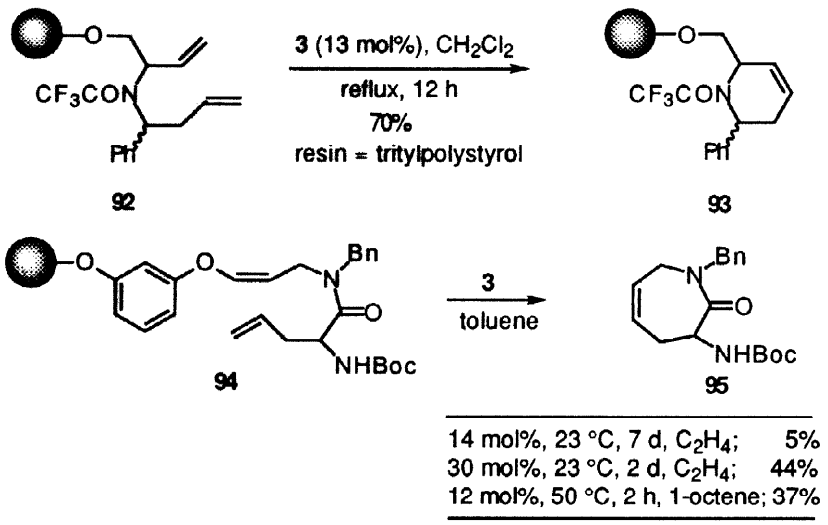
Performing organic transformations on a solid support has seen increased uses during the past few years. Olefin metathesis methodology has been also shown to be compatible on solid support bound substrates. There are two potential strategies depending on the olefin's position on the solid support as depicted in Scheme 42. A diene which contains a variety of functional groups (for instance, alcohol, carboxylic acid, amine *etc.*) may be covalently bound by a linker to a solid support and heterogeneous RCM can be carried out on the resultant solid-bound substrates (equation A). A different approach (B) is the "cyclization/cleavage method" in which the desired cyclic olefin is directly liberated from RCM of a diene attached at one end to solid support and therefore no additional step for removing the linker from the resin is necessary.

**Scheme 42.**




Examples of each strategy have been recently documented (Scheme 43). Poly-styrene bound diene **92** was converted quickly to the cycloolefin **93** which remains bound to the resin.[74,75] Despite the conceptual merit that RCM of dienes such as **94** directly releases the desired cycloolefinic product, the actual metathesis of these substrates has been found to be quite sluggish under standard reaction conditions to afford **95**.[76]

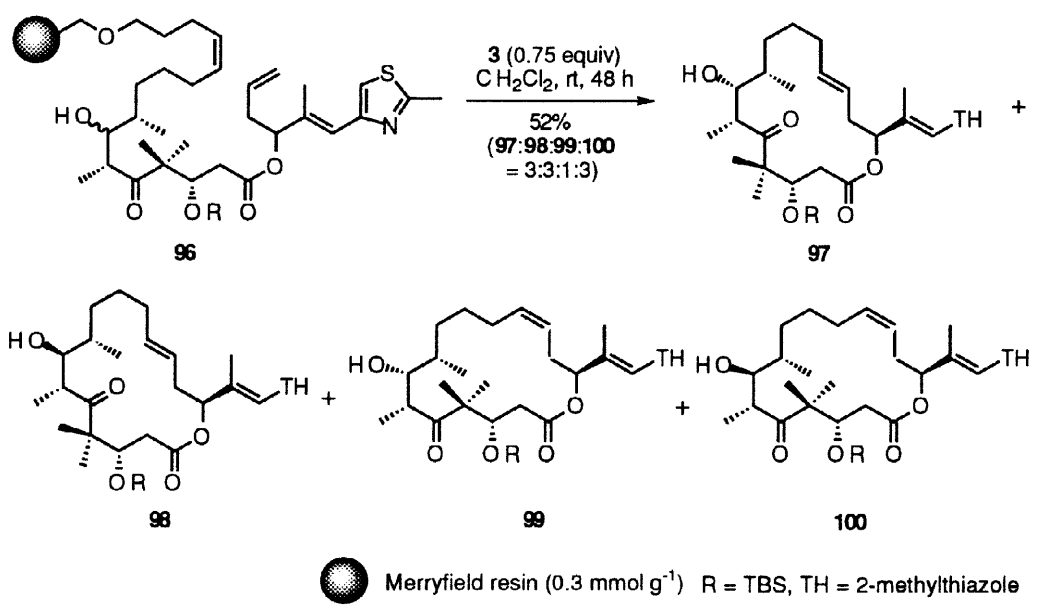
**Scheme 43.**




The authors attribute this low rate of RCM mainly to immobilization of the metal carbene complex on the resin during the course of the metathesis, and therefore the catalyst is not available for further reaction. Addition of a terminal olefin such as ethylene or 1-octene largely obviated this problem, presumably by detaching the immobilized catalyst to provide a recyclable active carbene intermediate.

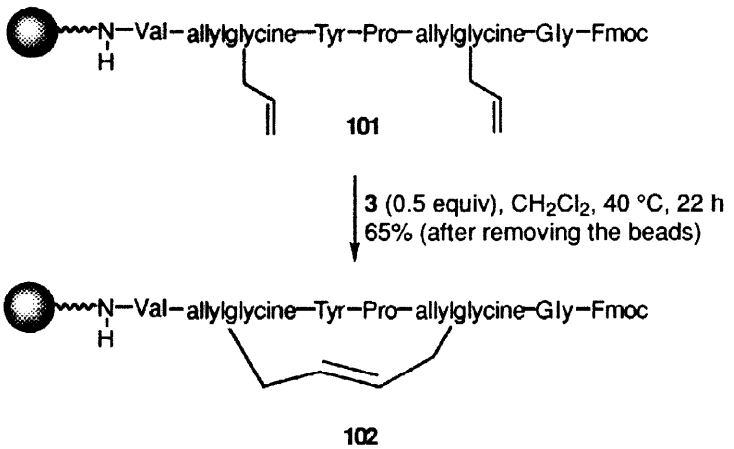
Nicolaou and co-workers have reported a solid-phase synthesis of epothilone A incorporating RCM (Scheme 44).[77] Upon treating solid support bound olefin **96** with 0.75 equiv of catalyst **3** in methylene chloride, 4 olefinic compounds **97-100** were released from the resin in total 52% yield as a separable mixture of 4 diastereomers. Desilylation and epoxidation of the cyclic olefins affords the biologically important epothilone A and its derivatives.

**Scheme 44.**



In the RCM of peptidic olefins containing greater than five amino acid residues, substrates commonly suffer from poor solubility in usual non-polar organic solvents where the metal carbene complexes display their highest activities. As a result, the feasibility of performing the RCM on solid support bound peptides was considered (Scheme 45).[53] Peptidic dienes were prepared by the standard solid phase peptide synthesis on a Tentagel resin, and heterogeneous RCM of **101** was effected under the conditions analogous to the solution phase RCM reaction. Upon cleavage of the cyclic peptide from the resin bound product **102**, efficiency of the solid phase reaction was revealed to be analogous to the solution phase cyclization.

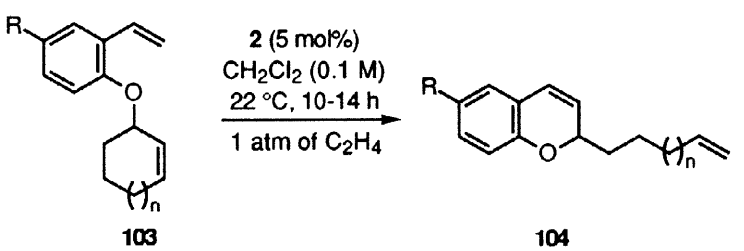
**Scheme 45.**




### 3.7. RCM Mediated Rearrangement

Recently olefin metathesis catalysts have been employed for the rearrangement of styrenyl ethers to yield isomeric heterocyclic products (Scheme 46).[78] Surprisingly, the yields of the desired rearranged-products were dramatically improved under an ethylene atmosphere as dimer formation was minimized. Chromenes **104** with different lengths of side chain and with diverse substituents were prepared in excellent yields from reaction of styrenyl ethers **103** with the Ru-carbene **2**. However, with substrates containing small size rings (**103**, $n \leq 1$), the rearrangement proceeds less efficiently than for 7- or 8-membered ring systems. For instance, cyclopentenyl styrenyl ether (**103**, n = 0) gave no rearranged product.

**Scheme 46.**

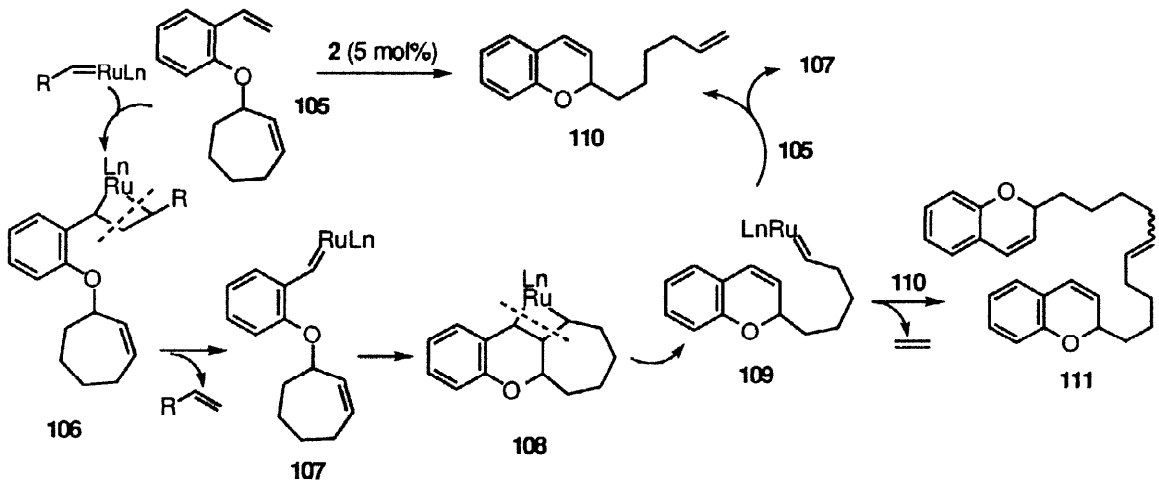



103 104

| | |
|---|---|
| n = 1, R = H, | 35% |
| n = 2, R = H, | 92% |
| R = OMe, | 100% |
| R = F, | 86% |
| n = 3, R = H, | 90% |
| R = $NO_2$, | 84% |

In light of added olefin (ethylene) effects, a mechanism for the above Ru-catalyzed rearrangement of styrenyl ethers has been proposed (Scheme 47). Reaction of the intermediate carbene **109** with a second equivalent of styrenyl ether **105** yields the desired product **110**. However, as increasing amounts of **110** are produced, **109** may react with **110** to afford the undesired dimer **111**. With ethylene present, dimer formation is reduced likely because the ethylene competitively reacts with **109** to deliver both **110** and the active ruthenium methylidene LnRu=$CH_2$ which goes on to form **106** in the catalytic cycle. The lower reactivity of the smaller ring systems probably results from strain in the formation of the metallacycle **108**.

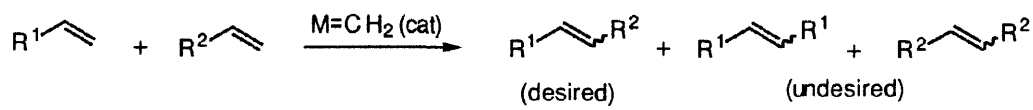
**Scheme 47.**




## 4. Cross Metathesis

Metal carbene catalyzed intermolecular coupling between two different olefins potentially yields 3 new types of alkenes as depicted in Scheme 48. Efficiency of the cross metathesis depends on the selectivity observed in the couplings. Minimization of unproductive alkenes from "self-metathesis" and consequently maximization of productive cross-metathized alkenes is a crucial issue to be optimized. In addition to the regioselectivity, stereocontrol of the newly formed double bonds is another important consideration in this chemistry.

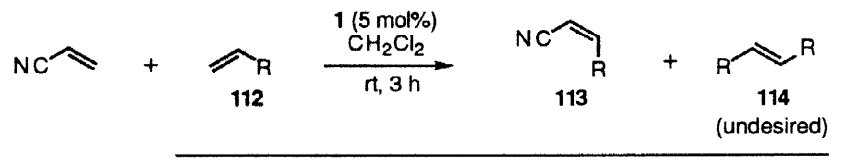
**Scheme 48.**




In contrast to the vast number of successful accounts of ring-closing metathesis reactions, there are only a few examples of selective cross-metathesis in the presence of functional groups.[79] This unique acyclic C-C double bond "interchanging strategy", therefore, has not found widespread application in organic synthesis because of the fact that general conditions giving high selectivity have not been discovered.

Cross metathesis in which acrylonitrile is used as one olefin is one of the few examples affording high selectivity (Scheme 49).[80] The reaction efficiency was found to be dependent on the type of the second substrate **112**. The yields are generally lower for alkyl-substituted olefins bearing electron-withdrawing groups. Even though its origin is not clear at present, the high *cis*-selectivity exerted with acrylonitrile is especially noteworthy because other metathetical coupling reactions between two different olefins invariably proceed with a high degree of *trans* pathway.

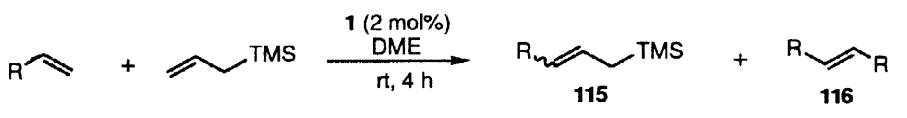
**Scheme 49.**




| | | | |
|---|---|---|---|
| R = | $(CH_2)_5CH_3$ | ***113***, 56% (*cis/trans* = 9:1) | **114**, 4% |
| | $(CH_2)Br$ | 17.5% (*cis/trans* = 9:1) | 20% |
| | $(CH_2)_3OBn$ | 60% (*cis/trans* = 7.6:1) | <1% |
| | $(CH_2)_5CH_3$ | 56% (*cis/trans* = 9:1) | 4% |
| | $CH_2TMS$ | 76% (*cis/trans* = 3:1) | 0% |
| | $(CH_2)_5CH_3$ | 56% (*cis/trans* = 9:1) | 4% |
| | $(CH_2)_6CH=CH_2$ | 53% (*cis/trans* = 8:1) | 19% |
| | $(CH_2)_2C(O)OBn$ | 44% (*cis/trans* = 5.6:1) | 6% |

Allylsilane coupling with terminal olefins is another example of regio- and stereoselective cross metathesis demonstrated by Crowe and co-workers (Scheme 50).[81] Reaction of allyltrimethylsilane with various *para*-substituted styrenes in the presence of Mo-catalyst **1** generated excellent stereoselectivity. More significantly, unproductive self-metathesized products were not formed. Even though the coupling with alkyl-substituted olefins afforded modest *trans*-selectivity (*ca.* 3-5:1), varying amounts of the self-metathesis dimers were formed in these cases. Increasing the size of the alkyl group (i.e., from trimethylsilyl- to triisopropylsilyl-) on the silyl alkenes led to increased *trans* selectivity without diminishing the overall yields.

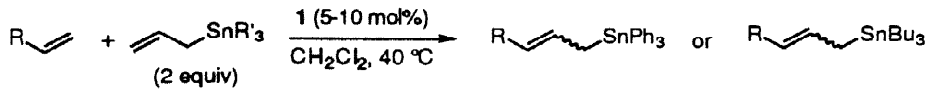
**Scheme 50.**

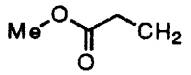
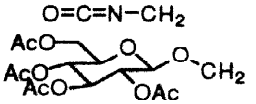



| | | | | |
|---|---|---|---|---|
| R = Ph, | **115**, 85% | *E/Z* = 100:0 | **116**, 0% |
| R = *o*-$NO_2C_6H_4$ | 40% | *E/Z* = 100:0 | 0% |
| R =CN | 76% | *E/Z* = 1:4.7 | 0% |
| R = $(CH_2)_2Br$ | 45% | *E/Z* = 2.8:1 | 12% |
| R = $(CH_2)_3OBn$ | 60% | *E/Z* = 4.6:1 | 26% |
| R = $(CH_2)_2CN$ | 37% | *E/Z* = 4.4:1 | 15% |

Cross metathesis of various terminal olefins with allyltriphenyl- or allyltributyl stannane has been reported by Blechert and co-workers (Scheme 51).[82] Even though the stereoselectivity observed is low to moderate, it is noteworthy that derivatives of various synthetically useful allyl stannanes can be prepared by this simple procedure.

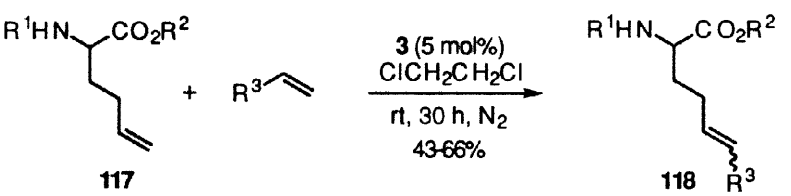
**Scheme 51.**




| | |
|---|---|
| R = $PhCH_2$ | R' = Ph, 74% (*E/Z* = 1.2:1); R' = Bu, 55% (*E/Z* = 1.4:1) |
|  | R' = Ph, 78% (*E/Z* = 2.7:1); R' = Bu, 74% (*E/Z* = 2.2:1) |
| $NCCH_2$ | R' = Ph, 72% (*E/Z* = 1.8:1); R' = Bu, 22% (*E/Z* = 1.0:1) |
| $O{=}C{=}N{-}CH_2$ | R' = Ph, no reaction; R' = Bu, no reaction |
|  | R' = Ph, 67% (*E/Z* = 2.3:1); R' = Bu, 21% (*E* only) |

Ru-carbene catalyzed cross metathesis of protected forms of unnatural amino acid homoallylglycine **117** with aryl- or alkylsubstituted terminal alkenes has recently been illustrated (Scheme 52).[83] Even though high *E*-stereoselectivity (>10/1) for the productive cross metathesis alkenes **118** was obtained with styrene, unproductive self-metathesized products were also formed in similar ratios. A steady stream of $N_2$ across the reaction mixture increased yields.

**Scheme 52.**

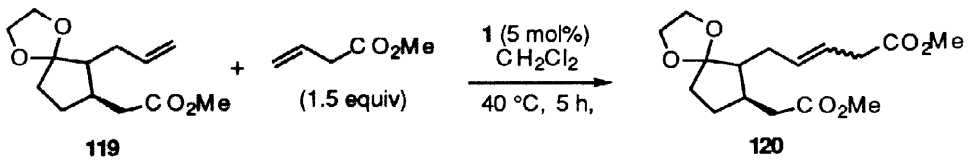



**117** **118**

R = Ph, *trans/cis* = >10/1, 43-55%
R = alkyl, *trans/cis* = 4/1, 55-66%

Using cross metathesis, derivatives of jasmonic acid **120** containing modified olefinic side chains were prepared to study their biological activities (Scheme 53).[84] Despite the broad functional tolerance of Mo-**1** and Ru-**3** catalysts, considerably lower coupling yields were obtained when a ketonic ester was employed in cross metathesis instead of the acetal ester **119**. It is possible that the ketone coordinates with the intermediate carbene complexes. With the exception of acrylonitrile, all olefins were coupled with **119** to afford a moderate *E*-selectivity.

**Scheme 53.**




119

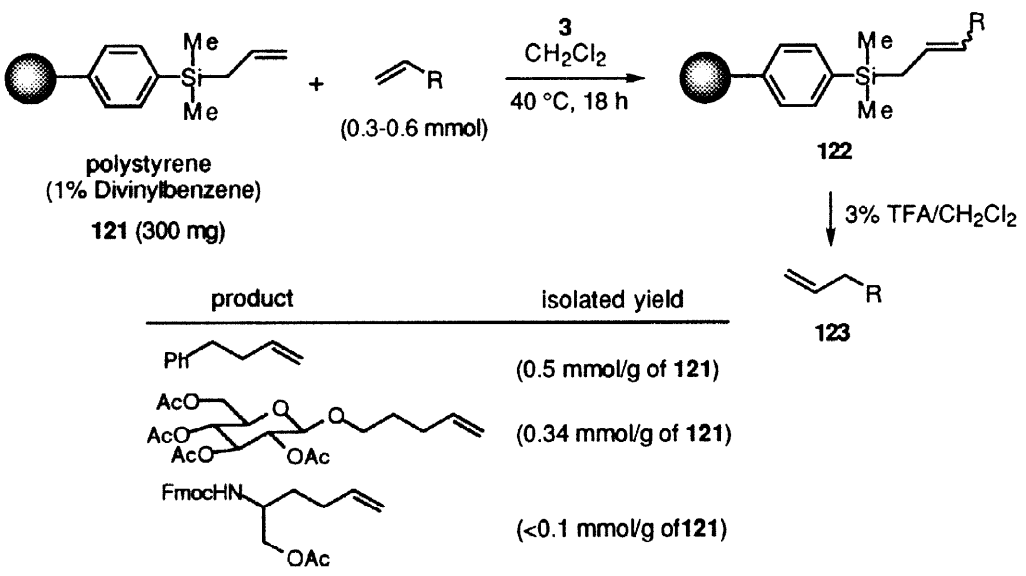
120

(83%, *E*/*Z* = 2:1)

| | | | |
|---|---|---|---|
| OAc | (2 equiv) | **3** (5 mol%) | (73%, *E*/*Z* = 2:1) |
| OH | (1.5 equiv) | **3** (8 mol%) | (70%, *E*/*Z* = 6:1) |
| CN | (2 equiv) | **1** (5 mol%) | (92%, *Z* only) |
| | (1.5 equiv) | **1** (5 mol%) | (65%, *E*/*Z* = 4:1) |

In contrast to the coupling of two alkenes in solution, cross metathesis involving polymer-bound olefins could give one potential benefit; self metathesis of solid support bound olefins could be theoretically prevented due to the site isolation on the solid support. Indeed high efficiency was obtained in the cross coupling of a immobilized alkene **121** with various aliphatic olefins giving new immobilized olefin products **122** (Scheme 54).[85] Products **122** were subjected to electrophilic cleavage to yield homologated alkenes **123**.

**Scheme 54.**




polystyrene
(1% Divinylbenzene)

**121** (300 mg)

**122**

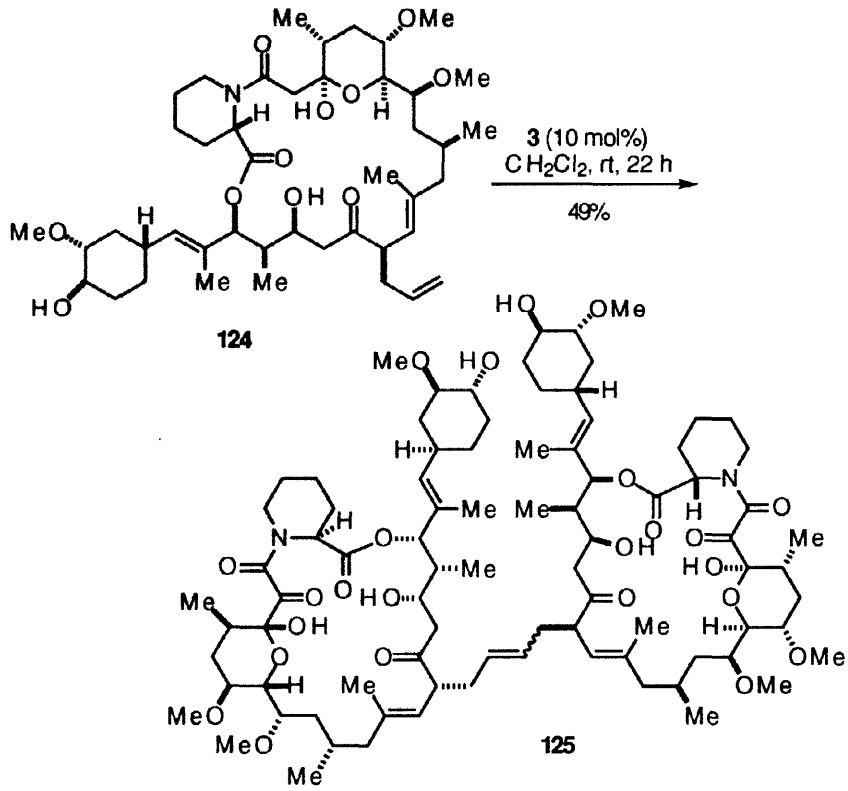
**123**

| product | isolated yield |
|---|---|
| Ph | (0.5 mmol/g of **121**) |
| AcO, AcO, AcO, OAc | (0.34 mmol/g of **121**) |
| FmocHN, OAc | (<0.1 mmol/g of**121**) |

In an interesting and biologically relevant application of cross metathesis, immunosuppressant FK 506 (**124**) was dimerized in 49% yield with the Ru-catalyst **3** (Scheme 55).[86] The potentially coordinating alcohol functionality at C-24 or C-32 were not protected. The yield of the dimeric product **125** (*ca.* 1:1 mixture of

alkene isomers) was improved (58%) by increasing the concentration of the diene **124** and replenishing the catalyst **3** (total 10 mol%) once during the reaction. Even though the stereoselectivity of the metathesis was relatively insensitive to both common organic solvents and reaction temperature, modest *E*-selectivity (4:1 *E*/*Z*) was obtained in refluxing *t*-BuOH (23% yield). Improved *Z*-selectivity (3:1 *Z*/*E*) was obtained by TBS protection of the C-24 hydroxyl group.

**Scheme 55.**



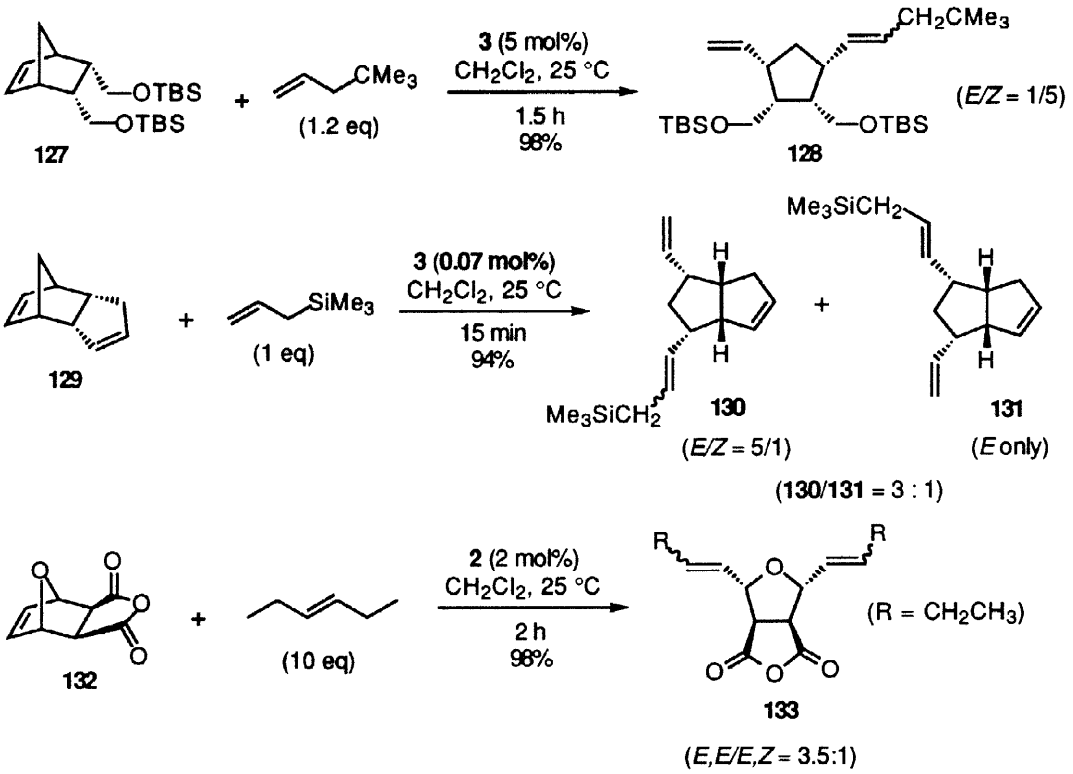

## 5. Ring-Opening Cross Metathesis

Another area of cross metathesis has been recently re-investigated from synthetic points of view. Ring-opening metathesis of strained ring systems and subsequent coupling with acyclic alkenes provides new types of diene products. To avoid polymerization of the cyclic olefins, the reaction is usually performed in relatively dilute concentrations (*ca.* 0.1 M) and an excess of acyclic alkenes is added. This modified cross metathesis uses the ring-opening of strained cyclic olefins as a driving force for the reaction. As in cross-metathesis, control of regio- and stereoselectivity of the newly forming double bonds appears to be the most important issue in order to make this reaction an appealing strategy in organic synthesis. The recent successful application of these reactions is surprising in light of the rapid equilibration of the end groups in cross metathesis reactions with classical catalysts. In fact the formation of scrambled cross products as the kinetic products with classical catalysts was one of the first clues implying that the mechanism involves carbenoid intermediates.[2a]

Ring-opening cross metathesis of strained norbornene derivatives with various types of olefins has been illustrated by Blechert and co-workers (Scheme 56).[87] With symmetrical norbornenes such as **127**, reaction

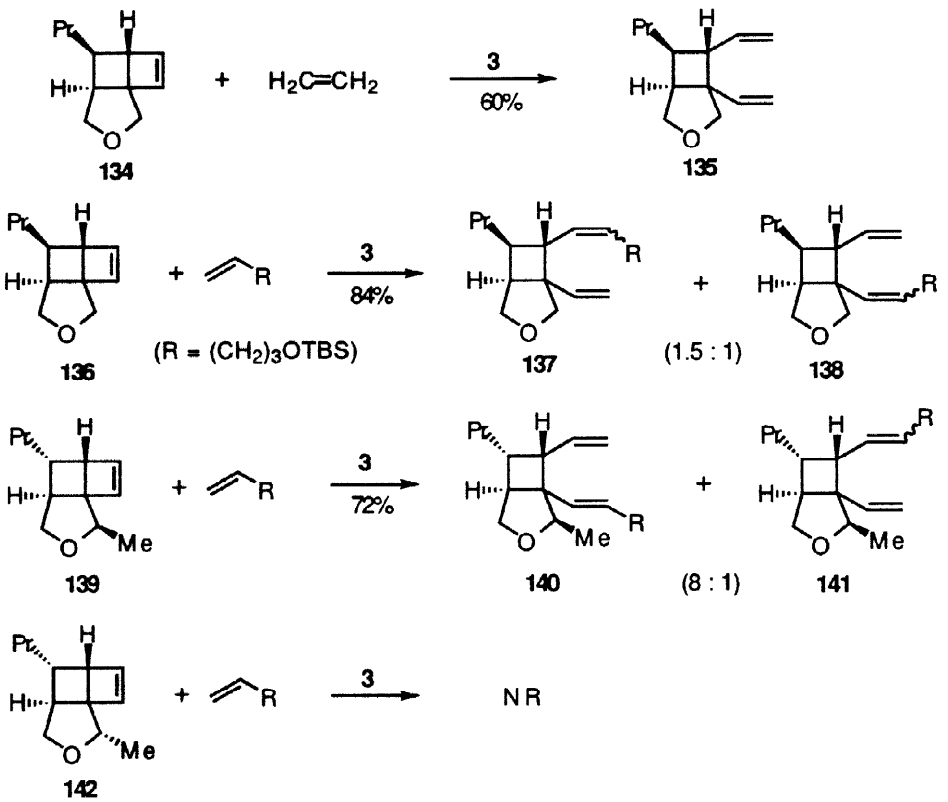
with a slight excess of terminal alkene produced only one regioproduct **128** in excellent yield using the Ru-catalyst **3**. Two regioisomeric products, however, would be formed from the reaction of unsymmetrical norbornenes. Indeed, reaction of dicyclopentadiene **129** with allylsilane afforded a 3:1 mixture of two regioisomeric products **130-131**. The efficiency of the reaction is truly remarkable, with only 0.07 mol% of the Ru-catalyst **3** being sufficient to complete the reaction in 15 min at room temperature. This increased efficiency is apparently due to the high reactivity of the strained olefins. If a disubstituted alkene is added to a strained cyclic olefin **132**, a new type of ring-opened internal olefin **133** is formed as a isomeric mixture.[88]

**Scheme 56.**



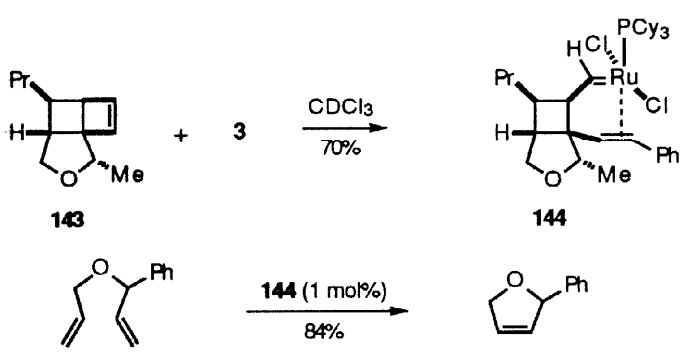

Regio- and stereoselective ring-opening cross metathesis of cyclobutene-containing substrates with suitable terminal olefins has been recently investigated by Snapper and co-workers (Scheme 57).[89,90] Unlike symmetrical alkenes (for instance, ethylene), reaction of unsymmetrically substituted olefins introduces new regio- and stereochemical questions. While cross-metathesis of **136** with TBS protected 4-penten-1-ol provided ring-opened products with little regiocontrol (**137/138** = 1.5:1), cycloadducts having substituents on the furan ring led to higher levels of regioselectivity (**140/141** = 8:1). Moreover, the newly formed olefin of the major regioisomer **140** was obtained with excellent *E*-selectivity (>20:1). As was observed for intramolecular ring-closing metathesis, subtle variations in substrate structure also play a critical role in the reactivity profile for ring-opening cross metathesis. In fact, no ring-opening metathesis occurred with cyclobutene **142**, the diastereomer of **139**. Stereospecific Cope rearrangement of the metathesis products affords bicyclo [6.3.0] ring systems in excellent yields.

**Scheme 57.**




During the above study, a new ruthenium alkylidene intermediate **144** was isolated from the reaction of cyclobutene adduct **143** with stoichiometric Ru-complex **3** and its structure was characterized (Scheme 58).[91] One of the phosphine ligands is replaced by a tethered olefin and the alkylidene hydrogen is *syn*-periplanar to the ruthenium-phosphine bond as shown by both NMR spectroscopy and an X-ray structure. The stable (even on silica gel) complex **144** has been found to have a catalytic activity in both ROMP and RCM.

**Scheme 58.**



At this time there are no general rules by which regio- and stereoselectivity can be reliably predicted in ring-opening cross metathesis. The stereoselectivity of the reaction often varies dramatically rather in a seemingly unpredictable way. However, in some cases, the reactions are highly efficient and provide diverse types of new alkenes which can not be easily obtained with any known chemistry. With improved selectivity, therefore, ring-opening cross metathesis could be a promising area for metathesis chemistry in the near future.

## 6. Conclusions and Future Outlook

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

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

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