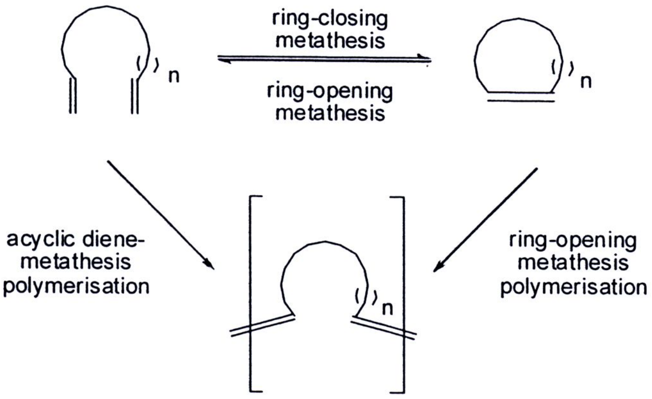
CHAPTER 1

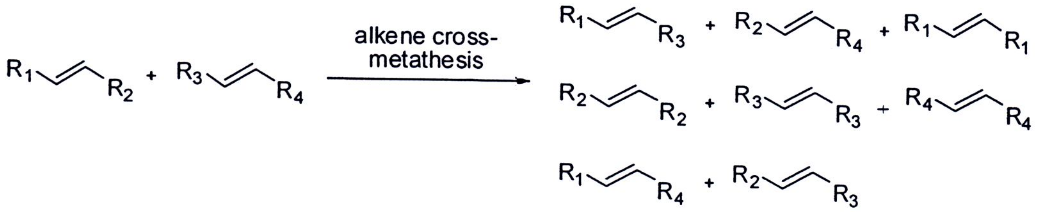
INTRODUCTION

General Ring-Closing Metathesis (RCM)

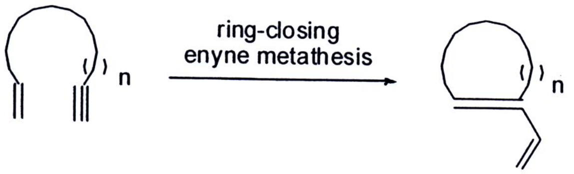
Olefin metathesis has been known for many years since 1950 involving rearrangement of unsaturated carbon-carbon bond in the presence of metal carbene complexes.[1-3] This reaction has become an extremely powerful tool in the synthesis of carbocycles[4,5] and heterocycles.[6-8] Especially, it was also developed to industrial and pharmaceutical method that are more efficient and less pollutant. The recognition of this chemistry suggests a big step in the development of new green methods for the synthesis of essential chemicals. The metathesis has been utilized in 3 types of reactions.[9] The first type is alkene metathesis reaction the second one is enyne metathesis reaction and final type is alkyne metathesis reaction.

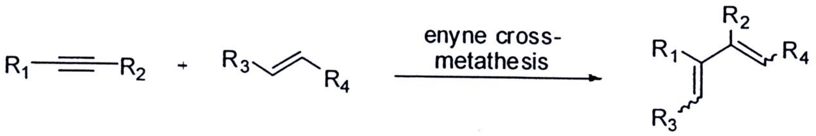
1. Alkene Metathesis reaction



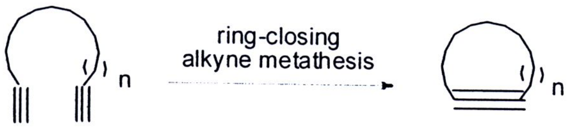


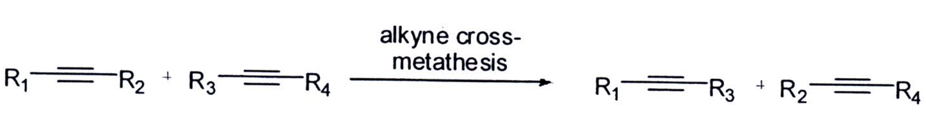
2. Enyne Metathesis reaction





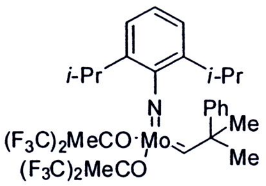
3. Alkyne Metathesis reaction





Ring-Closing Metathesis (RCM) of dienes is one of the most important methodologies now in use for the assembly of cyclic organic compounds. Progress in the development of the metathesis reaction has been directly correlated to improvement in the functional group compatibility and the reactivity of the catalysts. There are two main types of catalysts in use today.

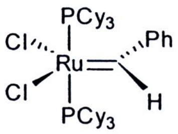
1. Molybdenum-complex (Schrock-type molybdenum complex **1**): It shows high reactivity to many diene substrates however it suffers from high sensitivity to air and moisture.[10,11]

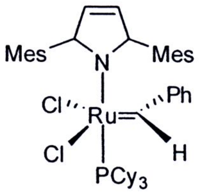


Schrock-type
molybdenum complex
1

Figure 1 Molybdenum-Complex (Schrock-type Molybdenum Complex)

2. Ruthenium-complexes **2** and **3**: Grubbs and co-workers introduced the first generation Grubbs catalyst (GI) **2** in 1995 and further developed by replacement of one of the phosphine ligands with *N*-heterocyclic carbene ligand led to the discovery of the second generation Grubbs catalyst (GII) **3** which shows greater reactivity and high stability to air and mositure.[12,13] GII is most commonly used for the RCM reaction throughout this thesis.





Mes = 2,4,6-trimethylphenyl

The first generation Grubbs catalyst

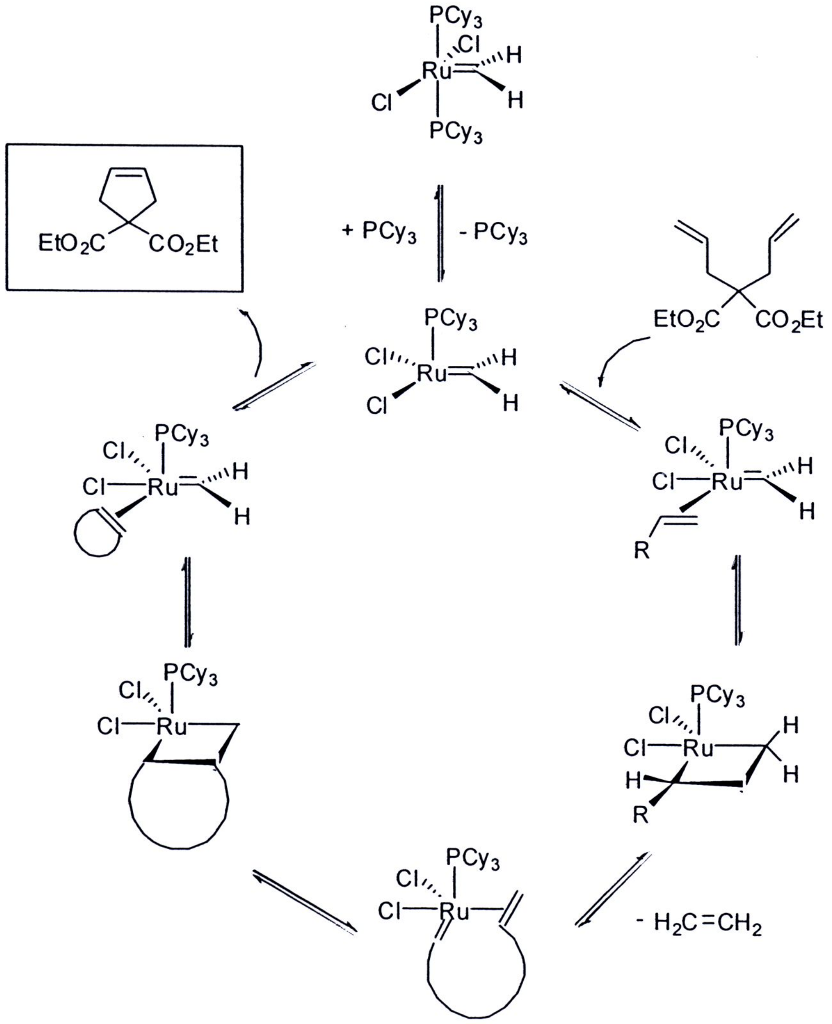
(GI) **2**

The second generation Grubbs catalyst

(GII) **3**

Figure 2 Ruthenium-Complexes (Grubbs Catalyst)

The generally accepted mechanism of RCM involves metal alkylidene complexes.[2] It has been found that the most significant operative pathway for Grubbs type ruthenium catalyst involves dissociation of a phosphine ligand to generate a more active species. Subsequent olefin-coordination forming metallacyclobutane and breakdown release a productive intermediate and following the similar process to afford the cyclised product.[2]

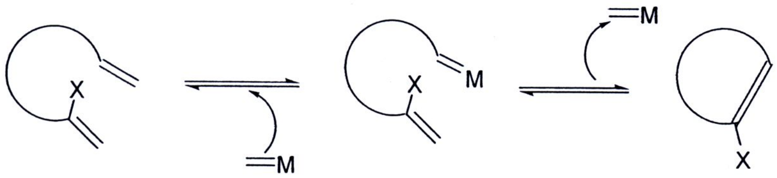


Scheme 1 Basic Catalytic Cycle of RCM

RCM of Vinyl Substituted Dienes

Ring-Closing Metathesis (RCM) has been extensively explored. This methodology has been widely applied to the construction of carbocyclic and heterocyclic systems.

After we have studied about catalysts and mechanism, we found that the scope of RCM has continuously increased from regular terminal olefins to variety of olefins ranging from electron-rich ones to electron-poor ones.[14] However, there are some limitations of metathesis reactions involving participation of heteroatom-substituted olefins.



Acylic Diene

Cyclic Olefin

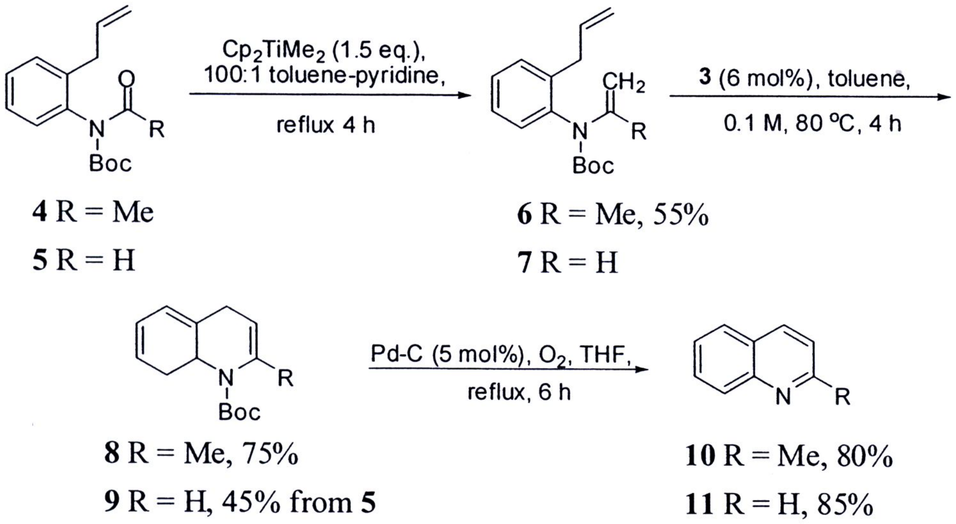
X = OH, NH_2, S, P, Si, B, and Halogen atoms

Scheme 2 RCM of Vinyl Substituted Dienes

In this section, RCM of heteroatom-substituted olefin will be summarized by using some representative examples.

1. RCM of Vinyl Amine-Containing Dienes

Bennasar *et. al.* reported the synthesis of benzo-fused *N*-heterocycles **10** and **11** by the carbonyl olefination RCM route.[15] Amide olefination of **4** and **5** using dimethyl titanocene (Cp_2TiMe_2) in the presence of pyridine produced the cyclized precursors **6** and **7** albeit in moderate yields. Subsequent RCM and oxidation of the resulting enamides gave the corresponding 1,4-dihydroquinoline products **8** and **9** in good yields.



4 R = Me
5 R = H

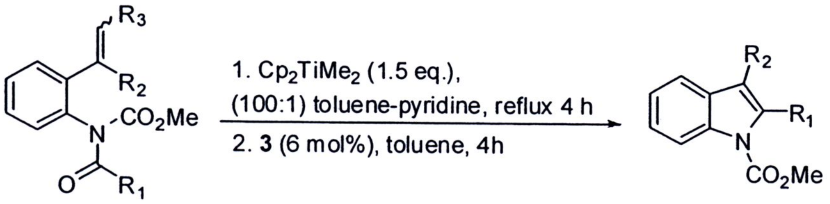
6 R = Me, 55%
7 R = H

8 R = Me, 75%
9 R = H, 45% from **5**

10 R = Me, 80%
11 R = H, 85%

Scheme 3 Synthesis of 1,4-Dihydroquinoline Compounds

A related study led to the synthesis of 5-membered cyclic enamide **15-17** using tandem methylation and subsequent RCM sequence in excellent yields.[16]



12 $R_1 = H, R_2 = Me, R_3 = H$
13 $R_1 = Me, R_2 = H, R_3 = Me$
14 $R_1 = R_2 = H, R_3 = Me$

15 $R_1 = H, R_2 = Me$, 90%
16 $R_1 = Me, R_2 = H$, 85%
17 $R_1 = R_2 = H$, 90%

Scheme 4 Synthesis of Indole System

Kinderman and co-workers presented the example of RCM of olefin containing enamides using Ru-based catalysts (the first generation Grubbs catalyst **2** or the second generation Grubbs catalyst **3**) to give 5- and 6-membered cyclic enamides in good yields.[17]

Table 1 RCM of Olefinic Enamides

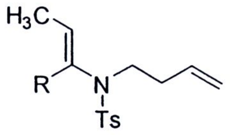
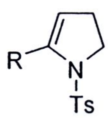
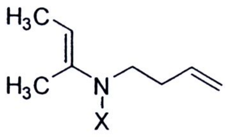
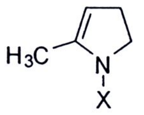
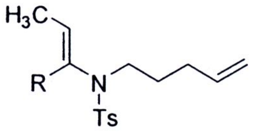
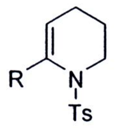
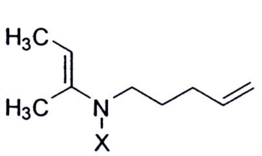
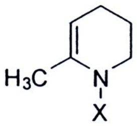
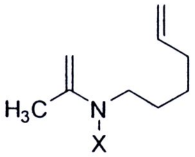
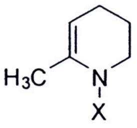
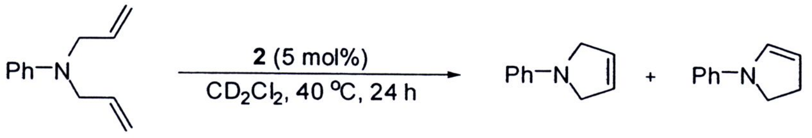
Entry	Enamide	Product	Yield
1			R = H (84%) R = CH_3 (86%)
2			X = Bz (63%) X = CO_2Et (62%)

Table 1 RCM of Olefinic Enamides (continued)

Entry	Enamide	Product	Yield
3			R = H (80%) R = CH_3 (75%)
4			X = Bz (93%) X = CO_2Et (57%)
5			X = Ts (62%)[a] X = Bz (24%)[a] X = CO_2Et (34%)[a]

a: isomerization products

Hong and colleagues published the RCM of *N,N*-diallyl aniline in 2005.[18] The author noted that addition of benzoquinone was found to reduce the amounts of unwanted isomerization-RCM product formed in some reactions. However, none of isomerization product **20** was observed in the case of RCM of diallyl phenyl amine.



18 **19** **20**

without addition of 1,4-dibenzoquinone	16%	84%
with 10 mol% of 1,4-dibenzoquinone	> 90%	0%

Scheme 5 RCM of *N,N*-Diallyl Aniline

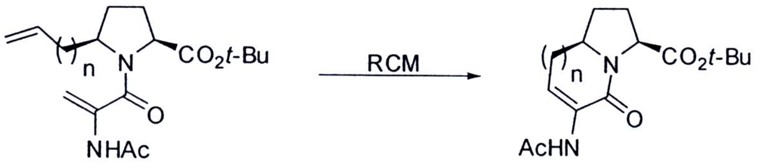
Katz and Overman presented the enamide-olefin RCM reaction to secure the intermediate dihydropyrrole **22** in good yield in the presence of a diversity of functionality, underscoring the excellent functional group tolerance of the Ru-catalyst.[19]

21 **22**

Scheme 6 Synthesis of Delivered Dihydropyrrole

Manzoni *et. al.* demonstrated the first RCM of dehydroamino acid **25**, **26**.[20] By changing the catalyst from Grubbs catalyst **2** to Grubbs catalyst **3**, RCM of the substrate **23** cyclized smoothly to afford the 6,5-fused bicyclic lactam **25** in excellent yield. Olefin **24** was subjected to RCM condition using

Grubbs catalyst **3** stirred at 40 °C to afford only 12% of the cyclized product **26**. Increasing the catalyst loading to 15 mol% at 80 °C, an improved yield of the cyclized product in 44% was observed. However, using Grubbs catalyst **3** for example at higher temperature at 100 °C and lower substrate concentration the starting material showed full conversion leading to an isolated yield of 53% of **26** after column chromatography accompanied by 14% of the bicyclic lactam **25**. Probably due to ruthenium catalysed isomerization to the more stable olefin, followed by RCM of isomerized intermediate to the 6-membered cyclic enamide **25**.



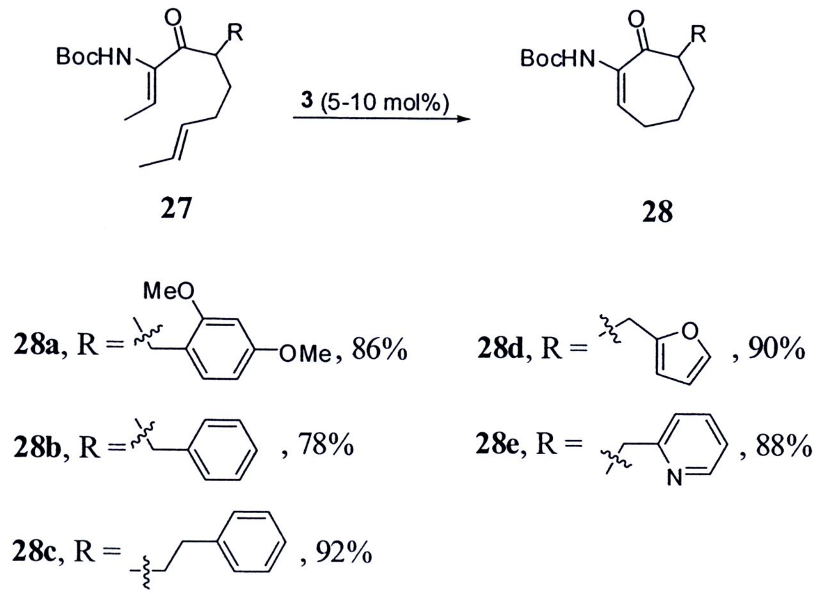
23 n = 1

24 n = 2

25 n = 1, **2** (5-10 mol%), 40 °C, 24 h, CH_2Cl_2, 4%
3 (5 mol%), 20 °C, 5 h, CH_2Cl_2, 89%
26 n = 2, **3** (5-10 mol%) , 25 °C, 24 h, CH_2Cl_2, 12%
3 (15 mol%), 80 °C, 72 h, toluene, 44%
3 (5-10 mol%), 100 °C, 72 h, toluene, 53%
(and **25** 14%)

Scheme 7 Synthesis of Dehydroamino Acid

Liu and co-workers established the facile synthesis of versatile functionalized amino caprolactams **28** using RCM reaction of α-amino acrylamide **27**.[21] The afforded α-amino α,β-unsaturated caprolactam **28** could be effectively hydrogenated to get a small library of α-amino caprolactam derivatives **28a-28e** in good to excellent yields.



27

28

28a, R = , 86%

28b, R = , 78%

28c, R = , 92%

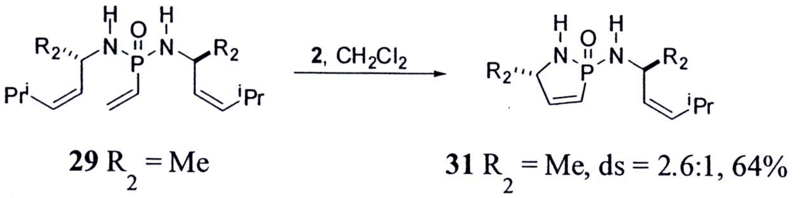
28d, R = , 90%

28e, R = , 88%

Scheme 8 Synthesis of α-Amino Caprolactam Analouge

2. RCM of Vinyl Phosphorus-Containing Dienes

Hanson and Stoianova reported the synthesis of cyclic compounds containing an asymmetric phosphorus atom (*p*-chiral heterocycles) **31** and **32** through application of RCM.[22] Cyclization of vinyl phosphonamides **29** and **30** using Grubbs catalyst **2** afforded 5,6-membered heterocycles with diastereoselectivities of 1:1 up to 15:1.

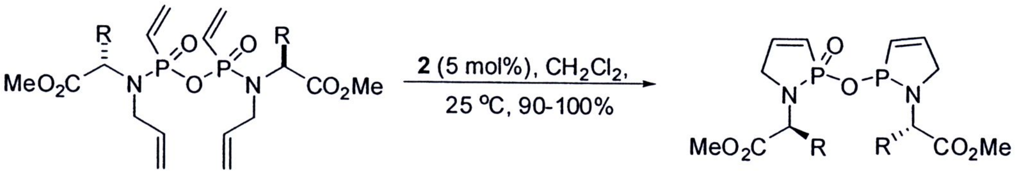


29 R_2 = Me
30 R_2 = *i*-Pr

31 R_2 = Me, ds = 2.6:1, 64%
32 R_2 = *i*-Pr, ds = 5.0:1, 80%

Scheme 9 Synthesis of *p*-Chiral Heterocycles

As extension of RCM of vinyl phosphonamides, the same group also demonstrated the synthesis of *p*-chiral amino acid-derived bicyclic phosphonamidic anhydride **34** by RCM, which proceeded in excellent yields using Grubbs catalyst **2**.[23]

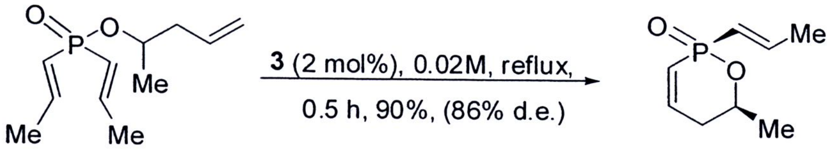


33 **34**

$R = CH_3, CH_2CHMe_2, Bn, CHMe_2$

Scheme 10 Synthesis of *p*-Chiral Amino Acid-Derived Bicyclic Phosphonamidic Anhydride

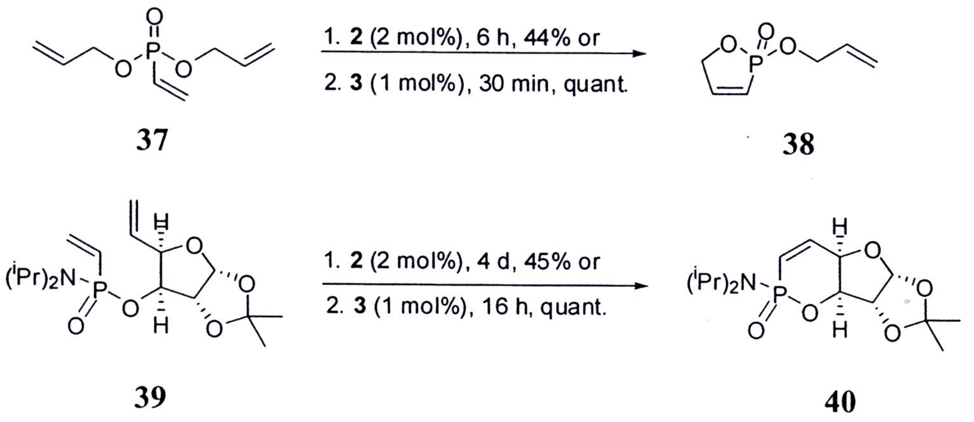
Dunne and co-workers presented the diastereoselective synthesis of *p*-stereogenic phosphinates **36** from trienes **35** using RCM with diastereoisomeric excesses of up to 86%.[24]



35 **36**

Scheme 11 Synthesis of *p*-Stereogenic Phosphinates

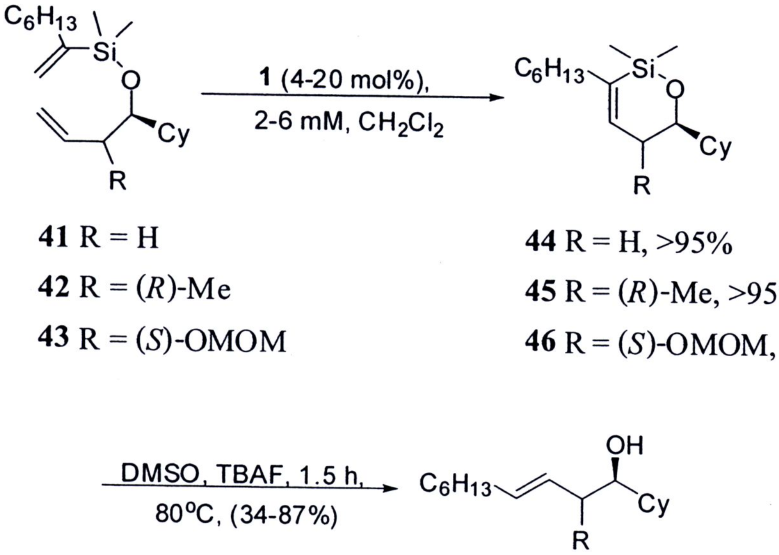
Timmer and colleagues reported the RCM of phosphonates **37** and phosphonamides **39** in the presence of Grubbs catalyst **3**, which enhanced performance in comparison to Grubbs catalyst **2**.[25] Under the reduced reaction times and less amount of Grubbs catalyst **3** promoted smooth cyclization of phosphonate **37** and phosphonamide **39** to furnish the corresponding heterocycles **38** and **40** in excellent yields.



Scheme 12 RCM of Phosphonates and Phosphonamides using Catalyst **2** or **3**

3. RCM of Vinyl Silane-Containing Dienes

Ahmed *et. al.* published the synthetic utility of the silicon-tethered RCM using Schrock catalyst **1**, however high catalyst loading (20 mol%) and low concentrated substrate (6 mM) were required for the conversion of diene **41-43**.[26] Protodesilylation of the vinylsilanes **44-46** produced the enantiomerically enriched homoallylic alcohols **47-49** with an *E*-configured disubstituted olefins.



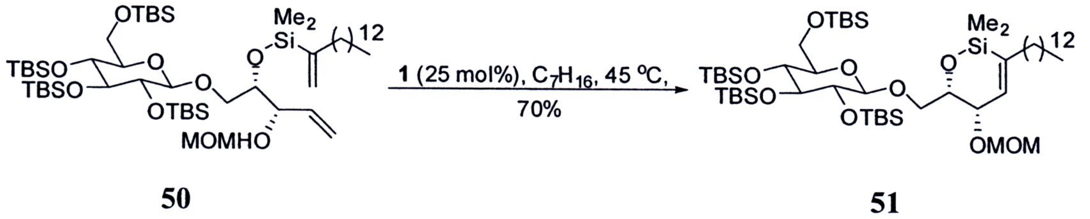
41 R = H
42 R = (*R*)-Me
43 R = (*S*)-OMOM

44 R = H, >95%
45 R = (*R*)-Me, >95%
46 R = (*S*)-OMOM, 34%

47 R = H, 87%
48 R = (*R*)-Me, 78%
49 R = (*S*)-OMOM, 66%

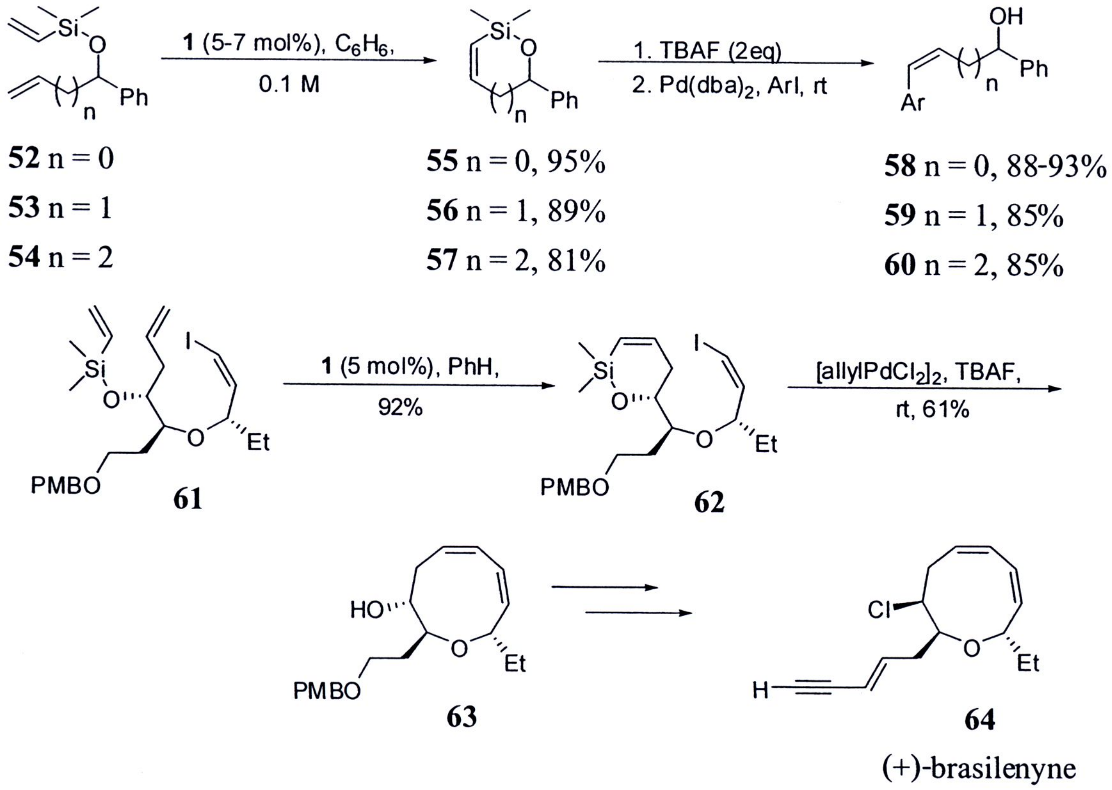
Scheme 13 Synthesis of *E*-Configured Homoallylic Alcohols *via* RCM of Vinyl Silyloxy Dienes

Barrett and co-workers reported the cyclization of the intermediate glycosphingolipids **50**. RCM of diene **50** using Grubbs catalyst **2** was unsuccessful probably due to the low reactivity of homoallylic vinyl siladiene substrates **50**.[27] Treatment of diene **50** with the Mo carbene **1** was then examined, initially in heptane to get the siloxacycle **51** in good yield (assessed by ^1H NMR) which was not isolated.



Scheme 14 Synthesis of Siloxacycle

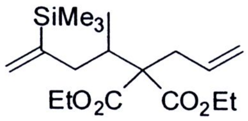
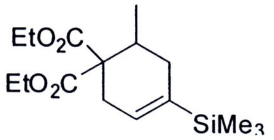
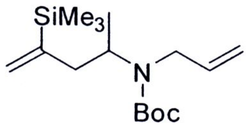
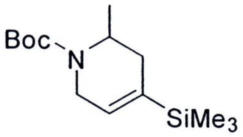
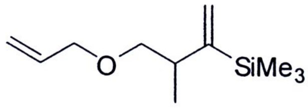
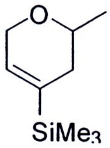
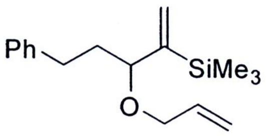
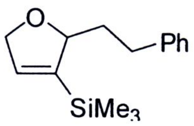
Denmark and Yang developed RCM in order to synthesis 5-, 6- and 7- membered cyclic vinylsilyl ethers **58-60**.[28] Optimization of the Pd(0)-catalyst was coupled with siloxane **55-57** and aryl iodides to afford *Z*-configured olefin **58-60**. They later went on to exploit this methodology during a total synthesis of (+)-brasilenyne **64**.[29-31]



Scheme 15 RCM and Subsequent Pd (0) Coupling Reaction of Vinyl silanes

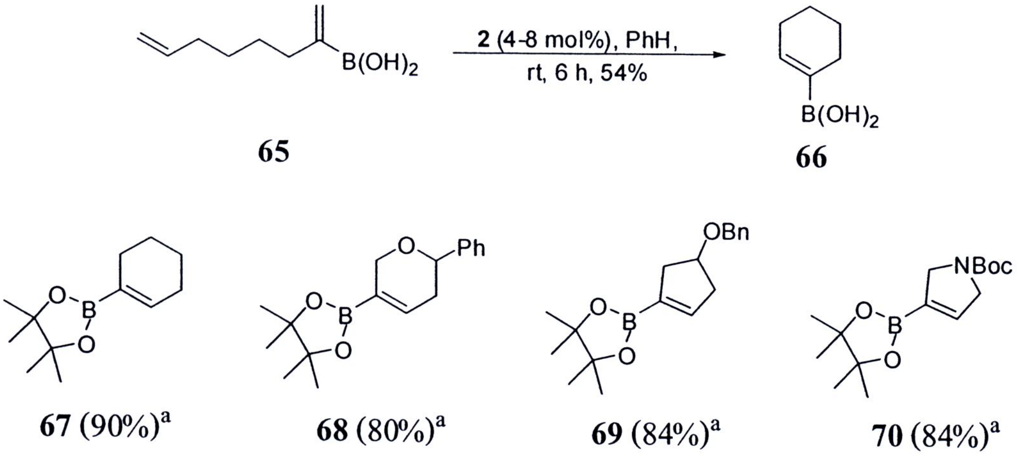
Schuman and Gouverneur presented the RCM of trimethylsilyl substituted precursors to provide a series of carbocycles and heterocycles analogues.[32]

Table 2 A Series of Trimethylsilyl Substituted Carbocycles and Heterocycles by RCM

Entry	Substrate	Product	Yield and conditions
1			98%, 3 mol%, 8 h
2			93%, 5 mol%, 18 h
3			93%, 3 mol%, 3 h
4			90%, 2 mol%, 1 h

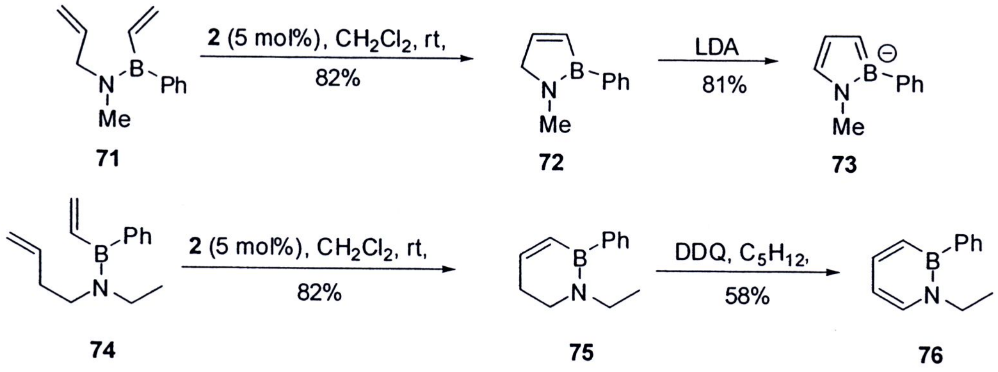
4. RCM of Vinyl Boronate-Containing Dienes

Alkyenylboronic esters and acids are well known to be versatile substrates for palladium-catalyzed coupling reaction.[33,34] Renaud and Ouellet developed a regioselective method for their RCM of acyclic dienylboronates **65**.[35] The Cyclization of the boronic acid **65** using Grubbs catalyst **2** gave the cyclized product **66** in moderate yield. Subsequently, boronic esters were shown to be useful substrate, affording 5- and 6-membered carbocyclic and heterocyclic alkenylboronates **67-70** in excellent yield. High dilution was required in some cases, when cyclization rates were slow, in order to minimize homo-metathesis of the unfunctionalized olefin.



Scheme 16 Alkenylboronate-Olefin RCM. [a] **2** (5-10 mol%), C_6H_6, 4-50 mM, rt

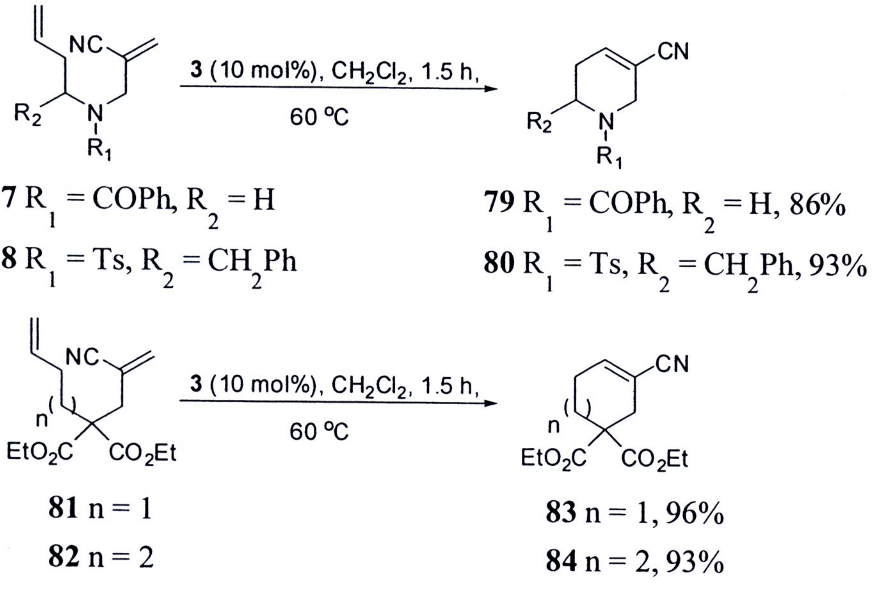
Kampf team reported a series of B-N heteroaromatic compounds which have been synthesized in good to excellent yields using vinylborane-olefin RCM as a key step.[36-38] Following deprotonation of **72**, the resulting heterocyclic cyclopentadiene (Cp) analogue **73** was used to prepare a Ru sandwich complexes. Oxidation of **75** using DDQ to get the final aromatic azaboracycle **76**.



Scheme 17 Synthesis of Boron-Containing Heterocycles

5. RCM of Vinyl Cyanide-Containing Dienes

Choi and co-workers published the synthesis of the cyano cyclic olefins **79**, **80** and **83**, **84** through RCM using Grubbs catalyst **3** to afford the cyclized products in excellent yields.[39]



77 R_1 = COPh, R_2 = H

78 R_1 = Ts, R_2 = CH_2Ph

79 R_1 = COPh, R_2 = H, 86%

80 R_1 = Ts, R_2 = CH_2Ph, 93%

81 n = 1

82 n = 2

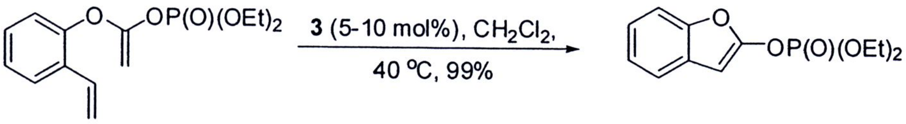
83 n = 1, 96%

84 n = 2, 93%

Scheme 18 RCM of Vinyl Nitrile

6. RCM of Vinyl Pseudohalides-Containing Dienes

Hanson and co-workers reported the preparation of enol phosphate **86** from simpler acyclic precursor **85**. The reaction was easily and successfully performed using ketene ketal phosphates. In terms of synthetic potential, the method is a good alternative to the difficult vinyl halide metathesis.[40]



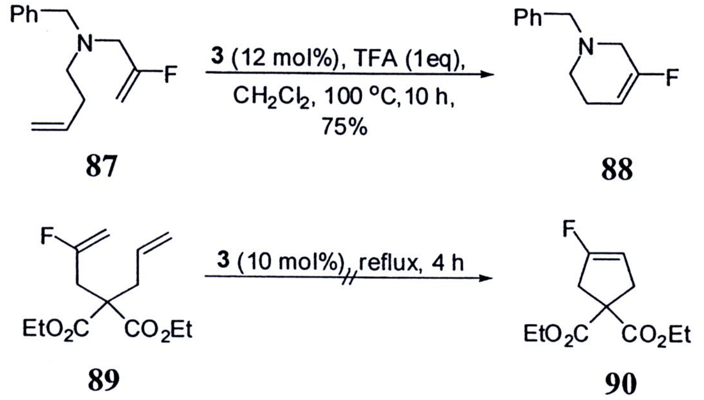
85 **86**

Scheme 19 Synthesis Vinyl Pseudohalides-Containing Dienes

7. RCM of Vinyl Halides-Containing Dienes

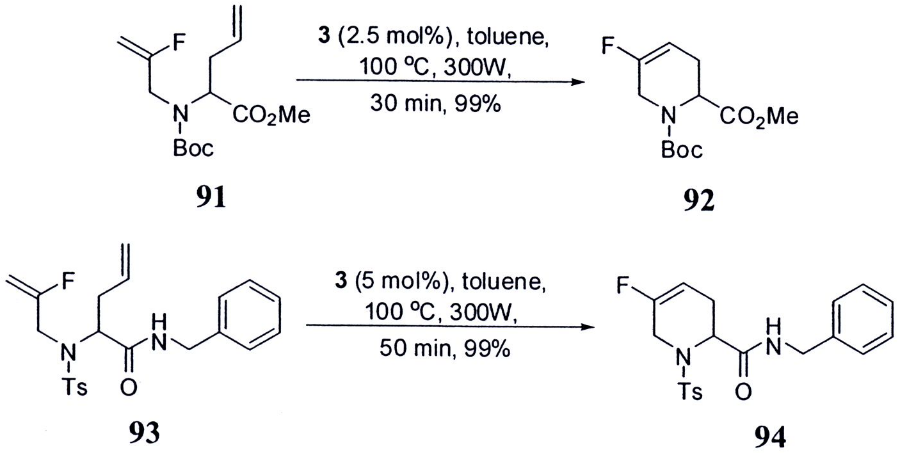
7.1 RCM of Vinyl Fluoro-Containing Dienes

Salim and co-workers reported the first synthesis of heterocyclic and carbocyclic fluoro-olefin **87** by RCM to provide 6-membered cyclic vinyl fluoride **88**.[41] However, the 5-membered vinyl fluoride **90** could not be generated from the carbocyclic fluoro-olefin **89**.[41] It was noted that the failure of the RCM reaction is a reflection of the lower reactivity of the fluoro-olefin double bond, combined with a greater ring strain energy developed in the formation of an intermediate. Thus, competed side-reactions or recovered starting material are observed.



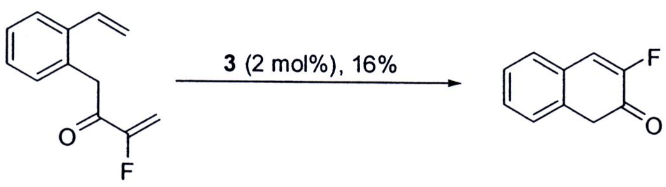
Scheme 20 Synthesis of Heterocyclic and Carbocyclic Fluoro-Olefins

Furthermore, De Matteis and co-workers published the RCM of fluoro olefins using Grubbs catalyst **3**, achieving some notable successes using α-fluoroacrylic acid derivatives **91**, **93** to afford 6-membered cyclic products **92**, **94**.[42,43] The addition of the Ru-complex **3** in portion over the course of the reaction was found to be very important otherwise it would result in catalyst decomposition and decrease yields.[40]



Scheme 21 RCM of Fluoro Olefins

Marhold and teams presented new opportunity for the synthesis of fluorinated heterocycles and carbocycles. In contrast, a rigid backbone was helpful in the reaction of the α-fluoroacrylated **95** to get 3-fluoro coumarin **96** using Grubbs catalyst **3** catalyzed RCM reaction.[45]

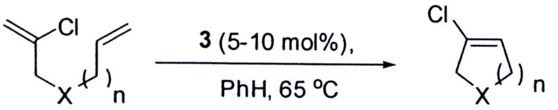


95 **96**

Scheme 22 Synthesis of 3-Fluoro Coumarin

7.2 RCM of Vinyl Chloro-Containing Dienes

Weinreb and Chao published the first example of RCM of vinyl chloride using Grubbs catalyst **3**, which provided a new route to regiodefined cyclic vinyl chloride **100-102** that would otherwise be difficult to access.[45,46]



97 n = 1-3, X = $C(CO_2Et)_2$

98 n = 2, X = NTs

99 n = 2, X = NBz

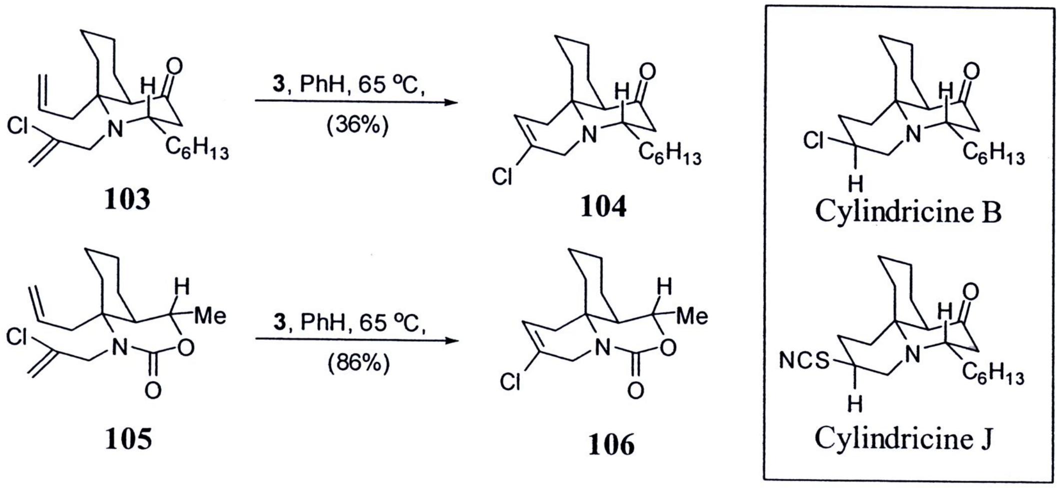
100 n = 1-3, X = $C(CO_2Et)_2$, 85-99%

101 n = 2, X = NTs, 92%

102 n = 2, X = NBz, 90%

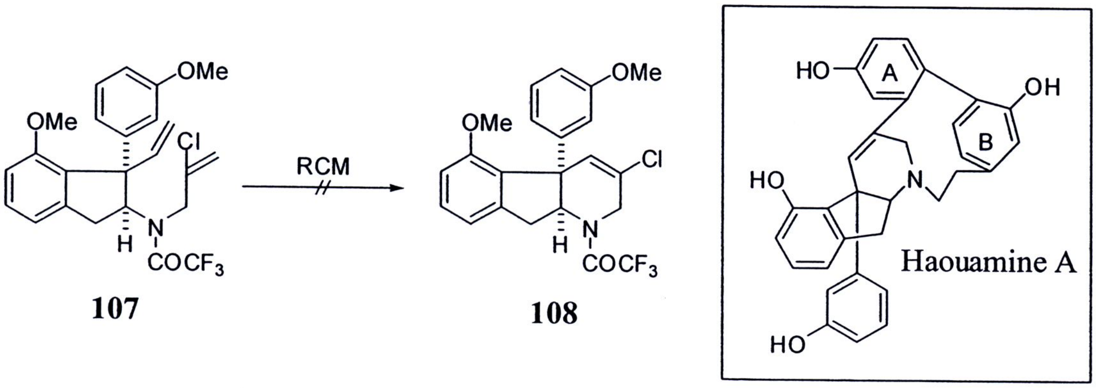
Scheme 23 RCM of Cyclic Vinyl Chloride

To highlight the application of RCM of vinyl chloride, Chao and co-workers published the RCM of vinyl chloride **103, 104** as a key step in the synthesis of the marine alkaloids cylindricines B and J respectively.[47]



Scheme 24 Synthesis of the Tricyclic Pyridoquinoline Framework of Cylindricine B and J

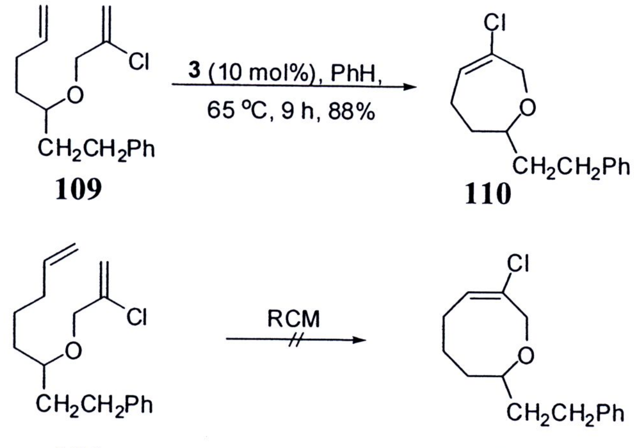
Weinreb and Jeong later reported the total synthesis of the cytotoxic marine ascidian alkaloid haouamine A. Unfortunately, all attempts to effect RCM of indene precursor **107** to produce indenotetrahydropyridine **108** failed.[48] They believe that the problem here is the steric hindrance in substrates because based on their earlier work it appears that the non-chlorinated olefin must initially form a metal carbene species for this RCM process to occur as desired.



107 **108**

Scheme 25 Attempted RCM of Indene Precursor

Chattopadhyay and co-workers published the RCM of **109** using Grubbs catalyst **3** to produce the chloro-substituted oxepin derivative **110** in excellent yields. Disappointingly, all attempts to synthesize the corresponding oxocin derivative **112** from **111** did not meet with success.[49]



109 **110** **111** **112**

Scheme 26 Synthesis of Oxocycles Derivative