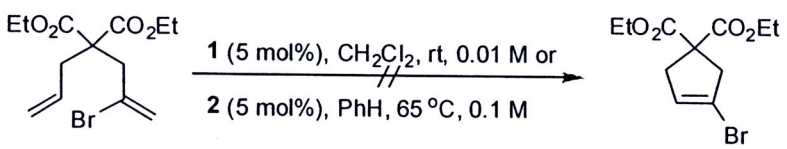
CHAPTER 2

RESULTS AND DISCUSSIONS

Previous Metathesis Reactions of Bromine-Containing Olefins

Research carried out on the RCM of vinyl bromide containing substrates is described in this section. A survey of the literatures revealed that few works of the metathesis of bromo containing olefins had been reported. In fact, Grubbs and co-workers were the only group reported the RCM of bromo-substituted dienes **113** with Mo-complex **1** and Grubbs catalyst **2**. As the results, none of the cyclized products was obtained, but only starting material remained unreacted upon such an attempt.[50]

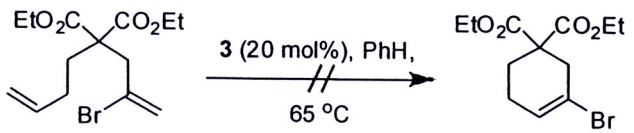


113 **114**

Scheme 27 Attempted Synthesis of 5-Membered Cyclic Vinyl Bromide

Since the discovery of new catalyst with high metathesis activity, for example the second generation Grubbs catalyst **3**, exposure of bromo dienes to the powerful Grubbs catalyst has been reported. Weinreb and Chao attempted RCM of vinyl bromide by using the conditions developed for vinyl

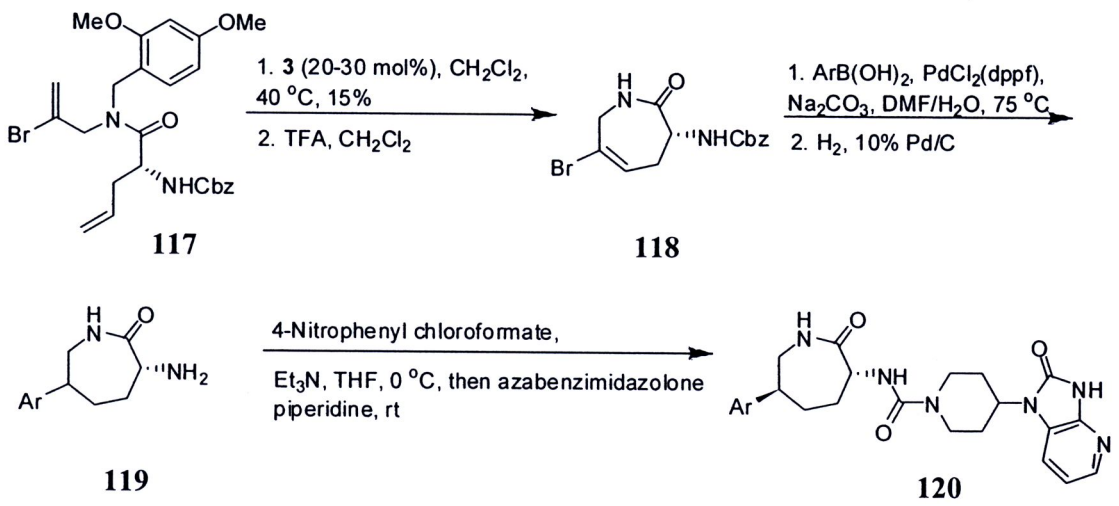
chloride.[46] However no cyclized product was observed. The author postulated that the vinyl bromide functionality would react with Grubbs catalyst leading to the formation of unstable Fischer-type carbene.



115 **116**

Scheme 28 Attempted Synthesis of 6-Membered Cyclic Vinyl Bromide

Group of Paone presented the synthesis of the urea-linked (*3R*)-amino-(*6S*)-phenylcaprolactam **120** to a Calcitonin Gene-Related Peptide receptor (CGRP recepter) privileged structure.[51] The key cyclization was accomplished with catalyst **3**. The unprecedented vinyl bromide RCM required high catalyst loading (20-30 mol%) to poorly obtain the caprolactam product **118** (15%). Suzuki couplings with various boronic acids proceeded cleanly, and hydrogenation of the styrene products. The desired product underwent smooth amide alkylation with various electrophiles, and followed by urea coupling with the azabenzimidazolone piperidine provided the final targets **120**.



Scheme 29 The Synthesis of (*3R*)-Amino-(*6S*)-Phenylcaprolactam Urea Linked to a CGRP Privileged Derivative

Despite of the previous report on the failure of metathesis of vinyl bromo containing substrates by Grubbs and Weinreb. It is indeed very challenging for us to investigate the viability of the analogue of vinyl bromide metathesis. Moreover, if this methodology was successful, it would provide an important new regioselective route to cyclic bromo-olefins ever, which is difficult to prepare by conventional methods. This thesis presents the most successful cyclization of vinyl bromo-olefins which have been demonstrated in 3 types of products. The first type is cyclic amine containing vinyl bromo-olefin. The second and the third types are cyclic sulfamide containing vinyl bromo-olefin and carbocycle containing vinyl bromo-olefin, respectively.

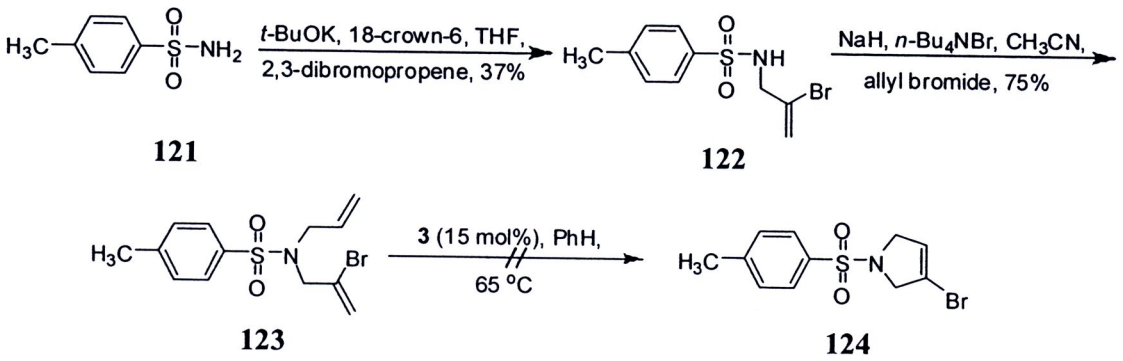
Synthesis and Metathesis of Vinyl Bromo-Containing Dienes

In order to investigate the RCM of vinyl bromides, we decided to prepare a variety of C, N, and sulfamide-linked substrates. Those efforts will be described in the following section.

1. Synthesis and Metathesis of Amine-Linked Vinyl Bromides

1.1 Synthesis of 5-Membered Cyclic Vinyl Bromo-Containing Amine

In order to investigate the RCM of monobrominated dienes with single heteroatom or multiple heteroatoms in the linking chain, a number of amine precursors were synthesized. Starting with alkylation of 4-toluenesulfonamide **121** with 2,3-dibromopropene in the presence of 18-crown-6 and *t*-BuOK in THF produced monobrominated dienes **122** and subsequent alkylation of sulfonamide **122** with allyl bromide afforded metathesis precursor **123** in good yield. The metathesis of precursor **123** were then exposed to RCM conditions using 15 mol% of the second generation Grubbs catalyst **3** under reflux in benzene for 18 hours. However, RCM reaction of vinyl bromide precursor **123** did not give the expected 5-membered product **124** and only starting material was recovered.

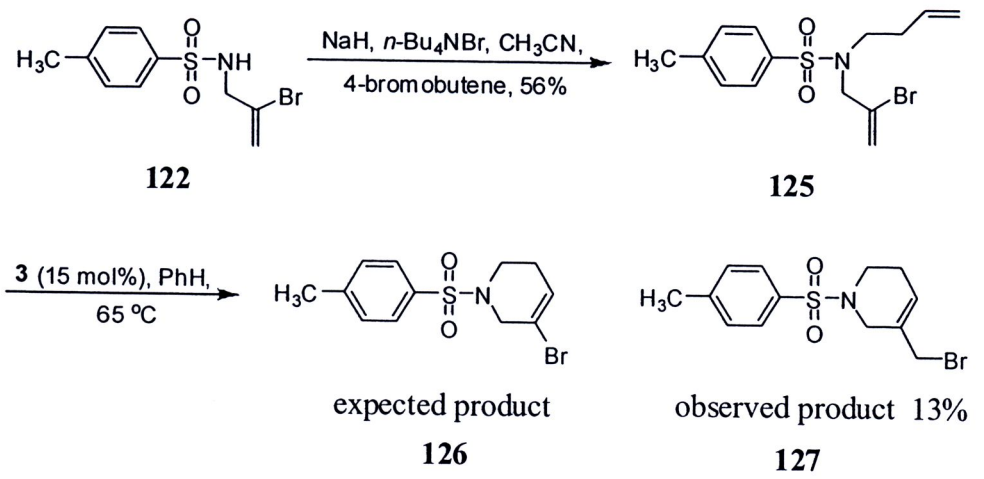


121 122 123 124

Scheme 30 Attempted Synthesis of 5-Membered Ring of Cyclic Amine Containing Vinyl Bromo-Olefin

1.2 Synthesis of 6-Membered Cyclic Vinyl Bromo-Containing Amine

Monobrominated sulfonamide precursor **125** was obtained by alkylation of sulfonamide **122** with 4-bromobutene under basic conditions in moderate yield. RCM reaction of **125** using 15 mol% of the second generation Grubbs catalyst **3** under reflux in benzene for 18 hours gained the cyclized product **127** in 13% yield without the production of the expected dihydropyridine derivative **126**.

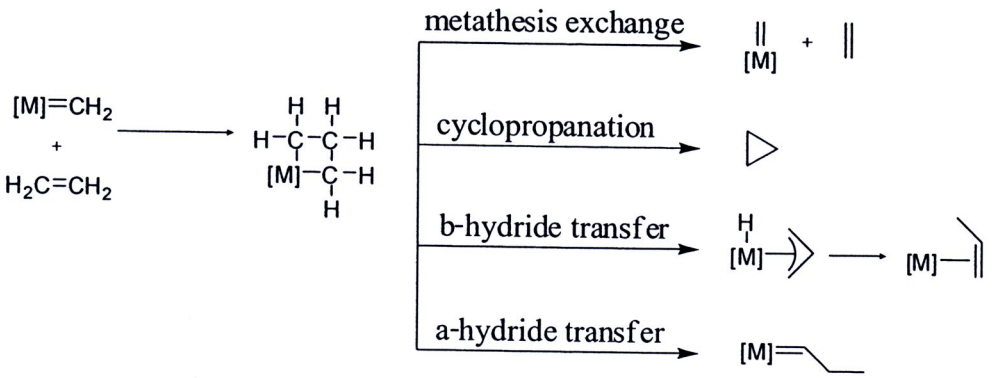


122 **125**

126 **127**

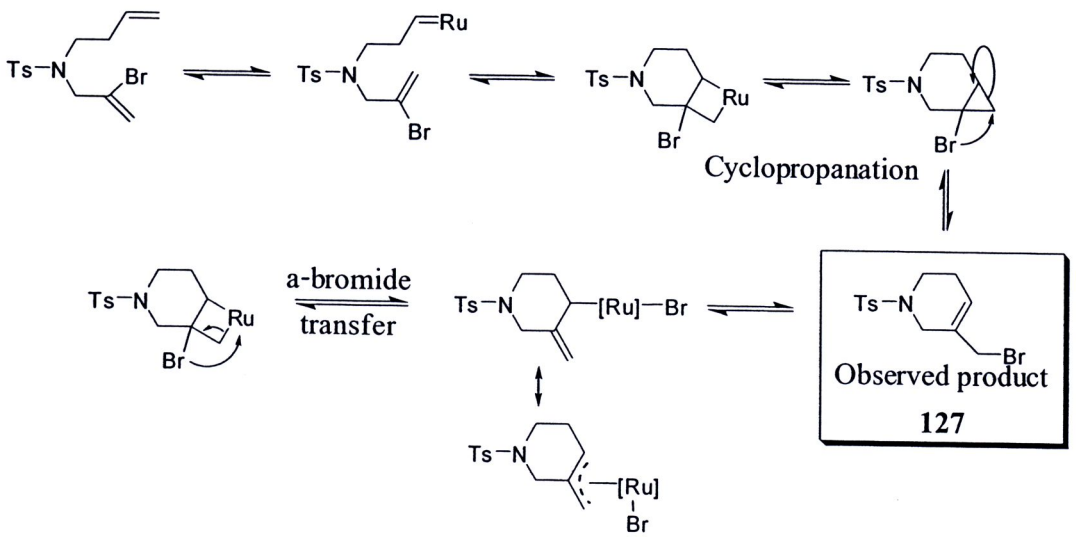
Scheme 31 Synthesis of 6-Membered Ring of Cyclic Amine Containing Vinyl Bromo-Olefin

According to the literature, the mechanism of RCM may follow the metallacyclobutane decomposition pathways as shown below.[52] Olefins would firstly react with carbene in a number of alternative ways that might complete with the α-hydride transfer. So the metallacycles might undergo metathesis exchange more readily than the rearrangement to a new carbene by α-hydride transfer. Also there are two other major pathways via cyclopropanation and β-hydride transfer reaction to get cyclopropane and olefin-π complex product.



Scheme 32 Metallacyclobutane Decomposition Pathways

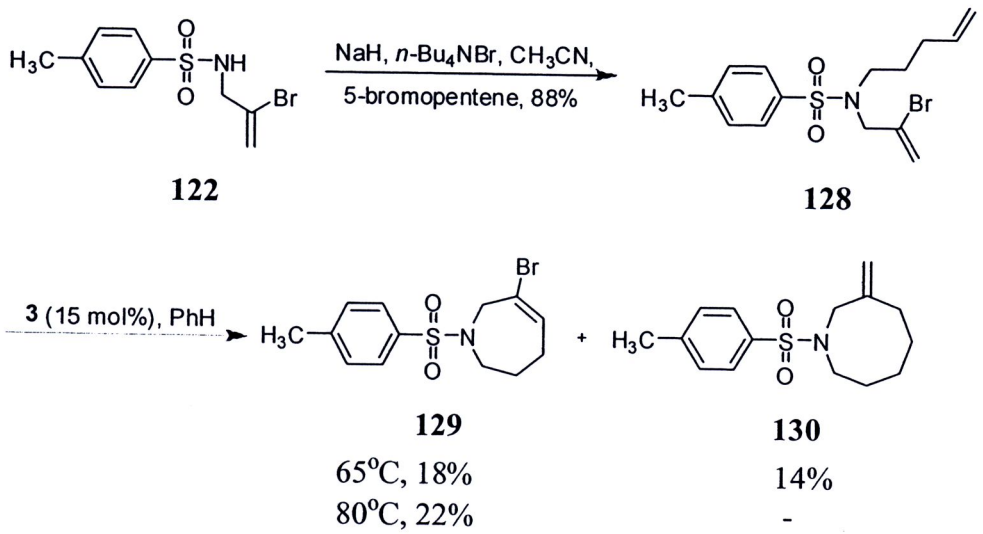
Based on the mechanistic studies of ruthenium carbene catalyzed reaction described above, two possible pathways for the reactions of bromo-olefins could be suggested. In the first pathway, a reaction might involve the reductive elimination from metallacycle to produce bromo-cyclopropanated intermediate and then rearrangement of this intermediate leading to the allylic bromide **127**. The second pathway might start from the formation of metallacycle and follow by the subsequent rearrangement of the bromine to release cyclized product **127**.



Scheme 33 Mechanism of Cyclopropanation and α-Bromide Transfer Pathway for the Cyclized Product

1.3 Synthesis of 7-Membered Cyclic Vinyl Bromo-Containing Amine

Finally, the alkylation of sulfonamide **122** with 5-bromopentene under basic conditions gave sulfonamide precursor **128** in moderate yield. RCM reaction of **128** using 15 mol% of the second generation Grubbs catalyst **3** heating at 65 °C in benzene for 18 hours produced the 7-membered ring product **129** and some of 8-membered ring product **130**. We believe that the unexpected product **130** was created from the metallacyclopentane type intermediate. However, at 80 °C ruthenium complex **3** proceeded smoothly to produce the expected product **129** (22%) and none of the unexpected product **130** was observed.



122 **128**

129 **130**

65°C, 18% 14%

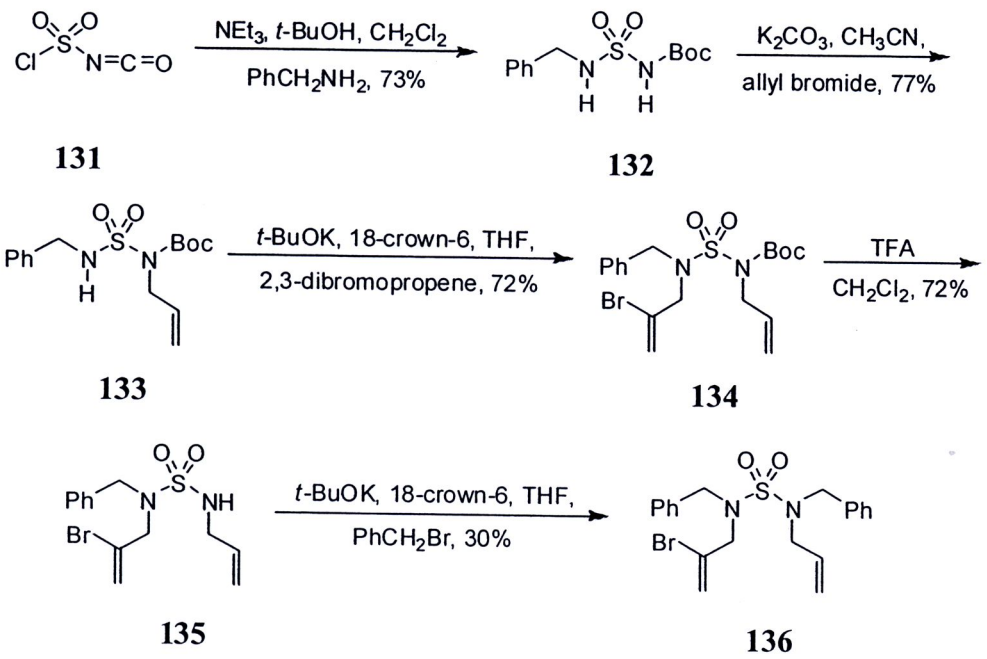
80°C, 22% -

Scheme 34 Synthesis of 7-Membered Ring of Amine Containing Vinyl Bromo-Olefin

2. Synthesis and Metathesis of Sulfamide-Linked Vinyl Bromides

To evaluate the feasibility of bromo-olefin metathesis, a number of sulfamide substrates were prepared following the established method.[42] Treatment of benzylamine with chlorosulfonyl isocyanate (CSI), NEt_3 and *tert*-butanol provided the sulfamide **132** in 77% yield. Mono-alkylation of sulfamide **132** was carried out in the presence of K_2CO_3 in CH_3CN to give the sulfamide **133** in good yield. The free amine was then coupled with the commercially available 2,3-dibromopropene using *t*-BuOK as a base to provide the desired sulfamide **134** in good yield and after the deprotection of the Boc-group, the sulfamide **135** was obtained in 72% yield. Subsequent alkylation of sulfamide **135** with benzyl bromide and *t*-BuOK in THF gave the sulfamide precursor **136** in low yield (30%). Probably, the last alkylation step may not

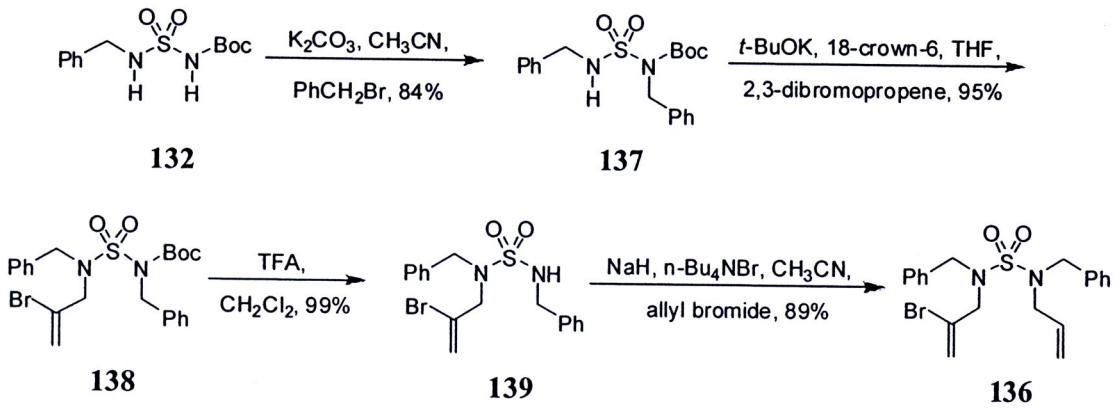
smoothly proceed due to the low reactivity of benzyl bromide used as alkylating reagent.



131 **132** **133** **134** **135** **136**

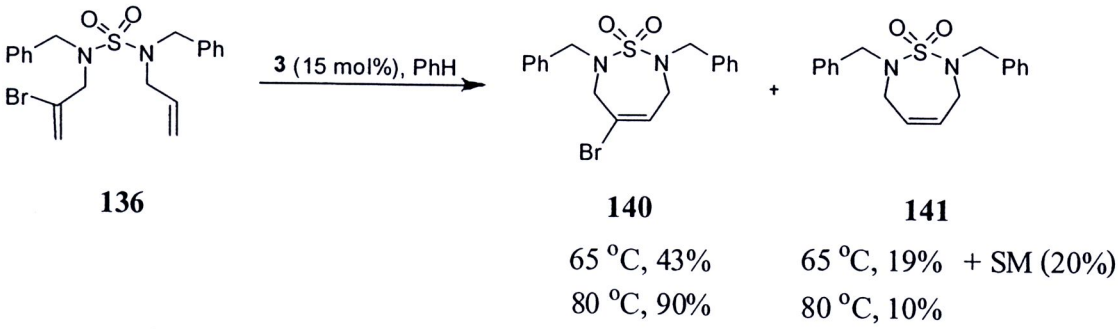
Scheme 35 Synthesis of Sulfamide Precursors (Method 1)

Therefore, the developed pathway in order to improve the overall yield for making sulfamide precursor **136** was carried out. Sulfamide **132** was treated with K_2CO_3 in CH_3CN and subsequence treatment with benzyl bromide to give the sulfamide **137** in 95% yield. The free amine was then coupled with the commercially available 2,3-dibromopropene using *t*-BuOK as a base to provide the desired sulfamide **138** in almost quantitative. After deprotection of the Boc- group and subsequent alkylation of sulfamide **139** with allyl bromide and *t*-BuOK in THF produced the sulfamide precursor **136** in excellent yield.



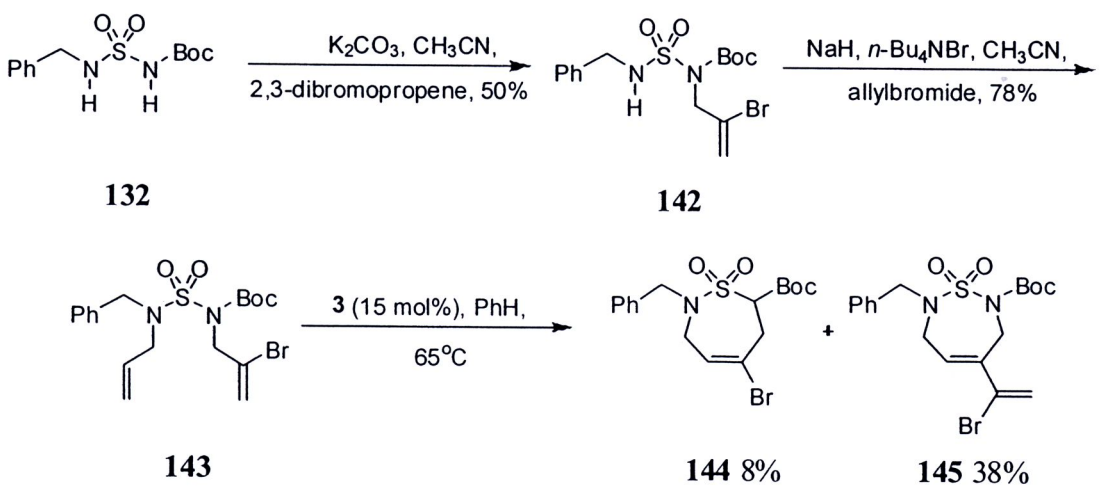
Scheme 36 Synthesis of Sulfamide Precursors (Method 2)

We were pleased to find that the RCM reactions of sulfamide **136** proceeded successfully in benzene using 15 mol% of the second generation Grubbs catalyst **3** adding in portion. It was found that the use of temperature at 65 °C for RCM reaction gave the desired 7-membered ring RCM product **140** with some **141**, but a substantial amount of starting material remained. However, at 80 °C, metathesis reaction proceeded smoothly to afford the cyclic sulfamide **140** in excellent yield (90%) as a major product and compound **141** (10%) as a minor product.



Scheme 37 Synthesis of Cyclic Sulfamide Containing Vinyl Bromide **140**

Mono-alkylation of sulfamide **132** was carried out by treatment with K_2CO_3 in CH_3CN followed by treatment with 2,3-dibromopropene to give sulfamide **142**. The free amine was then coupled with commercially available allyl bromide using *t*-BuOK as a base to fairly provide the desired sulfamide **143**. RCM was carried out on the Boc-protected sulfamide **143** which cyclized in refluxing benzene with 15 mol% ruthenium complex **3** to give the desired product **144** (8%) and unexpected product **145** (38%).



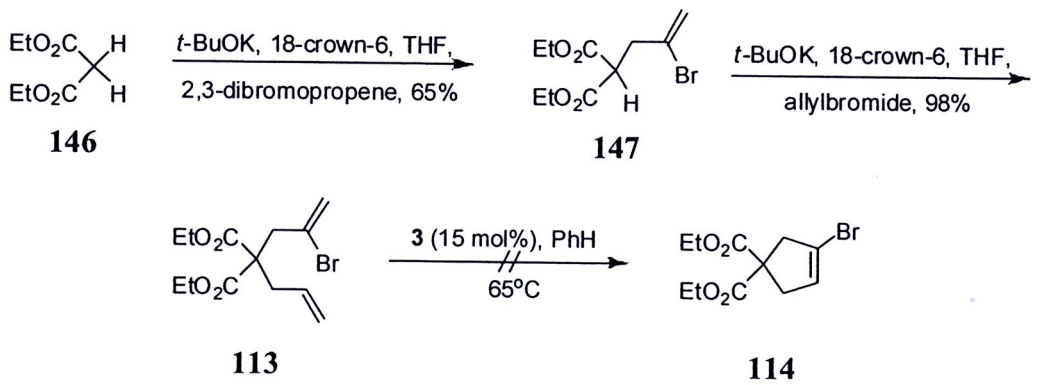
Scheme 38 Synthesis of Cyclic Sulfamide Containing Vinyl Bromide **144**

3. Synthesis of Carbocyclic-Linked Vinyl Bromides

3.1 Synthesis of 5-Membered Carbocyclic Vinyl Bromide

It was of interest to investigate whether this methodology could be applied to other classes of compounds. Carbocyclic precursor **147** was easily obtained via mono-alkylation of diethylmalonate with *t*-BuOK in THF followed by treatment with 2,3-dibromopropene. The free proton was then alkylation with allyl bromide in the presence of *t*-BuOK and 18-crown-6 to provide the

desired precursor **113** in excellent yield. The RCM reaction conditions of precursor **113** using 15 mol% of Grubbs catalyst **3** in portion under refluxing in benzene for 18 hours none of the require product **114** was observed and the starting material was recovered.

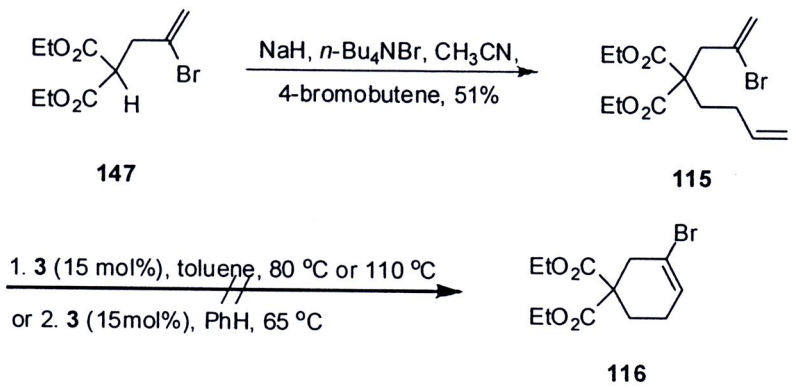


Scheme 39 Attemped Synthesis of 5-Membered Ring Carbocyclic Containing Vinyl Bromide

3.2 Synthesis of 6-Membered Carbocyclic Vinyl Bromide

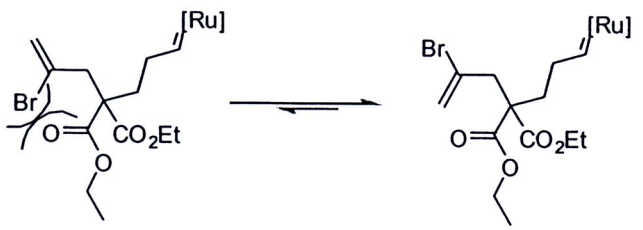
Alkylation of the monoalkylation product **147** was carried out by treatment with NaH in CH_3CN and subsequent treatment with 4-bromobutene to give carbocyclic precursor **115**. The first attempted RCM reaction of precursor **115** was carried out by using 15 mol% of Grubbs catalyst **3** at concentration of 0.05 M heating at 80 °C in toluene. However, only some decomposed starting material was observed. The second attempt, decreasing the concentration of substrate (0.01 M) and heating at 80 °C in toluene also did not give the expected cyclization. However, even heating up to 110 °C none of cyclized product was observed and again some decomposed starting material

was obtained. The final attempted RCM reaction conditions using 15 mol% of Grubbs catalyst **3** under refluxing in benzene for 18 hours at concentration of substrate (0.01 M) none of the cyclized product was observed, but only starting material was recovered.



Scheme 40 Attemped Synthesis of 6-Membered Ring Carbocyclic ContainingVinyl Bromide

The failure of the RCM of vinyl bromo olefins in order to make 6-membered ring systems may probably due to the lower reactivity of the bromo-olefin double bond together with a steric hindrance between bromine atom and carbonyl group of the ester which can lead to the formation of the intermediate **115**.

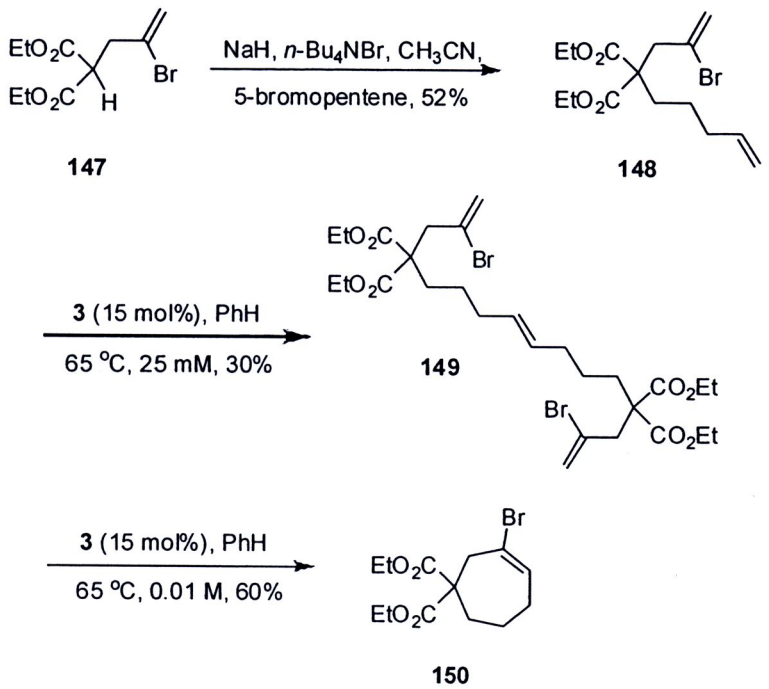


115

Scheme 41 Steric Hindrance Between Bromine Atom and Carbonyl Group of the Ester Effect

3.3 Synthesis of 7-Membered Carbocyclic Vinyl Bromide

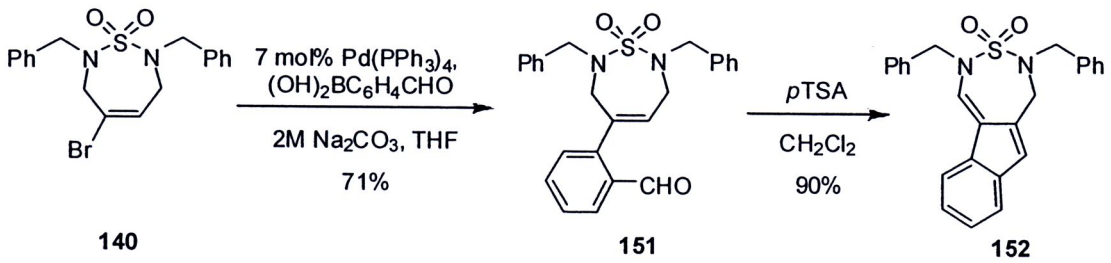
Finally, the alkylation of monobrominated product **147** with 5-bromopentene under basic conditions gave carbocyclic precursor **148** in moderate yield. The first exposure of precursor **148** to RCM condition using 15 mol% of Grubbs catalyst **3** at substrate concentration of 25 mM at 65 °C in benzene for 18 hours produced cross product **149** in 30% yield. The second trial, dilution of the reaction at substrate concentration of 0.01 M under heating at 65 °C in benzene afforded the cyclized product **150** in good yield (60%).



Scheme 42 Synthesis of 7-Membered Ring Carbocyclic Containing Vinyl Bromide

Synthetic Application of Cyclic Vinyl Bromides

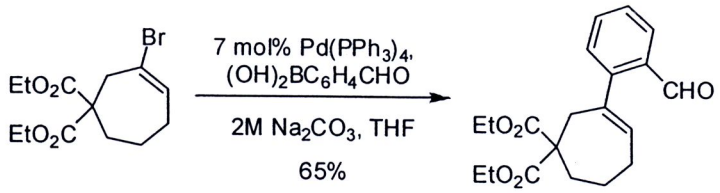
The metathesis product **140** can be useful for the subsequent synthetic transformations. An example of Suzuki cross coupling reaction was carried out by treatment of the cyclized product **140** with aq. Na_2CO_3 and 2-formyl phenyl boronic acid in the presence of $Pd(PPh_3)_4$ as a catalyst to provide the coupled product **151** in good yield. Treatment of the aldehyde **151** with *p*TSA furnished tricyclic compound **152** in excellent yield.



140 151 152

Scheme 43 Synthetic Application of Cyclic Sulfamide Containing Vinyl Bromide

In addition, the vinyl bromide moiety of the metathesis products **150** can undergo Suzuki cross coupling reaction by treatment with aq. Na_2CO_3 and 2-formyl phenyl boronic acid in the presence of $Pd(PPh_3)_4$ as a catalyst to produce the coupled product **153** in good yield.



150 153

Scheme 44 Synthesis of Carbocyclic Containing Vinyl Bromide