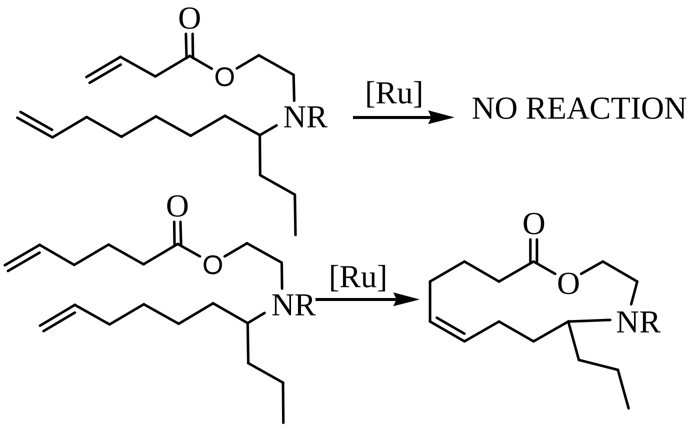
1. INTRODUCTION

This dissertation is concerned with the formation of benzo-fused heterocycles by ring closing metathesis (RCM). In this introductory chapter, the background to the research is presented in the following order. Firstly, the topic of olefin metathesis is introduced, with emphasis on RCM. Then follows a description of various catalysts used for metathesis especially ruthenium-containing catalysts. Also important for this dissertation is the use of catalysts for the positional isomerisation of olefins, and some relevant information is presented. The chapter then describes some reported syntheses of 6-, 7-, 8- and 9-membered benzo-fused heterocycles before going to survey syntheses of these systems by RCM in the laboratories at this University. Finally, the specific aims of this project are presented.

1.1 OLEFIN METATHESIS

The origin of the word metathesis is thought to have come from the phrase “move out of my sun” spoken by Diogenes to Alexander the great.[1] Metathesis thus means moving from one place to another. The metathesis reaction of olefins was discovered during the early studies on the attempted polymerization of olefins by the Ziegler process. A number of early patents described the catalysis of olefin polymerization and among these documents was a report by Eleuterio in 1960 describing the formation of carbon chains with double bonds, *i.e*. unsaturated polymers.[2] These studies on the attempted polymerization of olefins using the Ziegler methods employed a first generation metathesis catalyst, which usually consisted of a mixture comprising a transition metal halide and a main group alkylating agent, *e.g*. $MoCl_5/Et_3Al$; $WCl_6/EtAlCl_2/EtOH$.[3] Olefin metathesis was found to allow the exchange of substituents between different olefins *i.e*. a transalkylidenation. This reaction was first used industrially in petroleum reformation for the synthesis of higher olefins, the so-called shell higher olefin process (SHOP), with nickel catalyst under pressure and high temperatures.[2] RCM on the other hand is a flexible technique used for the synthesis of cyclic olefins and it has witnessed an explosive growth in application in the last decade.[4] It has been shown to be a versatile method for the construction of small and medium size ring systems.[5]

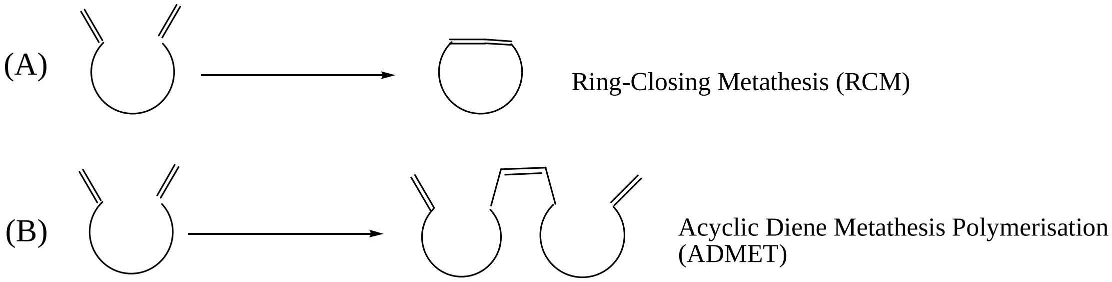
Olefin metathesis is thus a unique carbon skeleton redistribution in which unsaturated carbon-carbon bonds are rearranged in the presence of a metal carbene complex.[6,7] With the advent of efficient catalysts, this reaction has emerged as a powerful tool for the formation of carbon-carbon bonds in chemistry. Of particular significance, this type of metathesis utilizes no additional reagent beyond a catalytic amount of metal carbene and in most cases releases only a volatile olefin.[8] Olefin metathesis is thus a popular and useful reaction. In the presence of certain transition-metal compounds, including various metal carbenes, olefins exchange the groups around the double bonds, resulting in several outcomes such as straight swapping of groups between two acyclic olefins (cross-metathesis-CM), closure of large rings (ring-closing metathesis-RCM), formation of dienes from acyclic and cyclic olefins (ring-opening metathesis-ROM), polymerization of cyclic olefins (ring-opening metathesis polymerization-ROMP) and polymerization of acyclic dienes (acyclic diene metathesis polymerization-ADMET).[9] The stereochemical outcome of RCM can presently not be accurately predicted for some ring sizes. Olefin metathesis is catalytic not stoichiometric, it is reversible, it is applicable to small molecules and there is a high level of chemo-, regio-, and stereoselectivity. Minimal substrate protection is required and it is applicable to diversity-oriented synthesis. Olefins which are used in commercial olefin metathesis are usually cheap and available in bulk quantities. Functional groups play an important role in olefin metathesis; they can promote the reaction by providing conformational bias *i.e.* bringing the “hands” together. An example of this is found in the work of Fürstner and Langemann, as shown in Scheme 1.[10]

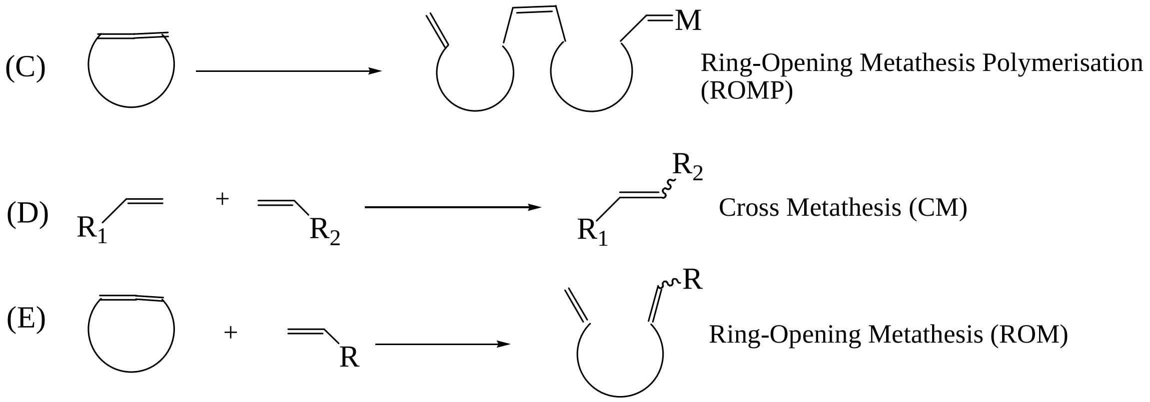


SCHEME 1

1.1.1 THE DIFFERENT TYPES OF OLEFIN METATHESIS.

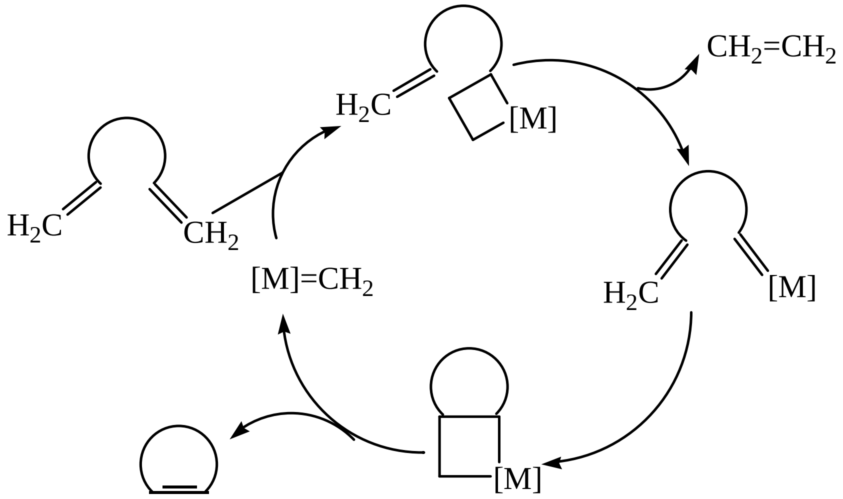
The use of metathesis in organic synthesis has been directly correlated to improvement in metal-carbene catalysts. The chemists mostly responsible for developing such catalysts have been chemistry professors Robert H. Grubbs, Yves Chauvin and Richard R. Schrock who shared a Nobel Prize in chemistry 2005 for the development of the metathesis reaction in organic synthesis.[9] Olefin metathesis can be utilized in the following types of reactions shown below (Scheme 2).





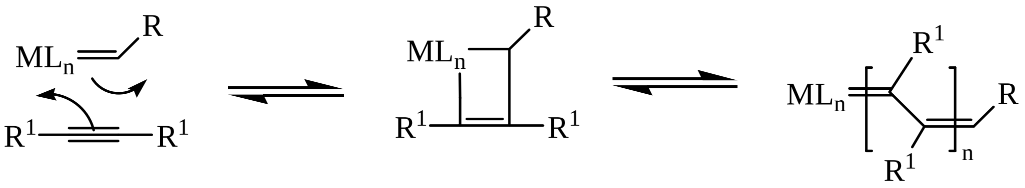
SCHEME 2: Different types of metathesis.

METATHESIS TYPE A: RCM. This type of metathesis is used for the synthesis of medium or large sized rings from acyclic diene precursors.[8] It is the reverse of a ring-opening metathesis reaction. Ring closing metathesis and ring opening metathesis processes involve equilibra. There is a limitation in the use of metathesis *i.e.* it cannot be used to form highly-strained rings but it is entropically driven because a molecule is released. The RCM is driven by loss of ethylene and if thermodynamics of the closure reaction are unfavorable, polymerization of the substrate can occur.[8,11-12] Below is the proposed catalytic cycle of RCM (Scheme 3).



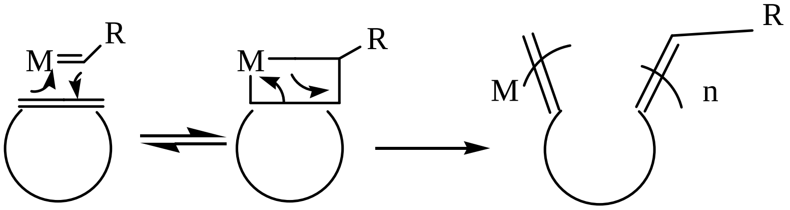
SCHEME 3

METATHESIS TYPE B: ADMET. This has been pioneered by Wagener[13] and Boncella[14] using alpha-omega dienes to produce polymers. The reaction is driven by the removal of ethylene from the system, which can be accomplished with a nitrogen purge.[15] The reverse of this reaction has been studied as a possible means of recycling automobile tyres. An example shown (Scheme 4) is in the polymerization of acetylene. When acetylene is reacted with an alkylidene, a [2+2] cycloaddition occurs resulting in a metallacyclobutene rather than metallocyclobutane. If this metallacycle opens in a productive fashion, the result is a growing polymer chain (Scheme 4).[15] In ADMET reactions, self dimerization reaction of the more valuable alkenes may be minimized by the use of an excess of the more readily available alkene.[8, 11-12]



SCHEME 4

METATHESIS TYPE C: ROMP. This type is thermodynamically favored for strained ring systems such as 3-, 4-, 8- and larger membered compounds.[8] 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.[8,15] When bridging groups are present *e.g.* with bicyclic olefins, the ΔG of polymerization is typically more negative as a result of increased strain energy in the monomers.[8, 11-12] The mechanism of the ROMP reaction involves an alkylidene catalyst and is identical to the mechanism of olefin metathesis with two important modifications. First, as the reaction involves a cyclic olefin, the new olefin that is generated remains unattached to the catalyst as part of a growing polymer chain with a generic strained cyclic olefin. The second difference is that the driving force for ROMP is the relief of the ring strain and the second step, shown below, is irreversible (Scheme 5).[15]



SCHEME 5

The catalysts used for ROMP are the same used in RCM. However, if the catalyst is too active, it can metathesize the unstrained olefinic bonds in the growing polymer chain (a process called ‘backbiting’), thereby reducing the molecular weight and increasing the molecular weight distribution.[16]

METATHESIS TYPE D: CM. This reaction is very versatile in its use and the scrambling of the mutual alkylidene fragments between two olefins is promoted by the metal carbene complexes.[8] It can be used to shorten unsaturated fatty acid esters or to extend them.[1,9] The CM reaction has various problems as such as low product selectivity, the fact that mixtures of homodimers and copolymers can be formed, poor selectivity in the produced olefins and that there is no large driving force such as in ROMP or RCM. At present there is a lack of a model that satisfactorily predicts *E*/*Z* selectivity.[18]

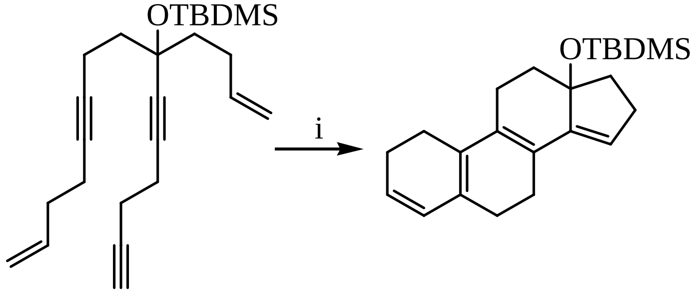
METATHESIS TYPE E: ROM. The driving force for this type of reaction is the relief of strained rings *i.e.* it is thermodynamically favored for strained ring systems. In the absence of excess of a second reaction partner, polymerization occurs (ROMP). The ROM reaction is similar to the ROMP reactions but the only difference is that in the ROM reactions, double bonds of the monomers are not preserved in the final product whereas; in ROMP reactions, the double bonds of the monomers are present both in the monomer and final polymer.[19] Strained rings may be opened by a ruthenium carbene-catalyzed reaction as in Scheme 5.

1.1.2 SOME APPLICATIONS OF RING-CLOSING METATHESIS.

A few selected pharmaceutical and material applications of the Grubbs catalyst will be described in the following section.

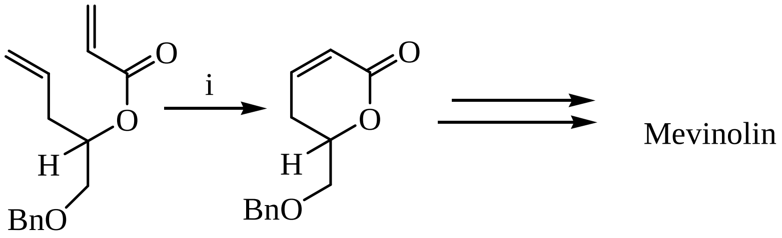
RING CLOSING METATHESIS IN PHARMACEUTICAL APPLICATIONS

The application of olefin metathesis in the manufacture of potential pharmaceutical intermediates is almost boundless. Most striking, RCM enables the efficient production of complex ring systems from simple acyclic precursors using Grubbs first generation catalyst, which will be described further in Section 1.4 (Scheme 6).[20] RCM has been utilized in a key step of the total synthesis of Mevinolin (Scheme 7),[21] a compound shown to reduce serum cholesterol levels in animals as well as in humans and in the synthesis of Ambruticin, an orally active antifungal agent (Scheme 8).[22] A further application is in the synthesis of alpha substituted amino acids.[17]

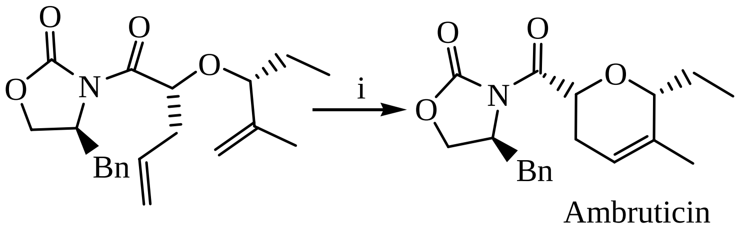


SCHEME 6

(i) 4 mol% Grubbs I, rt., 4 hrs, 70%



SCHEME 7(i) 10 mol% Grubbs I, 40°C, 15 hrs, 91%.



SCHEME 8

(i) 0.05 equiv. Grubbs I, 40°C, 3 hrs, 98%.

RING CLOSING METATHESIS IN MATERIALS APPLICATIONS

RCM has shown remarkable utility in the production of fine chemicals on an industrial scale *e.g.* the SHOP process has been extensively used in the field of material science to produce polymers with unique properties. One such example is the ROMP of dicyclopentadiene (DCPD) to give resins. The polymerization is highly exothermic because of relief of strain energy, and it can be initiated by transition-metal/alkylidene complexes. These resins exhibit remarkable impact and corrosion resistance, much tensile strength, impact, or HDT up to 200°C versus the current 120-130°C.[23] In Japan, Grubbs I ruthenium catalyst has been used for the manufacture of materials used in making shower stalls and basins. DCPD polymers are used for body parts for trucks, agricultural earth moving equipment[23] and microelectronics.[17] RCM combined with CM has also been used to produce functionalized oligomers, commonly known as telechelic materials. These materials are normally difficult to prepare in high yield and are finding growing application in the production of multi-block polymers such as styrene-butadiene-styrene and thermoplastic polyurethanes.[24,25]

1.2 CATALYSTS FOR OLEFIN METATHESIS

1.2.1 SURVEY OF CATALYSTS.

The first metathesis catalysts used consisted of Ziegler-type mixtures comprising a transition metal halide and a main group alkylating agent, *e.g.* $MoCl_5/Et_3Al$,

$WCl/EtAlCl_2/EtOH$. A significant evolution in the development of olefin metathesis catalysts involved the use of molybdenum and ruthenium-based catalysts; for example catalysts **1**, **2**, **3**, **4**, and **5**. The synthetic utility of the ruthenium-based catalysts is derived from their ability to orchestrate additional metathetic transformations including RCM, ROMP, ROM and ADMET.[9] Below are various types of carbene complexes of molybdenum (compound **1**) and ruthenium (compound **2**, **3**, **4** and **5**) that have been discovered as efficient precatalysts for olefin metathesis (Figure 1):

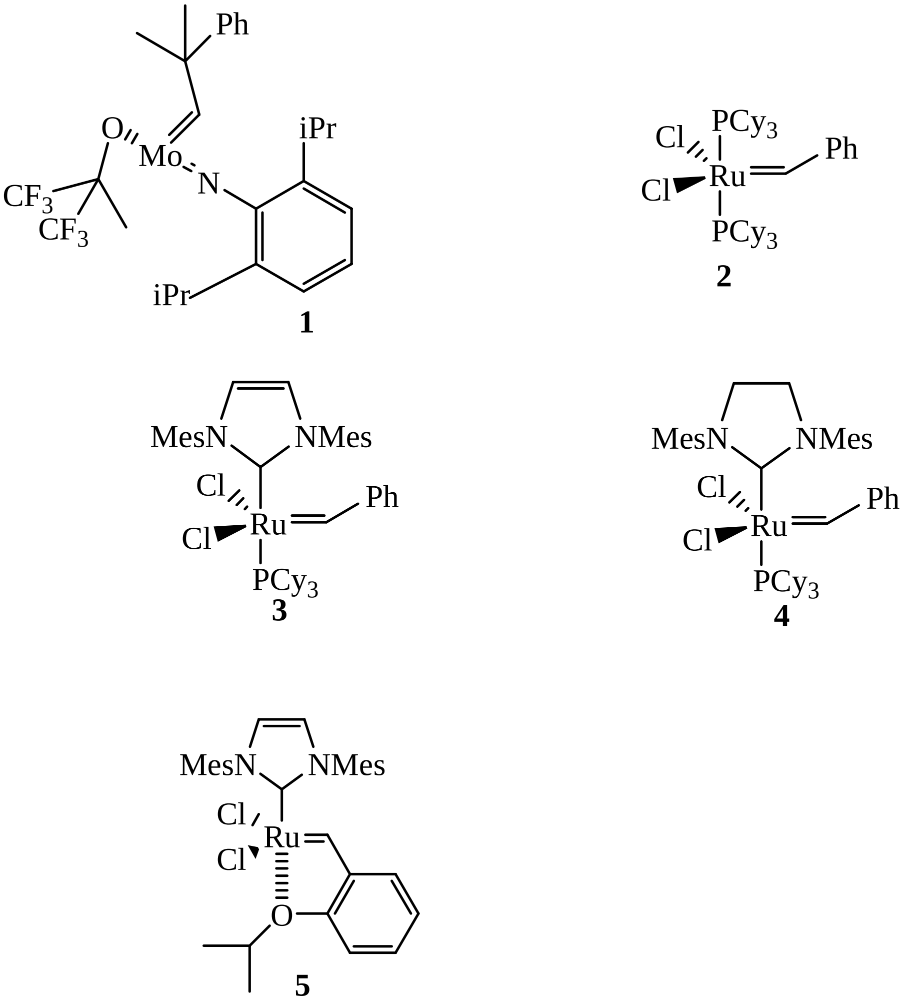
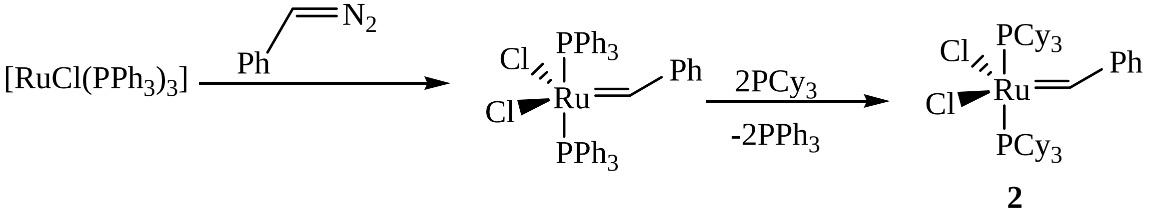


FIGURE 1.

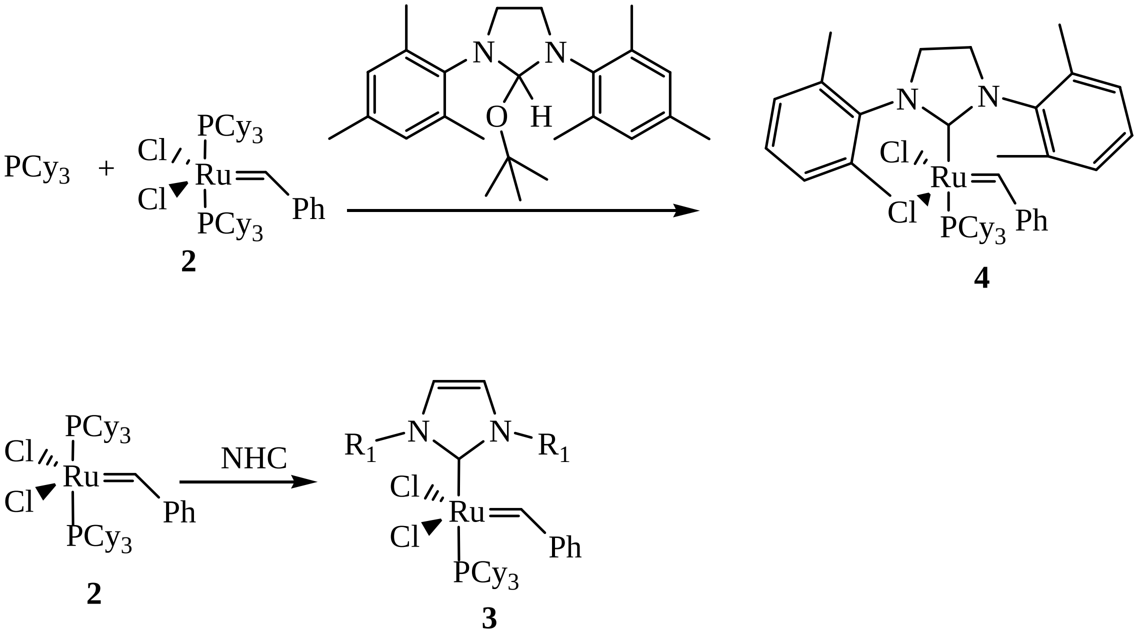
The Schrock molybdenum complex **1** has a high reactivity towards a broad range of substrates with many steric or electronic variations. In addition, the alkoxides in the molybdenum system can be readily altered to adjust their activities.[8] A critical drawback of this molybdenum-based carbene complex is 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.[8] The Grubbs catalyst **2** is a first generation ruthenium-based catalyst, and is commercially available. When compared to catalyst **1**, it is tolerant to a wide range of functionality under normal reaction conditions, although it is not as reactive as the molybdenum catalyst. In addition it is relatively intolerant of steric effects. The complex **2** can be readily prepared using phenyldiazomethane (Scheme 9).



2

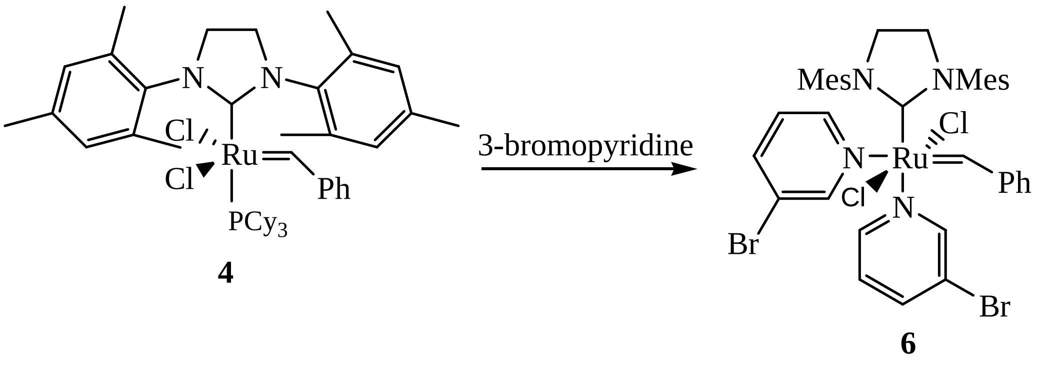
SCHEME 9

Complexes **3, 4** and **5** are examples of second generation ruthenium-based catalysts. They contain *N*-heterocyclic carbene (NHC) ligands that do not come off easily. In addition, the NHC ligands are bulky, kinetically inert and electron rich. In the original Grubbs catalysts **2**, PCy_3 dissociation occurred readily, but recombination was competitive with substrate binding whereas in the second generation catalyst **3**, PCy_3 dissociation is relatively inefficient. However, once the phosphine leaves, coordination of the olefin is very facile.[26] The second generation catalysts also exhibit high reactivity in variety of ROMP, CM and RCM reactions under mild conditions. In addition, the ruthenium-based systems have a remarkable tolerance towards many different functional groups.[8] Catalytic activity is not reduced significantly in the presence of air, moisture or minor impurities in solvents.[8] In addition, they can be conveniently stored in air for several weeks without severe decomposition. Ruthenium NHC systems often exhibit relatively lower propagation rates, especially with sterically bulky substrates, when compared to the molybdenum catalyst. To their advantage, the ruthenium complexes are commercially available and do not require Lewis acid co-catalysts or promoters. The second generation catalysts are generally prepared from the first generation catalysts using the addition of the NHC ligands as shown in (Scheme 10).



SCHEME 10

The so-called “third generation” catalyst **6** is the fastest metathetic initiator to date and it is even effective in the CM of acrylonitrile which has been known to be problematic even for the active second generation catalysts. It can be prepared from the second generation catalyst using 3-bromopyridine as shown in the scheme below (Scheme 11).[27]



Mes = 2,4,6 trimethylphenyl

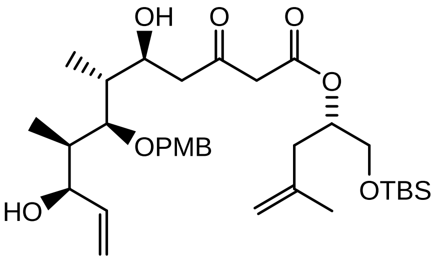
SCHEME 11

The Hoveyda-Grubbs catalyst **5** is an example of a second generation catalyst. It shows efficiencies similar to those of the Grubbs II catalyst **3** and **4** but with different substrate specificity. It is recycleable and can catalyze RCM, ROMP and CM with highly electron-deficient substrates.[16] It was designed to be a more active and robust version of Grubb II catalyst **2**. The *N*-heterocyclic carbene significantly increases the lifetime of the active catalyst while the chelating alkylidene increases the activity of the catalyst. Initiation is slow and the ruthenium fragments at the end of the reaction.[28]

1.2.2 NON-METATHETIC BEHAVIOUR OF RUTHENIUM-BASED CATALYSTS

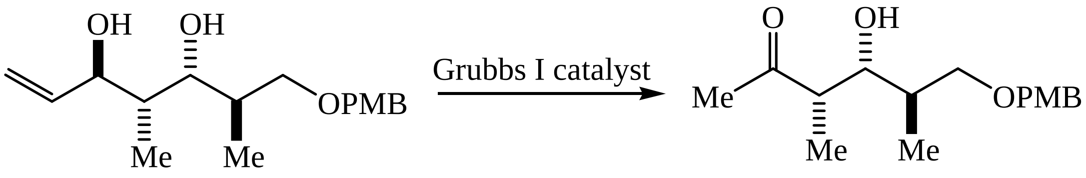
A number of non-metathetic properties of Grubbs carbene-containing catalysts have been noted. These include isomerisations,[30] hydrogenation/oxidations, fragmentations *etc*. A number of these have been listed in the section below and have been summarized from a recent review by Almendros.[29]

1. DEGRADATION OF ALLYLIC ALCOHOLS:- A degradation of allylic alcohol that required stoichiometric amount of ruthenium catalyst was observed by Hoye and Zhao in the synthesis of Callipeltoside A, **7** (Figure 2). The authors observed that the RCM of **7** did not occur in the presence of the first generation catalyst but that the carbene was consumed instead and that the allylic alcohol was degraded to a methyl ketone **8** (Scheme 12). [31,32]



7

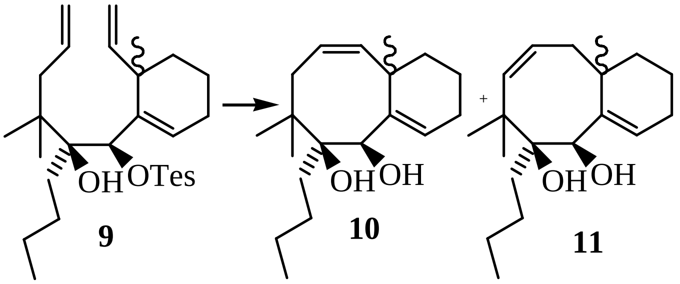
FIGURE 2



8

SCHEME 12

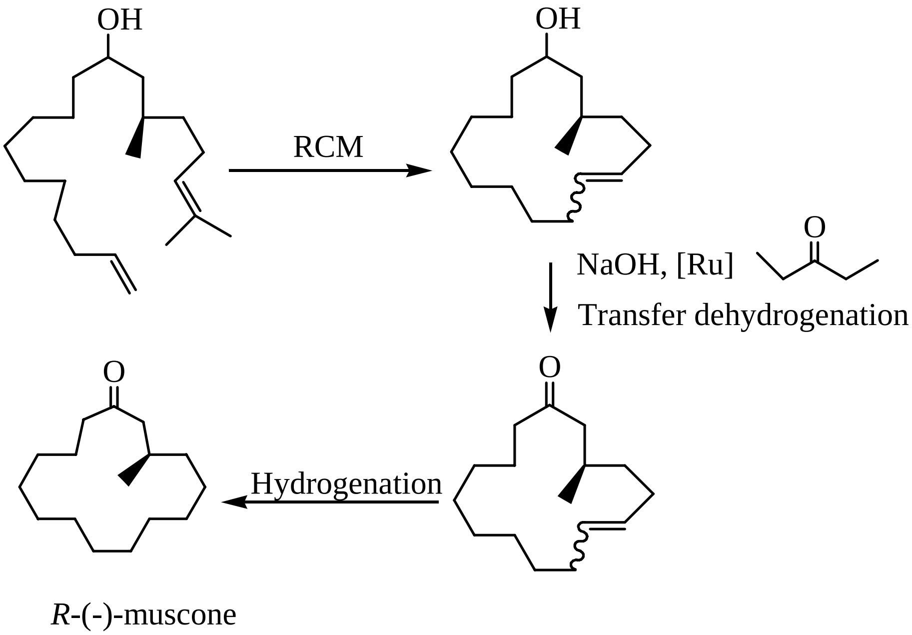
2. ISOMERISATION:- Isomerisations has been noted to interfer with RCM. In a synthetic example, when Prunnet *et al*. were attempting to synthesize taxol derivatives by the RCM of **9**, two cyclized products were isolated. There were the expected cyclooctane **10** and the unexpected isomer **11** which is a result of isomerisation after RCM (Scheme 13).[33, 34]



9 **10** **11**

SCHEME 13

3. TRANSFER HYDROGENATION/DEHYDROGENATION:- The ruthenium complex [RuCl$_2$(PPh$_3$)$_3$] was observed by Grubbs and co-workers to do catalytic transfer and dehydrogenative oxidations. This observation was put to use in a one-pot synthesis of (*R*)-(-)-muscone (Scheme 14).[35]



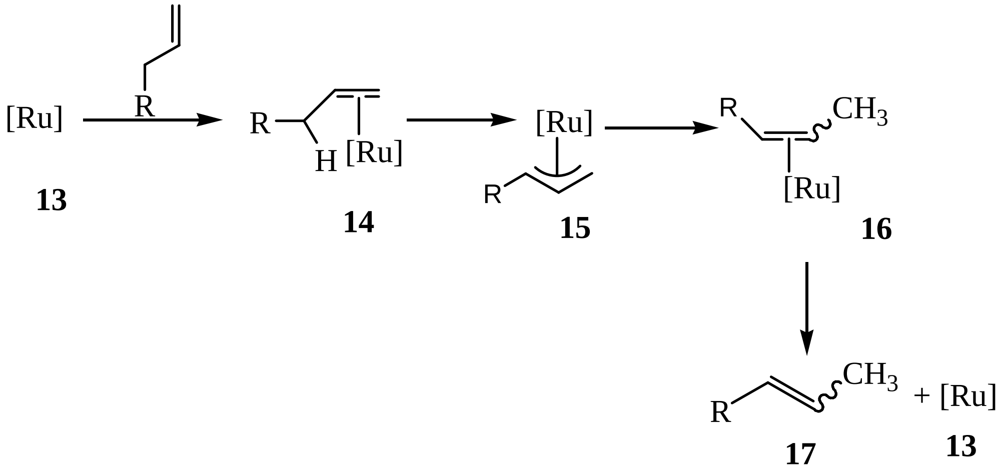
SCHEME 14

1.3 METAL-MEDIATED OLEFIN ISOMERISATION

The ruthenium catalyst **12** has gained popularity in that it can be used for the isomerisation of terminal alkenes.[36] In an allyl isomerisation reaction, the double bond migrates to the more thermodynamically favoured position. One of the proposed mechanisms for allyl isomerisation is given below (Scheme 15).[8]

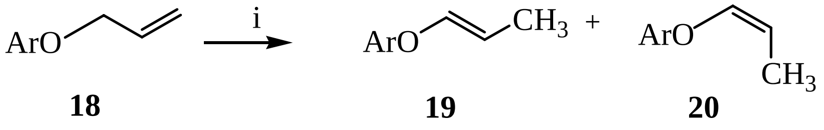
$[RuClH(CO)(PPh_3)_3]$

12



SCHEME 15

The intermediate **15** is assumed to result from the migration of the hydride from the allylic position of the alkene substrate to the metal center. Reductive elimination then gives **16**, from which the substrate dissociates to regenerate **17** and the catalytically active species **13**. The ruthenium isomerisation catalyst **12** has been used extensively by Krompiec and co-workers and it was used in the isomerisation of allyl-aryl ethers. Propenyl ethers **19** and **20** were prepared from the allyl ether **18** using the ruthenium catalyst **12**, with benzene at 50-60°C, for 2-16 hrs under an argon atmosphere (Scheme 16).[37]

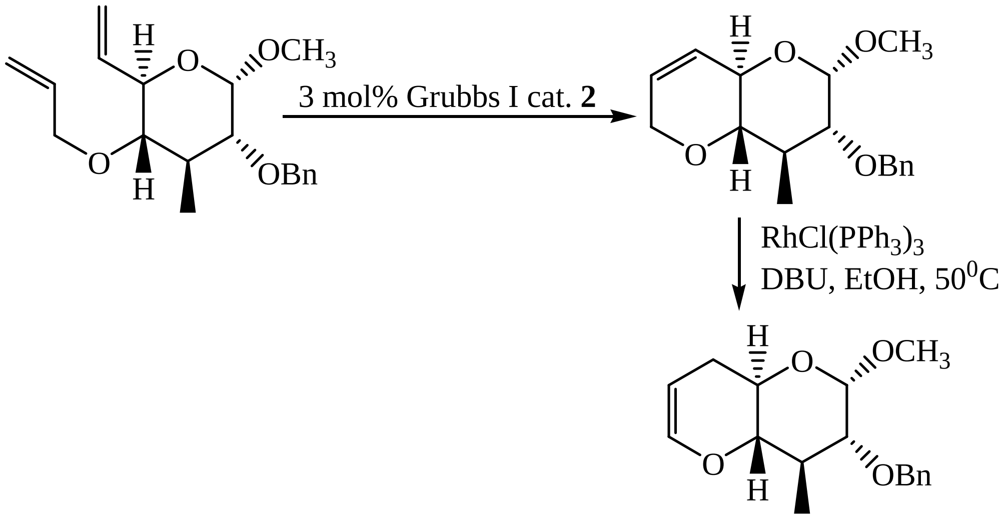


SCHEME 16

(i) Ruthenium catalyst **12**, benzene, 50-60°C, 2-16 hrs.

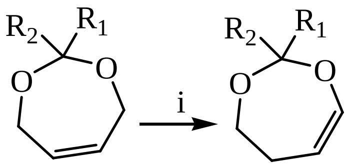
Where Ar = X-C_6H_4, X = H (94%); *o*, *p*-Cl (90, 95%)

The selective isomerisation of one or both double bonds in a metathesis substrate can sometime facilitate the synthesis of the precursor and significantly enhance the flexibility of a synthetic strategy by making various chain and ring sizes accessible from the same set of starting materials.[38] This principle has been exploited in the synthesis of benzo-fused heterocycles and some examples are included in this dissertation. Isomerisations followed by RCM have also been developed. An example where this method has been applied is in the synthesis of trans-fused polyethers by van Boom *et al.* in which the internal alkene formed after metathesis was isomerized by a catalytic amount of $RhCl(PPh_3)_3$ (Scheme 17).[38]



SCHEME 17

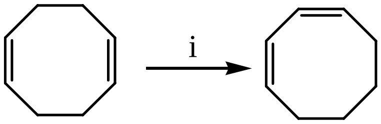
Olefinic compounds are isomerised under a great variety of conditions; catalysts such as acids, bases and organometallic complexes are effective for promoting the migration of double bonds.[39] Applications of the double bond migration catalyzed by transition metal complexes to organic ligands have been successfully performed by several investigators.[40-42] Pd and its complexes have served as catalysts for isomerisation of alkenes and alkynes via a series of hydropalladation-dehydropalladation reactions, *i.e.* a 1,2-*H* shift and some examples are described briefly below.[43] Suzuki and co-workers used ruthenium hydride complexes to synthesize 4,7-dihydro-1,3-dioxepine (Scheme 18).[44]



SCHEME 18

(i) Ruthenium hydride, 100°C, 1 hr, quantitative yield.

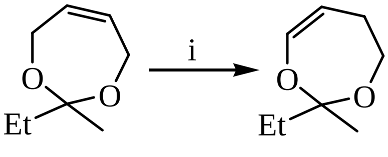
In 1968, an example of a Pd-catalyzed highly regioselective isomerisation reaction was reported. 1,3-Cyclooctadiene was synthesized by the isomerisation of 1,5-cyclooctadiene and this represented an isolated investigation of a class of isomerisation reactions (Scheme 19).[45]



SCHEME 19

(i) $Cl_2Pd(PhCN)_2$ catalyst, 140-145°C, 1.5 hr, 99.5%.

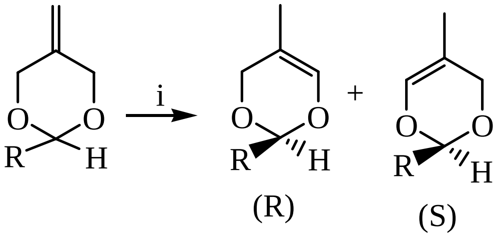
Malanga *et al*. performed an isomerisation of cyclic but-2-ene-1,4-diol derivatives to but-1-ene-1,4-diol derivatives which was mediated by nickel complexes (Scheme 20).[46]



SCHEME 20

(i) $Ni(dppe)Cl_2$, *i*-PrMgBr, Me_3SiCl, 100%.

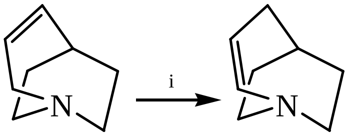
Frauenrath *et al.* did research on the asymmetric isomerisation of 2-substituted 5-methylene-1,3-dioxanes to 5-methyl-4*H*-1,3-dioxins which was catalyzed by ruthenium complex of ((R,R)-DIOP) under nitrogen atmosphere. These cyclic acetals are promising starting materials for macrolide antibiotics and other polyketide-derived natural products (Scheme 21).[47]



SCHEME 21

(i) $Ru_4Cl_4(DIOP)_3$, H_2, EtOH, 80°C.

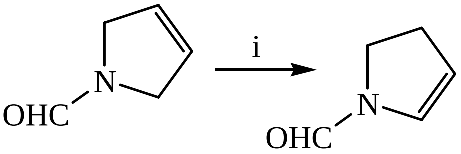
Systematic studies on the isomerisation of *N*-allylamines and imines to aliphatic enamines were carried out with iron, rhodium and ruthenium complexes as catalyst. Doering *et al*. did a study on the isomerisation of 1-azabicyclo[3.2.2]non-2-ene to orthogonal enamines catalyzed by *t*-BuOK. The enamines formation was calculated to be favored by ~4 Kcal mol^{-1}(Scheme 22).[48]



SCHEME 22

(i) $RuH(PPh_3)_3(NO)$, benzene, 80°C, 48 hrs.

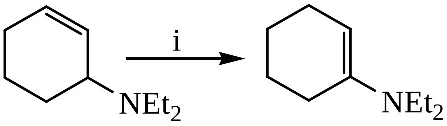
Recently, the palladium-catalyzed isomerisation of *N*-formyl-2,5-dihydropyrroles to form *N*-formyl-2,3-dihydropyrroles was reported by Sonesson *et al*. (Scheme 23).[49]



SCHEME 23

(i) $Pd(OAc)_2$, dppp, Ni(*i*-Pr)$_2$Et, CF_3COOH, 78%.

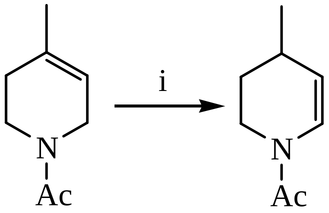
The isomerisation of allylamines were studied extensively by employing Rh-BINAP complexes as a catalyst in THF at 60°C. A cyclic allylamine, 3-diethylaminocyclohexene was isomerised selectively to its corresponding enamine. This isomerisation reaction was most effectively applicable to allylamines at the γ,γ'-positions (Scheme 24).[39]



SCHEME 24

(i) Rh-BINAP, 95%.

Lastly in this section, the isomerisation of tetrahydropyridine derivatives by the Rh-BINAP catalyst at 150°C gave the enamides (Scheme 25).[50]



SCHEME 25

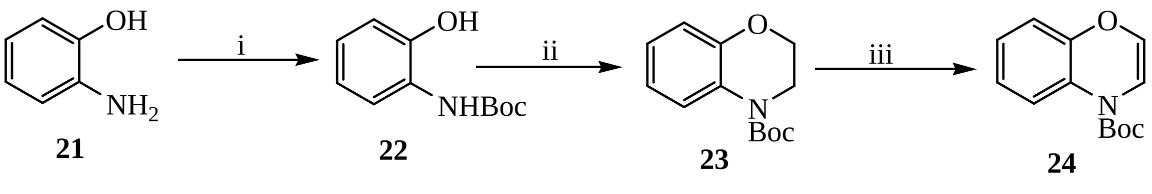
(i) [Rh((*R*)-BINAP)(cod)], 150°C, 72%.

1.4 SELECTIVE SYNTHESIS OF BENZO-FUSED HETEROCYCLIC COMPOUNDS

The following section will describe some non-metathetic approaches to 6-, 7-, 8- and 9-membered benzo-fused ring systems. Please note that this section is not exhaustive.

1.4.1 SOME REPORTED SYNTHESES OF 6- AND 7- MEMBERED BENZO-FUSED HETEROCYCLIC COMPOUNDS

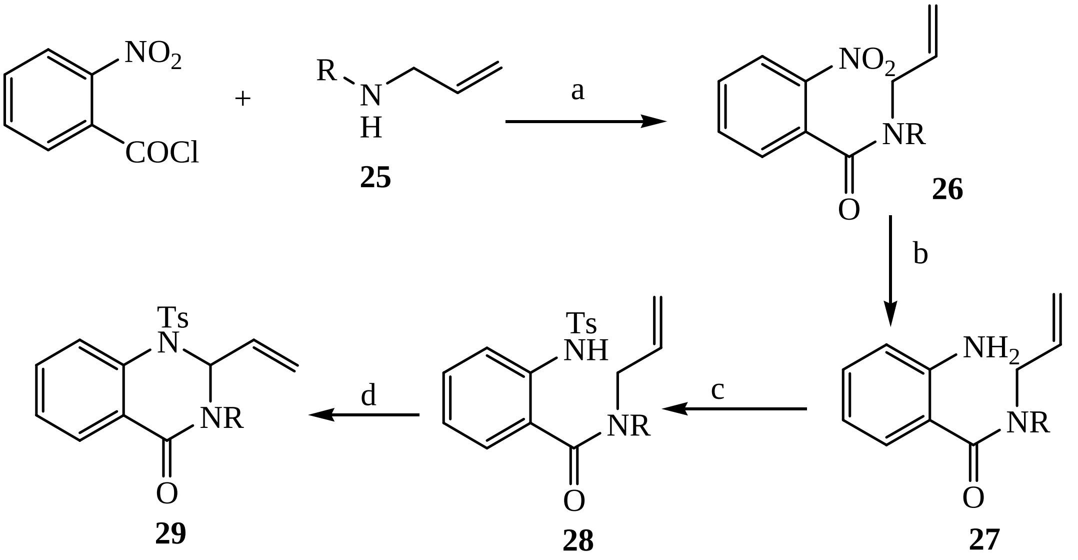
Boun *et al.* have synthesized a number of 6-membered benzo-fused heterocyclic compounds such as the 2,3 disubstituted benzoxazines **24**.[51] Benzoxazines are biologically active compounds and a large number of derivatives can be obtained from the 2,3 disubstituted benzoxazines. The first step in their synthesis involved the treatment of 2-aminophenol **21** with Boc_2O in THF at room temperature to afford the *N*-Boc phenolic compound **22** in a good yield of 96%. Compound **22** was then heated with 1,2-dibromoethane under reflux in acetone for 20 hrs, in the presence of K_2CO_3 to afford 4-(*tert*-butoxycarbonyl)-3,4-dihydro-2*H*-1,4-benzoxazine **23** in a yield of 75%. This compound was then treated with NBS and Bz_2O_2 in CCl_4 at reflux for 45 mins. The reaction was then cooled after which NaI was added with acetone and the reaction was stirred for 2 hrs at room temperature to afford the unsaturated 6-membered benzo-fused compound **24** in a yield of 86% (Scheme 26).[51]



SCHEME 26

(i) Boc_2O, THF, r.t. (ii) 1,2-dibromoethane, K_2CO_3, acetone, reflux, 18 hrs, 75%. (iii) a. NBS, Bz_2O_2, CCl_4, reflux. b. NaI, acetone, r.t., 86%.

Beccalli *et al*. used a Pd-catalyzed intramolecular cyclization approach to synthesize a 6-membered nitrogen-containing heterocyclic ring system. Nitrogen-containing compounds are biologically interesting heterocyclic derivatives. The 6-membered ring system was synthesized from commercially available allylamines **25** which were reacted with *o*-nitrobenzoyl chloride to afford *o*-nitrobenzamides **26**. Subsequent reduction of **26** with Fe/EtOH in aqueous AcOH gave aminoamides **27**. These were then tosylated to produce **28**. Pd-catalysed cyclization was performed on **28** to afford the 6-membered ring system **29** in a good yield (Scheme 27)**.** [52]

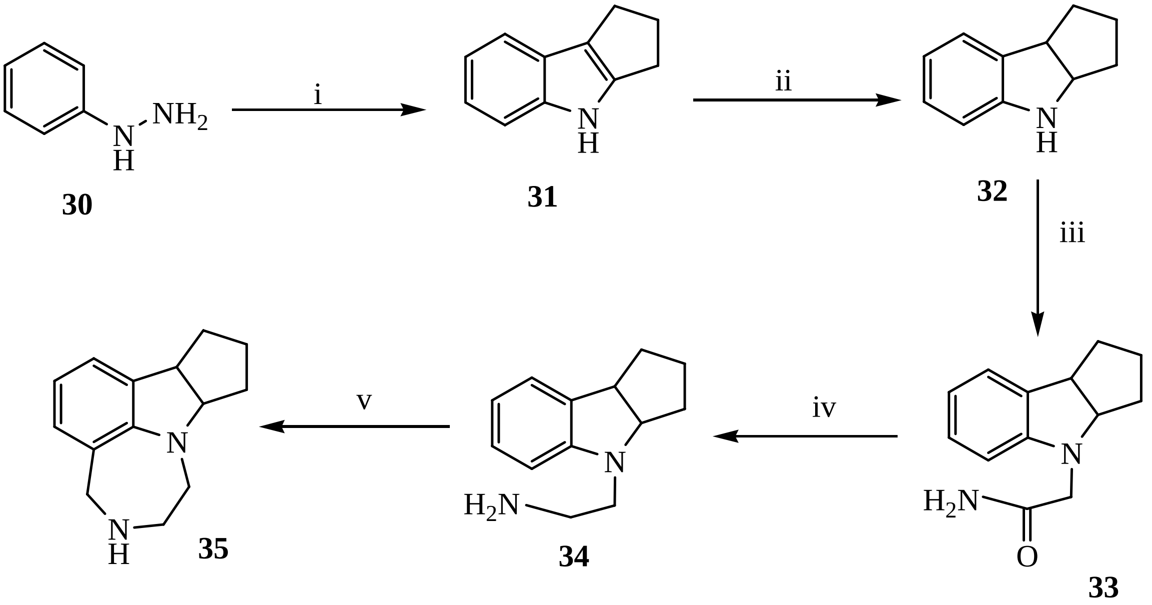


SCHEME 27

Where R = $CH_2CH=CH_2$

(a) DCM, TEA, 0°C, 2 hrs, 93%. (b) AcOH, Fe, EtOH, 50°C, 75% (c) TEA, DCM, *p*TsCl, 2 hrs, 78%. (d) DMSO, AcONa, $Pd(OAc)_2$, 96%.

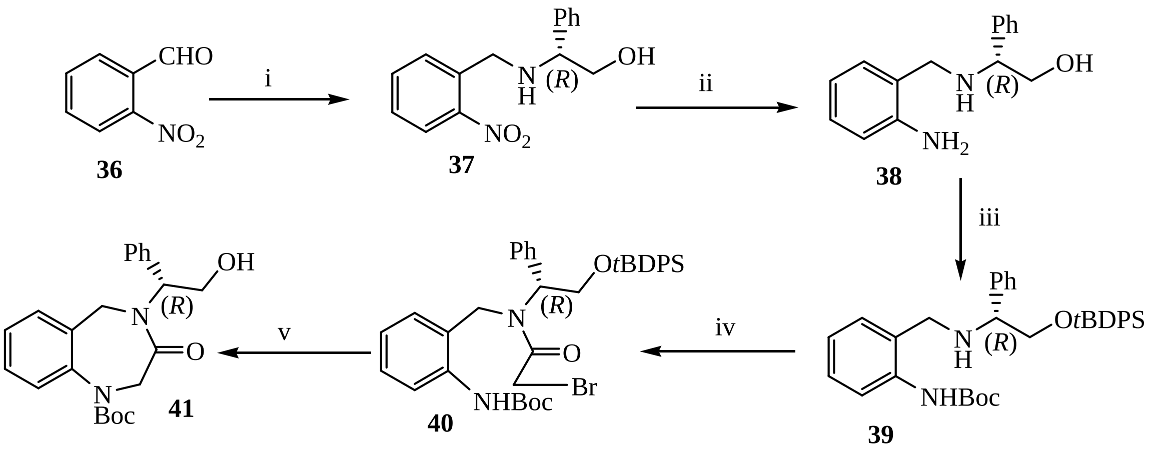
Welmaker and Sabalski synthesized the 7-membered benzo-fused ring system 1,4-benzodiazepin-3-one **35**. Benzodiazepines are a widely used class of hypnotics-anxiolytics, previously considered both safe and effective. Benzodiazepines have depressant properties and are used in the treatment of panic disorder. Due to its biological properties, Welmaker and Sabalski developed a new practical synthetic route toward the synthesis of substituted benzodiazepine **35**. The first step was a cyclization using the standard Fischer indole cyclization of **30** with cyclopentanone to afford an indole **31** which was then hydrogenated under acidic conditions to provide an indoline **32**. The indoline **32** was then coupled with 2-chloroacetamide to provide the amide **33**, which was subsequently reduced to primary amine **34**. The primary amine was then treated with formaldehyde to obtain the benzodiazepine **35** (Scheme 28).[53]



SCHEME 28

(i) Cyclopentanone, conc. H_2SO_4, H_2O. (ii) H_2, 5% Pd/C, HCl, EtOH. (iii) 2-Chloroacetamide, $EtN(i\text{-}Pr)_2$, DMF, 100°C. (iv) BH_3, THF, reflux. (v) CH_2O, TFA, EtOH, reflux.

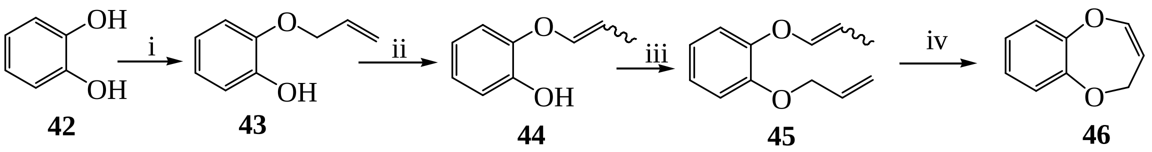
1,4-Benzodiazepin-3-one compounds have been extensively investigated due to their biological properties and their structure has been used as a molecular scaffold.[54] Several nitrogen-containing heterocyclic compounds have been identified to have antitumour, antibiotic,[55] anti-HIV,[56] antithrombotic[57] and anti-convulsant properties.[58] Cabedo *et al*. synthesized the 1,4-benzodiazepin-3-one from (*R*)-phenylglycinol and the first step was a reductive amination of the aldehyde **36**. The nitro group was then readily reduced by hydrogenation using 10% Pd/C in ethanol to afford **38**. The next step was the selective protection of the primary alcohol with *t*-BuPh$_2$SiCl and the aromatic amine with Boc$_2$O to afford **39**. The resulting amine was then treated with bromoacetyl chloride to give the *N*-acylated derivative **40**. Intramolecular cyclisation followed by silyl group deprotection was performed in a one-pot procedure to afford the 7-membered ring lactams **41** in 57% yield (Scheme 29).[54]



SCHEME 29

(i) a. (*R*)-phenylglycinol, MeOH, reflux, 3 hrs. b. NaBH$_4$, r.t., overnight. (ii) H$_2$ (1 atm)/10% Pd/C, EtOH, r.t., 18 hrs, 83%. (iii) a. *t*-BuPh$_2$SiCl, imidazole, DMF, r.t., 18 hrs, 72%. b. NaH, THF, 15 min, Boc$_2$O, r.t., 66%. (iv) ClCOCH$_2$Br, NEt$_3$, CHCl$_3$, -20°C, r.t., 71%. (v) NaH, DMF, r.t., 3 hrs, 57%.

In recent years, several research groups have reported RCM approaches to benzo-fused rings. Recently, Guillaumet and co-workers synthesized 2*H*-1,5-benzodioxepin derivatives using RCM. 2*H*-1,5-benzodioxepin ring systems constitute a common structural element in natural products and a similar feature is found in the antifungal Strobilurin G.[59] The starting material phenol **43** was synthesized by *O*-alkylation of diol **42** with allyl bromide in the presence of potassium carbonate in acetone at reflux to afford **43** in a yield of 70%. Isomerisation of **43** was carried out by treatment with *t*-BuOK in DMSO at high temperature to afford **44** as a mixture of *E* and *Z* isomers. Compound **44** was then treated with allyl bromide in the presence of potassium carbonate in acetone at reflux to afford **45** in a good yield. RCM was then done on **45** to afford product **46** in a yield of 53% (Scheme 30).[60]

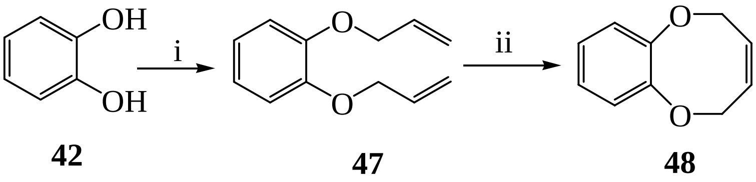


SCHEME 30

(i) Allyl bromide, K_2CO_3, acetone, reflux, 70%. (ii) *t*-BuOK, DMSO, r.t., 6 hrs, 90%. (iii) Allyl bromide, K_2CO_3, acetone, reflux, 10 hrs, 80%. (iii) Grubbs II catalyst **2**, benzene, 55°C, 53%.

1.4.2. SOME REPORTED SYNTHESES OF 8- AND 9- MEMBERED BENZO-FUSED HETEROCYCLIC COMPOUNDS BY RCM.

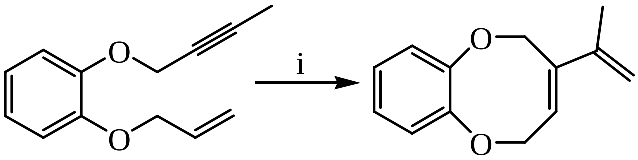
Guillaumet and co-workers have also synthesized 2,5-dihydro-1,6-benzodioxocin derivatives by RCM from a commercially available material, cathecol **42**. The precursor **42** was treated with allyl bromide in the presence of potassium carbonate in acetone at reflux to afford a diallylated compound **47**. RCM was done on the diallylated compound to afford the 8-membered ring system **48** in a yield of 60% (Scheme 31).[60]



SCHEME 31

(i) Allyl bromide, K_2CO_3, acetone, reflux, 18-20 hrs, 50%. (ii) Grubbs II catalyst **4**, benzene, 55°C, 17 hrs, 60%.

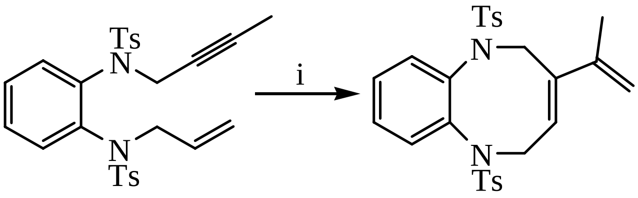
Mori and co-workers used enyne metathesis to synthesize 8- and 9-membered benzo-fused ring systems. The 8-membered benzo-fused *O*,*O*-ring was prepared from substrate **49** using Grubbs I catalyst **2** in DCM for 50 hrs to afford the 8-membered **50** in a yield of 61% (Scheme 32).[61] The 8-membered benzo-fused *N*,*N*-ring systems were prepared from substrate **51** in DCM using Grubbs I catalyst **2** for 7 hrs to afford the 8-membered benzo-fused *N*,*N*-ring **52** in a yield of 97% (Scheme 33).[61]



49 **50**

SCHEME 32

(i) DCM, Grubbs I catalyst **2**, 50 hrs, 61%.

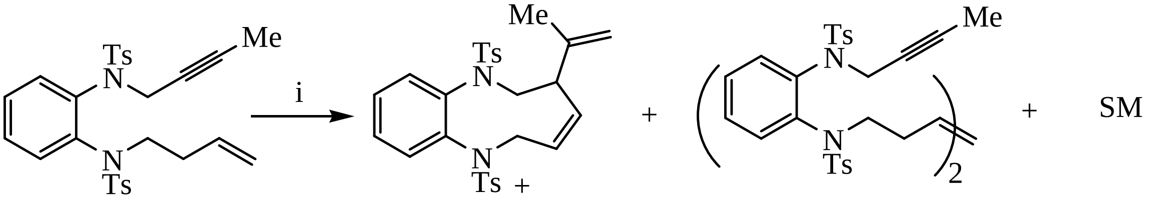


51 **52**

SCHEME 33

(i) DCM, Grubbs I catalyst **2**, 7 hrs, 97%.

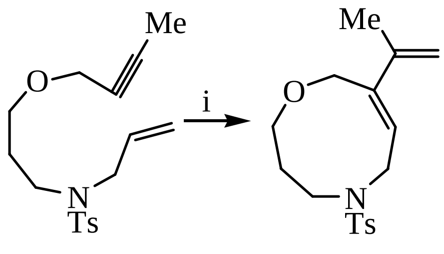
On the other hand, Mori and co-workers attempted the synthesis of 9-membered benzo-fused *N*,*N*-compounds from substrate **53** using Grubbs I catalyst **2** in DCM at room temperature for 20 hrs to afford the 9-membered benzo-fused *N*,*N*-compounds **54** in only 5% yield. A dimeric compound **55** was isolated in 22% yield, and the starting material was recovered in 62% yield (Scheme 34).[62]



53 **54** **55**

SCHEME 34 (i) Grubbs I catalyst **2**, DCM, r.t., 20 hrs, 5%.

They also attempted the synthesis of 9-membered *O*,*N*-compounds from substrate **56** using Grubbs I catalyst **2** in DCM at reflux for 24 hrs to afford the cyclized compound **57** in 74% yield as a single isomer (Scheme 35).[62]



56 **57**

SCHEME 35

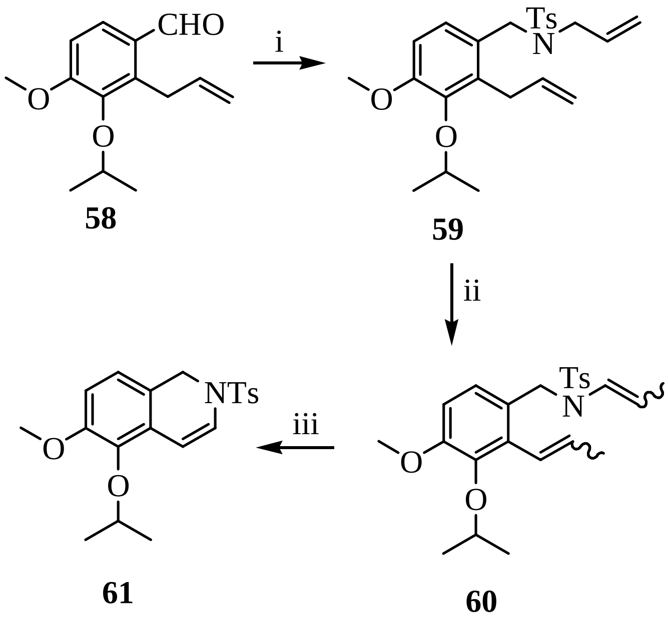
(i) Grubbs I catalyst **2**, DCM, reflux, 24 hrs, 74%.

1.4.3 THE WITS APPROACH TOWARDS THE SYNTHESIS OF BENZO-FUSED COMPOUNDS USING ISOMERISATION AND RING CLOSING METATHESIS

Isomerisation followed by metathesis has been used in a number of syntheses in our research group. Our laboratory has been able to synthesize 6-, 7-, and 8-membered benzo-fused compounds containing oxygen and nitrogen atoms. The scheme for this approach is shown below and it is based on the PhD work of Dr. R. Pathak.[5]

(a) 6-MEMBERED BENZO-FUSED HETEROCYCLIC COMPOUNDS

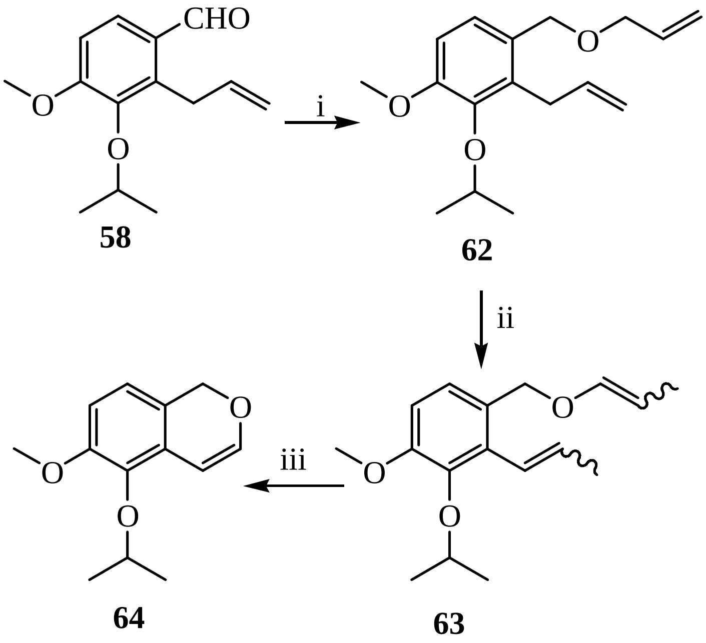
The 6-membered benzo-fused compound was synthesized from a readily available substituted benzaldehyde **58**.[63] A two step reductive amination of **58** with allylamine and $NaBH_4$ gave the amine which was converted into the *N*-tosylamine **59**. The bis-allyl compound **59** was subjected to an *in situ* isomerisation using ruthenium catalyst **12** to afford the product **54**. The isomerised compound was then subjected to RCM using Grubbs II catalyst to afford the 6-membered nitrogen-containing compound **61** in a yield of 76% (Scheme 36).[5]



SCHEME 36

(i) (a) Allylamine, toluene, *p*-TsOH (catalyst), Dean Stark apparatus, 110°C, 4 days, 20%. (b) $NaBH_4$, MeOH, 0°C. (ii) a. TsCl, Et_3N, CH_2Cl_2, rt., 4 hrs. b. Ruthenium catalyst **12**, toluene, 110°C, 2 hrs. (iii) Grubbs II catalyst **4**, toluene, 110°C, 3 hrs, 76%.

The 6-membered benzo-fused oxygen-containing compound was also synthesized from **58**. The aldehyde **58** was converted into **62** by reduction with $LiAlH_4$ followed by *O*-alkylation using allyl bromide. The bis-allyl compound **62** was then subjected to isomerisation using ruthenium catalyst **12** to afford **63**. RCM was then performed on **63** using Grubbs II catalyst **4** to afford a 6-membered benzo-fused oxygen-containing compound **64** in a yield of 83% (Scheme 37).[5]

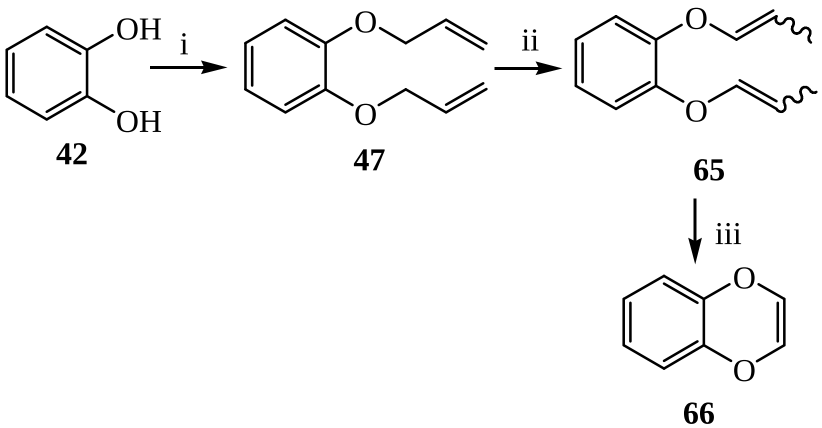


58 **62** **63** **64**

SCHEME 37

(i) a. $LiAlH_4$, THF, 40°C, 12 hrs, 86%. b. Allyl bromide, NaH, THF, reflux, 20 hrs, 77%. (ii) Ruthenium catalyst **12**, toluene, 80°C, quantitative. (iii) Grubbs II catalyst **4**, toluene, 60°C, 83%.

In the synthesis of benzo-1,4-dioxins, catechol **42** which is a commercially available starting material, was used. The first step in the synthesis was the bis(*o*-allylation) of the catechol **42** to afford **47**. This was then followed by *in situ* isomerisation to afford aryl bis(vinyl) ether **65**. Grubbs II catalyst **3** was then added directly to the reaction mixture and the desired benzo-1,4-dioxin **66** was deemed to have been formed in a good yield of greater than 70% (Scheme 38).[64]



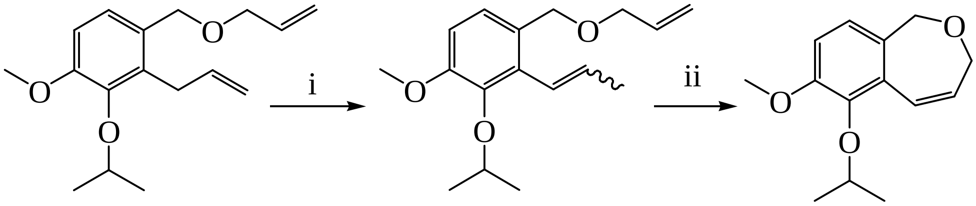
42 **47** **65** **66**

SCHEME 38

(i) Allyl bromide, K_2CO_3, acetone, reflux, 76%. (ii) Ruthenium catalyst **12**, 80°C. (iii) Grubbs II catalyst **4**, toluene-d_8, > 70%.

(b) 7- AND 8-MEMBERED BENZO-FUSED HETEROCYCLIC COMPOUNDS

In addition, the 7-membered oxygen containing benzo-fused compound was also synthesized by an allyl isomerisation method. The allylated compound **62** was isomerised selectively with *t*-BuOK as base to afford **67** followed by RCM to afford 1,3-dihydro-2-benzoxepines **68** in 64% yield (Scheme 39).[5]

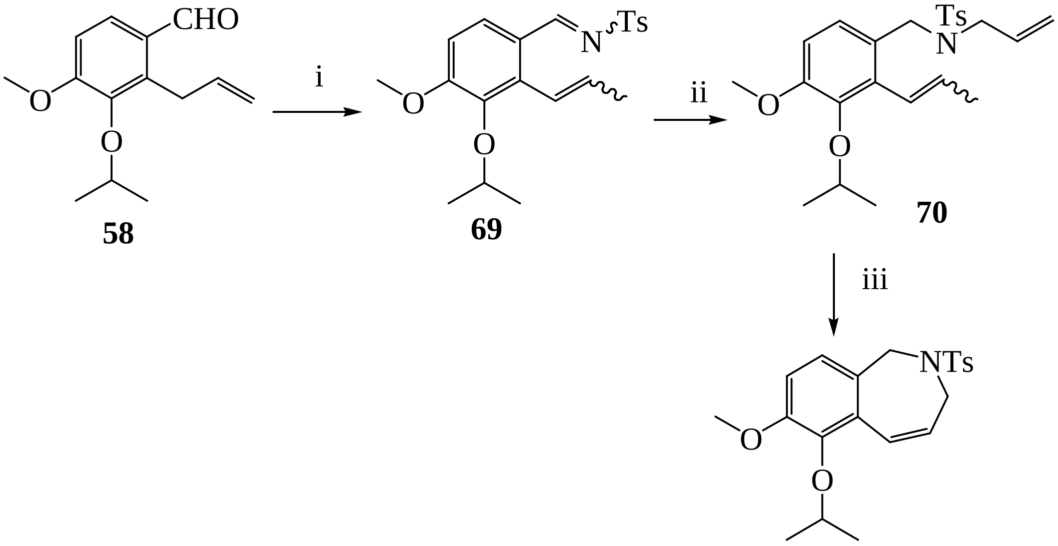


62 **67** **68**

SCHEME 39

(i) *t*-BuOK, DMF, r.t., 18 hrs, quantitative yield. (ii) 5mol% Grubbs II catalyst **4**, toluene, 2 hrs, 80°C, 64%.

The synthesis of the 7-membered benzannelated system **71** was approached in a slightly different way. The readily available substituted benzaldehyde **58** was first converted into the *N*-tosylimine and then isomerised to afford the styrene **69** using ruthenium complex **12**. The *N*-tosylimine **69** was then reduced with $NaBH_4$ and the resultant amine was alkylated with allyl bromide under standard conditions to afford **70**. This compound was then converted into the desired 2,3-dihydro-1*H*-2-benzazepine **71** by treatment with Grubbs II catalyst **4** (Scheme 40).[5]

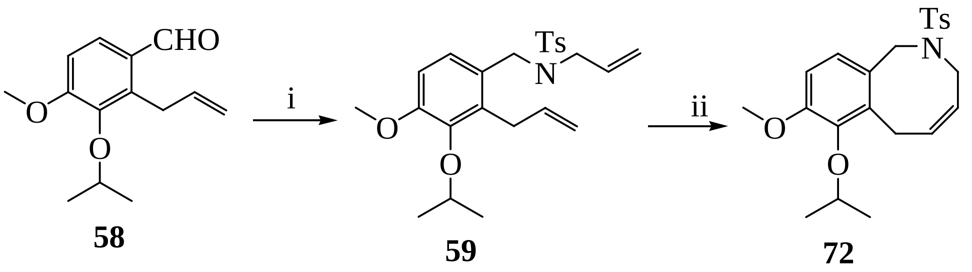


58 **69** **70** **71**

SCHEME 40

(i) a. $TsNH_2$, toluene, 110°C, 4 days, 20%. b. 1mol% catalyst **12**, 80°C, quantitative yield. (ii) a. $NaBH_4$, MeOH, 0°C, 30 mins, 98%. b. Allyl bromide, NaH, THF, 6 hrs, r.t., 64%. (iii) 5 mol% Grubbs II catalyst **4**, toluene, 2 hrs, 60°C, quantitative yield.

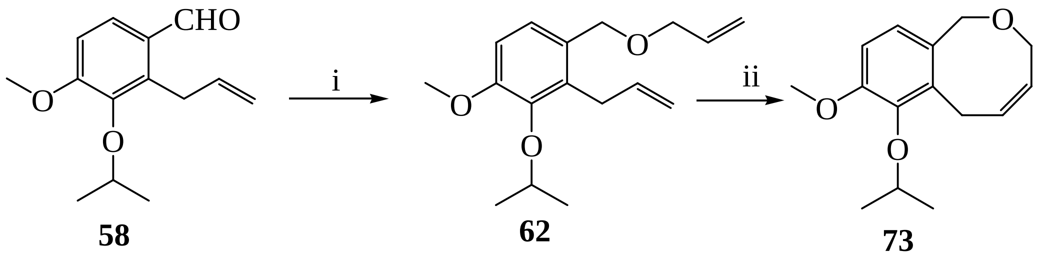
In addition, the 8-membered benzo-fused compound was synthesized from a readily available substituted benzaldehyde **58.**[63] A two step reductive amination of **58** with allyl amine and $NaBH_4$ gave the amine which was converted to the *N*-tosylamine **59**. Subsequent RCM of **59** with catalyst **4** afforded the 1,2,3,6-tetrahydro-2-benzazocine **72** in excellent yield (Scheme 41).[5]



SCHEME 41

(i) a. Allylamine, toluene, *p*-TsOH (catalyst), Dean Stark apparatus, 110°C, 4 days, 20%. b. $NaBH_4$, MeOH, 0°C. c. TsCl, Et_3N, CH_2Cl_2, r.t., 4 hrs. (ii) 5 mol%, Grubbs II catalyst **4**, toluene, 60°C, 1 hr, quantitative yield.

The synthesis of the 8-membered benzo-fused oxygen-containing compound was done by first converting the benzaldehyde **58** into **62** by reduction using $LiAlH_4$ followed by *O*-alkylation using allyl bromide. RCM was then successfully performed using Grubb's catalyst **4** on **62** in toluene to afford the 3,6-dihydro-1*H*-2-benzoxocine ring **73** in a yield of 52% (Scheme 42).[5]

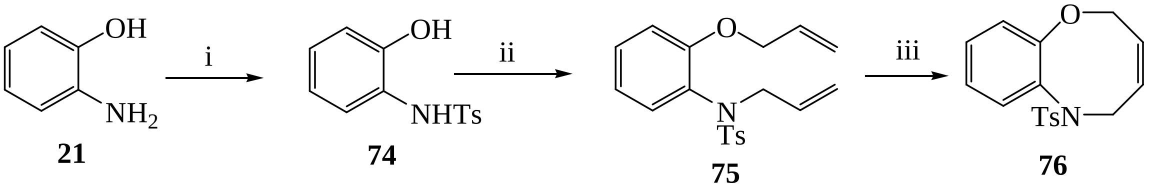


SCHEME 42

(i) a. $LiAlH_4$, THF, 40°C, 12 hrs, 86%. b. Allyl bromide, NaH, THF, reflux, 20 hrs, 77%. (ii) 1 mol% Grubbs II catalyst **4**, toluene, 60°C, 52%.

(c) THE WITS APPROACH TOWARDS THE SYNTHESIS OF 7- AND 8-MEMBERED BENZO- AND PYRIDO-FUSED *N*,*N*-, *N*,*O*- AND *N*,*S*- COMPOUNDS

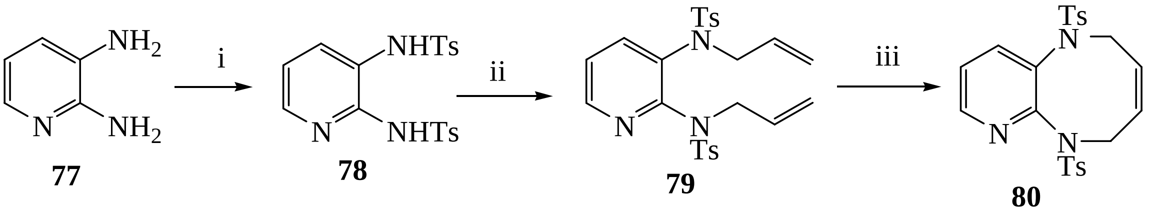
Rambo Khanye, an Honours student, carried out the synthesis of 8-membered benzo- and pyrido-fused *N*,*N*- and *N*,*O*- compounds using commercially available materials such as 2-aminophenol and 2-amino-3-hydroxypyridine. 2-Aminophenol **21** was protected using a tosyl group to afford **74** which was then subjected to an allylation reaction using allyl bromide to afford **75**. This compound was treated with Grubbs II catalyst **4** to afford an 8-membered benzo-fused *N*,*O*- compound **76** (Scheme 43).[65]



SCHEME 43

(i) TsCl, 60°C, 23 hrs, 93%. (ii) Allyl bromide, acetone, K_2CO_3, 3 hrs, 99%. (iii) 5 mol% Grubbs II catalyst **4**, toluene, r.t., 5 hrs, 70%.

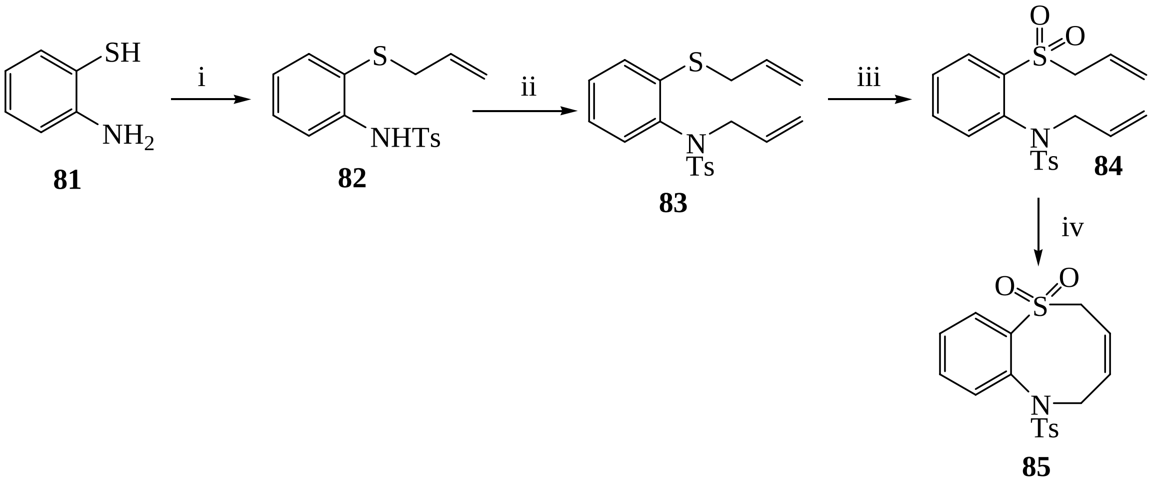
On the other hand, the 8-membered pyrido-fused *N*,*N*-compound was synthesized from commercially available 2,3-diaminopyridine **77**. It was first protected using the tosyl group to afford **78** which was then subjected to an allylation reaction using allyl bromide acetone to afford **79**. This compound was then treated with Grubbs II catalyst **4** to afford an 8-membered pyrido-fused *N*,*N*- compound **80** in excellent yield (Scheme 44).[65]



SCHEME 44

(i) TsCl, pyridine, 20-23 hrs, 60%. (ii) K_2CO_3, acetone, allyl bromide, 60°C, 20-30 hrs, 24%. (iii) 5 mol% Grubbs II catalyst **4**, toluene, r.t., 5 hrs, 94%.

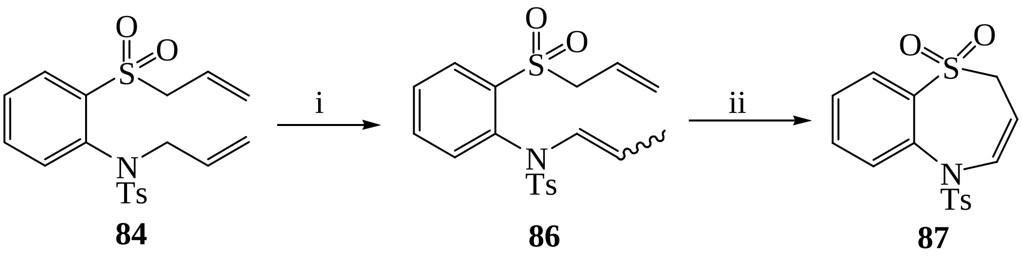
Garreth L. Morgans, a PhD student, carried out the synthesis of some 7- and 8-membered benzo-fused *N,S*-compounds using commercially available materials such as 2-aminobenzenethiol **81**. The 2-aminobenzenethiol **81** was monoallylated with allyl bromide to afford **82.** Furthermore, after protection of the amine group, an allylation then afforded the diallylated compound **83** which was oxidized using MCPBA to afford a sulphone **84**. This oxidized compound was then treated with Grubbs II catalyst **4** to afford **85** (Scheme 45).[65]



SCHEME 45

(i) a. Allyl bromide, MeOH, H_2O, r.t., 2 hrs. b. TsCl, pyridine, CH_2Cl_2, 45°C, 24 hrs, 97%. (ii) Allyl bromide, K_2CO_3, acetone, 60°C, 24 hrs, 99%. (iii) MCPBA, CH_2Cl_2, -5°C, 71%. (iv) 5 mol% Grubbs II catalyst **4**, DCM, r.t., 24 hrs, 95%.

For the synthesis of the 7-membered benzo-fused *N,S*-compound, the oxidized diallylated compound **84** was isomerised using ruthenium catalyst **12** to afford compound **86** which was then treated with Grubbs II catalyst **4** to afford the 7-membered benzo-fused *N,S* ring **87** in moderate yield (Scheme 46).[65]



84 **86** **87**

SCHEME 46

(i) Ruthenium isomerisation catalyst **12**, 24 hrs, toluene, 105°C, 84%. (ii) 5mol%, Grubbs II catalyst **4**, toluene, 80°C, 24 hrs, 41%.

1.5 SPECIFIC AIMS OF THIS PROJECT

(A) ESTABLISHED METHODOLOGY USED IN THE SYNTHESIS OF COMPOUNDS.

In the synthesis of 8- and 9-membered benzo-fused ring compounds, we will first perform protection reactions where necessary followed by diallylation reactions. After the diallylation reactions, we intend to do a RCM. In the case of the 6-membered benzo-fused ring compounds, after the protection reaction and diallylation reaction, we will do an isomerisation reaction before doing the RCM. For the 7-membered benzo-fused ring compounds, after the protection reaction, a mono-allylation reaction will be done followed by isomerisation reaction. A further allylation reaction will then be performed on the isomerised compound before RCM.

(B) SUMMARY OF AIMS

1. To use established methodology to synthesize a series of 6-, 7-, 8-, and 9-membered benzo-fused ring compounds with different protecting groups. The starting scaffolds to be used are 2-aminophenol, 2-amino-3-hydroxypyridine, *o*-phenylenediamine, 2-hydroxybenzyl alcohol, 2-aminobenzylamine and 2-aminobenzyl alcohol, 2-ethyl salicylate and catechol. Below are the structures of benzo-fused ring systems we have attempted and prepared (Figure 3).

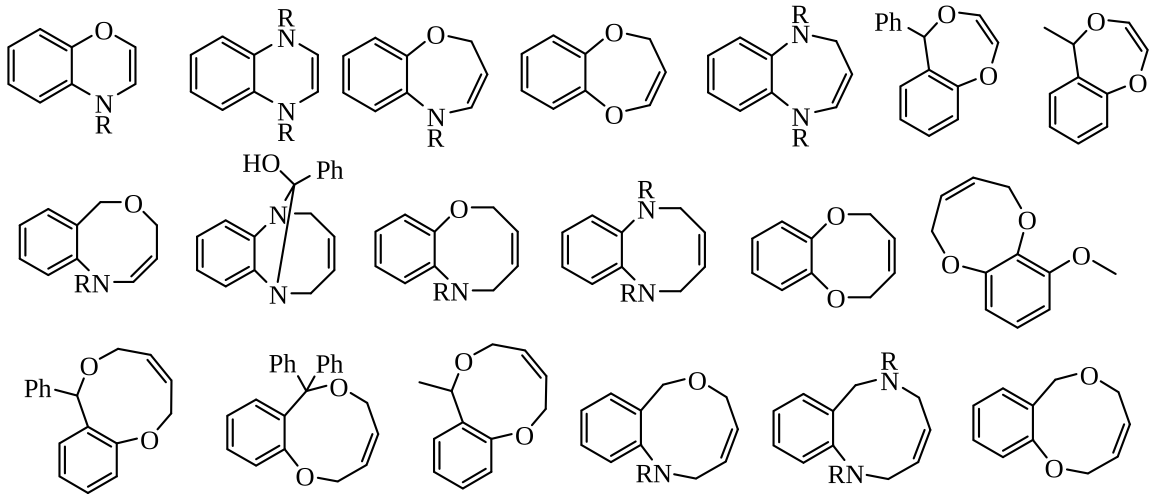


FIGURE 3

2. To do an internal isomerisation on some of the above benzo-fused ring systems with different protecting groups. We want to test if internal isomerisation is viable on the above systems. Below are the structures of the compounds on which internal isomerisation was successful (Figure 4).

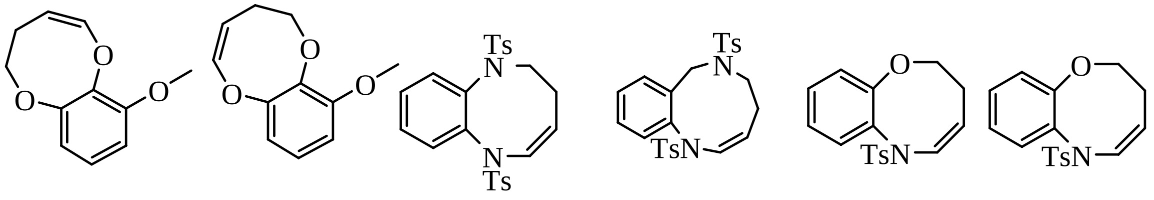


FIGURE 4

3. To do deprotection reactions on the benzo-fused ring systems.

4. To optimize the yield of the reactions.