THE SYNTHESIS OF NATURAL PRODUCTS CONTANING NITROGEN HETROCYCLES VIA RING CLOSING METATHESIS

A MSc Dissertation report by:

PRATIKSHA .B. GAWAS

DEPARTMENT OF CHEMISTRY

GOA UNIVERSITY

TALEIGAO PLATEAU

GOA 403206

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Dissertation report submitted to Goa University in partial fulfilment of the requirement for the degree of

MASTER OF SCIENCE IN CHEMISTRY

By

PRATIKSHA B GAWAS

Organic chemistry

Under the guidance of

DR. SANDESH BUGDE

Assistant professor

School of Chemical Sciences

Goa University

Taleigao Plateau, Goa

STATEMENT

I hereby declare that the matter presented in this dissertation entitled “THE SYNTHESIS OF NATURAL PRODUCTS CONTANING NITROGEN HETROCYCLES VIA RING CLOSING METATHESIS” is the result of investigation carried out by me in the School of Chemical Sciences, Goa University, Goa under the supervision of Assistant Professor Dr. Sandesh Bugde and the same has not been submitted elsewhere for the award of a degree or diploma.

Pratiksha B Gawas

20P0490032

CERTIFICATE

This is to certify that the dissertation entitled "THE SYNTHESIS OF NATURAL PRODUCTS CONTANING NITROGEN HETROCYCLES VIA RING CLOSING METATHESIS" is bonified work carried out by Ms. Pratiksha B Gawas under my supervision in partial fulfilment of the requirements for the award of the degree of Master of Science in Chemistry at the school of sciences, Goa University.

Dr. Sandesh Bugde

Assistant Professor

School of Sciences

Goa University

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Prof. Dr. Vidyadatta Verenkar

Dean

School of Chemical Sciences

Goa University

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Contents

THE SYNTHESIS OF NATURAL PRODUCTS CONTANING NITROGEN HETROCYCLES VIA RING CLOSING METATHESIS

INTRODUCTION

Heterocyclic compounds are cyclic compounds containing atoms of at least two different elements. Hetrocycles containing nitrogen are building blocks of life as they are key constituent of DNA, RNA and protein synthesizing ribosome[1].Nitrogen hetrocycles are central to chemical reactions that occur in all organisms.eg: Piperidine and pyrrolidine are subunits found in naturally occurring alkaloids such as coniine and kainic acid in which Coniine is a powerful neurotoxin and kainic acid is a potent central nervous system stimulant, which makes it useful in the study of epilepsy and Alzheimer's disease[2]. Since these and many other alkaloids serve as the primary source of pharmaceuticals and compounds used in the studies of many biological systems, the development of new methods for their synthesis is of considerable interest to organic and medicinal chemists.

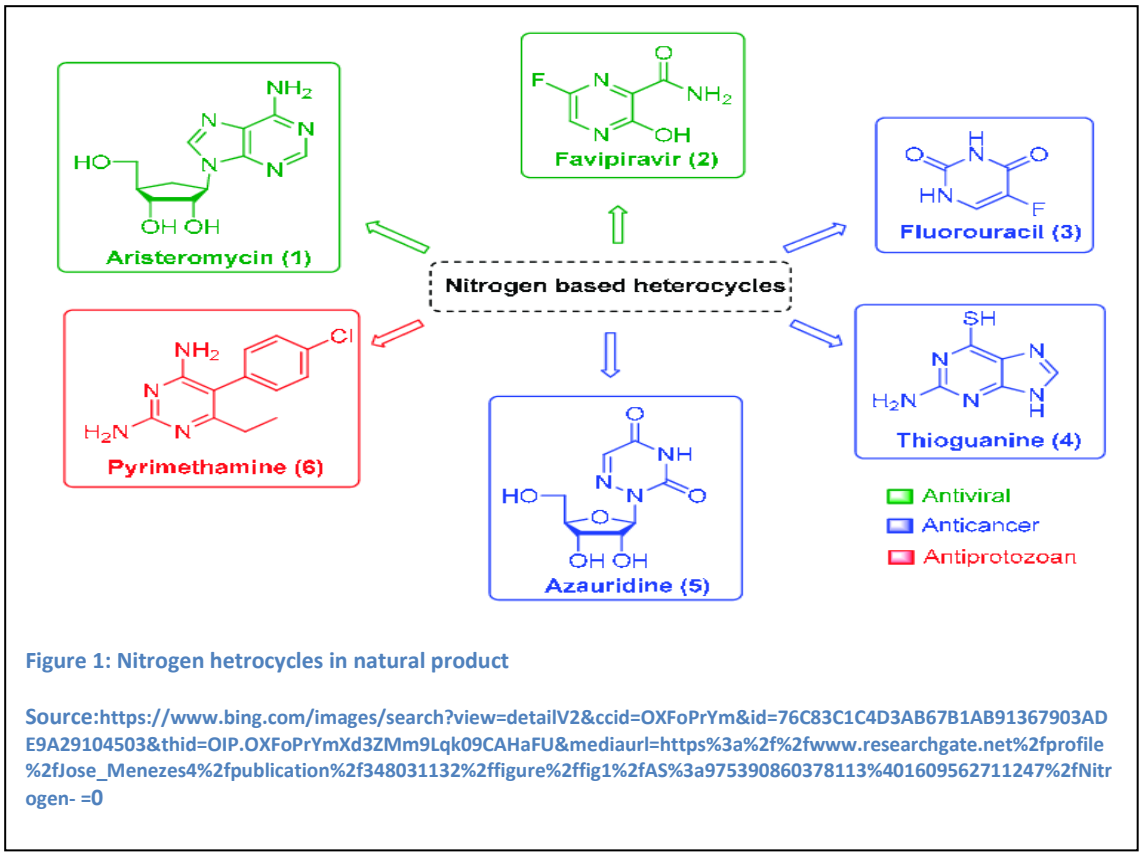


Figure 1: Nitrogen hetrocycles in natural product

Source:https://www.bing.com/images/search?view=detailV2&ccid=OXFoPrYm&id=76C83C1C4D3AB67B1AB91367903ADE9A29104503&thid=OIP.OXFoPrYmXd3ZMm9Lqk09CAHaFU&mediaurl=https%3a%2f%2fwww.researchgate.net%2fprofile%2fJose_Menezes4%2fpublication%2f348031132%2ffigure%2ffig1%2fAS%3a975390860378113%401609562711247%2fNitrogen- =0

A number of approaches for the synthesis of nitrogen-containing hetrocycles have been developed, most leading to the formation of five- and six membered ring systems, while the construction of seven-membered and larger hetrocycles is still quite limited. A great number of the existing ring-forming methodologies rely on metal catalyzed processes. Ruthenium is one such efficient catalyst used from the transitions metal series.[3] A number of natural and biologically active compounds can be synthesized via ruthenium catalysis, as ruthenium is the cheapest noble metal and can be extensively used to synthesize a variety of catalysts, for synthesis of chemotherapeutic agents, polymers, biopolymers and agrochemicals. Ruthenium-based catalysts are well famous because of their broad range of functional group, air and moisture tolerance. Different organic reactions such as alkylation, arylation, isomerisation and olefin metathesis are efficiently carried out in the presence of these catalysts within short reaction time [4]. In 1992, Robert H. Grubbs first time introduced ruthenium-based catalyst, known as Grubbs first-generation catalyst (G-1) to carry out olefin metathesis effectively. Later on, Grubbs second-generation (G-2), third-generation catalyst (G-3) and Hoveyda–Grubbs catalysts such as (HG-1) and (HG-2) were also obtained by changing different ligands with ruthenium. In this report, synthesis of natural products containing nitrogen hetrocycles using ruthenium-based Grubbs catalysts via ring closing metathesis (RCM) is discussed briefly.

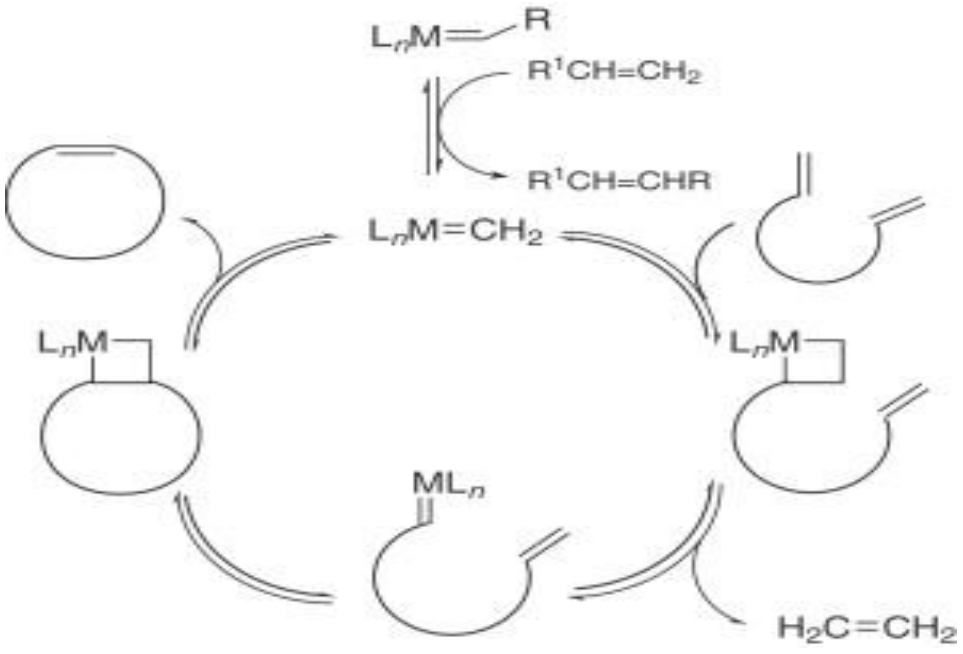
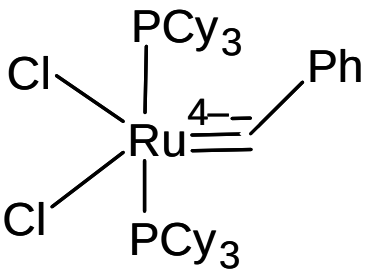


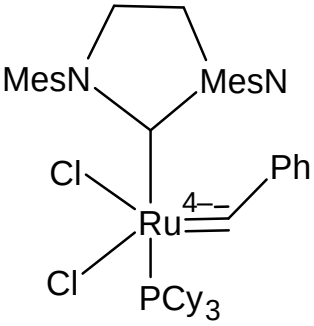
Figure 2: Mechanism of RCM

Source: https://www.sciencedirect.com/topics/biochemistry-genetics-and-molecular-biology/grubbs-catalyst



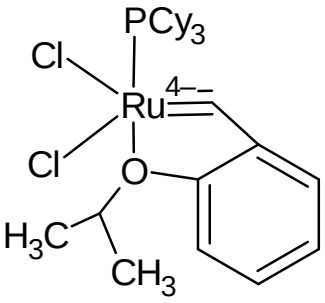
1

Grubbs first- generation



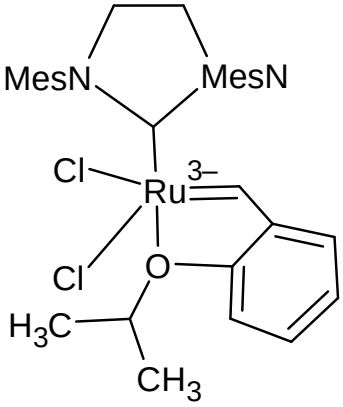
2

Grubbs second-generation



3

Hoveyda-Grubbs first generation



4

Hoveyda-Grubbs second generation

Literature review

1) A general synthesis of Quinolinones and benzothiazine 1,1-dioxides via ring closing metathesis [5]

The paper includes synthesis of Quinolinones and benzothiazine 1,1-dioxides which are an important class of hetrocycles present in many biologically active natural products. These compounds are the core structures of antibiotics and many other medicinally valuable compounds. Among the several procedures reported which involved use of strong base, high temperature and had limited functional group compatibility, ring closing metathesis represented as a powerful method for formation of such heterocyclic rings. N-phenylacrylamide was model substrates used which on treatment with 10% Grubbs 2nd

generation catalyst in dichloromethane cleanly yielded the desired quinolinones in 95% isolated yield (scheme 1). When the catalyst loading was reduced to 5% or 2% the time taken for the reaction was increased however there was no erosion in the efficiency of the cyclisation details in Table No 1. A variety of analogs of 1 was prepared varying the substituent's to study the effects of different substituent. The general yield of the different analogs was exceptionally good including electron withdrawing groups, bromine and CF3 (82% & 86%) however phenyl analog was sluggish and provided modest yield of 38% only.

Scheme 1

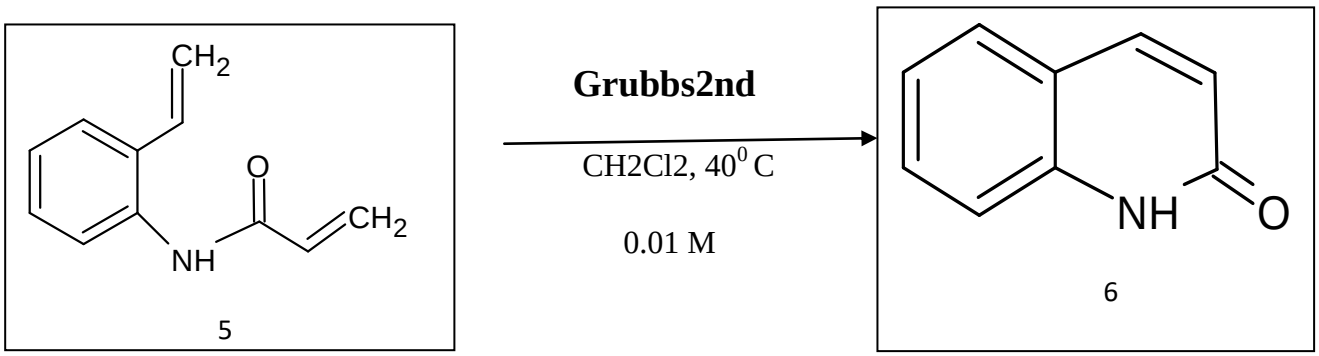


Table No 1

Entry	Catalyst loading (mol %)	Time (h)	Yield (%)
1	10	2.5	95
2	5	7.5	88
3	2	96	91

The required benzothiazine 1,1-dioxides was prepared from N-phenylethylenesulfonamides via ring closing metathesis (Scheme 2). The effect of decrease in catalyst loading with different solvents for benzothiazine 1,1-dioxides was now found showing negative impact on the products yields in contrast to what was seen in the case of Quinolinones (Table 2).The effect of various substituent's on the benzene ring was studied and seen showing similar results to that for Quinolinones .The electron donating and electron withdrawing substituent's gave excellent yield of desired products while the phenyl analog completely shuts down the RCM reaction similar to was observed for Quinolinones series.

Scheme 2:

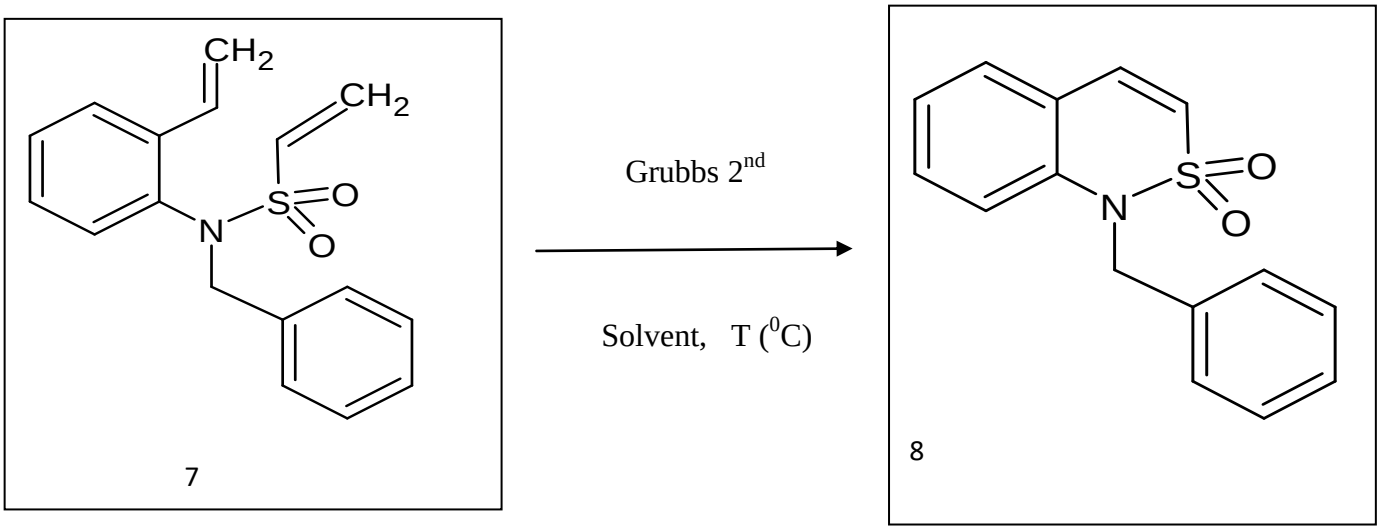


Table No 2:

Entry	Solvent	Catalyst loading (mol%)	Yield (%)
1	CH2Cl2	10	85
2	CH2Cl2	5	54
3	C6H6	10	0

2 Assisted tandem catalytic RCM-aromatization in the synthesis of pyrroles and furans[6]

In this paper N-aryl pyrroles were synthesised by catalytic transformation of diallyl amines and diallyl ether. The sequence relies on ring closing metathesis followed by dehydrogenation of the initially formed dihydropyrroles where both the steps are Ru catalysed. Synthesis of aromatic hetrocycles is considerable interest from a synthetic point of view, because of their occurrence in medicinal and natural products like bile, heme and chlorophyll pigments. Hence there is a constant need for novel synthetic methods in this field. A set of N-aryldiallyl amines was synthesized from the corresponding anilines by allylation and converted to aromatic pyrroles under microwave assisted RCM conditions. In the presence of 2.5 mol% of G-I, dihydro- pyrroles gave in quantitative yield, indicating that the spontaneous aromatization, which is not specific for this particular substrate but most likely was caused due to the microwave conditions (Scheme 3). With the increased in catalysts loading (from 2.5% to 5% mol) there was increased in the product yield. These reactions

were carried out in presence of series of different catalyst concentration in presences of different solvents and the data obtained is presented below in Table No 3.Lastly, the electronic conditions of the N-aryl substituent had no significant influence on the reaction, as electron rich and electron deficient aryl groups give comparable yields.

Scheme 3:

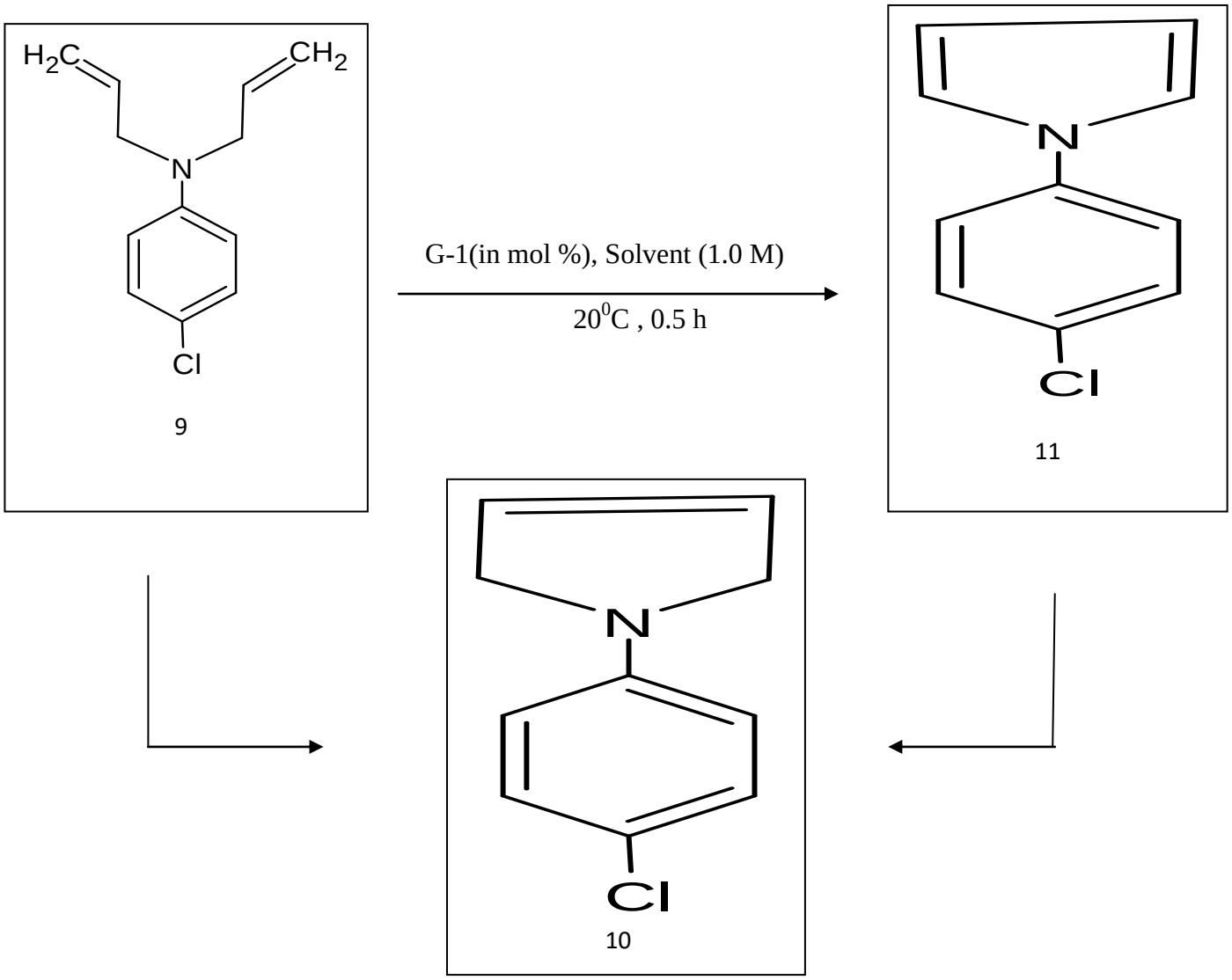


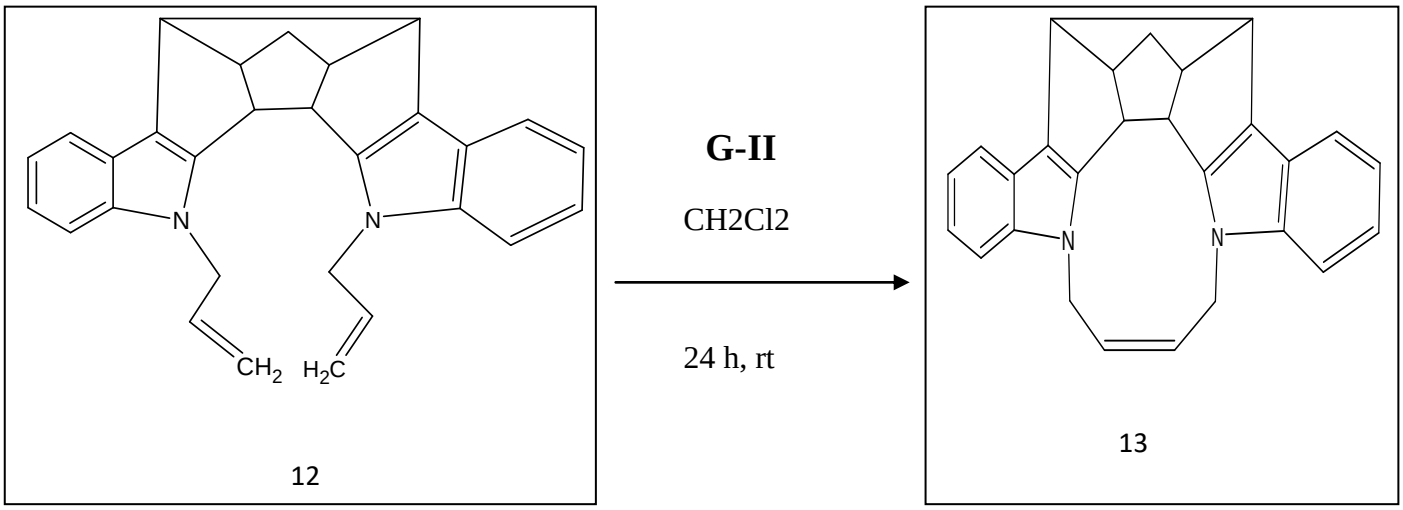
Table No: 3

Entry	Solvent	Starting material	Catalyst loading (Mol %)	Product	Yield (5%)
1	Benzene	9	2.5	10	99
2	CH2Cl2	9	5.0	11	71
3	Ethyl acetate	9	5.0	11	71
4	Toluene	9	5.0	11	96

3) Design and synthesis of polycyclic bisindoles via Fischer indolization and ring- closing metathesis as key steps[7]

Several bisindoles derivatives have been synthesised in this paper from a readily available tetracyclic dione via Fischer indolization and further ring-closing metathesis. The Fischer indolization was achieved under deep eutectic reaction conditions using L-tartaric acid and dimethyl urea. Various indole derivatives synthesized here are C2-symmetrical in nature which due to its binding ability exhibits inhibitory activities against to HIV-1 protease, Gram-positive bacteria Bacillus subtilis and Micrococcus luteus. Mixtures of L-tartaric acid and dimethyl urea were used, for synthesizing macrocyclic bisindole. And mono indole and hydrazone intermediate in 20%, 19% and 29% yields, respectively the structure of bisindole derivative has been established on the basis of 1H and 13C NMR spectral data. Diallyl hydrazone derivative was subjected to Fischer indolization with ZnCl2 under toluene reflux conditions to generate the diindole derivative. Desired diindole (12) derivative was subjected to ring-closure by Grubb's 2nd generation (G-II) Metathesis catalyst in dry CH2Cl2 to deliver the cyclised product (13) in 75% yield (Scheme 4).

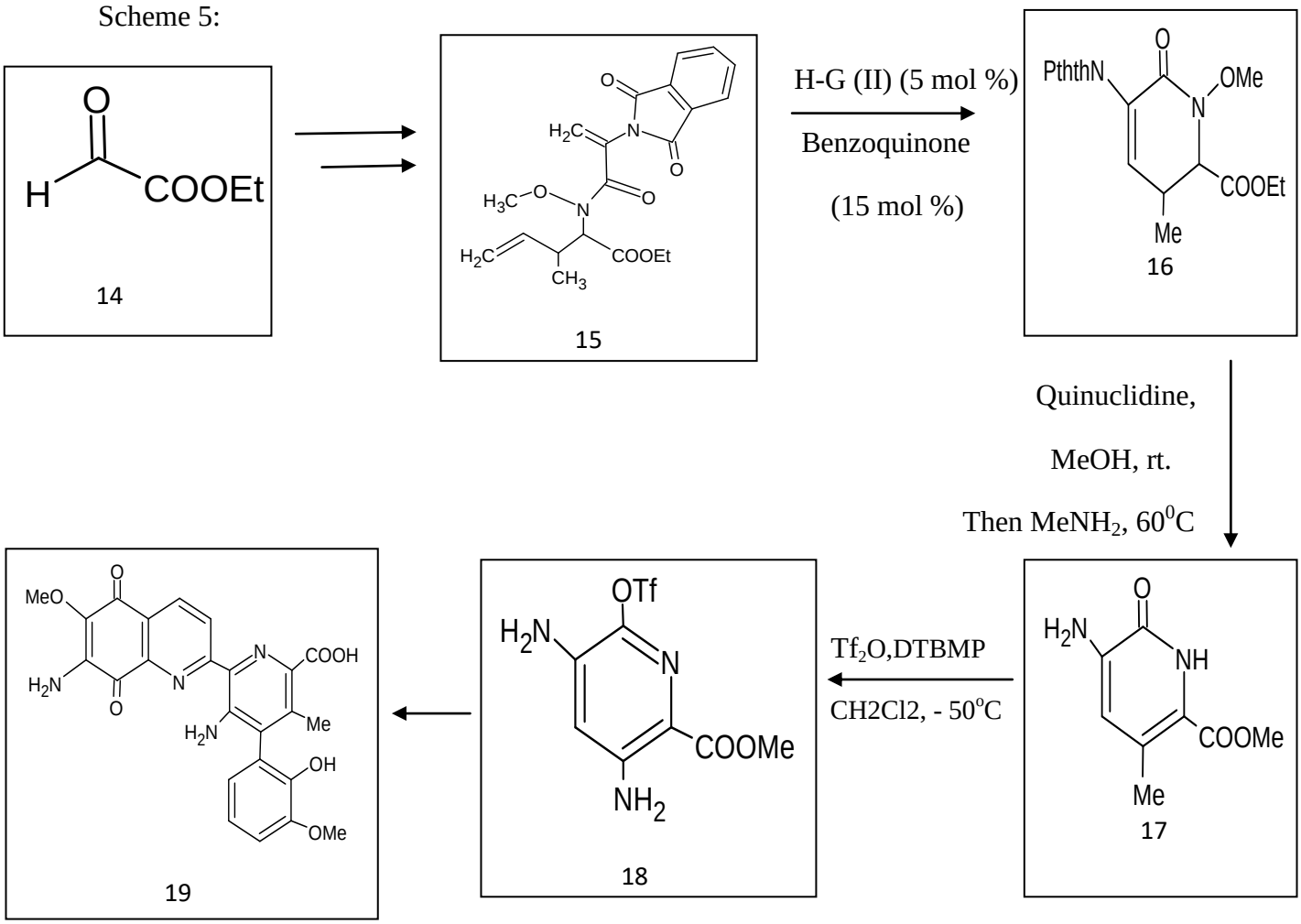
Scheme 4:



4) Synthesis of Aromatic Hetrocycles Using Ring-Closing Metathesis[8]

In this paper, RCM approaches for the synthesis of heteroaromatics are exemplified which are natural products having the application in medicinal field. Streptonigrin in which the heterocyclic core containing pyridine is an antibiotic and antitumor agent was synthesised by ring closing metathesis. The acyclic diene RCM precursor was readily available in a three-step synthesis involving condensation of methoxyamine with ethyl glyoxalate, followed by zinc-mediated crotylation and acylation. The crucial RCM reaction of the 1,1-disubstituted alkene was accomplished using Hoveydae Grubbs second-generation catalyst to provide (16) in 76% yield. This reaction proved to be challenging and slow addition of the catalyst along with the use of benzoquinone to quench any in situ formed Ru-H species was key to the success of this reaction Elimination of the leaving group (N-OMe) was effected using quinuclidine in methanol, which also resulted in transesterification. 2-pyridone (17) in 85% yield was then converted to the pyridine (18) in 84% yield using triflic anhydride, 2,6-di-tert-butyl-4-methyl pyridine, and hexafluoroisopropanol. Further synthetic manipulations resulted in the completion of synthesis of Streptonigrin with 11% of overall yield.

Scheme 5:

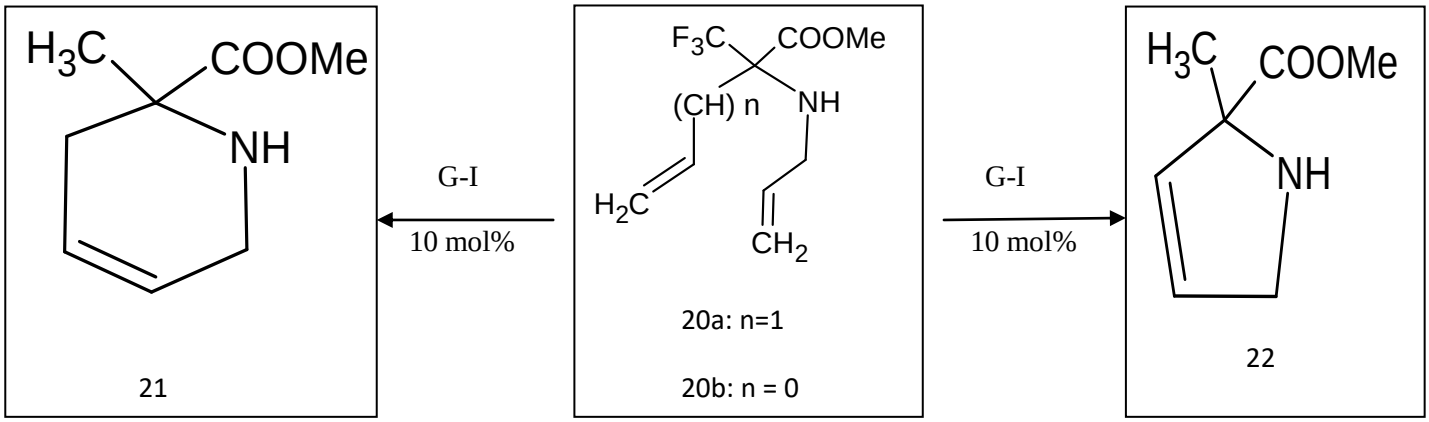


5) Synthesis of fluorine-containing cyclic amino acid derivatives via ring closing olefin metathesis[9]

In this paper new N-protected α-CF3 amino esters with two alkene chains (1,7-dienes 20a and 1,6-dienes 20b) were reacted with the ring closing metathesis catalyst Ru=CHPh(Cl)2(PCy3)2 (1) to give the α-CF3 dehydropipecolinate and prolinate derivatives 21 and 22 . Among various classes of biologically active compounds, fluorinated amino acids attract considerable attention as they are useful candidates for peptide modification, and potent as irreversible inhibitors of pyridoxal phosphate dependent enzymes. Dehydroproline derivatives have also found use as starting materials for kainic acid derivatives which was discussed previously in introduction.[10]Several imines with different protecting groups on

nitrogen, like PhSO2 and Boc were successfully applied to give the amino acid derivative. This was transformed to1, 7-diene derivative 20a and 1, 6-diene 20b respectively by treating with ally bromide and vinyl magnesium bromide respectively. The intramolecular ring closing metathesis reaction was attempted from the 20a and 20b in CH2Cl2 at room temperature in the presence of 10 mol% of the Grubbs first generation catalyst and the cyclisation took 10 h to give the dehydropipecolinate derivative in high yield (21 = 93% and 22 = 98% (Scheme 6).

Scheme 6:

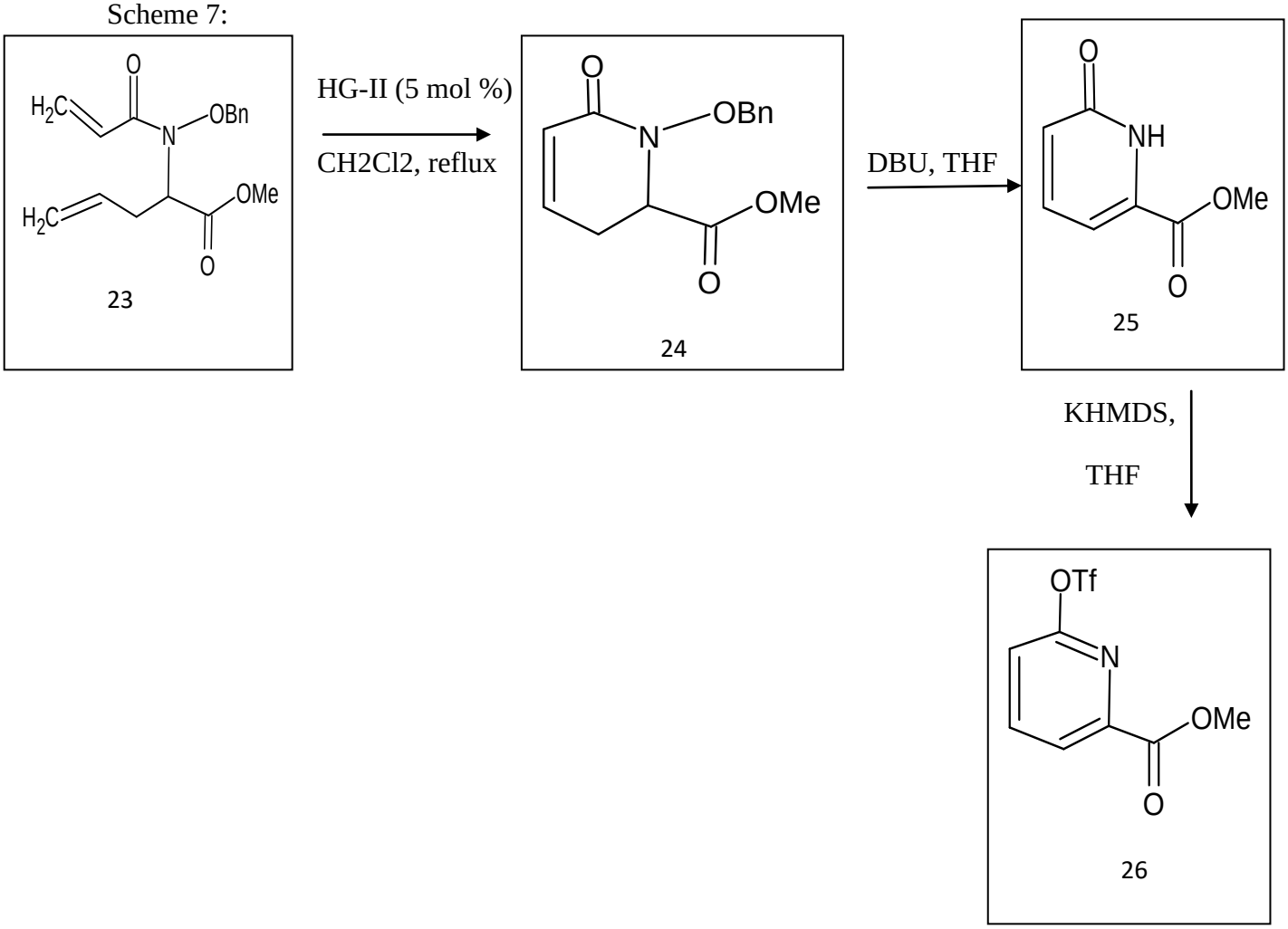


6) A Metathesis-Based Approach to the Synthesis of 2-Pyridones and Pyridines[11]

This paper reveals that the ring-closing metathesis reaction has been successfully employed to form a range of dihydropyridone intermediates, which undergo a base-induced elimination to reveal the aromatic 2-pyridone. This mild and novel approach to six-membered heteroaromatic compounds then provides access to a wide variety of substituted pyridines in excellent overall yield. The importance of this aromatic heterocycle in medicinal chemistry is evident. The synthetic route proceeds with, amine was generated by employing a zinc-mediated allylation of the oxime ether using allyl bromide. Treatment of this substrate with acryloyl chloride yielded the corresponding amide (23), which was then transformed into the dihydropyridone using Hoveyda-Grubbs second generation catalyst (4) in excellent yield of 98% (24). An extensive screen of bases revealed that DBU in THF provided the best result

for the elimination. This protocol provided an impressive overall yield of 79 %.(Scheme 7) But it was seen that when RCM and elimination reaction was carried out in one pot with the DBU and metathesis mixture provided the pyridone in a yield of 81% from amide. However the first procedure was preferred as the overall yield of pyridone product as it was obtained in greater purity.

Scheme 7:

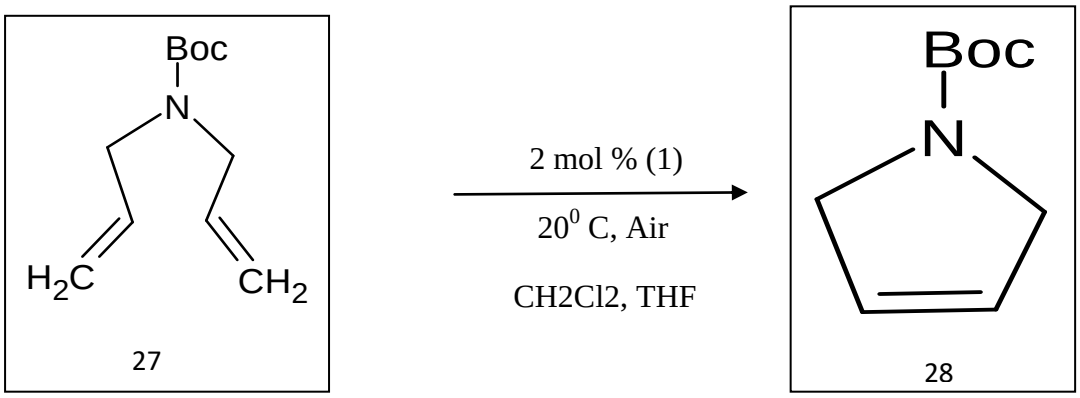


7) Catalytic Ring-Closing Metathesis of Functionalized Dienes by a Ruthenium Carbene Complex[12]

This paper describes the discovery of a family of well-defined ruthenium carbene complexes capable of metathesizing both strained and unstrained olefins. As part of their previously ongoing program directed towards the development of transition metal reagents for organic synthesis it was established that ruthenium carbene is an efficient catalyst for ring-closing olefin metathesis than molybdenum. The two important advantages of ruthenium over

molybdenum is diminished sensitivity to atmospheric oxygen and moisture and increased tolerance of most functionalities. Treatment of dienes with 2-4 mol % (1) at room temperature results in the formation of a variety of unsaturated hetrocycles in good yields. The catalyst efficiently generates five- six- and seven-membered nitrogen hetrocycles, and it tolerates common protecting groups, including trifluoroacetyl tBoc and benzyl. These nitrogen hetrocycles are the core structure of many natural products. Finally it was observed that ruthenium carbene (1) can cyclize dienes in the presence of air in reagent-grade solvents this provides an indication of the relative insensitivity of the reaction to oxygen, moisture, and adventitious impurities (Scheme 8)

Scheme 8

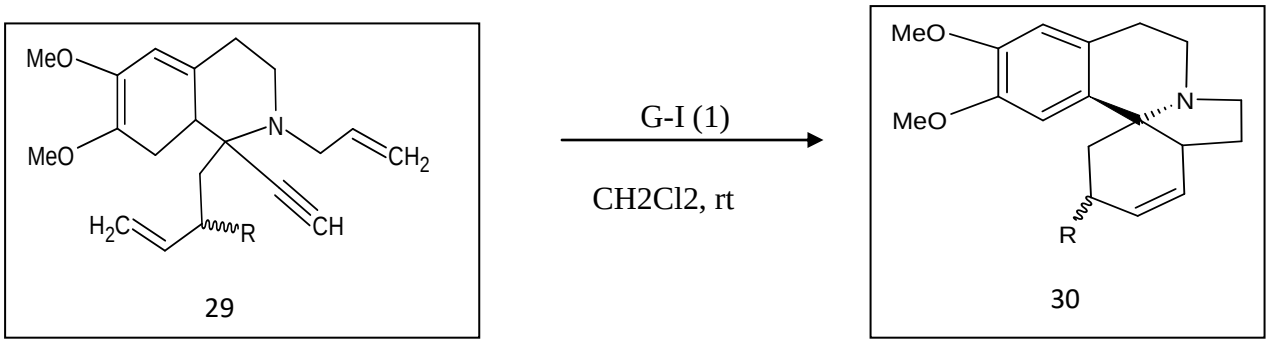


8) Total synthesis of (±)-erythravine based on ring closing dienyne metathesis[13]

The paper includes synthesis of (±)-erythravine, a Dienoid-type erythrinan alkaloids. These are major group of the Erythrina family of natural products [14]. These compounds have received considerable attention over the past few decades due to their various intriguing biological activity Although a wide variety of methods have already been developed for the synthesis of this family of alkaloids,[15] new approach which relies on ring closing metathesis (RCM) of dienyne on the basis of the Grubbs' protocol was applied. The reaction proceeded with 3,4-Dimethoxyphenethylamine which was first protected with Boc group, further it was reacted with diethyl propiolate in boiling trifluoroacetic acid to give diester via Pictet–Spengler type reaction [161718]. Reduction of with LiAlH4 followed by selective silylation gave TBDPS–ether. Swern oxidation of this ether resulted into an aldehyde with Bestmann's reagent[19] [20]afforded enyne (29). The crucial tandem RCM process was examined using Grubbs' catalysts (1 and 2) under various conditions. When alcohol(R=OH) was treated with 10–20 mol% of either Grubbs' catalyst in CH2Cl2 or toluene, no reaction occurred at room

temperature and only partial decomposition of R was observed at elevated temperature. On the other hand, upon treatment of acetate(R=OAc) with 10 mol% of in CH2Cl2 at reflux, the reaction completed after 8h, obtaining α and β isomer in a ratio of 63:37 in 78% yield(Scheme 9). In this particular case, the reaction turned out to be very sluggish at room temperature, possibly because of the coordination of the free tertiary amine to the ruthenium catalyst. Interestingly, in each reaction, the two epimeric products were not equally produced even though a 1:1 epimeric mixture was used as the starting material. Finally, treatment of 30 with K2CO3 in methanol furnished (±)-erythravine.

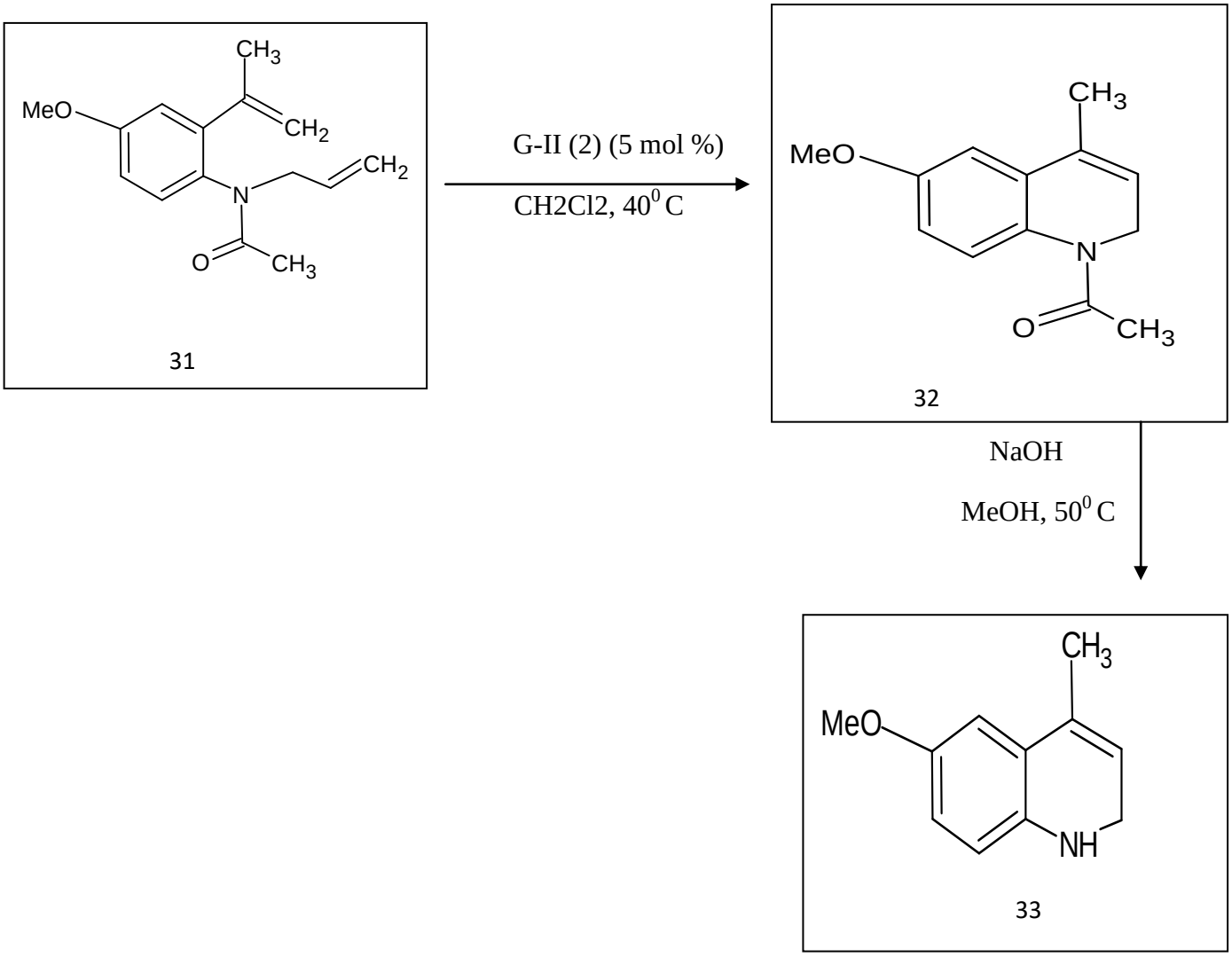
Scheme 9:



9) Ring-Closing Metathesis: Novel Routes to Aromatic Hetrocycles[21]

In this research paper, an early strategy was employed to gain access to aromatic compounds using the RCM transformation and allylic oxidation on the newly formed cyclic olefin. A number of carbocycles and heteroaromatic rings were synthesised using RCM in the paper, including substituted pyrroles, furans, dipyridone, quinolines and indoles. In the investigating it was found that the formation of a series of protected 1,2-dihydroquinolines by RCM of the corresponding acyclic diene the dihydroquinoline was isolated in good yield following RCM, but as the protecting groups on nitrogen were removed during silica gel column chromatography the, resulting dihydroquinoline was spontaneously auto-oxidised to give 4-methylquinoline. The group also applied this Procedure to the synthesis of quinolines (33), which are intermediates in the synthesis of the antimalarial agent's, quinine (Scheme 10)

Scheme 10:

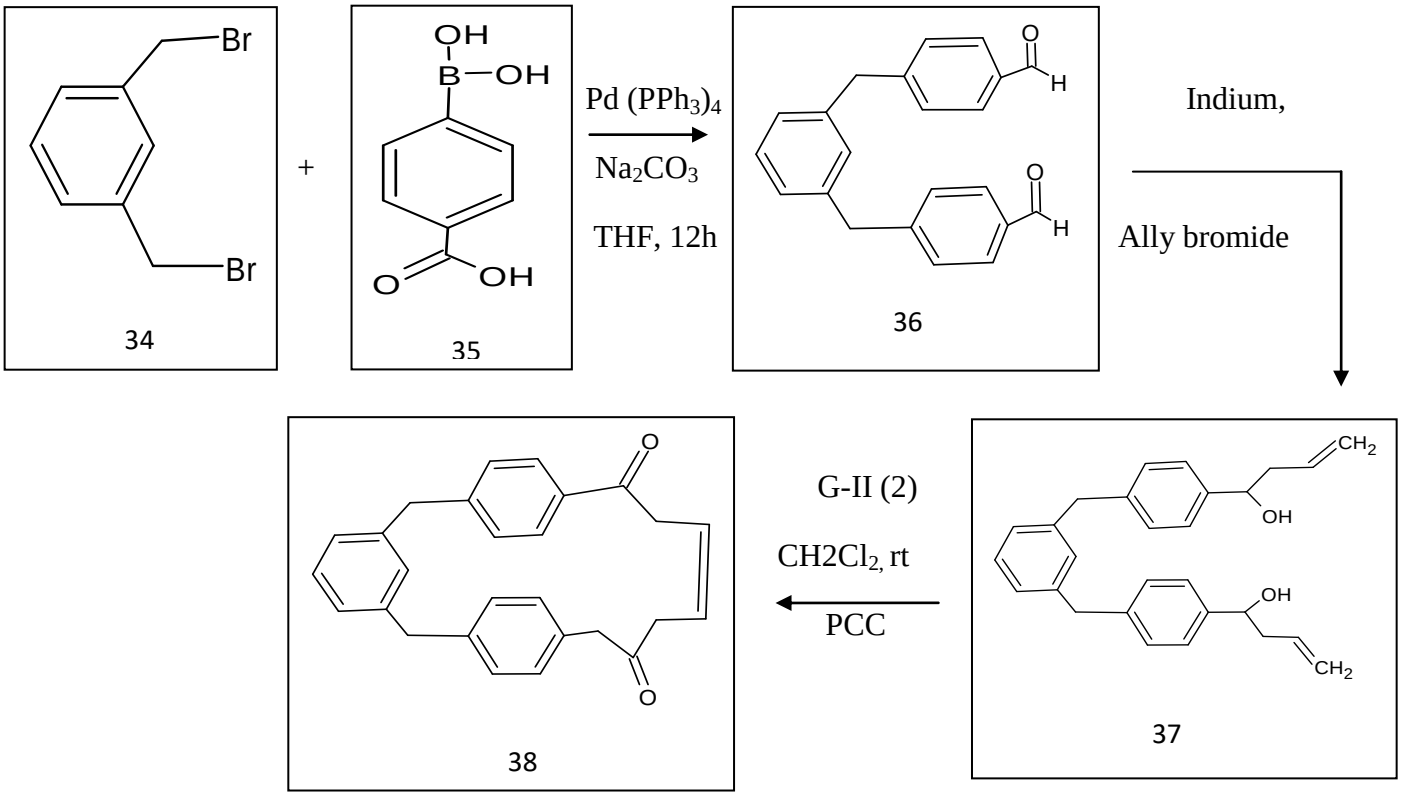


10) Design and Synthesis of Polycycles, Heterocycle, and Macrocycles via Strategic Utilization of Ring-Closing Metathesis[22]

The paper summarizes new synthetic approaches for the construction of various polycyclic compounds involving ring-closing metathesis as a key step. In this regard, ring-closing metathesis was used in combination with other popular reactions like Suzuki-Miyaura coupling, Claisen rearrangement, Fischer indolization, Grignard addition, Diels-Alder reaction, and [2+2] cycloaddition reaction etc. To this end, a variety of functional molecules such as α- amino acids, cyclophanes, heterocycles, propellanes, spirocycles, and macrocycles have been prepared.. Among the various molecules synthesised as mentioned above, the nitrogen containing hetrocycles present in nature was Cyclophanes. These are interesting molecules useful in the area of “host-guest” molecular recognition, and they canact as charge

transfer agents. Many natural products such as macrocidin, and ,nostocyclyne contains the cyclophane framework as a core structural unit [23].In addition, various heteroatom containing cyclophanes are known to exhibit important biological activities such as antimicrobial, anti-inflammatory, and antifungal properties. To construct diverse cyclophanes dialdehyde(36) was prepared via Suzuki-Miyaura (SM) coupling of dibromo compound(34) with boronic acid(35) and the key building block(37) was synthesized by treating the dialdehyde(36) with allyl bromide in the presence of indium powder. Next, the unsaturated diol(37) was subjected to RCM with Grubbs 2nd followed by oxidation with pyridinium chlorochromate (PCC) at room temperature to deliver the desired macrocycle (38) in 75% (Scheme 11). The highlight of this approach is, no usage of protecting groups was done and employment of two green processes such as SM coupling and olefin metathesis.

Scheme 11

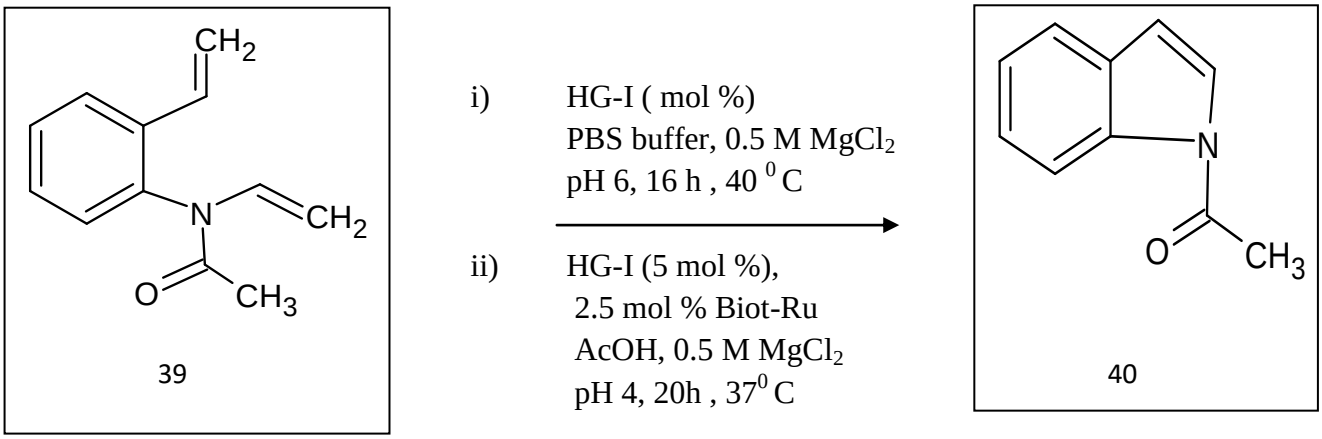


11) Synthesis of N- Substituted Indoles via Aqueous Ring- Closing Metathesis[24]

The report herein includes the synthesis of N-substituted indoles resulting from the ring-closing metathesis of indole precursors bearing N-terminal alkenes. The aqueous metathesis

of the indole precursors gave good yields of N-substituted indoles with commercial metathesis catalysts and with artificial metalloenzymes based on the biotin-streptavidin technology (Biot-Ru). Indoles are important synthetic scaffold and its core is present in many compounds which possess biological activity, such as naturally-occurring alkaloids and chemotherapeutic drugs Synthesis of N-vinylanilide derivatives via aqueous RCM using HG-I (3) yielded up to 72% of N-acetylindole in PBS buffer at pH 6 and 2–5% (V/V) organic co solvents (Scheme 12i). In the presence of ArMs (artificial metalloenzymes) based on the biotin-streptavidin technology, up to 42% of N-acetylindole was achieved.(Scheme 12ii)

Scheme 12:

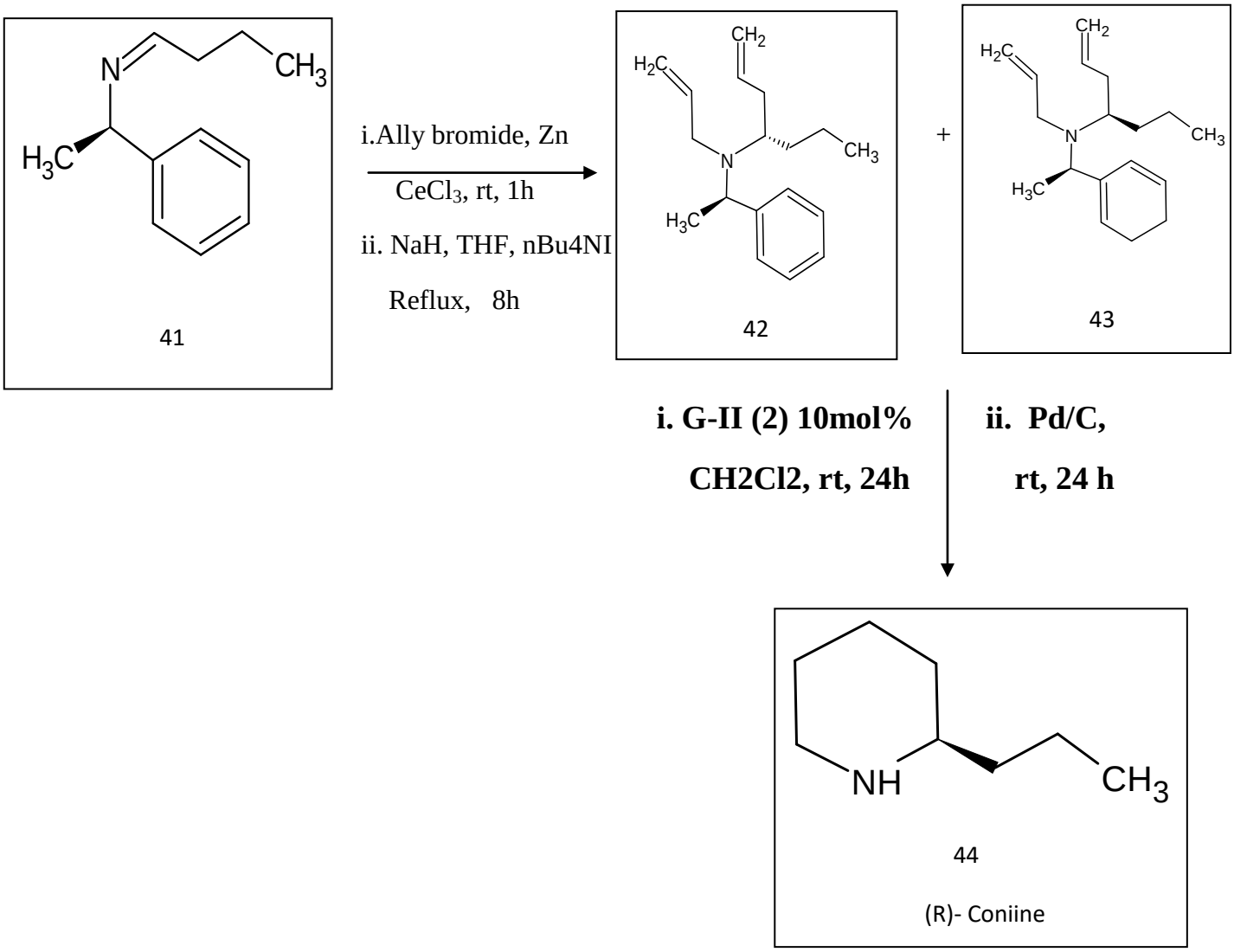


12) Chiral oxime ethers in asymmetric synthesis. Part 5.Asymmetric synthesis of 2-substituted 5- to 8-membered nitrogen heterocycles by oxime addition–ring-closing metathesis [25]

This article focuses on synthesis of piperidines and 4, 5-dehydropiperidines by ring- closing metathesis reaction (RCM) Piperidines are cores for many natural alkaloids. Some natural examples of Enantioselective members of this family includes coniine pipecoline, anabasine ,anatabine ,β- conhydrine , pipecolic acid, baikiain and sedamine. Among them, the efficient synthesis of these natural products by use of an RCM reaction as the key step has recently been reported. Coniine, one of the simplest alkaloids and one of the poisonous alkaloids is a popular target for the demonstration of new synthetic methodology in the piperidine Treatment of chiral imine, derived from butanal and (R)-α-methylbenzylamine with allylzinc bromide provided the secondary amine, which was then N-alkylated to give an inseparable

diastereoisomeric mixture of dienes in a ratio of 15:85. This diene mixture was subjected to an RCM reaction in the presence of Grubbs' catalyst 2 to furnish, after separation by chromatography on silica gel, the desired cyclised diastereoisomer. This was then hydrogenated to afford (R)- coniine in 58% overall yield. In a similar manner, starting from acetaldehyde, (R)-pipecoline has been synthesized in five steps with 33% overall yield (Scheme 13).

Scheme 13

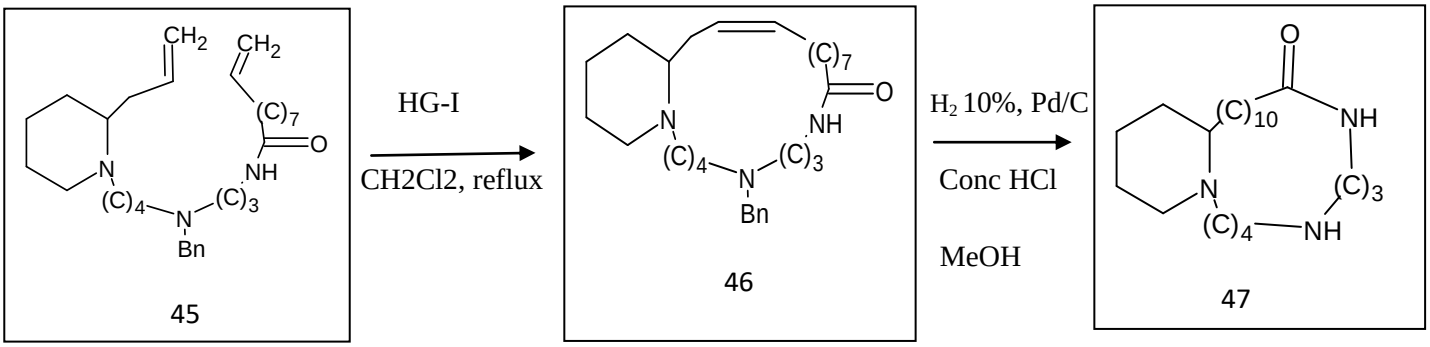


13) Efficient, asymmetric synthesis of (L)-isooncinotine[26]

This paper focuses on synthesis of (L)-isooncinotine, a 22-membered lactam of spermidine, natural alkaloid. These Polyamines, such as putrescine, spermidine, and spermine, are essential for the growth and function of normal cells.1 Studies on N-alkylated polyamines

revealed that these com- pounds possess antineoplastic activity against a number of murine and human tumor lines. Synthesis starts from resolution of 2- piperidineethanol with (S)-10-camphorsulfonic acid followed Michael addition. Amidations, and aluminum hydride reduction were applied to form the moiety of spermidine.The final synthesis of the skeleton of this macrolide is achieved with ring-closing metathesis using HG-I (3) of the diene prepared from acylation of the spermidine. Hydrogenation and then debenzylation of lactam 46 gave isooncinotine in 53% yield.(Scheme 14)

Scheme 14



14) Ring closing metathesis of unprotected peptides[27]

The paper reported an efficient and expedient route to the synthesis of dicarba peptides free from protecting group using Ru-alkylidenes catalysed olefin metathesis. A range of cyclic peptides was prepared from linear peptides containing two Z-crotyl glycine residues. Free amine groups were masked as salts with Bronsted acids preventing in situ catalyst decomposition. Excellent RCM conversion was obtained in both DMF and methanol solvents. Product purification by RP-HPLC was conducted for dicarba oxytocin providing cis and trans-isomers, in ratio of 55:45 (cis: trans), and >97%.This approach was exemplified by RCM of five structurally diverse peptide sequences.

15) The synthesis of Nitrogen hetrocycles via catalytic ring closing metathesis of dienes[28]

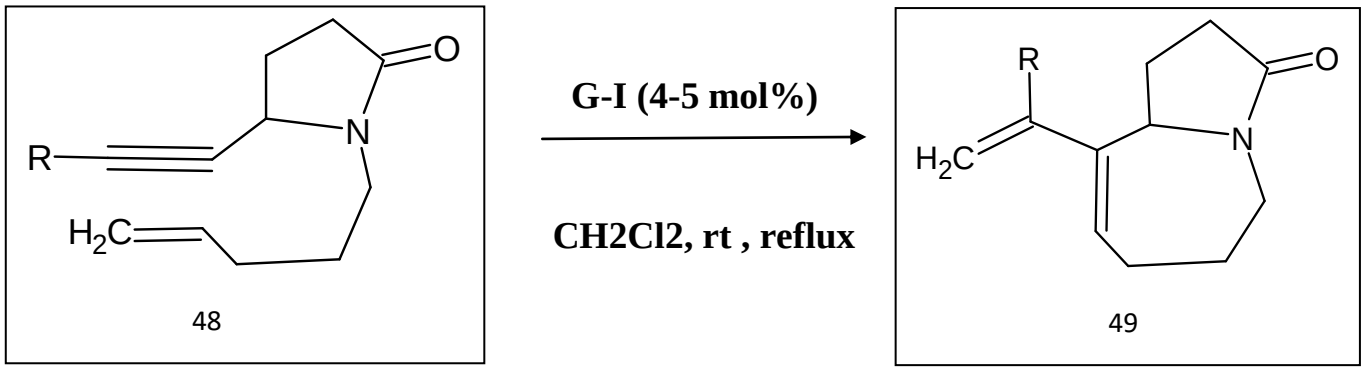
The paper has described an approach to the generation of unsaturated nitrogen hetrocycles based upon transition metal alkylidene- catalyzed ring-closing olefin metathesis. Successful application of this cyclisation process to the synthesis of a variety of nitrogen

heterocycles is done. The catalytic ring-closing olefin metathesis strategy is used of unsaturated nitrogen heterocycles from acyclic diene-amines.Tetrahydroazepines and seven-membered lactams can be were generated efficiently in good yield. Amides, too, are compatible with these metathesis conditions. Single and double cyclisation to form N-acyl-3- pyrrolines proceed smoothly within minutes at room temperature. Finally ring closure to form unsaturated five- and six- membered lactams were also tried to synthesised but turns out unsuccessful, due to the formation of stable chelated species. Generation of the corresponding amide chelate were accounted for the failure to observe cyclisation. It was reasoned that because metathesis of monosubstituted olefin is known to be more rapid than that of disubstituted olefins, addition of an alkyl substituent to the appropriate double bond might disfavour formation of the undesired intermediates. In practice, this strategy proved successful. Impurities in the reaction mixture (e.g., water or acids) can result in significant inhibition of the ring-closing metathesis process. The reaction also proceeds smoothly in CH2CI2, whereas use of a coordinating solvent such as THF results in a slower reaction.

16) Total Synthesis of (-)-Stemoamide Using Ruthenium-Catalyzed Enyne Metathesis Reaction[29]

The paper includes synthesis of Stemoamide, which was first isolated from the roots and rhizomes of Stemonaceous plants, is a polycyclic alkaloid possessing powerful insecticidal activity. This report have the total synthesis of (-)stemoamide from (-)-pyroglutamic acid using a ruthenium-catalyzed enyne metathesis developed by Grubbs. by Grubbs. The important characteristic features of intramolecularly enyne metathesis are that the carbon-carbon bond formation between the alkene and alkyne occurs to give a cyclization product, and the alkylidene part of the alkene moiety migrates to the alkyne carbon. The resultant diene moiety can be used for subsequent synthetic transformations. The starting enyne was prepared from (-)-pyroglutamic acid, When benzene solution of enyne and a catalytic amount of ruthenium catalyst(1) (5 mol %) was stirred at 50 °C for 11 h, enyne metathesis proceeded smoothly to give a 5,7-fused compound in 73% yield(Scheme 15). The total synthesis of (-)-stemoamide was accomplished from (-)-pyroglutamic acid in 14 steps in 9% overall yield

Scheme 15



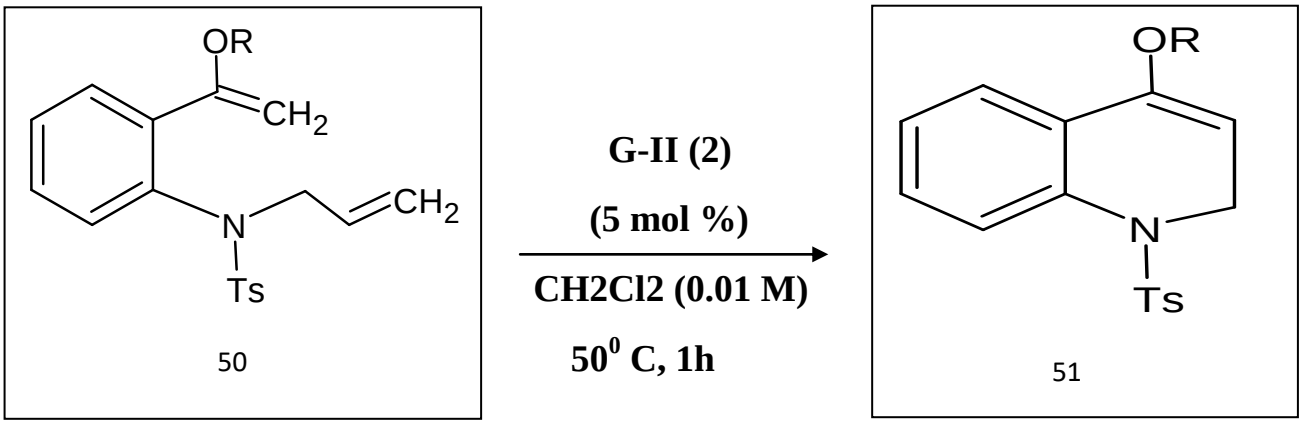
17) Enantioselective Total Syntheses of Manzamines A and Related Alkaloids[30]

In this research paper synthesis of manzamines A, which is constitute of growing and important family of structurally complex indole alkaloids that have been isolated from marine sponges. Manzamine A attracted considerable attention because of its potent antitumor and antimalarial activity and also was the first member of this group of alkaloids to be isolated. Related manzamine alkaloids are ircinol A and ircinal A. The synthesis of ircinal A required a total of 24 operations from commercially available starting materials, and the longest linear sequence was only 21 steps. The readily accessible chiral dihydropyrrole was first converted into the key tricyclic intermediate. The concise approach detailed herein highlights a novel strategy for assembling this tricyclic ABC ring core by a domino Stille /DielsAlder reaction. An unusual aspect of the key intramolecular Diels-Alder cycloaddition was the use of a vinylogous N-acyl urea as the dienophile. The synthesis of these complex indole alkaloids also demonstrates the power and versatility of RCM reactions for constructing 13- and 8-membered heterocyclic rings in highly functionalized setting.

18) Preparation of nitrogen-containing heterocycles using ring-closing metathesis (RCM) and its application to natural product synthesis [31]

The synthetic study of nitrogen-containing heterocycles using ring-closing metathesis (RCM) was seen for natural hetrocycles such as chiral bicyclic lactams, azacycloundecenes, axially chiral macrolactam, 1-2-dihydroquinolines,2-quinolinone and indoles; including a development of silyl-enol ether ene metathesis and isomerisation of terminal alkenes. All these natural hetrocycles were synthesised using Grubbs catalyst via RCM as mentioned in the previous reviews. Many quinolines alkaloids which shows important biologically activities such as quinine and chloroquinine contain substituent at 4-position. 4-siloxy-1,2-dihydroquinolines was synthesised using ene-enol ether metathesis. Enol methyl ether and enol siyil ether were prepared from commercially available o-aminoacetophenonen which was subjected to RCM conditions using G-I (1) the cyclised product was not obtained and the reactants was regenerated. In contrast when the same substrate was treated with G-II the product obtained in 95% yield (scheme 16)

Scheme 16:



R= Me,TBS

19) Highly Selective Synthesis of Bicyclic Quinolizidine Alkaloids and Their Analogues via Double RCM Reaction of *N*-Alkynyl-*N*-(1,ω)-alkadienyl Acrylamides[32]

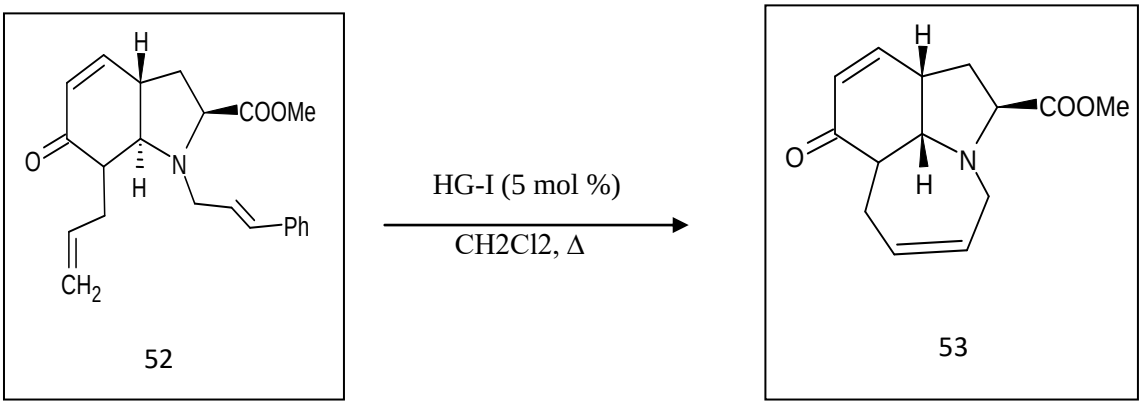
This paper includes synthesis of fused bicyclic lactams having quinolizidine alkaloid skeleton. These are common structural units of many important compounds displaying a broad range of biological activities. Ma and co-workers reported highly stereoselective

synthesis of bicyclic quinolizidine alkaloids and their analogues bearing 1,3-diene moiety via tandem ring closing metathesis reaction of N-alkenyl-(1,ω)-alkedienyl acrylamides using Grubbs catalyst I or II (1 or 2). The excellent stereo selectivity of the fused/dumbbell-mode cyclisation has been realized by the higher reactivity of the electron rich double bond or carbon-carbon triple bond combined with the lower reactivity of the electron deficient C=C towards metallocarbenes. The RCM precursors, N-containing trienynes were subjected to tandem RCM using 5 mol% of Grubbs' catalyst I or II in refluxing CH2Cl2 for 7-11 h to afford the desired fused bicyclic lactams that are suitable substrates for the preparation of polycyclic quinolizidine and other alkaloid derivatives via Diels-Alder reaction.

20) Total Synthesis of (−)-Tuberostemonine[33]

The paper includes first total synthesis of the complex pentacyclic, *Stemona* alkaloid, tuberostemonine. The desired product was accomplished in 24 steps and in 1.4% overall yield. The azepane subunit in the Stemona alkaloid (-)-tuberostemoninewas synthesised by substrate (52) which was synthesized in 10 steps from Cbz-protected L-tyrosine. In presence HG-I (3) led to the ring closure of the terminal double bond in (52) (Scheme 17).The presence of the α-unsaturated ketone moiety in (53) did not allow selective reduction of the isolated double bond in the azepane ring, so it was necessary to employ a three-step sequence to convert (53) (-)-tuberostemonine via a series of reactions in which the two γ-butyrolactone rings and the ethyl substituent were installed.

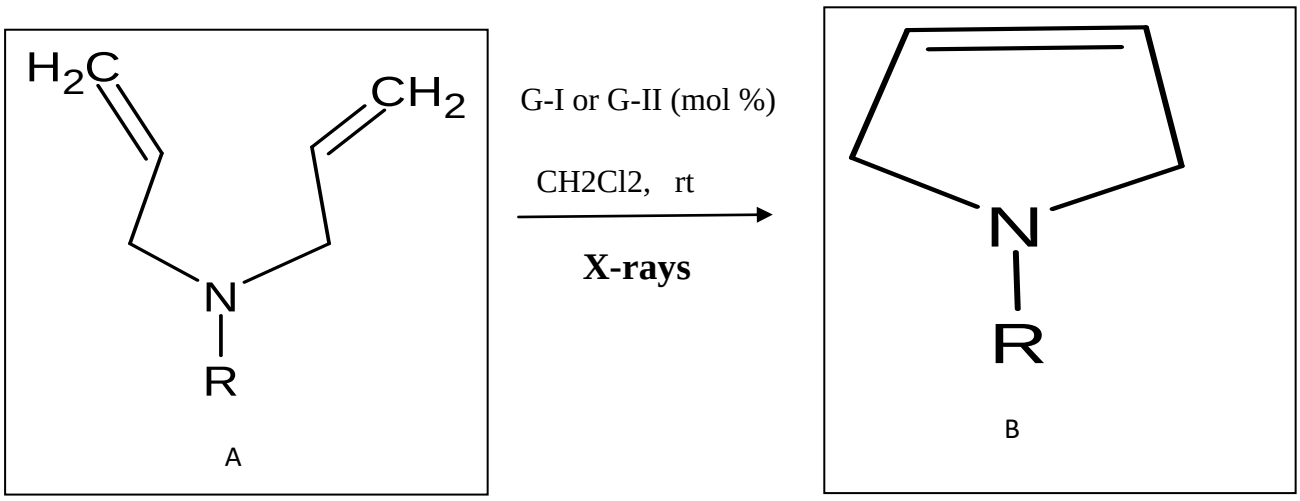
Scheme 17:



Methodology:

It is seen from the above reviewed research papers that, various natural nitrogen containing hetrocycles can be synthesises using ring closing metathesis using Grubbs catalyst. Over the past few years the need for the strategies for the incorporation of olefin metathesis has attracted considerable interest. Rapidly increasing demand has led to the development of many improved methods for the preparation of hetrocycles. Few examples of photo-assisted RCM were reported using microwaves and Ultraviolet rays for N-hetrocycles synthesis where high yields of product was obtained compared to normal RCM conditions due to photo-raditions[3435]. To add in it I would like to propose a new photo-assisted ring closing metathesis method using soft x-rays irradiation. N-aryldiallyl substrate can be synthesized from the corresponding aniline by allylation with allyl bromide in present of suitable base and solvent (A). RCM can be conducted on A to obtain the cyclised product (B) under X-rays conditions using Grubbs catalyst (1) or (2) in presence of DCM (solvent) at room temperature. The effects of X-rays on the reaction speed yield of product and catalyst can be studied varying the catalyst concentrations and starting N-hetrocycles.

Probable scheme:



Conclusion:

Alkaloids are an important class of natural compounds characterized by aromatic and heterocyclic fused rings which have significant biological activity. Nitrogen containing hetrocycles are backbone in many of the pharmaceuticals natural product, and plays vital role in modern drug design and drug discovery. A number of approaches for the synthesis of nitrogen-containing hetrocycles have been developed; one of the efficient method is by ring closing metathesis using Ruthenium catalyst. The progress of olefin metathesis since its discovery in the 1950s by Robert Grubbs has proved to be a compelling tool in materials science, medicinal, polymer and organic chemistry due to their stability, functional group tolerance, easy handling and commercial availability. Several important alkaloid families like pyrrolidine, pyrrolizidine, piperidine, indolizidine and quinolizidine was synthesised by RCM, carried on appropriate diene substrates, yielding in different ring sized heterocyclic units incorporated into molecules.

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