A Metathesis Based Approach to the Synthesis of Heteroaromatic Compounds

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Declaration

The work described in this thesis is entirely my own, except where I have either acknowledged help from a named person or given reference to a published source. Text taken from another source will be enclosed in quotation marks and a reference given.

Signature:  Date: 24th July, 2011

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Abstract

A Metathesis Based Approach to the Synthesis of Heteroaromatic Compounds

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The olefin metathesis reaction is a well established and powerful method for the synthesis of alkenes. This reaction can be further classified into the intermolecular process known as cross-metathesis and the intramolecular process known as ring-closing metathesis. The aim of these studies is the use of the two variants of the metathesis reaction for the development of new methods for the synthesis of heteroaromatic structures, in particular the synthesis of polysubstituted pyridines (Figure 1).

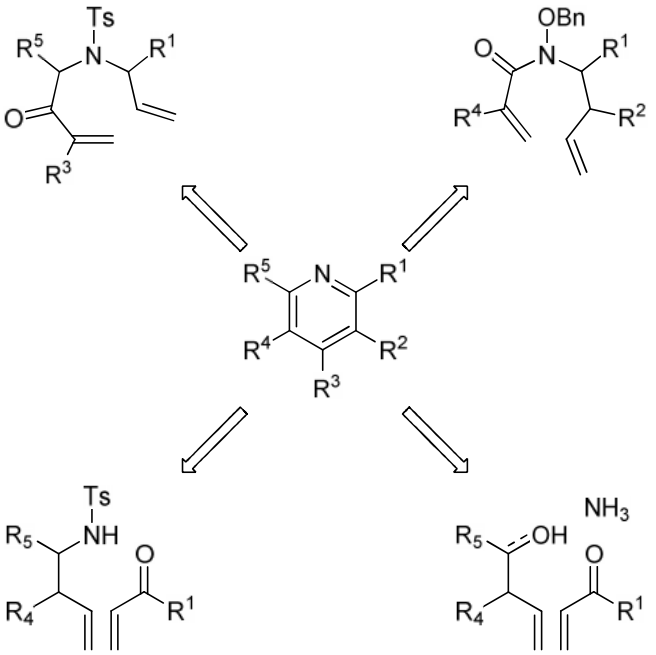

***Figure 1**-Different retrosynthetic analysis of pyridine.*

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Of all the bonds I have made, ours is the strongest

Abbreviations

Ac	acetyl
ADMET	acyclic diene metathesis polymerisation
app	apparent
aq.	aqueous
Ar	aromatic
Bn	benzyl
Boc	*t*-butoxycarbonyl
br	broad
Bu	butyl
ca.	*circa*
cat.	catalytic
CI	chemical ionisation
conc.	concentrated
COSY	correlation spectroscopy
Cp	cyclopentadienyl
Cy	cyclohexyl
DABCO	1,4-diazabicyclo-(2,2,2)octane
DBU	1,8-diazabicyclo[5.4.0]-undec-7-ene
1,2-DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-*p*-benzoquinone
DEPT	distortionless enhancement by polarisation transfer
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutyl aluminium hydride
DMA	*N*,*N*-dimethylacetamide
DMAP	4-dimethylaminopyridine
DMB	3,5-dimethoxybenzoin
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
dppp	diphenylphosphino propane
dr	diastereomeric ratio
E1	unimolecular elimination
E1cB	unimolecular elimination-conjugate base
EDCI	*N*-(3-dimethylamino propyl)-*N*'-ethyl carbodiimide
eq.	equivalent(s)
ESI	electron spray ionisation
Et	ethyl
FI	field ionisation
g	gram(s)
G-I	Grubbs' first generation catalyst
G-II	Grubbs' second generation catalyst
GC	gas chromatography
h	hour(s)
HG-I	Hoveyda-Grubbs' first generation catalyst
HG-II	Hoveyda-Grubbs' second generation catalyst
HMDS	hexamethyldisilazane
HMPA	hexamethyl-phosphoramide
HMQC	heteronuclear multiple quantum correlation
HOBt	1-hydroxybenzotriazole

HRMS	high resolution mass spectroscopy	ppm	parts per million
		Pr	propyl
i	*iso*/*ipso*	R	generic organic substituent
IR	infra-red	RCM	ring-closing metathesis
J	coupling constant	ROM	ring-opening metathesis
KHMDS	potassium bis-(trimethylsilyl)amide	ROMP	ring-opening metathesis polymerisation
LC	liquid chromatography	rr	Ratio of regioisomers
LDA	lithium diisopropylamide	RRCM	relay ring-closing metathesis
LG	leaving group	rt	room temperature
lit.	literature	*s*	*secondary (sec)*
m	*meta*	sat.	Saturated
M	molar	SES	2-trimethylsilylethane-sulsonyl
max	maximum		
m-CPBA	*m*-chloroperbenzoic acid	*t*	*tertiary (tert)*
Me	methyl	TBAF	tetrabutylammounim fluoride
Mes	2,4,6-trimethylphenyl	TBAI	tetrabutylammonium iodide
min	minute(s)	TBS	*t*-butyldimethylsilyl
mol	mole	Tf	trifluoromethylsulfonyl
m.p.	melting point	TFA	trifluoroacetic acid
MS	mass spectrometry	TFAA	trifluoroacetic anhydride
m/z	mass/charge ratio	THF	tetrahydrofuran
n	*normal*	TIPS	triisopropylsilyl
NBS	*N*-bromosuccinimide	TLC	thin layer chromatography
NHC	*N*-heterocyclic carbene	TMEDA	*N*,*N*,*N*',*N*'-tetramethyl-ethylenediamine
NMR	nuclear magnetic resonance		
n.O.e	nuclear Overhauser effect	TMS	trimethylsilyl
o	*ortho*	Ts	*para*-toluenesulfonyl
p	*para*	X	generic heteroatom
PCC	pyridinium chlorochromate	Z-1B	Zhan-1B catalyst
Ph	phenyl		
PMB	*para*-methoxybenzyl		

Chapter one: Introduction

Chapter one: Introduction

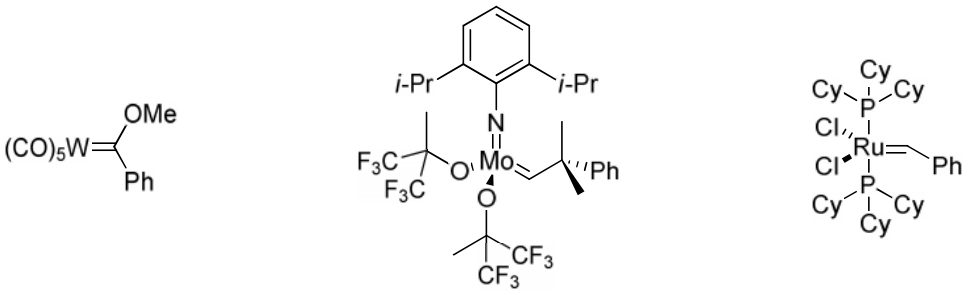
1.1 The olefin metathesis reaction

The synthesis of alkenes represents an important challenge in organic chemistry. The formation and functionalization of this functional group has been intensively studied and the development of methods to achieve this goal has made a contribution of paramount importance in organic chemistry.[1]

During investigations towards the development of new polymer products, several investigators started applying transition metal catalyzed polymerisation to new olefin starting materials and this led to the discovery of products arising from ring-opening polymerisation and olefin disproportionation.[2]

Calderon and co-workers studied these findings and postulated that these processes are mediated byte same reaction. They introduced the term "olefin metathesis" in 1967.[3]

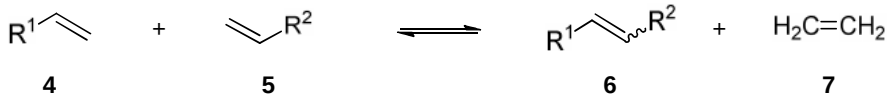
From this point onward, extensive works to better understand this transformation was undertaken.[4] The discovery of well defined metathesis catalysts **1**, **2** (S-I) and **3** (G-I) (Figure 1.1), have made this reaction robust and tolerable to many functional groups, to the point that it is now a standard method to consider for the synthesis of any unsaturated molecule or to solve a wide range of synthetic problems.[4]



1 **2 (S-I)** **3 (G-I)**

***Figure 1.1**- Well defined olefin metathesis catalysts.*

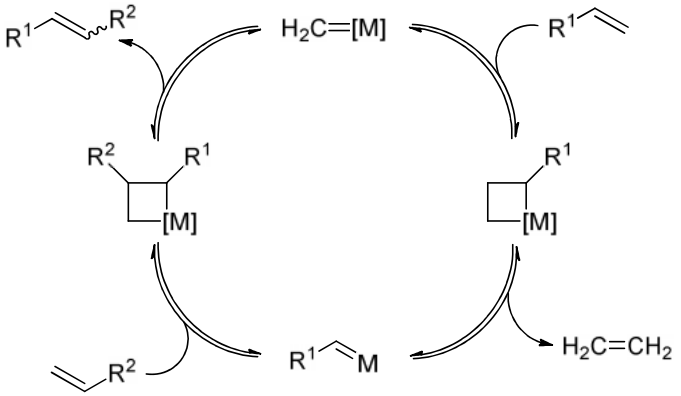
The olefin metathesis reaction involves a metal-catalyzed exchange of alkylidene groups of two olefins **4** and **5** to afford a truncated product **6** and by-product **7** (Scheme 1.1). The importance of this process is that the exchange of two synthetically simple olefins gives rise to a more complex alkene.



4 **5** **6** **7**

Scheme 1.1 *- Cross Metathesis.*

The mechanism proposed by Chauvin is the most consistent with the experimental data and involves the interconversion of an olefin and metal alkylidene *via* alternating [2+2] cycloaddition and cycloreversion (Scheme 1.2).[5]



Scheme 1.2 *- Olefin metathesis reaction mechanism.*

There are two main driving forces for the metathesis reaction; the release of highly volatile ethylene gas **7**, and in the case of ring-opening metathesis the release of ring strain.

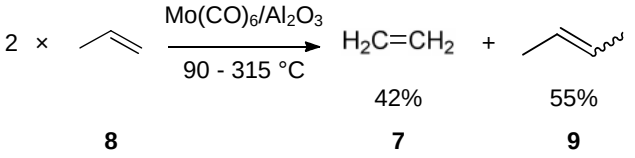
1.2 Development of well-defined olefin metathesis catalysts

1.2.1 Early catalysts

Since the discovery of the olefin metathesis reaction a great deal of effort has been put into the development of an air-stable catalyst that is capable of converting starting material to the desired product in the presence of a wide array of functional groups.[4] In the early stages of

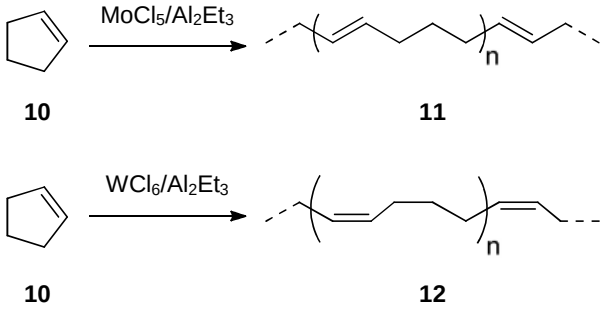
discovery, this reaction was performed by utilizing a mixture of metal salts, which were only active in the presence of simple olefins.[6] These catalysts were derived from the Ziegler catalyst system ($TiCl_4/Al(C_2H_5)_2Cl$) and they work essentially as a black box, in which several additives were needed and there was not a real understanding of how they work.[6]

In 1964, Banks and Bailey reported a new catalytic disproportionation reaction of linear olefins (Scheme 1.3).This reaction was mediated by a molybdenum hexacarbonylalumina catalyst or a tungsten hexacarbonylalumina catalyst.[6]



***Scheme 1.3**-Disproportionation reaction of linear olefins.*

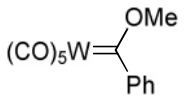
In the same year, Natta and co-workers reported the ring-opening polymerisation of cyclic olefin **10** using both a molybdenum pentachloride triethyl aluminium and a tungstenium hexachloride triethyl aluminium system to generate olefin **11** and **12** (Scheme 1.4).[7]



***Scheme 1.4** - Ring-opening polymerisation.*

1.2.2 Fisher carbenes

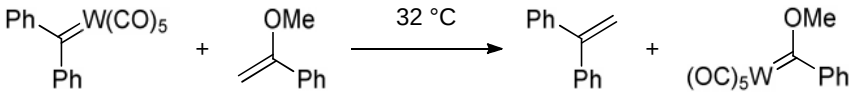
An important development was the isolation of a new type of organometallic compound **1**, which was later termed a Fisher metal carbene (Figure 1.2). These complexes contained a divalent organic ligand coordinated to the metal centre.[8]



1

Figure 1.2 *- A tungsten-based Fisher carbene.*

These compounds had a new type of metal-carbon bond and their appearance was a source of inspiration in understanding the basic mechanism of olefin metathesis. For example, when carbene **13** was combined with alkene **14**, a new metal carbene **1** and olefin **15** was obtained.[9] This alkylidene exchange is a key step in Chauvin's proposed mechanism for the olefin metathesis reaction (Scheme 1.5).[6]



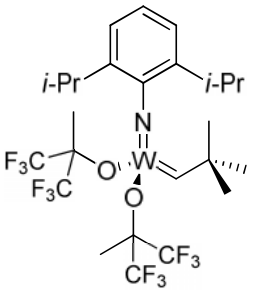
13 **14** **15** **1**

Scheme 1.5 *- Olefin exchange in Fisher carbene.*

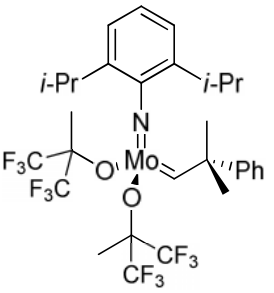
Despite some Fisher carbenes possessing the requisite properties to catalyze the olefin metathesis reaction, they usually have low catalytic activity and the reliable synthesis of a range of alkenes would not be a viable task using them.[10 - 13]

1.2.3 Molybdenum catalysts

Based on these findings, several investigators started to prepare different carbenes and studied their catalytic properties on the metathesis reaction. Schrock and co-workers developed a number of efficient tungstenium based catalysts such as **16** (Figure 1.3).[14] An important breakthrough was the synthesis of the molybdenum variants of these catalysts, for example S-I, because of the increased activity that was achieved when used in a metathesis reaction.[15]



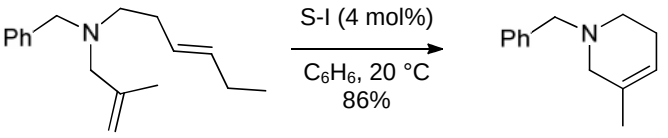
16



S-I

Figure 1.3 *- Schrock's catalysts.*

Catalyst S-I is known as Schrock's catalyst and it was used to catalyze many metathesis processes.[16 - 18] Grubbs and Fu showed the ring-closing metathesis (RCM) of several terminal olefins to prepare a variety of heterocycles in good yields, for example, the conversion of diene **17** into unsaturated piperidine **18** (Scheme 1.6).[19]



17 **18**

Scheme 1.6 *- RCM of terminal olefins using Schrock's catalyst 2.*

The disadvantage of S-I, and many of the high oxidation state early-transition metal complexes used as metathesis catalysts, is their sensitivity to air and moisture. In addition, they do not tolerate well the presence of protic or polar functional groups, due to the electrophilicity of the active metal species.[4]

Complexes of late transition metals which would be less electrophilic were thought to solve this problem. Schrock and co-workers started developing rhenium based catalysts, but they never achieved the required activity to be successfully employed in organic chemistry.[20]

1.2.4 Ruthenium catalysts

The importance of the metathesis reaction promoted the development of catalysts that were more resilient towards moisture and air. Particularly important was the development of a catalyst that was able to tolerate a wide range of functional groups.[4]

The culmination of many years of effort to meet this challenge can be summarized in the discovery by Grubbs and Fu of a series of ruthenium carbene based catalysts **19** (G-0) and G-I, known as Grubb's first generation catalyst (Figure 1.4).[21]

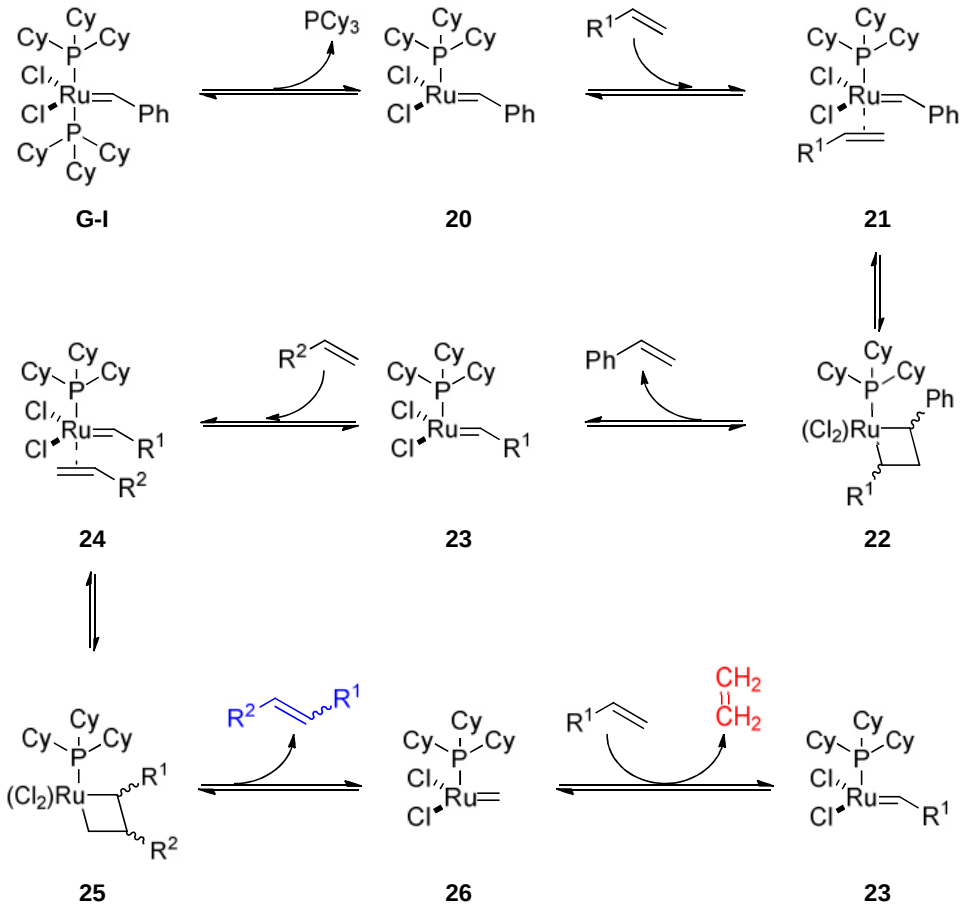


19 (G-0) **G-I**

Figure 1.4*- Grubbs' first generation catalysts.*

Mechanistic studies on the catalytic cycle of G-I indicated that the first step involves a dissociation of one tricyclohexylphosphine ligand, leading to a 14 electron intermediate **20**, which reacts with an olefin to produce a monophosphine-olefin complex **21**. In the third step, coupling of the olefin and complex **21** leads to the formation of metallacyclobutane **22** (Scheme 1.7).[22]

There are two alternative isomeric metallacycles that can be formed, one is a 1,3-disubstituted metallacyclobutane **22** which collapses to form a new olefin and new alkylidene species **23**. Another is a 1,2-disubstituted metallacyclobutane **25**, which leads to the desired cross product and new alkylidene species **26**.[22]



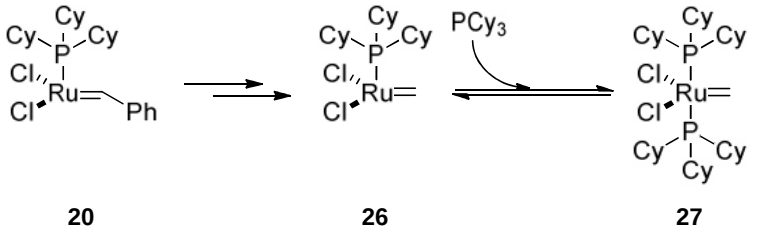
Scheme 1.7 *- Mechanism of catalyst activation.*

This series of steps are reversible and the direction in which the metallacycle can collapse is driven by the formation of ethylene as a volatile gas, when alkylidene species **26** is converted to **23**.[23]

In accordance with this mechanism, Grubbs determined that the overall catalytic activity of G-I is mediated by the relative rates of three processes: (1) phosphine dissociation, (2) phosphine re-coordination and (3) olefin binding. The key to high catalytic activity is the 14 electron intermediate **20** being able to coordinate with an olefin faster than reassociation with any free phosphine.[4]

It is noteworthy to mention that after the first turnover the catalytically-active species is more likely to be **26** than **20** (Scheme 1.8). The 14 electron catalyst **26** would associate with a tricyclohexylphosphine ligand to form **27**. Studies on the decomposition of **27** reveal that

this is a thermally unstable system. The half-life of **27** is 40 minutes at 55 °C, while the half-life of G-I is 8 days at the same temperature.[24]



Scheme 1.8*-Catalyst deactivation mode.*

Adding CuCl as a phosphine scavenger facilitates the formation of the active species **26**, but this does not represent an overall increase in catalytic turnover, since it also increases the rate of catalyst decomposition.[24]

With the intention of finding a ligand that would facilitate phosphine disassociation, Nolan[25] and Grubbs[26]independently reported similar ruthenium based catalysts which have a tricyclohexylphosphine ligand replaced by an *N*-heterocyclic carbene (NHC) ligand (Figure 1.5).

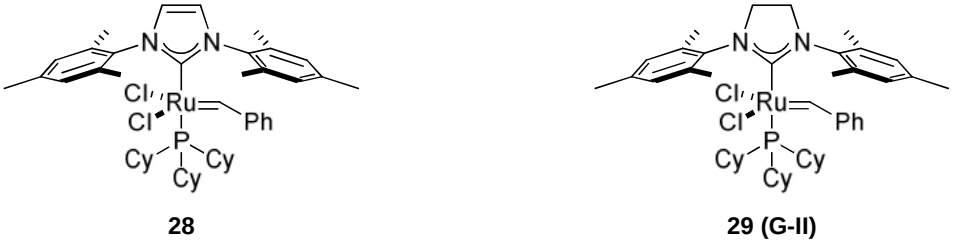
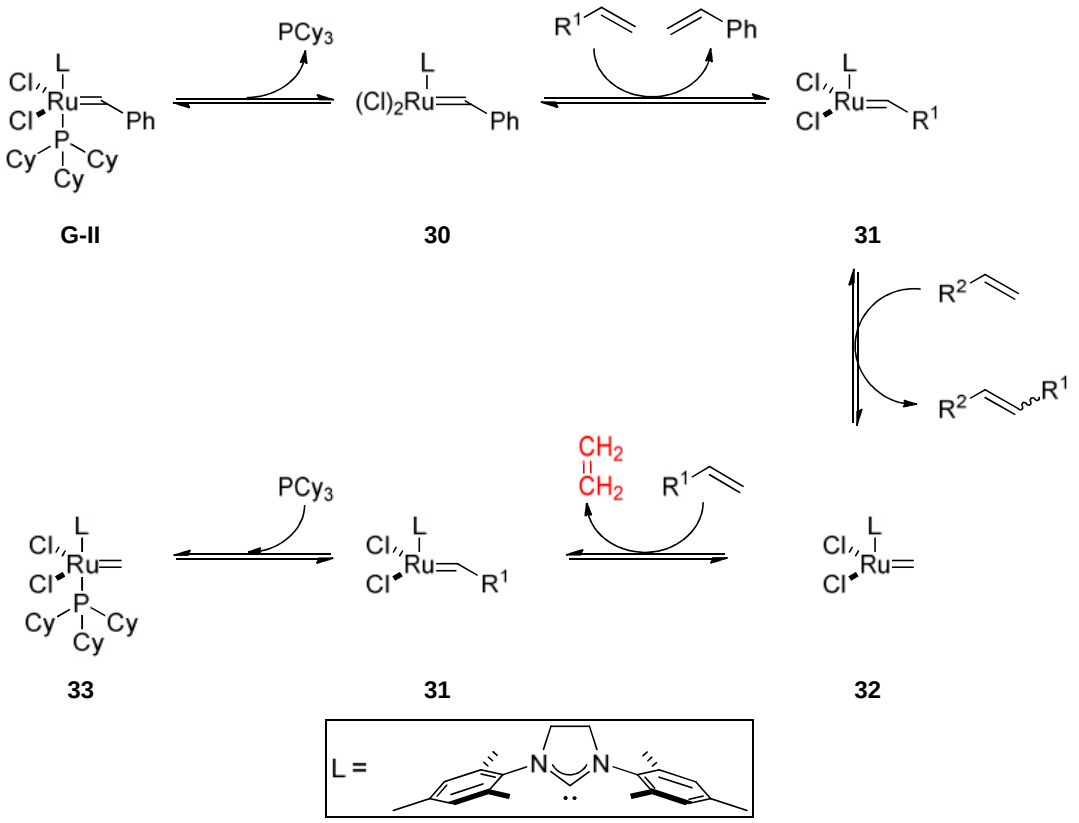


Figure 1.5 *- NHC based metathesis catalysts.*

Catalyst **29** (G-II) is known as Grubbs' second generation catalyst and is now commercially available. This catalyst represented a breakthrough in olefin metathesis and it has transformed this reaction into a well established method for organic synthesis. This is mainly because the second generation catalyst G-II can perform metathesis reactions of highly substituted olefins, as well as electron poor olefins, while maintaining a wide range of functional group compatibility.[25-31]

Phosphine dissociation has been proven to be slower in this second generation system, and the increase in catalytic activity is explained by a preference to coordinate an olefinic substrate, thereby significantly slowing down catalyst decomposition (Scheme 1.9).[32]

The mechanism by which carbene G-II catalyses the metathesis reaction is also dissociative and involves the loss of a tricyclohexylphosphine ligand to produce the catalytically active species **30**, **31** and **32**. The loss of ethylene is the main driving force of this reaction (Scheme 1.9).[32]



Scheme 1.9 *- Formation of metal alkylidene species in catalyst G-II.*

Is also important to point out that methylidene complex **33**, obtained from the recombination of the 14 electron intermediate **32** and free phosphine ligand, is a poor initiator that decomposes rapidly.[32]

In 1999, Hoveyda and co-workers designed a system based on catalyst G-I, which was thought to be more resilient to moisture and air. By treatment of carbene G-I with 2-isopropoxystyrene, catalyst **34** (HG-I)was obtained which could then be isolated by flash

column chromatography (Figure 1.6). This carbene is chelated by an oxygen ligand that is tethered to the aromatic portion of the alkylidene.[33]

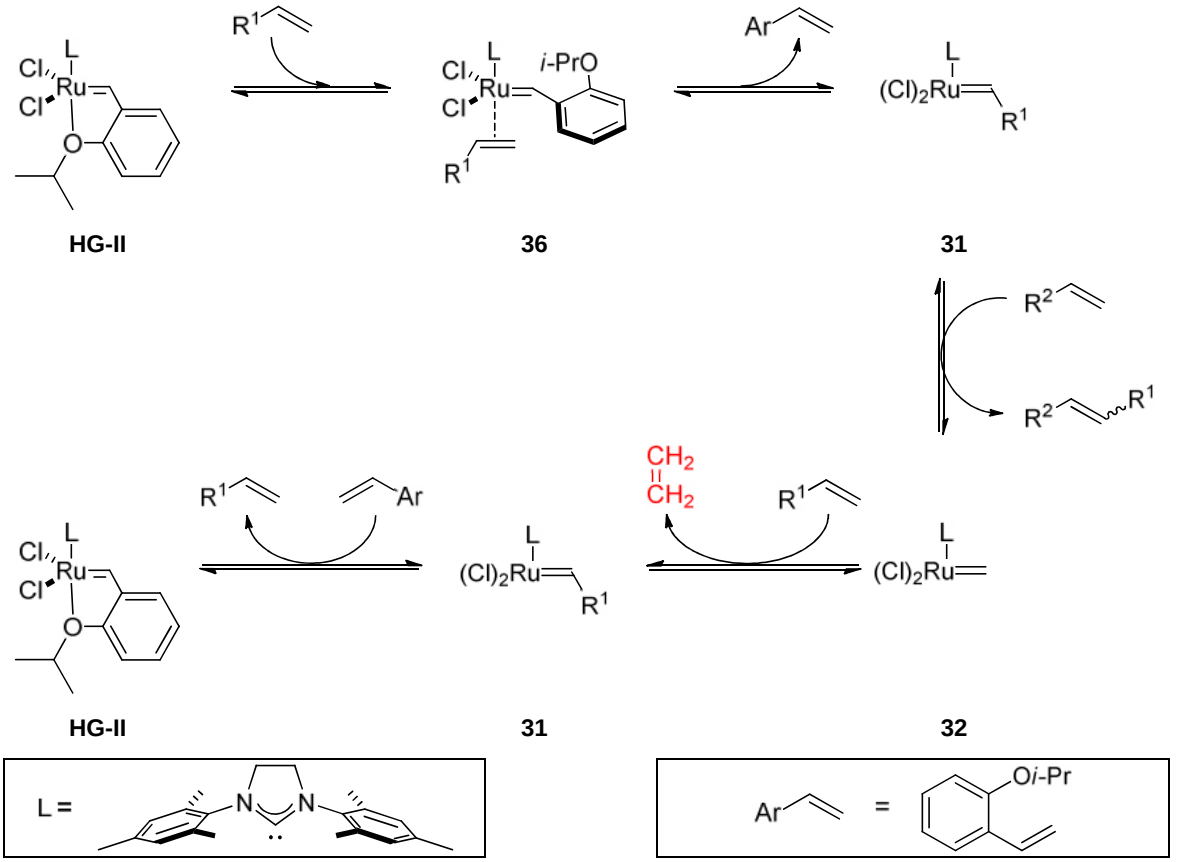


34 (HG-I) **35 (HG-II)**

***Figure 1.6**-Hoveyda-Grubbs'1st and 2nd generation catalysts.*

Hoveyda also prepared a second generation system **35** (HG-II), from catalyst G-II, which gave a much higher catalytic activity; this catalyst is known as Hoveyda-Grubbs' second generation catalyst and is now commercially available (Figure 1.6).[34]

In 2010, Vorfalt and Wannowius studied in detail the mechanism of initiation of carbene HG-II, showing that the olefinic substrate participates in the initiation step, opposite to catalyst G-II. This study reveals an associative type mechanism and it explains why catalyst HG-II initiates at a much lower rate (Scheme 1.10).[35]



Scheme 1.10 *- Proposed mechanism for catalyst* ***HG-II****.*

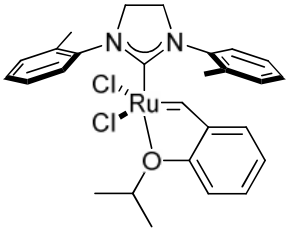
The higher catalytic activity of carbene HG-II is mainly due to its stability, as there is no phosphine ligand present that can recombine with the 14 electron species **32**. Instead, this species can recombine with 2-isopropoxystyrene to form carbene HG-II and regenerate the catalyst.[34]

1.2.5 Recent catalysts for the olefin metathesis

Catalysts G-I, G-II and HG-I are all capable of forming di-substituted olefins *via* RCM and in some cases *via* CM. Catalyst HG-II can be used for the synthesis of di-substituted and in some cases tri-substituted olefins.[27,36]

Despite the major advances in olefin metathesis, catalyst HG-II is not capable of initiating in the presence of terminal olefins that are 1,1-di-substituted and for this reason the synthesis of tetra-substituted alkenes *via* a metathesis reaction is still a major limitation and catalyst

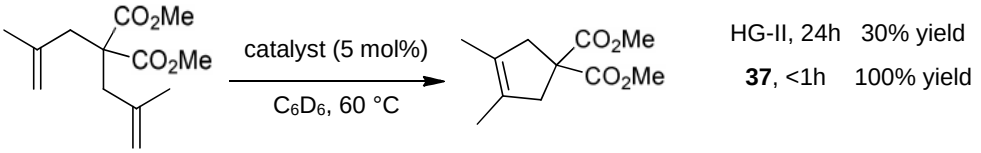
improvement is an ongoing effort. To this end, Grubbs and co-workers designed a new NHC ligand and synthesized carbene **37** (Figure 1.7).[37]



37

Figure 1.7*-Grubbs' catalyst for 1,1-disubstituted olefin.*

It was demonstrated that diene **38** is readily converted to the cyclopentene derivative **39** *via* RCM in the presence of the new catalyst **37**. In contrast, when catalyst HG-II is used only 30% conversion is observed (Scheme 1.11).[37]



38 **39**

Scheme 1.11 *- RCM of diene **38**.*

This new system has a much smaller aromatic portion in the NHC ligand in order to reduce steric congestion in the transition state, allowing it in some cases to initiate on 1,1-disubstituted olefins. The transition state **40**, which would lead to the formation of a 1,3-disubstituted metallacyclobutane, and the transition state **41**, which would lead to the formation of a 1,2-disubstituted metallacyclobutane, and subsequently to the desired RCM product, are less congested compared to **42** and **43** obtained from catalyst HG-II (Figure 1.8).[23]

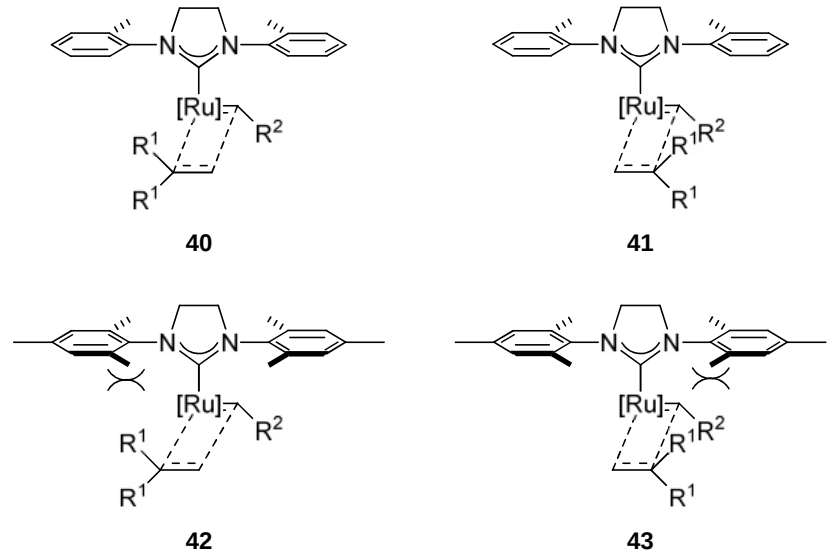


***Figure 1.8**- transition state for the formation of metallacyclobutanes.*

Grubbs and co-workers also prepared catalyst **44** which has a more bulky aromatic portion in the NHC ligand compared to catalyst **37** and HG-II. The reactivity in a CM of a series of 1,1-disubstituted olefins was studied (Figure 1.9).[23]

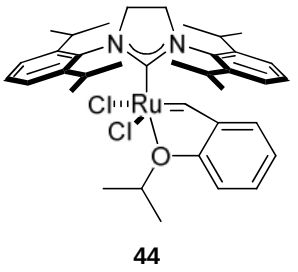
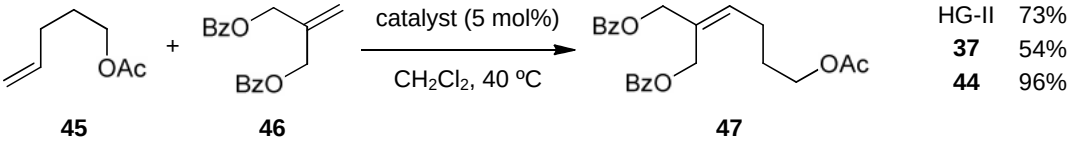


***Figure 1.9** - Catalyst for selective CM of 1,1-disubstituted olefin.*

Alkene **45** and 1,1-disubstituted olefin **46** were subjected to a cross-metathesis (CM) to obtain the trisubstituted olefin **47**. Catalyst **44** was more effective than using catalyst HG-II or **37** (Scheme 1.12).[23]



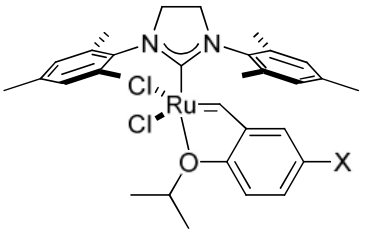
***Scheme 1.12** - CM of 1,1-disubstituted olefin **49**.*

The yield of the CM product is much higher using catalyst **44**, because when using a less bulky catalyst like **37** there is an increase in the selectivity for the formation of **40** versus **41** (Figure 1.8), while with the bulky ligand this selectivity is much smaller and therefore the rate of formation of the 1,2-disubstituted metallacyclobutane, which leads to the desired CM product, is increased.[23]

In order to obtain more active catalysts, several investigators have prepared a series of carbenes based on catalyst HG-II, but with an electron deficient styrene portion**.** Zhan prepared the arylsulfonamide system **48** (Z-1B) and obtained a catalyst that showed a much faster rate of initiation (Figure 1.10).[38]

In 2002, Grela and co-workers synthesized catalyst **49** which incorporated an aryl nitro group in order increase the rate of initiation in the catalytic cycle (Figure 1.10).[39]

Maudit and co-workers also prepared carbene **50**, which has similar electronic properties to catalyst **49**, but utilizes a triflouroacetamide as an electron-withdrawing group in the styrene portion of the catalyst (Figure 1.10).[40]

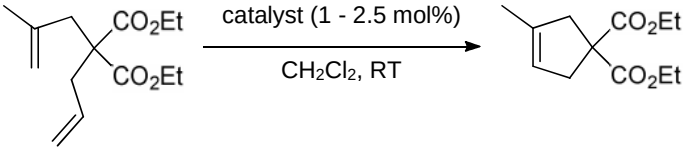


X = SO_2NMe_2	**48 (Z-1B)**	Zhan
X = NO_2	**49**	Grela
X = $NHCOCF_3$	**50**	Maudit

Figure 1.10 *- Catalysts with higher rates of initiation.*

These catalysts show a significant improvement in their activity while having comparable stability to the parent system, catalyst HG-II. The higher rates of initiation are due to the decrease of electron density in the chelating oxygen, facilitating the displacement of this oxygen, and opening of the chelate, by an olefinic substrate.

For example, the rate of conversion of **51** to **52** *via* RCM was examined for different catalysts (Scheme 1.13).[39] Grela's catalyst **49** was compared to catalyst G-II and HG-II and after two hours, Grela's catalyst achieved 100% conversion (Table 1.1).[39]



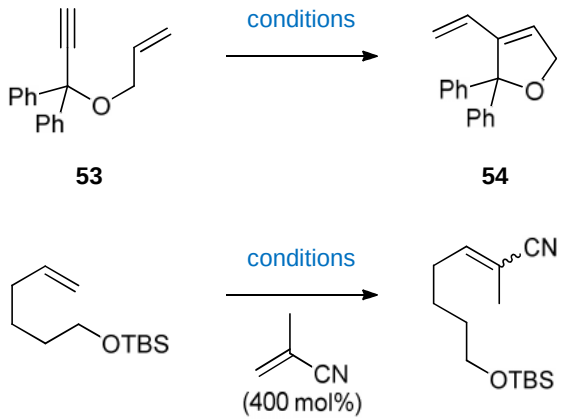
51 **52**

Scheme 1.13 *- RCM of diene **51**.*

Catalyst	Yield after 2 hours
49 (1.0 mol%)	100%
G-II (1.0 mol%)	100%
HG-II (2.5 mol%)	15%

Table 1.1 *- RCM conversion of **51**.*

A series of alkenes were constructed using metathesis in order to compare more difficult transformations (Scheme 1.14).[39,40] These experiments demonstrate the higher catalytic activity of catalyst **49** and **50** over second generation catalyst G-II and HG-II.



53 **54**

55 **56**

49 (1.0 mol%), RT, 2 hours 99%
HG-II (2.5 mol%), RT, 18 hours 50%
28 (2.5 mol%), 80 ºC, 1 hour 85%
50 (0.3 mol%), RT, 0.5 hours 98%

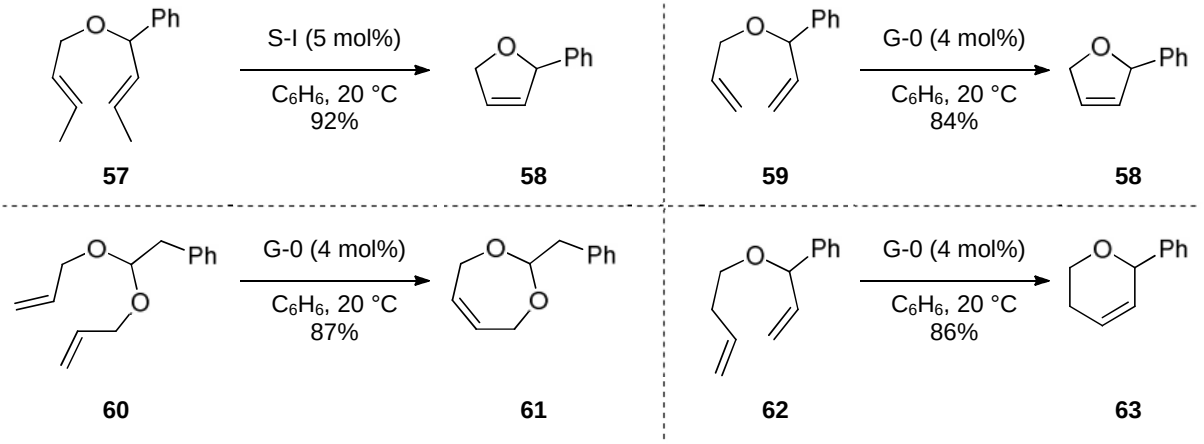
49 (5.0 mol%), 40 ºC, 16 hours 58%
G-II (5.0 mol%), 80 ºC, 24 hours 0%

Scheme 1.14 *- Catalyst comparison using different substrate.*

1.3 Synthesis of heterocycles by ring-closing metathesis

1.3.1 Synthesis of oxygen containing heterocycles

In 1992, Grubbs and co-workers described the application of the metathesis reaction for the synthesis of five, six and seven membered ring oxygen-containing heterocycles using catalyst S-I (Scheme 1.15).[41]They subsequently demonstrated that similar heterocycles, plus some new oxygen-containing heterocycles, could be catalyst G-0.[42]



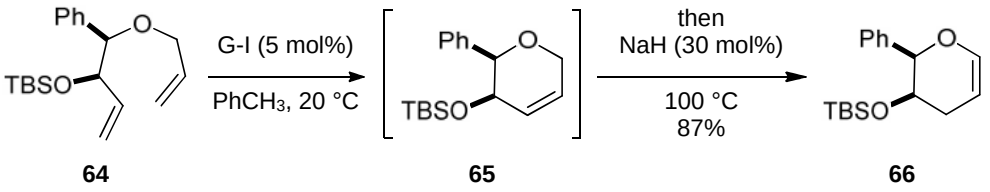
Scheme 1.15 *- Synthesis of heterocycles via RCM.*

This seminal work demonstrated the value of the metathesis reaction in organic chemistry due to the simplicity with which an important class of organic compounds could be achieved in a short sequence. These findings served as a platform on which many investigators used the metathesis reaction for the construction of several heterocyclic frameworks.[43]

The synthesis of 3,6-dihydropyrans **63** is a relatively simple task since the starting allylic-homoallylic ether **62** can be easily prepared. However, a RCM approach to the synthesis of a 3,4-dihydropyran **66** using a similar approach would require an enol ether to be used as the starting material. The synthesis of enol ethers is more challenging and makes this approach less attractive,

An elegant solution to this problem is the use of a two step, one pot, protocol in which the carbene serves first as a metathesis catalyst and is then converted to a metal hydride species

capable of performing a double bond isomerisation. Schimdt and co-workers use this tandem process to synthesize the 3,4-dihydropyran **66** from allylic-homoallylic alcohol **64** *via* 3,6-dihydropyran **65** (Scheme 1.16).[44]



64 **65** **66**

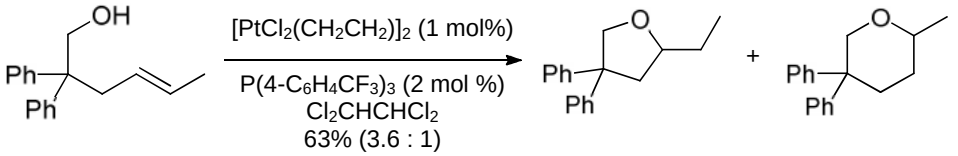
Scheme 1.16 *- Synthesis of 3,4-dihydropyran **66**.*

A general methodology for the synthesis of heterocyclic compounds based on RCM was demonstrated by these seminal reports, using an acyclic diene followed by a RCM to form the desired cyclic product.

While the synthesis of heterocycles is an important endeavour in organic chemistry, there are few general methods that are capable of making an array of different size heterocyclic rings.

An attractive tactic to the synthesis of cyclic ethers is *via* the intramolecular attack of a tethered hydroxyl group to an electron deficient carbon, generated from an alkene.

For example, Widenhoefer and co-workers developed a platinum-catalyzed hydroalkoxylation.[45] Hydroxyalkene **67** was converted to a mixture of tetrahydrofuran **68** and tetrahydropyran **69** (Scheme 1.17).

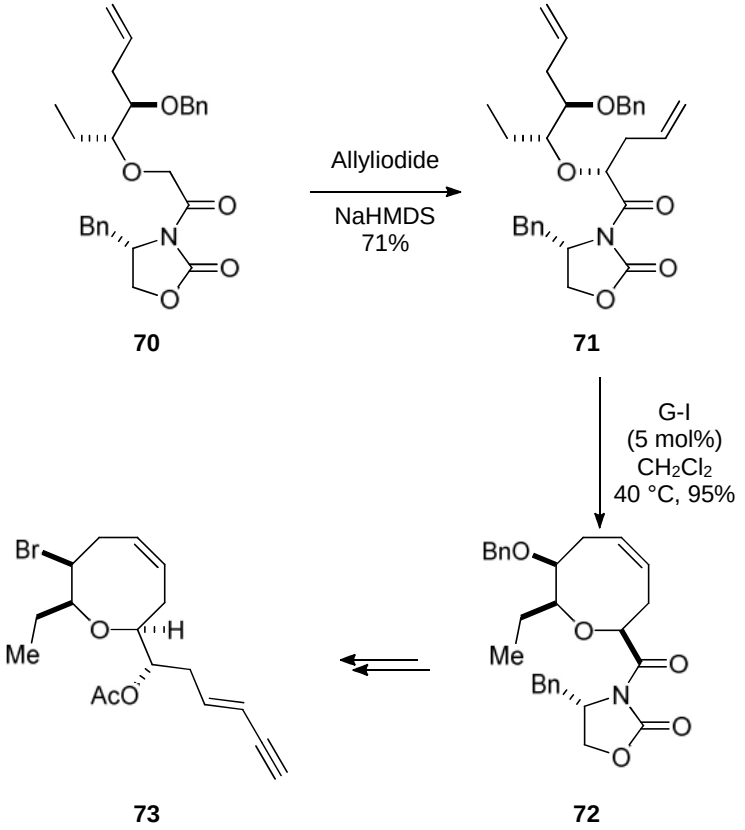


67 **68** **69**

Scheme 1.17 *- Hydroalkoxylation of alkenes.*

The main advantage of a RCM approach to cyclic structures relies on the predictable regiocontrolled outcome of this reaction. Furthermore a RCM approach is modular in the sense that the required diene is formed from two fragments joined by the desired heteroatom.

Using this approach, several natural products containing an oxygen heterocycle have been prepared. In 1999, Crimmins and co-workers employed a RCM approach for the synthesis of (+)-laurencin **73**. This target consists of an eight membered oxygen-containing ring. The diene **71** is formed *via* a stereoselective Evans' auxiliary-controlled alkylation of **70**, which is then converted to ring **72** *via* a RCM (Scheme 1.18).[46 - 48]

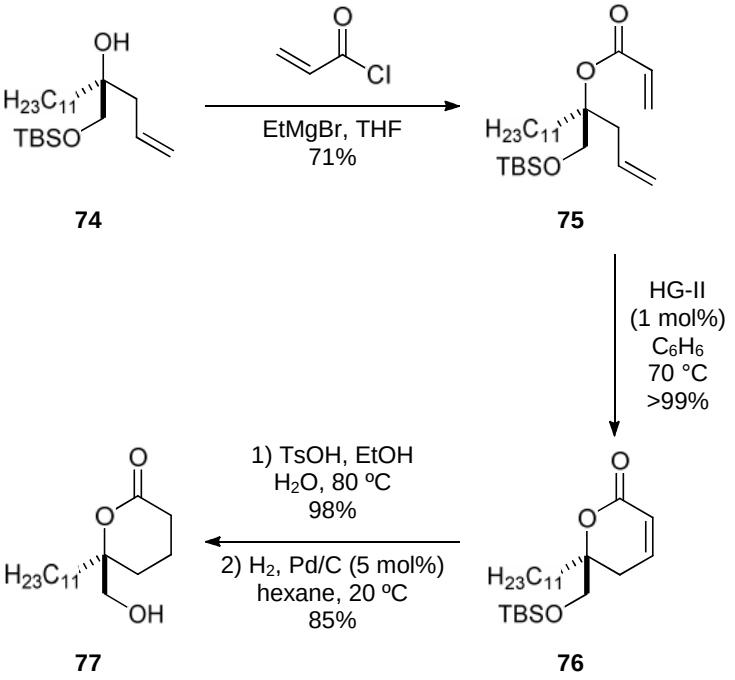


Scheme 1.18 *- Crimmins' synthesis of (+)-laurencin**73**.*

The synthesis of five- and six-membered lactones as well as macrolactones has also been achieved by a RCM approach.[49,50] A common strategy has emerged, consisting of a diene synthesis from an unsaturated acid derivative and an alcohol, followed by RCM of this diene to afford the desired unsaturated heterocycle.

In 2002, Honda and co-workers utilized this approach to achieve the total synthesis of several natural products, for example (+)-tanikolide **77** (Scheme 1.19).[51] The homoallylic alcohol **74** undergoes esterification with acryloyl chloride to produce diene **75**. RCM of

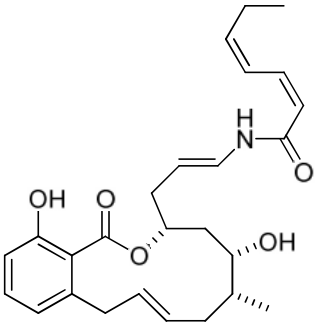
diene **75** using catalyst HG-II afforded the unsaturated lactone **76**, which was readily converted to (+)-tanikolide **77** in two further more steps.



Scheme 1.19 *- Honda's synthesis of (+)-tanikolide.*

The synthesis of macrocyclic lactones using this approach can be challenging depending on the ring size, nevertheless this strategy has been widely used to achieve many important targets.[52]

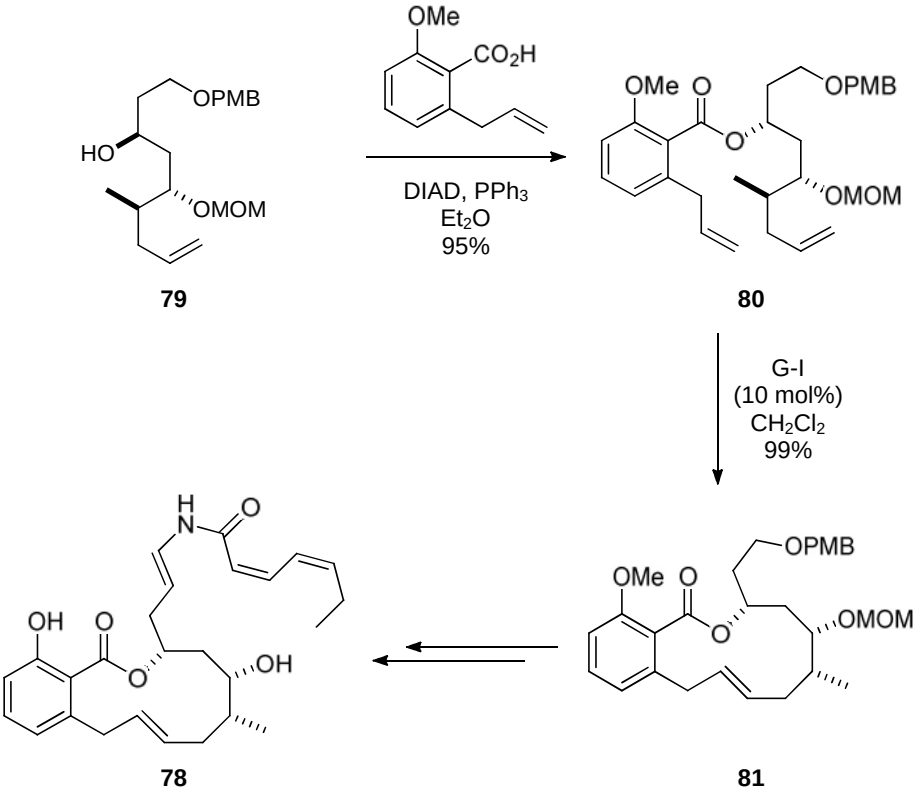
(+)-Salicylihalamide A **78** was isolated from Haliclona by Body in 1997 and it consists of a 12-membered salicylate macrolide (Figure 1.11).[53,54]This target displays potent cytotoxicity in the NCI 60-cell line human tumour assay and a total synthesis of this molecule was sought in order to prepare quantities needed for a thorough biological evaluation.



78

Figure 1.11 *- (+)-salicylihalamide A.*

In 2000, De Brabander and co-workers achieved the total synthesis of **78**using a RCM approach (Scheme 1.20). The synthesis of diene **80** was accomplished by esterification of alcohol **79** with the corresponding acid *via* a Mitsunobu reaction. RCM of **80** using catalyst G-I affords the macrocycle **81** in excellent yields and this is then converted to the desired target **78** in ten more steps.[55 - 57]



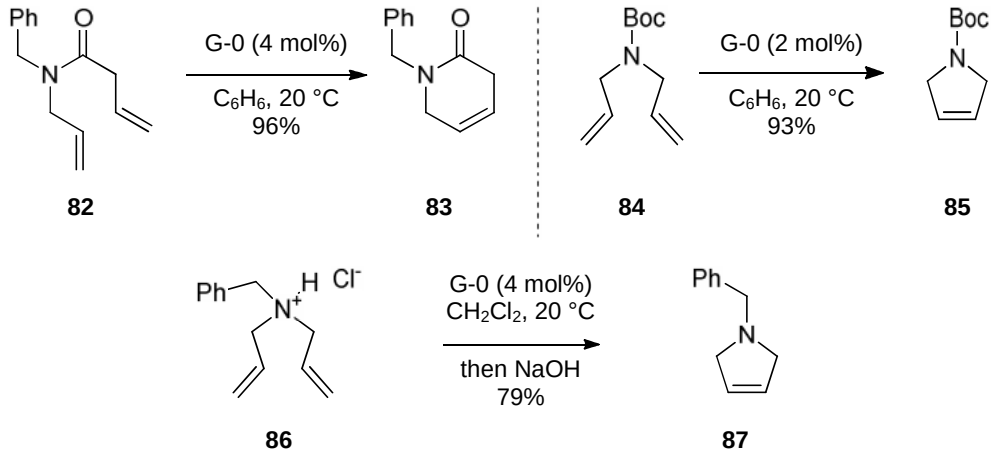
Scheme 1.20 *- De Brabander's synthesis of (+)-salicylihalamide A.*

1.3.2 Synthesis of nitrogen containing heterocycles

The use of a RCM approach for the synthesis of nitrogen containing heterocycles has also been the focus of research due to the importance of these compounds. Many of these structural motifs are of paramount interest in organic chemistry, inorganic chemistry, medicinal chemistry, material science, pharmaceutical and agrochemical industries.[58]

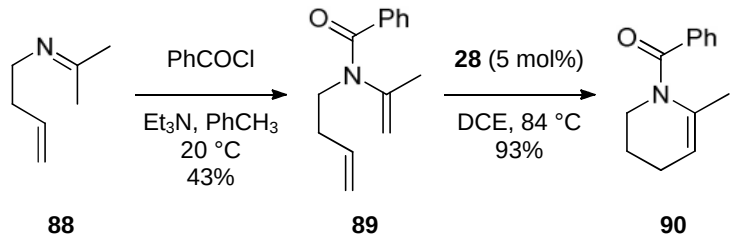
The main difference in this approach compared to the synthesis of oxygen-containing heterocycles, is that not all amino functional groups are tolerated by the catalyst systems, and therefore protecting groups are often required prior to the RCM step.

Initial investigations by Grubbs and co-workers demonstrated that it is possible to construct such nitrogen heterocycles using catalyst G-0 (Scheme 1.21).[42] They showed that RCM was an efficient process using tertiary amide **82** and tertiary carbamate **84**. They also showed that hydrochloride salts of a tertiary amine **86** could undergo RCM to form the dihydropyrrole **87**.



Scheme 1.21- *Synthesis of N-heterocycles.*

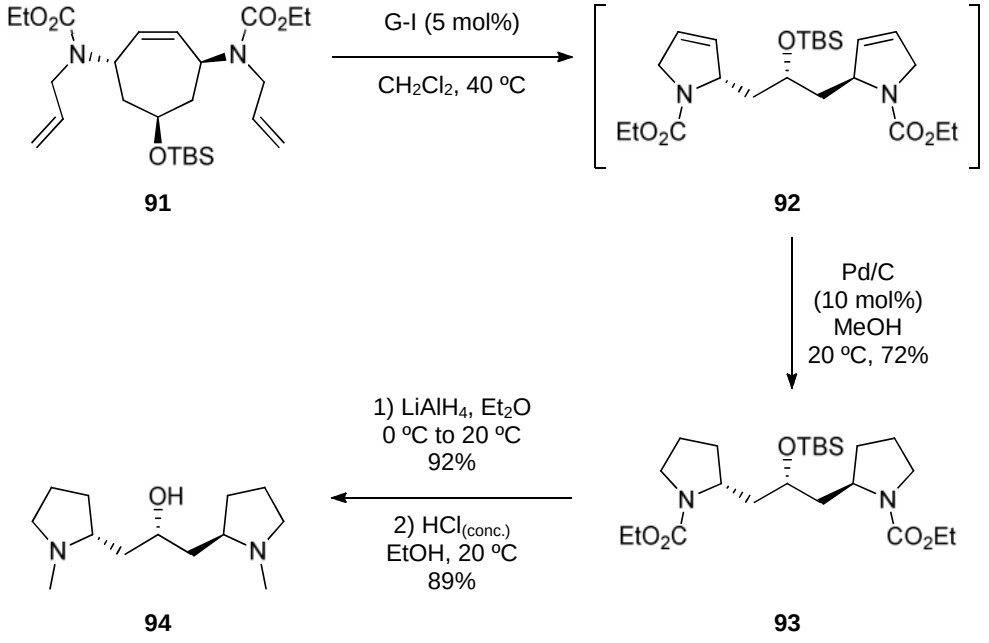
In 2001, Rutjes and co-workers demonstrated that acyclic enamide **89** could undergo RCM, using second generation catalyst **28**, to produce a 1,2,3,4-tetrahydropyridine **90** (Scheme 1.22).[59]



Scheme 1.22*- Synthesis of cyclic enamides.*

To emphasize the synthetic utilities of the metathesis reaction, a RCM process can be combined with a ring-opening metathesis (ROM) event in such a way that a tandem reaction is obtained and a complex product can be derived in a single step.

In 2002, Blechert and Stapper produced an enantioselective synthesis of (+)-dihydrocuscohygrine **94** using such a sequence (Scheme 1.23).[60] After the tandem RCM-ROM process is finished, the intermediate unsaturated heterocycle **92** was subjected to a hydrogenation so as to avoid decomposition. Heterocycle **93** was then converted to the desired target **94** in two further more steps.



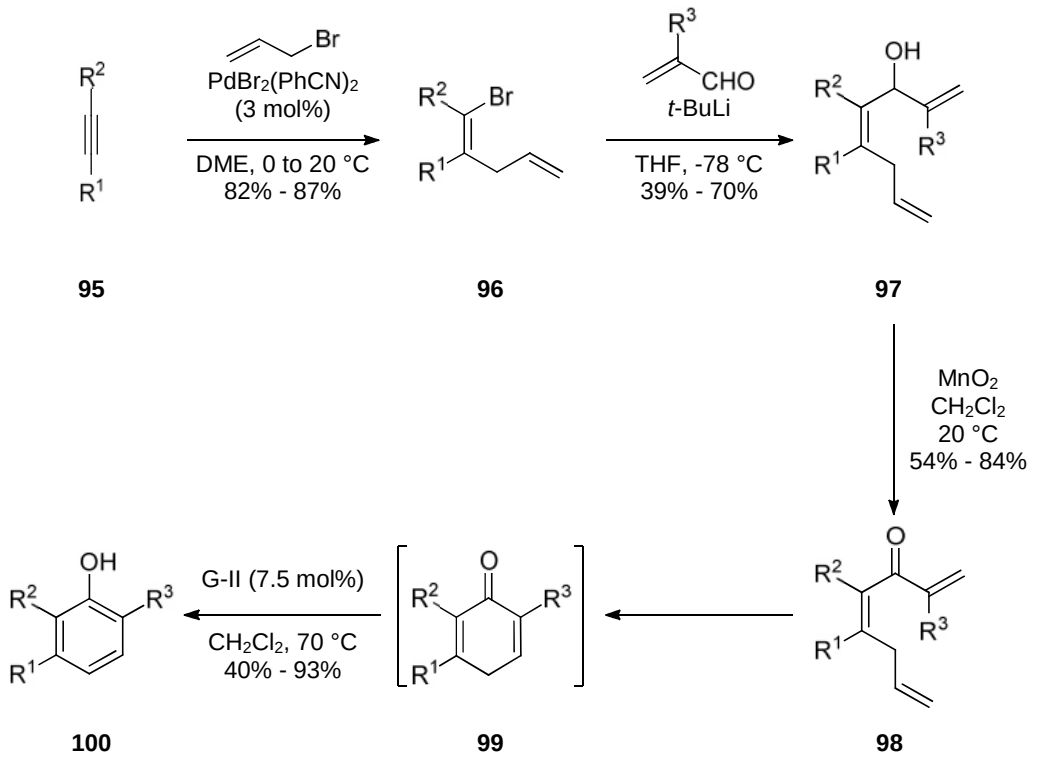
Scheme 1.23*-Blechert and Stapper's synthesis of (+)-dihydrocuscohygrine.*

1.4 Synthesis of heteroaromatic compounds *via* RCM

Having demonstrated the simplicity of the RCM reaction to construct different cyclic structures, a new approach to the synthesis of aromatic compounds was devised. In order to achieve this goal, a RCM event that forms a carbocycle is then followed by an aromatisation protocol. The utility of this method depends on different factors: ease of preparation of the starting materials, the efficiency of the RCM, the type of aromatisation protocol needed and the number of substituents and substitution patterns that can be produced.

In 2005, Yoshida and Imamoto reported some methodology for the synthesis of phenols based on a RCM approach (Scheme 1.24).[61] The construction of carbocycle **100**, starting from the 1,4,7-triene-3-one **98**, using catalyst G-II was an effective process, and aromatisation was achieved by spontaneous tautomerisation of the cyclic enone intermediate **99**.

Triene **98** was prepared in three steps: alkyne **95** undergoes Pd-catalyzed bromo-allylation to afford the vinyl halide **96**,[62] which is reacted with *t*-butyl lithium and coupled with an acrylaldehyde. The resulting alcohol **97** was oxidized to afford the desired 1,4,7-triene-3-one **98**. RCM of triene **98** produced the intermediate enone **99** which tautomerize in situ to give the desired aromatic target **100** (Scheme 1.24).[63]



Scheme 1.24*- RCM approach to the synthesis of phenols.*

This methodology inspired the design of other synthetic routes for the synthesis of polysubstituted benzenes.[63]

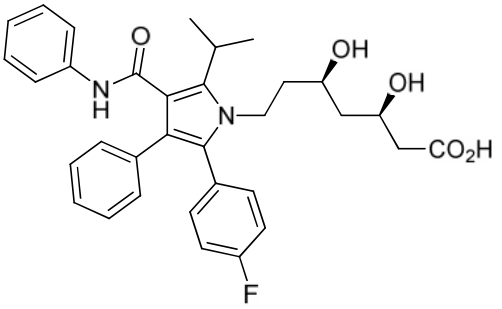
The synthesis of heteroaromatic compounds using RCM is an emerging area of research driven by the utility of these products in the pharmaceutical and agrochemical industries, material science and ligands for catalyst design.

As a result, the Donohoe group has dedicated a program of research towards the development of metathesis based methods that facilitate the synthesis of heteroaromatic compounds.

The investigations described herein are included in this area of research, where modular, fast and reliable methods are required for the construction of a large number of synthetic units that contain a heteroaromatic moiety.

1.4.1 Synthesis of pyrroles

Pyrroles are five membered nitrogen containing aromatic compounds that occur in many biologically active molecules. For example, Atorvastatin **101** which is used for the treatment of high levels of cholesterol and is the top selling drug in the world (11.4 billon US dollars on sales in 2009), contains a polyfunctionalized pyrrole.[64]

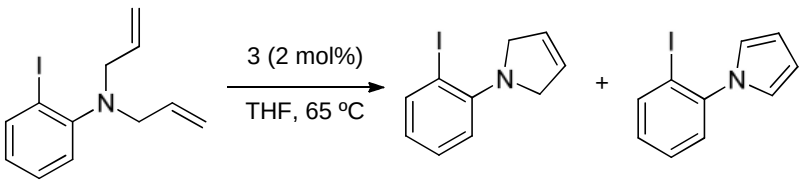


101

Figure 1.12 *- Atorvastatin.*

The formation of pyrroles after a RCM reaction was first observed because the desired dihydropyrroles from a RCM would slowly oxidize to produce the aromatic compound. These pyrroles were unwanted but they served to inspire the development of methods that would purposefully generate pyrroles *via* a RCM-oxidation sequence.

For example, Griggs and co-workers use a RCM to convert diene **102** into the dihydropyrrole **103** in 93% yield, and upon standing they also found that some pyrrole **104** had formed (Scheme 1.25).[65]

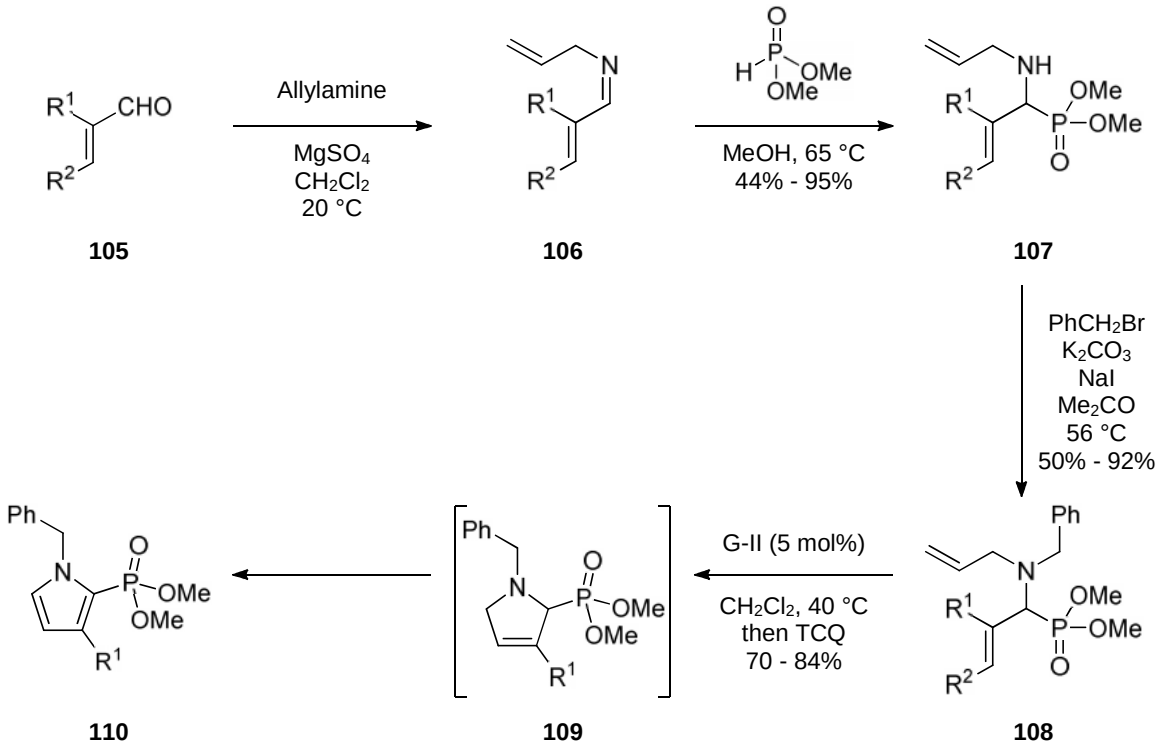


102 **103** **104**

Scheme 1.25 *- RCM of diene **102**.*

In 2006, Stevens and co-workers used these findings to develop a method based on RCM to produce 2,3-disubstituted pyrroles (Scheme 1.26). The aromatisation protocol of this method

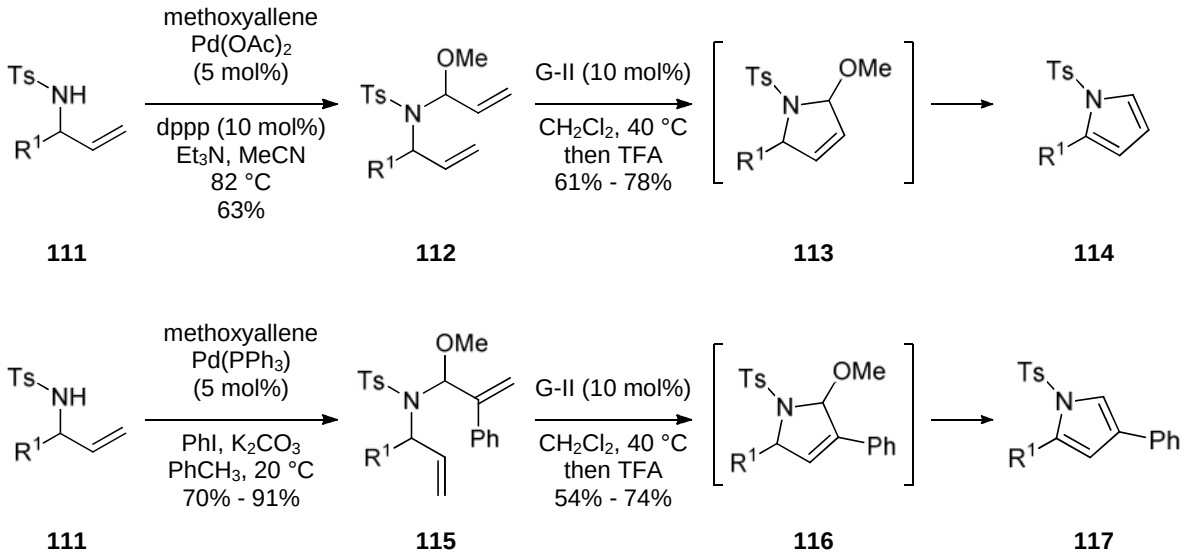
was an oxidation of the dihydropyrrole intermediates using tetrachloroquinone (TCQ). Imine **106** is prepared from acrylaldehyde **105** by condensation and a Pudovik-type reaction of the imine **106** formed diene **107**. Protection of this diene was required in order to render the substrate compatible with the metathesis catalyst. Catalyst G-II was used for the RCM step and the reaction was monitored by ^{31}PNMR spectroscopy. After the starting diene **108** was consumed, TCQ was added and pyrrole **110** obtained in very good yields.[66]



***Scheme 1.26**-Stevens' synthesis of pyrroles.*

A more general approach to the synthesis of pyrroles was introduced in 2005 by Donohoe and co-workers (Scheme 1.27).[67,68] This method allows the formation of 2-, 4- and 2,4-disubstituted pyrroles. Palladium-catalyzed coupling of sulfonamide **111** with methoxyallene afforded diene **112**. RCM of diene **112**, using catalyst-II, formed the dihydropyrrole intermediate **113** which was converted to the desired pyrrole **114** after addition of acid.

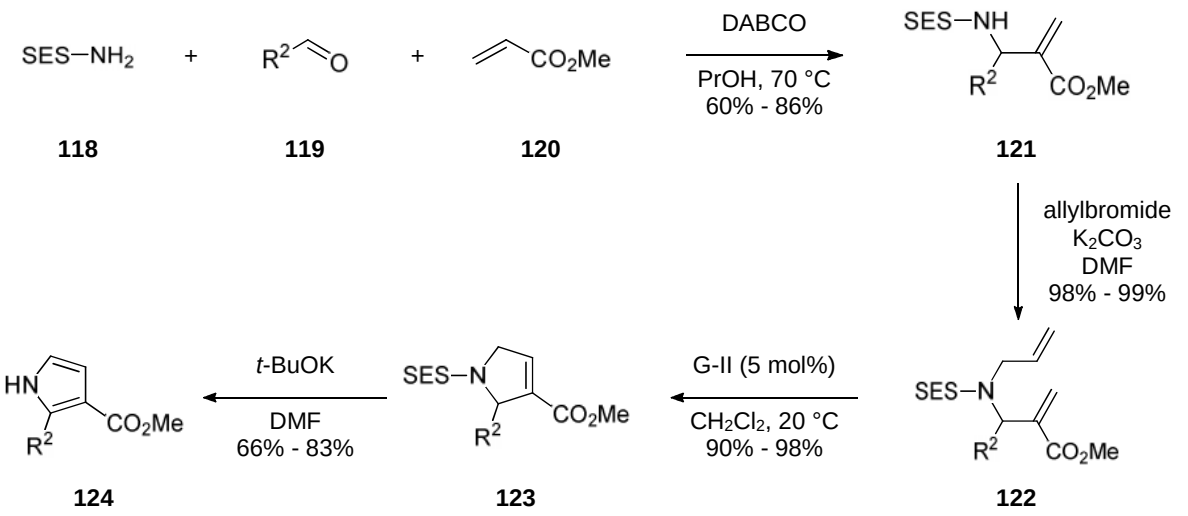
A three-component coupling using sulfonamide **111**, methoxyallene and phenyliodide is a viable route for the synthesis of diene **115**. This diene was readily converted to the desired pyrrole **117** by a RCM-acid catalyzed aromatisation sequence (Scheme 1.27).



Scheme 1.27*-Donohoe's synthesis of pyrroles.*

In 2006, Lamaty and co-workers developed a synthesis of pyrroles *via* a RCM in which a 2-trimethylsilylethanesulfonyl (SES) protecting group on nitrogen was used, and then conveniently removed in the last step of the sequence by the use of base with concomitant aromatisation (Scheme 1.28).[69]

Sulfonamide **118** was converted to allylic sulfonamide **121** by an aza-Baylis-Hillman reaction which was subsequently allylated to form diene **122**. RCM using catalyst G-II afforded the pyrrolidine **123**. Base induced SES deprotection afforded pyrrole **124** in good yields.

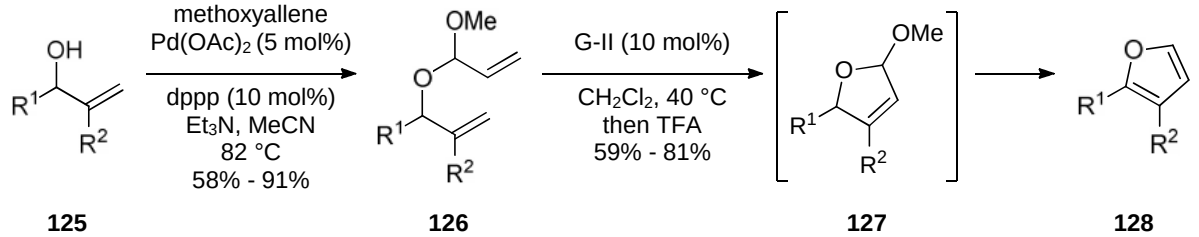


Scheme 1.28*- Lamaty's synthesis of pyrroles.*

1.4.2 A metathesis based synthesis of furans

Furans are an important class of heterocycles and are often encountered in natural products. Efforts towards a general method for their synthesis have generated a series of RCM-based approaches.

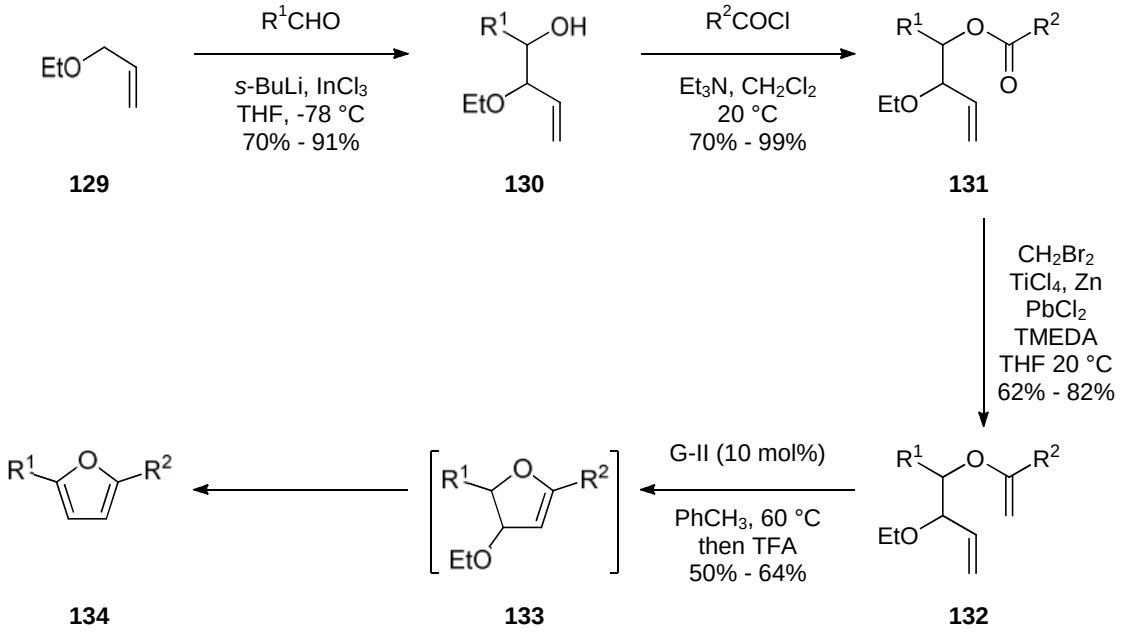
In 2005, Donohoe and co-workers devised a synthetic method for the construction of furans based on a RCM (Scheme 1.29).[67] The method consists of the formation of a mixed acetal **126** from allylic alcohol **125** under palladium catalyzed conditions. RCM of the mixed acetal **126**, using catalyst G-II, afforded the dihydrofuran intermediate **127**, which is converted *in situ* to the desired furan **128** by an acid catalyzed elimination of methanol. This elimination is driven by aromatisation by a very simple and efficient process.



Scheme 1.29*-Donohoe's RCM approach to the synthesis of furans.*

The limitation of this method is that only 2,3-disubstituted furans can be obtained in good yields. It is important to point out that the aromatisation protocol does not rely on an oxidation of the dihydrofuran intermediate, which is sometimes problematic.

In order to synthesize furans with a different substitution pattern, Donohoe and co-workers developed a second route for the synthesis of furans (Scheme 1.30).[70] This route is capable of forming 2,5-disubstituted furans using a RCM. Likewise in this method, the aromatisation of the RCM product is *via* an acid catalyzed elimination of a leaving group, ethanol.



Scheme 1.30 *- Synthesis of 2,5-disubstituted furans.*

It is well established that deprotonation of allylic ether **129** in the presence of $InCl_3$ forms a γ-alkoxy allylindium reagent that gives high levels of regiocontrol when coupled with an aldehyde.[71] This method was used to synthesize alcohol **130**, which was esterified with acid chloride to form ester **131**. Takai-Utimoto titanium-based olefination was then used to form diene **132** which underwent a facile RCM-aromatisation protocol to afford the 2,5-disubstituted furan **134**.

From these RCM based methods it is clear that the synthesis of other heteroaromatic structures would benefit from similar approaches.

The importance of heteroaromatic compounds in organic chemistry drives the need for methods that are fast, modular and produce a desired target with high levels of regiochemical control.

Many of the current methods are based on transition metal catalyzed cross-couplings, which require prior functionalisation of the heteroaromatic moiety and this can be difficult to control, often requiring directing groups.[72,73]

Methods for a direct C-H functionalisation of the heteroaromatic moiety are scarce, an example of such process is the iridium mediated borylation.[74]

A new approach which can deliver a heteroaromatic moiety with the appropriate substitution pattern would benefit organic chemistry in general.

The pyridine functionality is an important class of heteroaromatic compound and the development of methods that use a metathesis reaction in order to obtain this target will be the focus of the investigations discussed herein. A great emphasis will be given to regiocontrolled processes that deliver specific substituents at specific positions.

Although many methods for the synthesis of this functional group have emerged, little attention has been applied to the use of a metathesis reaction to form this important target. Many of these methods have specialised substituents that are required as directing groups and this contains some limitations.

The initial focus of these investigations involves the use of a RCM approach to the synthesis of pyridines.[75]

Chapter two: The synthesis of 2-pyridones and pyridines

Chapter two: The synthesis of 2-pyridones and pyridines

2.1 Introduction

Substituted pyridines are a privileged structure in organic chemistry, being of importance to the pharmaceutical and agrochemical industries. They also play a role in coordination chemistry and preparative chemistry.[76,77]

Pyridine**135** is a six-membered heteroaromatic compound with a molecular formula of C_5H_5N which corresponds to three double bonds in a ring structure (Figure 2.1).



135 **135**

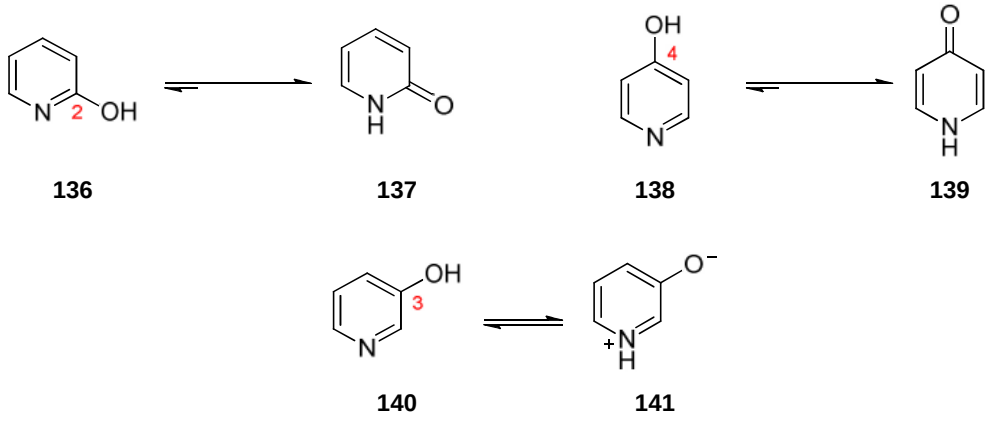
Figure 2.1*- Pyridine.*

This molecule is planar and has a slightly distorted hexagonal shape, where all the carbons are sp^2-hybridised. This distortion arises from the shorter C-N bond compared to the C-C ones. Also, the electron density distribution is not even because of the electron-withdrawing effect of the nitrogen atom. The number of π-electrons in this molecule is six, which according to Hückel's rule there would be a strong indication that this molecule is aromatic. Important evidence is seen in that the ^1H NMR spectrum of pyridine indicates three signals at 7.5 ppm, 7.1 ppm and 8.5 ppm. These signals are due to the three distinctive hydrogen atoms environments in pyridines and importantly the chemical shifts are found in the aromatic region of the spectra.[78]

In this molecule, all the carbons have a p-orbital orthogonal to the plane of the molecule and so does the nitrogen, which also has a lone pair in the plane of the ring. The nitrogen in

pyridine can be considered as a stable imine, which means that it is weakly basic, the pKa of its conjugated acid is 5.25,[79] and it is reasonably nucleophilic.[78]

There are five possibilities for substitution on carbon in a pyridine ring, and there are many examples of nitrogen being functionalized to form a pyridinium salt. When a free hydroxyl group is occupying a substitution place, there are corresponding tautomeric forms that are important to consider in their structure. Thus, 2-hydroxypyridine **136** almost exclusively exists in the carbonyl tautomeric form **137** and this structure is called 2-pyridone (Scheme 2.1).[80]



136 **137** **138** **139**

140 **141**

Scheme 2.1 *- 2-Pyridone, 4-Pyridone and 3-Hydroxypyridine.*

This is also true when the hydroxyl group is located at the 4-position **138**, as the keto is still the prevalent tautomeric form **139** (Scheme 2.1).[80] Traces of the hydroxyl tautomeric forms **138** and **136** could be seen in diluted solutions using non-polar solvents.[81]

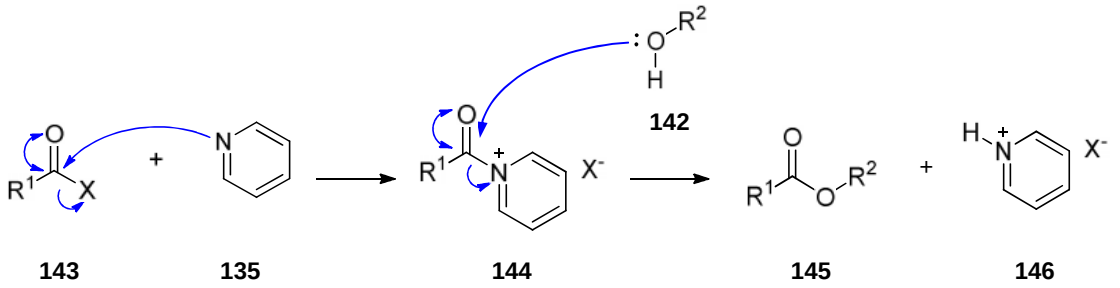
However, the 3-hydroxylpyridine **140** is observed in many non-polar solvents, like $CDCl_3$ and CCl_4. In aqueous solutions it has been demonstrated that the zwitterionic species **141** is observed in comparable proportion to neutral species **140**.[82-84]

2.1.1 Application of pyridine-based molecules in synthesis

There are many applications of pyridine-based molecules that can be easily found in different industries. In organic chemistry, pyridines may serve as nucleophilic catalysts for acylation reactions.

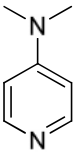
The reaction of alcohols with acetic anhydride in the presence of pyridine was known as early as 1901.[85] This reaction was later extended to the use of acid chlorides for the esterification of alcohols in carbohydrate chemistry.[85]

The mechanism of this reaction involves the nucleophilic attack of pyridine **135** to the carboxylic acid derivative **143**, and this intermediate activated species is more susceptible to the attack of the hydroxyl group in alcohol **142**, leading to the desired ester **145** (Scheme 2.2).[86]



Scheme 2.2 *- Pyridine catalyzed acylation of alcohols.*

In 1967, Litvinenko and Kirichenko found that there was a 10^4 increase in the rate of benzylation of *m*-chloroaniline by replacing pyridine with 4-dimethylaminopyridine **147** (DMAP) (Figure 2.2).[87]Sieglich and Höfle independently discovered that the use of DMAP **147** had a dramatic influence on the rate of acylation reactions.[88]



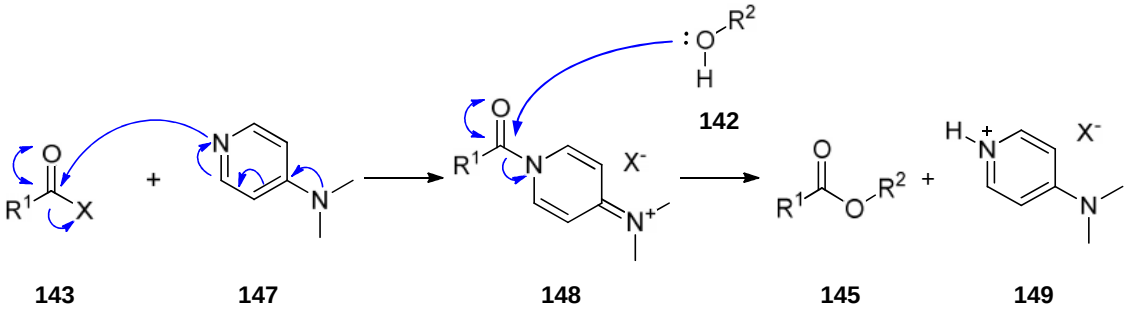
147

Figure 2.2 *- 4-Dimethylamino pyridine.*

Due to its high catalytic activity, DMAP is used for the acylation of amines, hindered alcohols and phenols, as well as the acylation of enolates (from CH-acid compounds) and the formation of amides from isocyanates.[85]

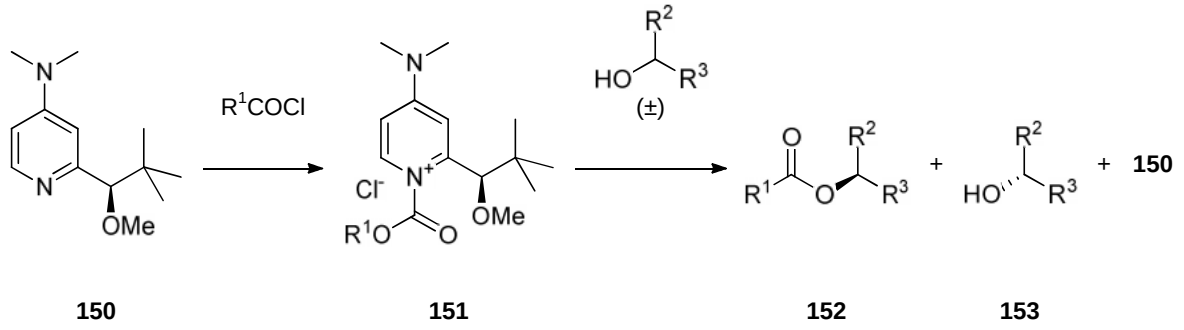
The electron rich dialkylamine group increases the nucleophilicity of the nitrogen in DMAP **147**, and also it stabilizes the intermediate **148** without having increased the steric congestion

around the carbonyl moiety, giving an overall increase in the rate of the reaction (Scheme 2.3).



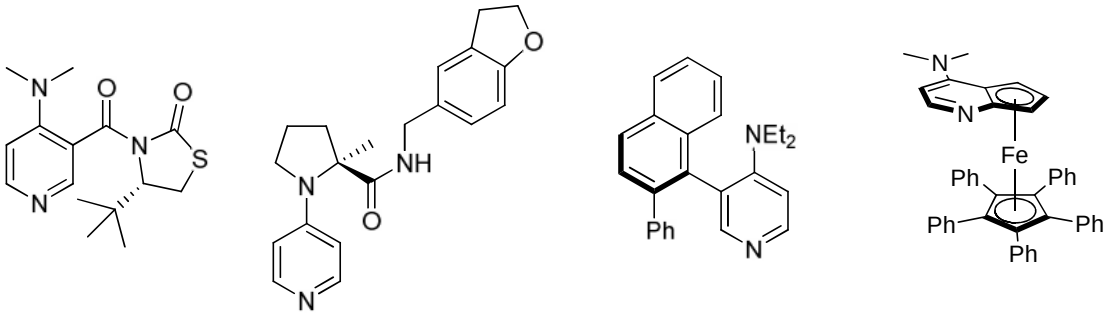
Scheme 2.3 *- Pyridine catalyzed acylation of alcohols.*

Chiral DMAP derivatives have been developed in order to separate racemic alcohols into their enantiomerically pure forms *via* kinetic resolution. Enantiopure secondary alcohols have a high importance due to their presence in natural products, bioactive molecules and chiral ligands. Vedejs and Chen reported in 1996 the first effective chiral DMAP which was substituted at the 2-position with a stereogenic centre which influences the outcome of the acylation reaction (Scheme 2.4).[89] - [92]



Scheme 2.4 *- Acylation using 2-substituted chiral DMAP.*

However, DMAP **150** was used in stoichiometric quantities because the substitution at the 2-position considerably slowed down the rate of the reaction. Several alternative pyridines were later synthesized (without substitution at the 2-position) which were able to be used in catalytic amounts to perform the kinetic resolution of alcohols (Figure 2.3).[93]



154 **155** **156** **157**

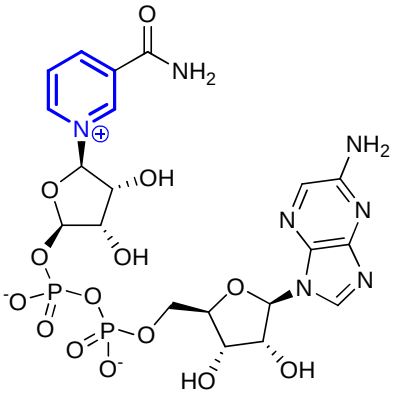
Figure 2.3 *- Chiral DMAP catalysts.*

2.1.2 Pyridine cores in bioactive molecules

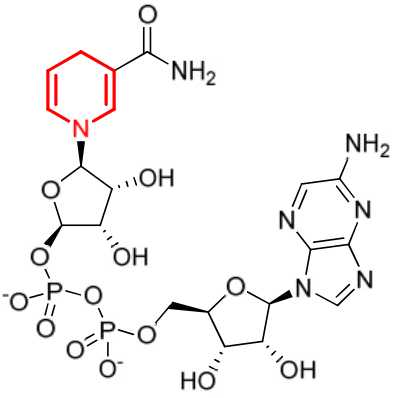
Heterocyclic compounds play a major role in many biochemical systems, and the number of bioactive molecules that contain substituted pyridines is vast. Hence it is of little surprise that there are so many therapeutic agents that contain a pyridine core.

All living cells contain nicotinamide adenine dinucleotide (NAD+) **158** and its reduced form (NADH) **159** and these two molecules are utilised to transfer electrons from one molecule to another. The pyridine core in **158** is in the form of a pyridinium salt, and is capable of being reduced by accepting electrons and forming the dihydropyridine **159**. Consequently these dihydropyridines can be oxidized to regain aromaticity and form **158** (Figure 2.4).

This process is controlled by enzymes called oxidoreductases and there are many other pyridine-based molecules that can block or influence this process and are therefore bioactive.



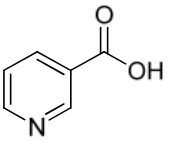
158



159

Figure 2.4 *- NAD+ and NADH.*

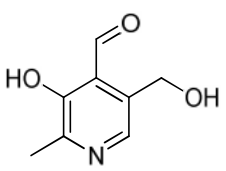
Niacin **160**, also known as vitamin B_3, is the precursor to NAD+ and is one of the essential nutrients for the human body (Figure 2.5). This essential compound is a 3-substituted pyridine, and is also utilised in the body for DNA repair and the production of steroid hormones in the adrenal gland.[94]



160

Figure 2.5 *- Vitamin B_3 Niacin.*

There are three forms of vitamin B6: pyridoxal **161**, pyridoxamine **162** and pyridoxine **163** (Figure 2.6).[95] These three compounds are converted to pyridoxal 5-phosphate **164** in the human body. A deficiency of these compounds can lead to serious illness.



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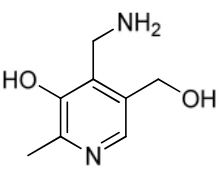
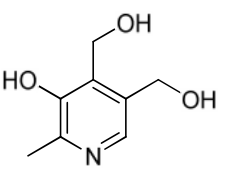
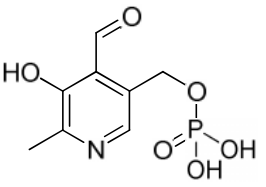


162



163



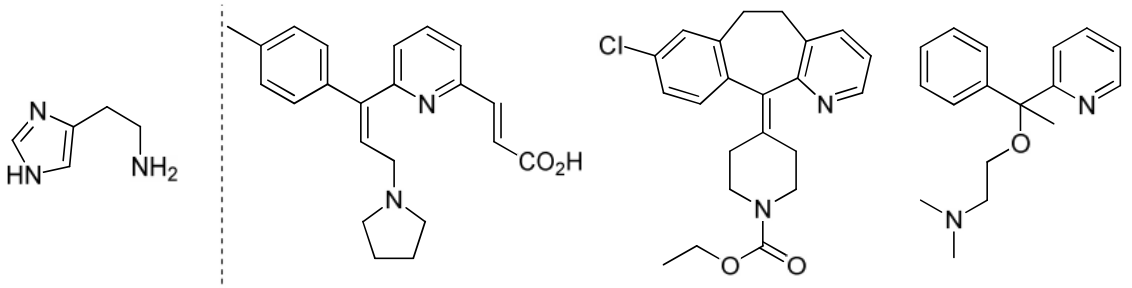
164

Figure 2.6 *- Vitamins B_6.*

Due to the occurrence or pyridine derivatives in many biological processes in the body, it is expected that there would be a number of pyridine-containing pharmaceutical compounds. In

addition, as the pyridine is a rigid structure, it can mimic ligands in enzyme pockets and it can have a large binding affinity depending on the receptor.

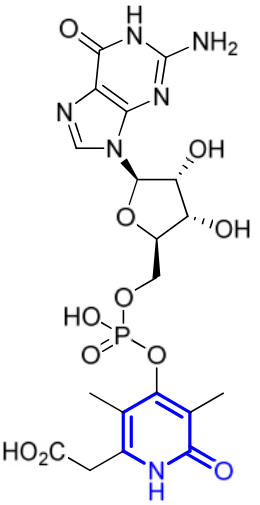
For example, there are a number of histamine **165** antagonists that are polysubstituted pyridines, such asacrivastine **166**, loratadine **167** and doxylamine **168** (Figure 2.7) amongst others.[96, 97]



165 **166** **167** **168**

Figure 2.7*- Histamine and pyridine based histamine antagonists.*

The2-pyridone core is also present in biological systems, for example the 2-pyridone derivative **169** is found as a cofactor in hydrogenase enzymes.[98]



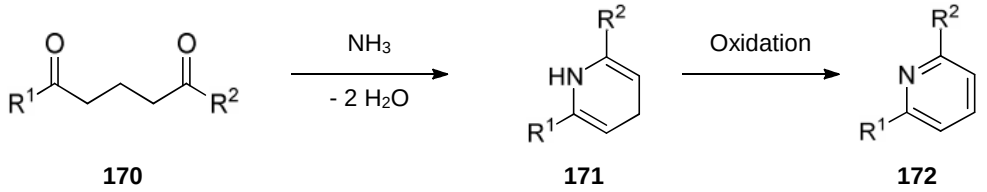
169

Figure 2.8 *- 2-Pyridone derivative cofactor.*

2.1.3 Synthesis of pyridines

The oldest method for the synthesis of substituted pyridines involves the condensation of a 1,5-diketone with ammonia followed by an oxidation step. In the first instance, condensation

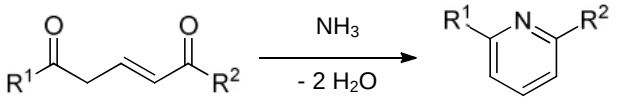
with ammonia of one of the carbonyls in 1,5-diketone **170** forms an imine which can undergo a second condensation with the other carbonyl, forming dihydropyridine **171**, which in some cases can be isolated. Spontaneous air oxidation, or oxidation in a second step, affords the pyridine **172**. The synthetic utility of this method depends on the availability of such 1,5-diketones (Scheme 2.5).[99, 100]



170 **171** **172**

Scheme 2.5*-Condensation of 1,5-diketones with ammonia.*

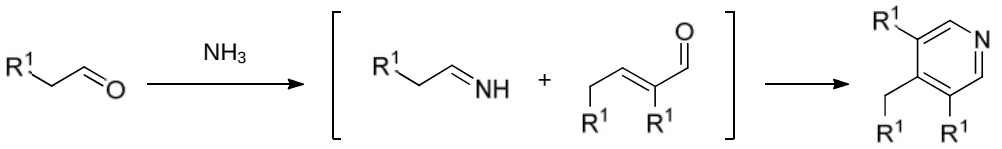
When the starting material is an unsaturated 1,5-diketone **173**, the condensation with ammonia would produce the desired pyridine **172** in one step (double bond geometry not withstanding), obviating the need for an oxidation procedure (Scheme 2.6).[101]



173 **172**

Scheme 2.6 *- Condensation of unsaturated 1,5-diketones.*

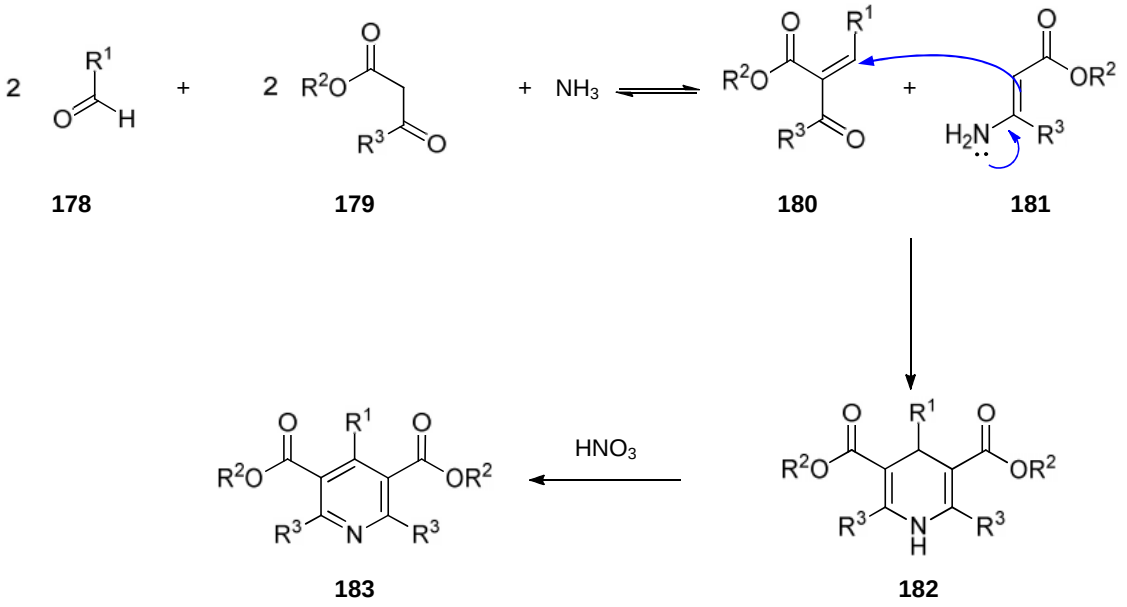
Tschitschibabin (Chichibabin) describe the synthesis of pyridines from the condensation of an aldehyde in liquid ammonia.[102] In this reaction media, the aldehyde **174** undergoes two reactions simultaneously: condensation to form imine **175** as well as an aldol reaction to form α,β-unsaturated aldehyde **176**. These two products react to form the desired pyridine **177** (Scheme 2.7).[102]



174 **175** **176** **177**

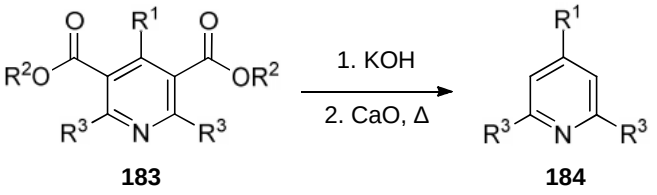
Scheme 2.7 *- Chichibabin synthesis of pyridines.*

The Hantzsch pyridine synthesis involves a multicomponent reaction, where an aldehyde **178**, a β-ketoester **179** and ammonia, or an ammonia source, are reacted together to form a dihydropyridine **182**. Dihydropyridine **182** can be oxidized to the pyridine **183** (Scheme 2.8).[103]



Scheme 2.8 *- Hantzsch pyridine synthesis.*

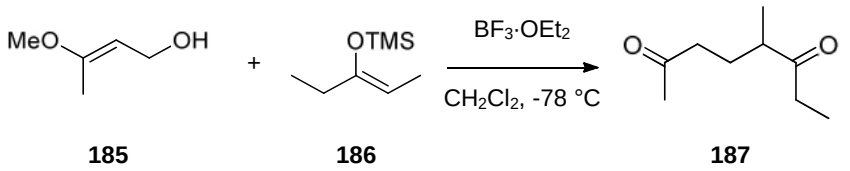
Furthermore, the ester groups at the 3- and 5-position on pyridine **183** can be removed by a saponification-decarboxylation protocol giving rise to a 2,4,6-trisubstituted pyridine **184**, but with the limitation that the 2- and 6-substituents are equivalent (Scheme 2.9).[104]



Scheme 2.9 *- Decarboxylation of Hantzsch pyridine products.*

There are a number of methods for the synthesis of 1,5-diketones, however a general procedure to prepare any 1,5-diketone remains elusive. Instead, these methods have the capacity to produce a limited number of pyridine precursors.

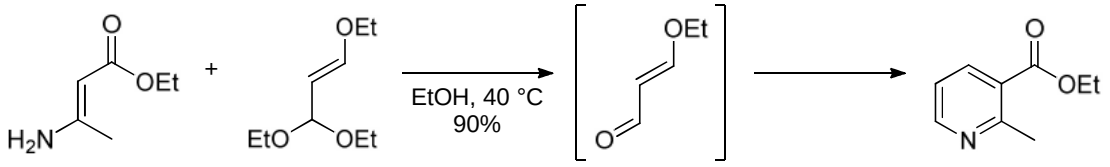
In 1986, Duhamel and co-workers reported a synthesis of 1,5-diketone **187** by a Lewis acid catalyzed condensation of 3-methoxyallylic alcohol **185** and silyl enol ethers **186** (Scheme 2.10).[105]



185 **186** **187**

Scheme 2.10 *- Lewis acid promoted synthesis of 1,5-diketones.*

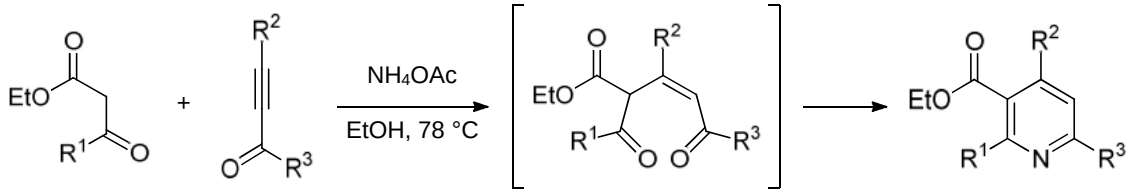
In 1957, Bohlmann and Rahtz reported that carbon nucleophile **188** undergoes a 1,4-addition to propargyl ketone **190**, which is generated *in situ* from acetal **189**, to give the desired heterocycle **191** (Scheme 2.11).[106]



188 **189** **190** **191**

Scheme 2.11*-Bohlmann-Rahtz pyridine synthesis.*

Bagley and co-workers demonstrated the utility of this method and developed a one pot protocol in which 1,3-ketoester **192** is used as the carbon nucleophile and 1,4-addition with propargyl ketone **193** affords the unsaturated 1,5-diketone **194**, which is subsequently converted to pyridine **195** (Scheme 2.12).[107]

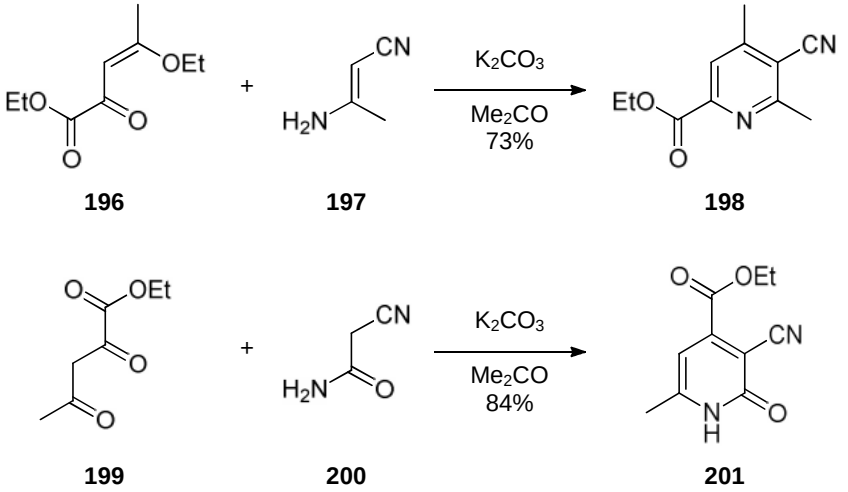


192 **193** **194** **195**

Scheme 2.12*-Bohlmann-Rahtz synthesis of pyridines from 1,3-ketoester **192**.*

The Guareschi synthesis of pyridines is similarly based on a carbon nucleophile that can add to a desired electrophile either by a 1,2- or a 1,4-addition. For example enone **196** is used as

a Michael acceptor and the enamine **197** is used as the carbon nucleophile, to afford pyridine **198** as the final product. Alternatively 1,3-dicarbonyl **199** can be used as the electrophile and in this case the α-cyano-acetamide **200** reacts selectively with the most electron-deficient carbonyl to generate the pyridine **201** (Scheme 2.13).[81]



Scheme 2.13 *- Guareschi synthesis of pyridines.*

It is noteworthy to mention that the Bohlmann-Rahtz method requires nucleophile **192**to have two carbonyl groups of different reactivity towards the condensation with ammonia, in order to obtain just a single regioisomer.[107]

Similarly, the Guareschi method needs two carbonyls of different reactivity in the electrophiles, **196** and **199**, to also obtain a single isomeric product.[81]

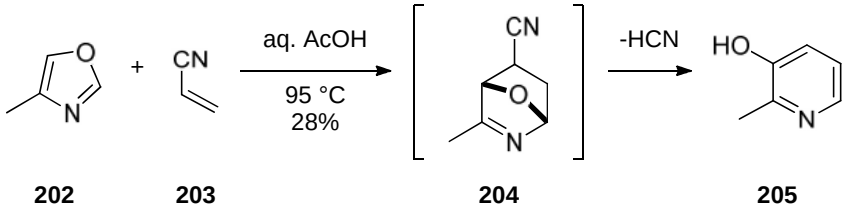
2.1.4 *De novo* approaches to pyridines

The above methods described for the synthesis of pyridines have the advantage that they can assemble this moiety from cheap starting materials in very short sequences. The limitation, however, arises from the required electron-deficient substituents to direct the regioselectivity or the limited access to a wide array of unsaturated 1,5-diketones substrates.[108]

In addition, the difficulties in functionalisation of the electron-deficient pyridine core have driven several investigators to develop different methodologies that would allow formation

of polysubstituted pyridines containing alternative functional groups, or other substitution patterns.[102]

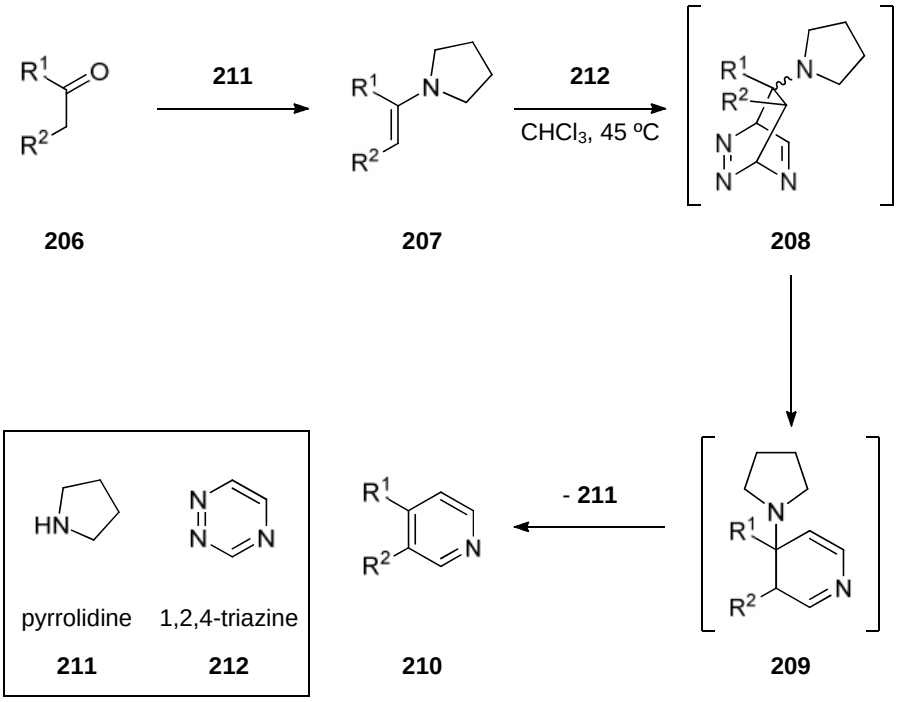
In 1965, Naito and co-workers showed the use of a [4+2]-cycloaddition reaction between oxazole **202** and cyano olefin **203** to form the unstable heterocycle **204** which loses hydrogen cyanide (HCN) and the rearranges to give the 3-hydroxy pyridine **205** (Scheme 2.14).[109]



202 **203** **204** **205**

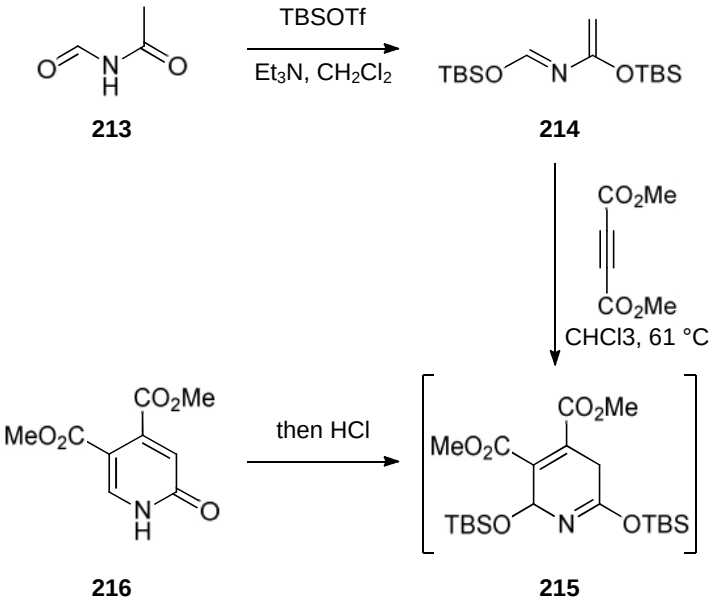
Scheme 2.14 *- 6π-Cycloaddition approach to pyridines.*

In 1981, Boger and Panek utilised a similar approach to pyridines in which a ketone **206** was converted to enamide **207**. The electron-rich olefin in this moiety can undergo an efficient [4+2]-cycloaddition in the presence of 1,2,4-triazine **212** to form the heterocycle **208**. Extrusion of nitrogen leads to the dihydropyridine intermediate **209** and aromatisation drives the elimination ofpyrrolidine **211** to afford the desired pyridine **210** (Scheme 2.15).[110]



Scheme 2.15 *- Boger's synthesis of pyridines.*

In 1982, Ghosez and co-workers demonstrated the use of a [4+2]-cycloaddition reaction to form pyridines. Amide **213** was converted into the imine-enamide **214** by bis *O*-protection, and these products can undergo the desired cycloaddition to form heterocyclic intermediate **215**. This is then treated with hydrochloric acid to deprotect the silyl enol ethers and to promote the elimination of one water molecule to form the 2-pyridone **216** (Scheme 2.16).[111]



213 **214** **216** **215**

Scheme 2.16 - *Ghosez's synthesis of pyridines.*

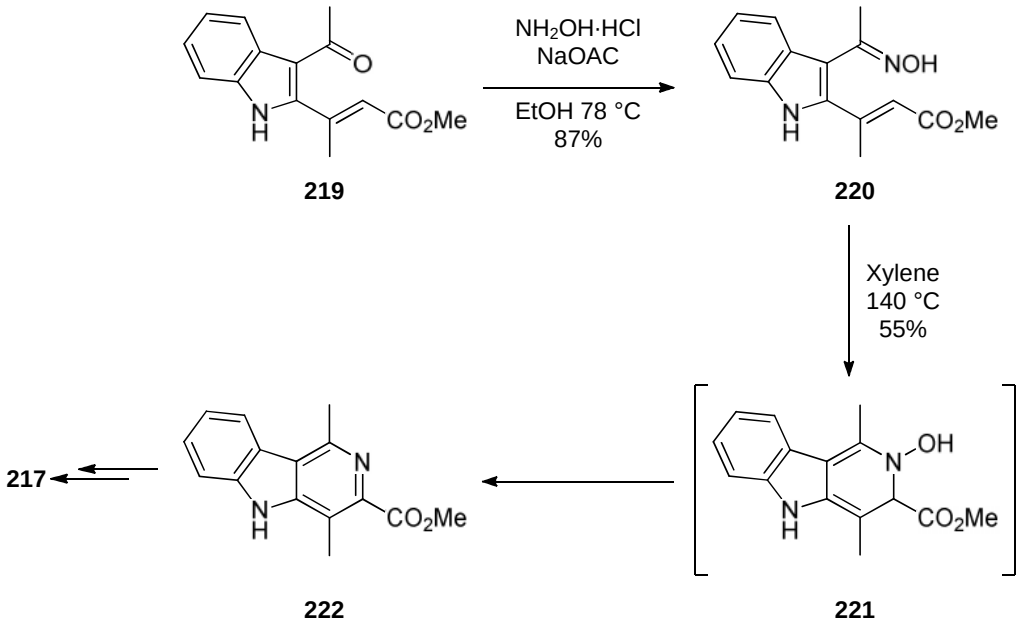
Hibino and co-workers achieved the total synthesis of the genotoxic heterocyclic amine Trp-P-1 **217** using a 6π-electrocyclisation reaction of a 1-aza-1,3,5-triene **218** to achieve the synthesis of the desired target (Figure 2.9).[112]



217 **218**

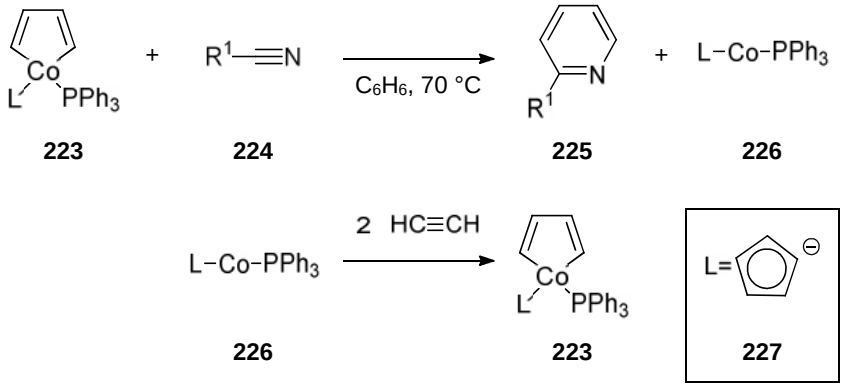
Figure 2.9 - *Genotoxic heterocyclic amine Trp-P-1**217**.*

Ketone **219** is treated with hydroxylamine hydrochloride ($NH_2OH{\cdot}HCl$) to form oxime**220** that can undergo a 6π-electrocyclisation reaction to form the dihydropyridine **221**. Elimination of water affords the desired pyridine **222** (Scheme 2.17).[112]



Scheme 2.17 *- Synthesis of pyridines via 6π-electrocyclasation reaction.*

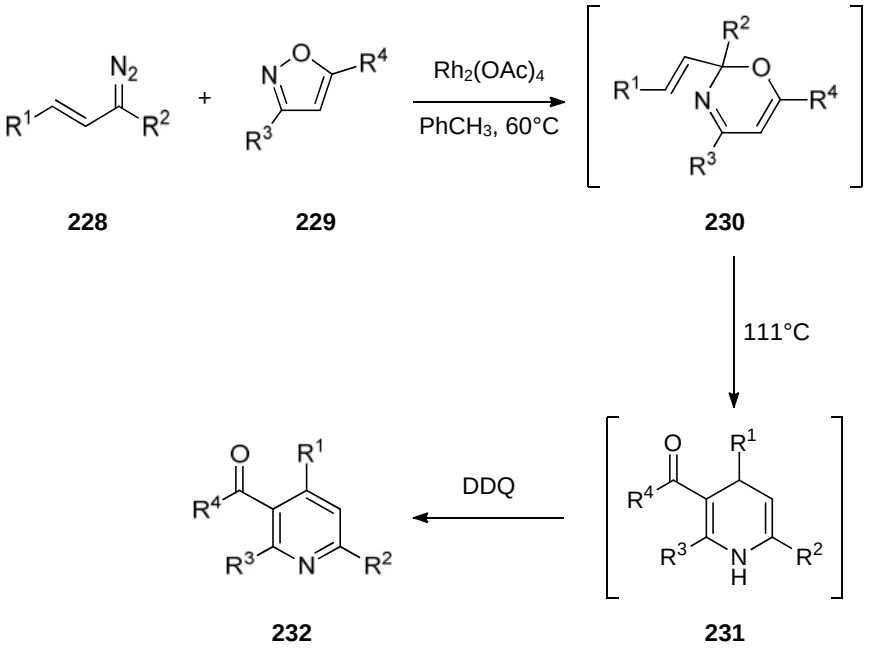
In 1973, Yamazaki and Wakatsuki first reported that cobalt (I) complex **223** could be used as a homogeneous catalyst for the cycloaddition reaction between acetylene and nitrile **224** to synthesize pyridine **225**. The reaction proceeds through an interaction of the pre-catalyst **226** and two molecules of acetylene to form the cyclopentanyl cobalt species **223** (Scheme 2.18).[113]



Scheme 2.18 *- Cobalt catalyzed synthesis of pyridines.*

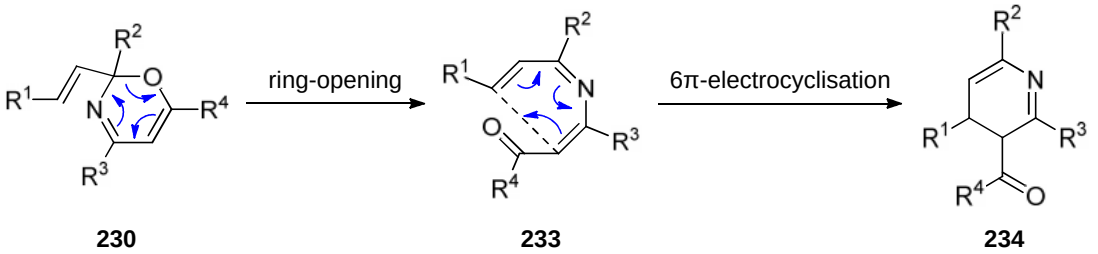
In 2008, Davis and Manning reported rhodium carbenoid-induced ring expansion of isoxazoles and they demonstrated that the product of this reaction can be converted easily to a dihydropyridine *via* a rearrangement (Scheme 2.19).[114] The combination of vinyl diazomethane **228** with $Rh_2(OAc)_4$ is likely to form a rhodium carbenoid that can insert into

the N-O bond of isoxazole **229** and form heterocycle **230**. Once the temperature is increased, dihydropyridine **231** can rearrange. Oxidation of dihydropyridine **231** with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) afforded the polysubstituted pyridine **232**.[114]

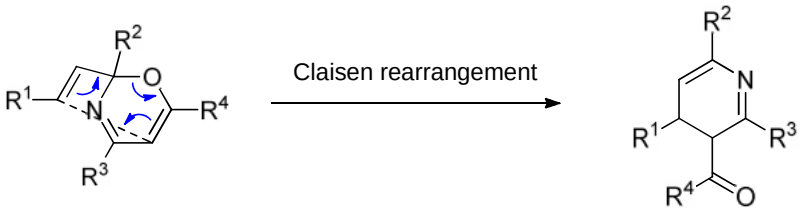


Scheme 2.19 *- Rhodium mediated synthesis of pyridines.*

The authors proposed that the ring expansion product **230** can either undergo a ring opening to form the azatriene **233** with subsequent 6π-electrocyclisation (Scheme 2.20), or it could undergo a Claisen rearrangement to form the dihydropyridine **234** (Scheme 2.21). Finally, dihydropyridine **234** can tautomerize into dihydropyridine **231** (Scheme 2.22)**.**[114]

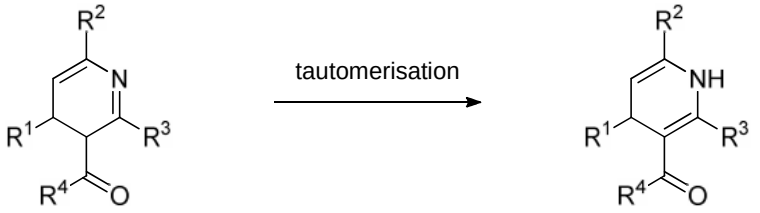


Scheme 2.20 *- 6π-Electrocyclasation for the formation of dihydropyridine **234**.*



230 **234**

Scheme 2.21 *- Claisen rearrangement for the formation of dihydropyridine* ***234****.*



234 **231**

Scheme 2.22 *- Tautomerisation for the formation of dihydropyridine* ***231****.*

Various methods for the synthesis of pyridines have been reported, and the development of such a number is driven by the importance of the pyridine core in many areas of chemistry. Although several of these methods are efficient in obtaining the pyridine core, each specializes in one type of substitution pattern and one type of substituent. A development of new synthetic methods to this class of heteroaromatic compound is of great importance in organic chemistry.

2.2 A metathesis approach to the synthesis of 2-pyridones

Given the success of the metathesis approach to the synthesis of pyrroles (Scheme 1.27) and furans (Scheme 1.29), it was decided that extending this methodology to the synthesis of pyridines was a viable and worthwhile task.

A route to the synthesis of pyridines was being developed in the Donohoe group by L. P. Fishlock which involved the formation of heterocycle **235** from the 2-pyridone moiety **236**

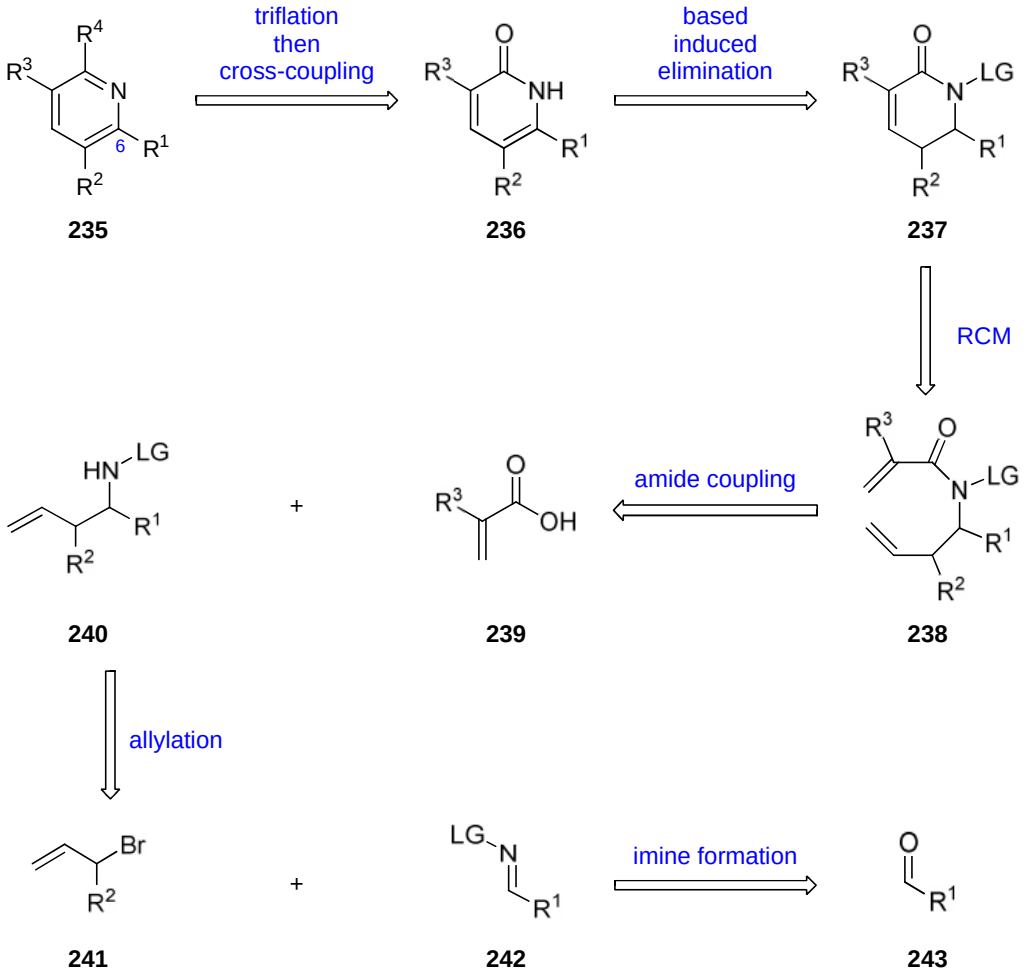
via an activation that was followed by a transition metal cross-coupling protocol (Scheme 2.23).

The 2-pyridone **236** moiety is obtained from a based-induced elimination of a leaving group from the dihydropyridone **237**, which is prepared by the key RCM of diene **238**.

Amide coupling between an acrylic acid **239** and homoallylic amine **240** would form the required diene **238** (Scheme 2.23).[75]

Homoallylic amine **240** can be formed from a zinc-mediated reaction between allylic bromide **241** and imine **242**, which is readily available from aldehyde **243**.

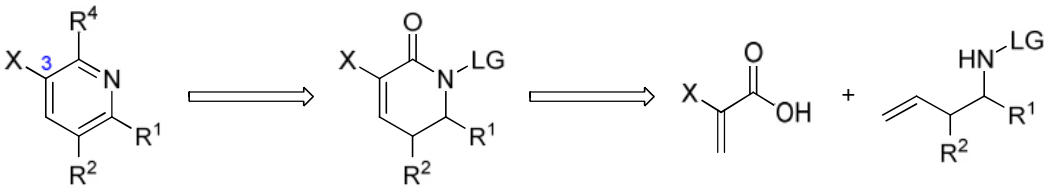
The limitation that arises from this approach is that it requires an electron-withdrawing group at the 6-position (R^1) to facilitate the base-induced elimination step.



Scheme 2.23 *- RCM approach to 2-Pyridones.*

2.2.1 Outline of research

Initial investigations focused on expansion of the methodology by demonstrating that the incorporation of heteroatom-derived substituents at the 3-position (X = OR, NR_2) can be easily accomplished using the above mentioned approach. Incorporating such substituents is of importance due to the number of synthetic targets that are present in Nature and because there is not an efficient method to form such compounds *via* a transition metal catalyzed coupling (Scheme 2.24).



Scheme 2.24*-Retrosynthetic analysis for the formation of substituted pyridines.*

According to the methodology, pyridine **244** would be formed from RCM product **245**, that would be obtained from acrylic acid **246**and homoallylic amine **240**(Scheme 2.24).

In 1995, Okuhara and co-workers isolated endothelin converting enzyme (ECE) inhibitors WS 75624 A **247**and WS 75624 B **248**. These compounds contained the structural motif with the requisite 3-alkoxy pyridine substitution pattern that would benefit from the expansion of the RCM methodology (Figure 2.10).[115]

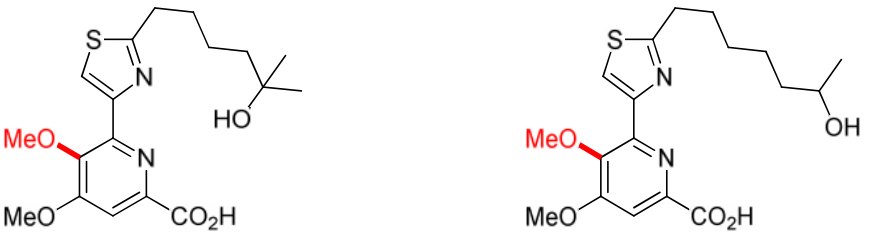
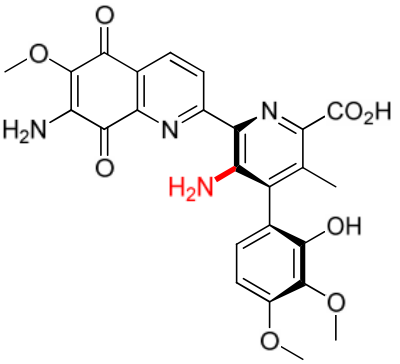


Figure 2.10 *- WS 75624 A**247** and WS 75624 B **248**.*

Streptonigrin **249** is a powerful metabolite that was shown to have high levels of toxicity but proves to be extremely potent in the treatment of a variety of human tumours. This natural

product was first isolated by Rao and Cullen in 1959 and contains a polysubstituted pyridine ring with an amino group at the 3-position (Figure 2.11).[116]



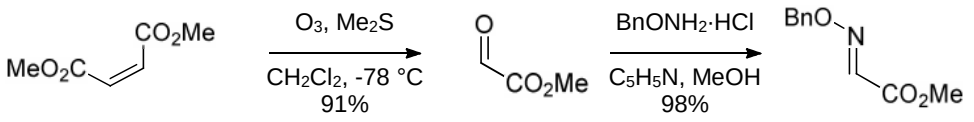
249

Figure 2.11 *- Streptonigrin.*

2.3 Result and discussion

2.3.1 The synthesis of 3-alkoxy 2-pyridones

The first step in the synthetic sequence involves the condensation of *O*-benzyl hydroxylamine hydrochloride and methyl 2-oxoacetate **251** to afford oxime **252**. A benzyloxy protective group has been found the most adequate for this method. Methyl glyoxalate **251** was obtained from an ozonolysis of methylmaleate **250** according to the procedure reported by Jung and co-workers.[117,118] Aldehyde **251** was converted to oxime **252** in very high yields (Scheme 2.25).

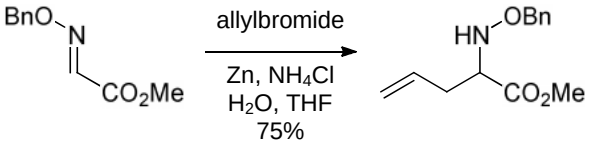


250 **251** **252**

Scheme 2.25 *- Synthesis of oxime 252.*

The formation of methyl ester **251** and of oxime **252** was demonstrated by comparison of the ^{1}H and ^{13}C NMR spectra with the previously reported spectroscopic data for these compounds.[70]

Once oxime **252** was obtained, it was then converted to the homoallylic amine **253** using a zinc-mediated allylation. This allylation is carried out in a mixture of THF and aqueous saturated ammonium chloride according to the procedure described by Hanessian and co-workers.[119]



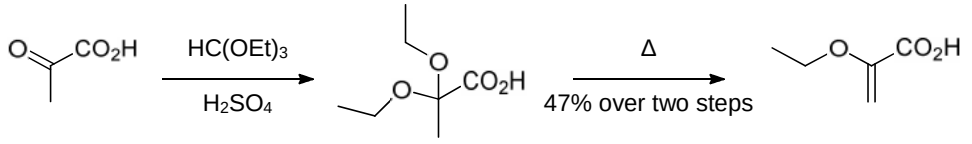
252 **253**

Scheme 2.26 *- Zinc-mediated allylation.*

The mechanism of this reaction is not completely known, and is likely that the formation of an organozinc is not possible since the reaction is carried out in an acidic aqueous medium that would rapidly quench such an organometallic species. Instead, it has been proposed that the reaction mechanism involves the formation of allylic radicals at the metal surface.[120,121]

The coupling partner to amine **253** would be an acrylic acid derivative with an alkoxy substituent at the alpha position to obtain the desired 3-alkoxy substituted pyridine.

In 1987, LaMattina and Muse reported the formation of 2-ethoxy-acrylic acid **256** by a distillation of the acetal **255**. Pyruvic acid **254** was converted to the diethyl acetal **255** in the presence of triethyl orthoformate and catalytic amounts of sulfuric acid (Scheme 2.27).[122]



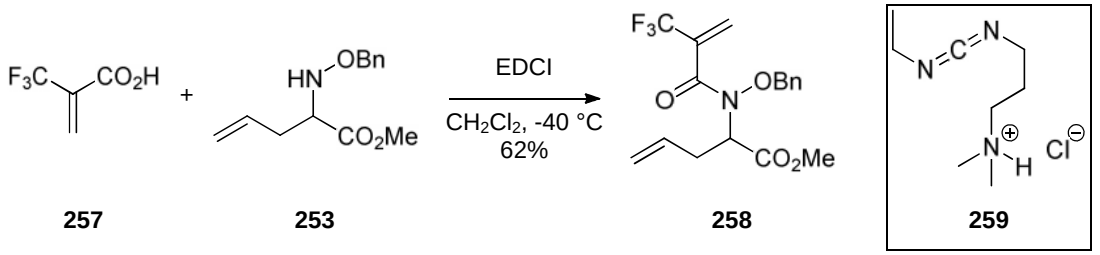
254 **255** **256**

Scheme 2.27 *- Synthesis of **256**.*

The crude acetal **255**, which is obtained with high levels of purity, was subjected to a distillation under reduced pressure. When the pressure was set to 1.5 mmHg and this crude acetal is heated, then elimination of ethanol occurs and the desired acrylic acid **256** distilled

above 100 °C. This surprising finding has allowed the simplification of the synthesis of this acid.[122]

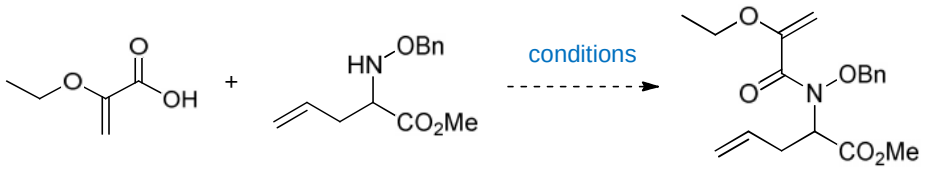
Next an amide coupling between amine **253** and acrylic acid **256** was sought. The use of coupling agent EDCI**259** was tested first, since it was known to promote the amide coupling of amine **253** and acrylic acid **257** (Scheme 2.28).[123]



257 **253** **258** **259**

Scheme 2.28 *- EDCI amide coupling.*

However, the use of EDCI did not yield any of the desired product. A series of reaction conditions were tried without success. Even when, TBTU **261** (Figure 1.13) was used as a more reactive amide coupling agent, there was no evidence of product formation (Table 2.1).

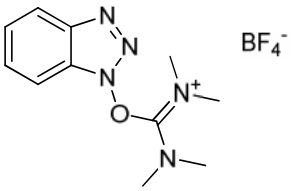


256 **253** **260**

Scheme 2.29 *- Amide coupling of acid **256** and amine **253**.*

Coupling agent	Additive	Solvent	Temperature	Yield
EDCI	none	CH_2Cl_2	-40 °C	None
EDCI	none	CH_2Cl_2	0 °C	None
EDCI	none	CH_2Cl_2	20 °C	None
EDCI	HOBt	DMF	60 °C	None
EDCI	HOBt	THF	20 °C	None
EDCI	4-DMAP, Et_3N	CH_2Cl_2	20 °C	None
EDCI	4-DMAP, Et_3N	CH_2Cl_2	40 °C	None
EDCI		DMF	80 °C	None
TBTU	Et_3N	DMF	20 °C	None
DCC		CH_2Cl_2	40 °C	<85%

Table 2.1 *- Conditions for amide coupling.*



261

Figure 1.13 *- Coupling agent TBTU.*

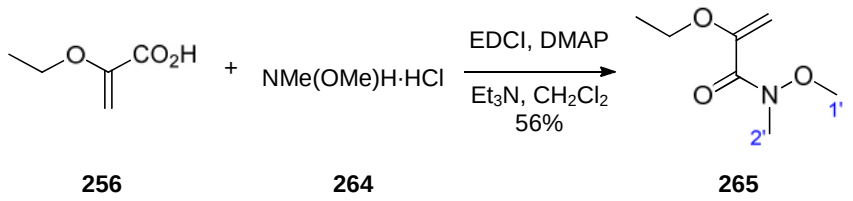
The use of DCC **262** yielded the desired product (Table 2.1), but complete purification from the by-product urea **263** remained elusive (Figure 2.12). The next step in the sequence was the RCM which was not possible to carry through because the urea **263** would inhibit the metathesis catalyst by coordination with ruthenium.



262 **263**

Figure 2.12 *- N,N'-dicyclohexylcarbodiimide (DCC)* ***262****and by-product urea****263****.***

In order to probe the relative nucleophilicity of the hydroxylamine **253**, a control experiment was carried out, in which the acrylic acid **256** was used in conjunction with N,O-dimethylhydroxylamine hydrochloride **264** and EDCI. The amide **265** was formed successfully (Scheme 2.30).



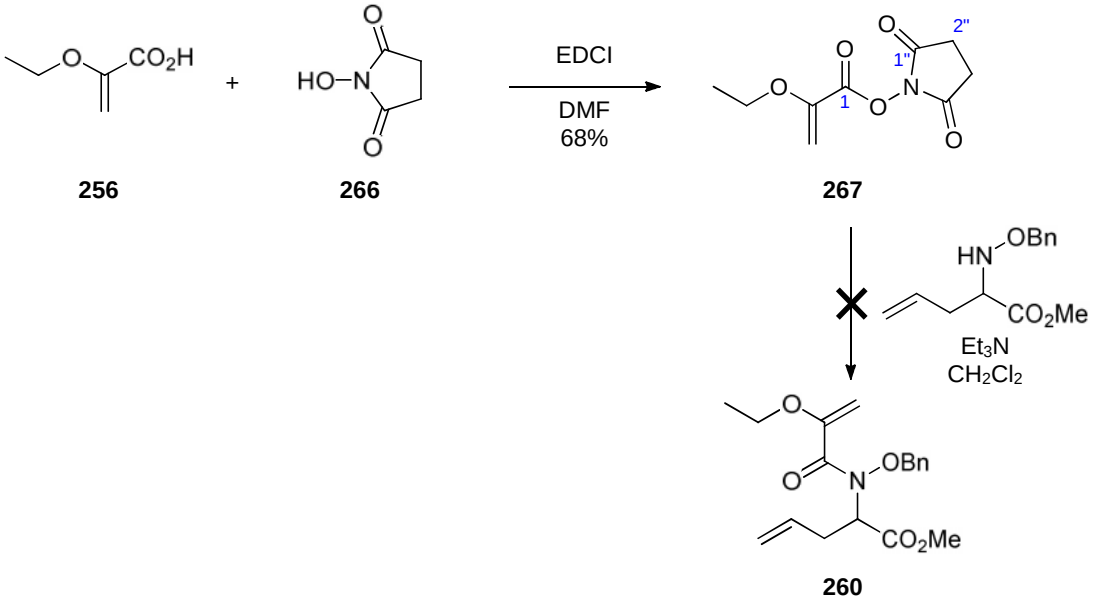
256 **264** **265**

Scheme 2.30 *- Amide coupling of acid **256** and amine **264**.*

The formation of amide **265** was evidenced by the appearance of two methyl singlet signals in the ^{1}H NMR spectrum at 3.68 ppm and 3.18 ppm, corresponding to C(1')H_3 and C(2')H_3 respectively.

That acrylic acid **256** participated successfully in an amide coupling gave an indication that the amine **253** is not able to displace the activated species generated from EDCI, and it was then decided to abandon the use of coupling agents and generate the amide through other means.

Acrylic acid **256** was coupled with *N*-hydroxysuccinamide **266** to form the activated derivative **267**, which was then subjected to a displacement with amine **253**, but again no product was observed.



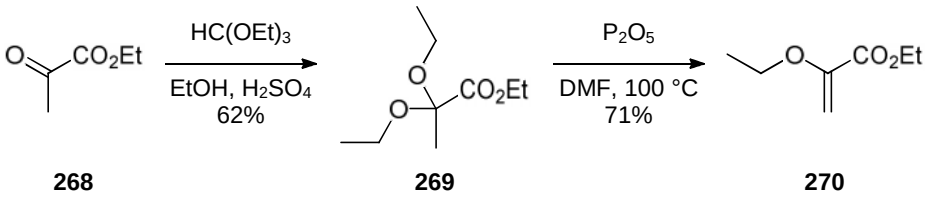
256 **266** **267** **260**

Scheme 2.31 *- Failed amide coupling.*

The formation of derivative **267** was evidenced by the appearance of a signal in the ^{1}H NMR spectrum at 2.80 ppm which was assigned to C(2")H_2 and corresponded to the four equivalent proton signals in the succinimide ring. Furthermore the appearance of signals in the ^{13}C NMR at 168.9 ppm and 158.3 ppm corresponded to C(1") and C(1) respectively.

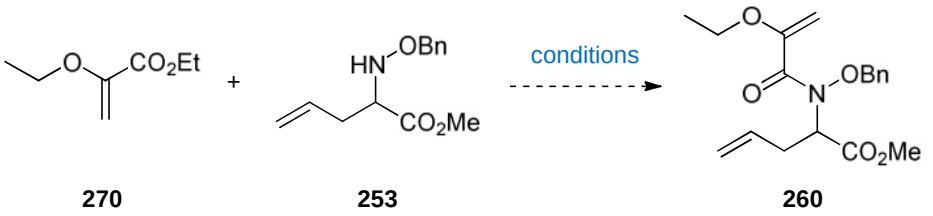
It was then decided to try an amination of ester **270** using trimethyl aluminium ($AlMe_3$) or isopropyl magnesium bromide as base. Ester **270** was prepared using a phosphorous pentoxide (P_2O_5) induced elimination of ethanol from the corresponding acetal.

Ethyl pyruvate **268** was converted to diethyl acetal **269** by standard conditions and then treated with P_2O_5 to form the ester **270** (Scheme 2.32).[124]



Scheme 2.32 *- Synthesis of ester **270**.*

Ester **270** was then subjected to a series of reaction conditions (Table 2.2).

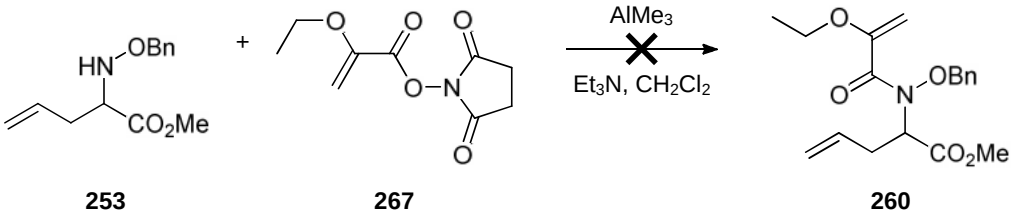


Scheme 2.33*- Amide coupling of ester **270** and amine **253**.*

Base	Solvent	Temperature	Yield of **260**
none	MeOH	20 ºC to 65 °C	none
none	none	20 ºC to 110 °C	none
isopropyl magnesium bromide	THF	20 °C	none
$AlMe_3$	CH_2Cl_2	20 °C	none

Table 2.2 *- Conditions for amide coupling*

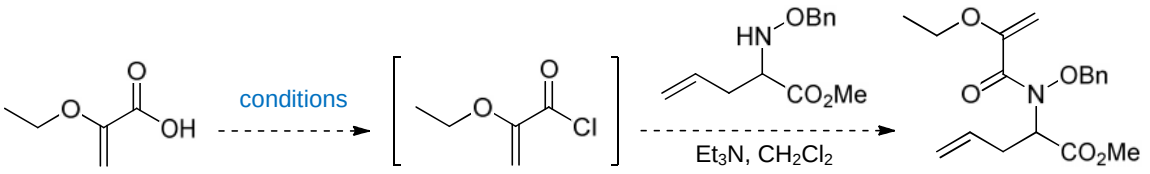
Subsequently, the reaction of activated derivative **267** and amine **253** using $AlMe_3$ was attempted but no product was observed (Scheme 2.34).



253 **267** **260**

Scheme 2.34 *- Failed amide coupling.*

The enol ether functionality in acrylic acid **270** is acid labile and therefore it was thought that this acid would be difficult to be convert to the acid chloride **271** since the reagents required for this conversion would decompose the substrate. Nevertheless, generating the carboxylate salt and then adding the chlorinating agent was thought to overcome the decomposition of the starting material (Table 2.3).



256 **271** **260**

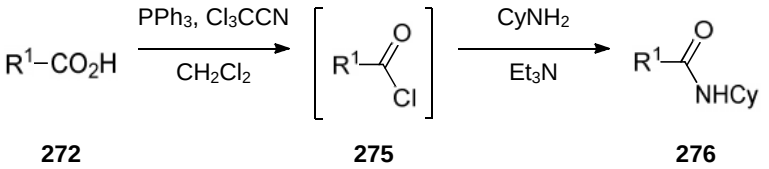
Scheme 2.35*-Attempted formation of acid chloride****271*** *and in situ amide coupling.*

Acid chloride reagent	Base	Solvent	Temperature	Yield
Thionyl chloride	K_2CO_3	Et_2O	20 °C	decomposition
Oxalyl chloride	K_2CO_3	Et_2O	20 °C	decomposition

Table 2.3*- Conditions for amide coupling.*

The formation of the acid chloride **271** was expected to be difficult, and a mild method to produce this target was investigated.

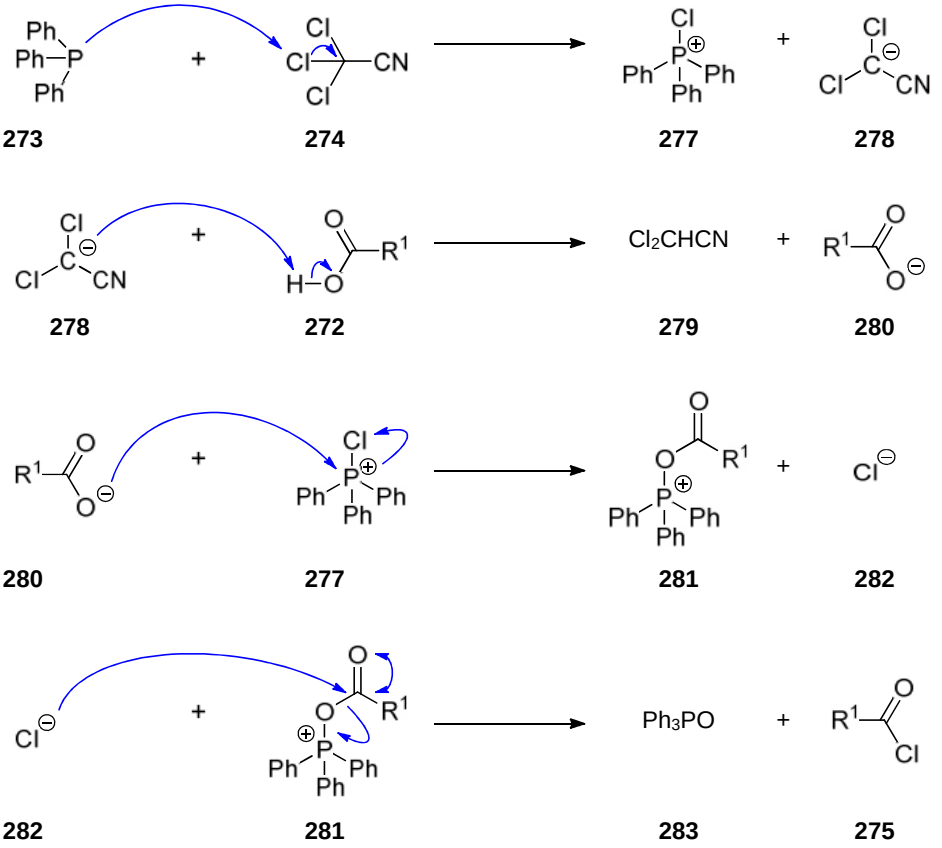
Jang and co-workers have demonstrated that when carboxylic acid **272** is reacted with triphenylphosphine **273** (Ph_3P) in conjunction with trichloroacetonitrile **274** (Cl_3CCN), the acid chloride **275** is produced, under neutral conditions, and this can be converted to the desired amide **276** (Scheme 2.36).[125]



Scheme 2.36 *- Amide coupling under neutral conditions.*

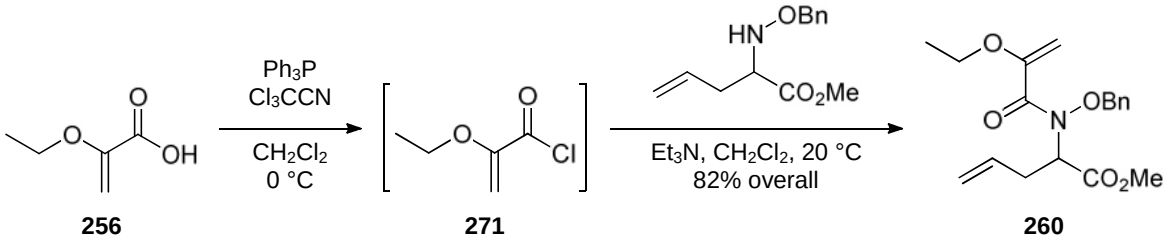
The mechanism of this reaction was not described, but the products formed initially are the acid chloride **275**, triphenylphosphine oxide **283** (Ph_3PO) and dichloroacetonitrile **279**.[125]

A plausible mechanism involves first the formation of triphenylphosphonium chloride **277** and deprotonation of the carboxylic acid **272** to form dichloroacetonitrile **279**. Carboxylate **280** can then displace the chloride from **277**, and this free chloride can now attack the activated carbonyl of intermediate **281**, to give Ph_3PO and acid chloride **275** (Scheme 2.37).



Scheme 2.37 *- Plausible mechanism of chlorination of acid **272**.*

These reaction conditions were employed with acrylic acid **256** and the corresponding acid chloride **271** was reacted with amine **253** to give the desired diene **260** in high yields (Scheme 2.38).[118]



Scheme 2.38 *- Amide coupling under neutral conditions.*

Formation of diene **260** was evidenced by the appearance of a signal in the ^{1}H NMR spectrum at 5.83 ppm which was assigned to the olefinic signal C(4)H. Further evidence is seen in the appearance of four signals at 5.18 ppm, 5.12 ppm, 5.07 ppm and 5.02 ppm which were assigned to the terminal olefin signals C(5)H_2 and the benzylidene signals C(1")H_2 (Figure 2.13).

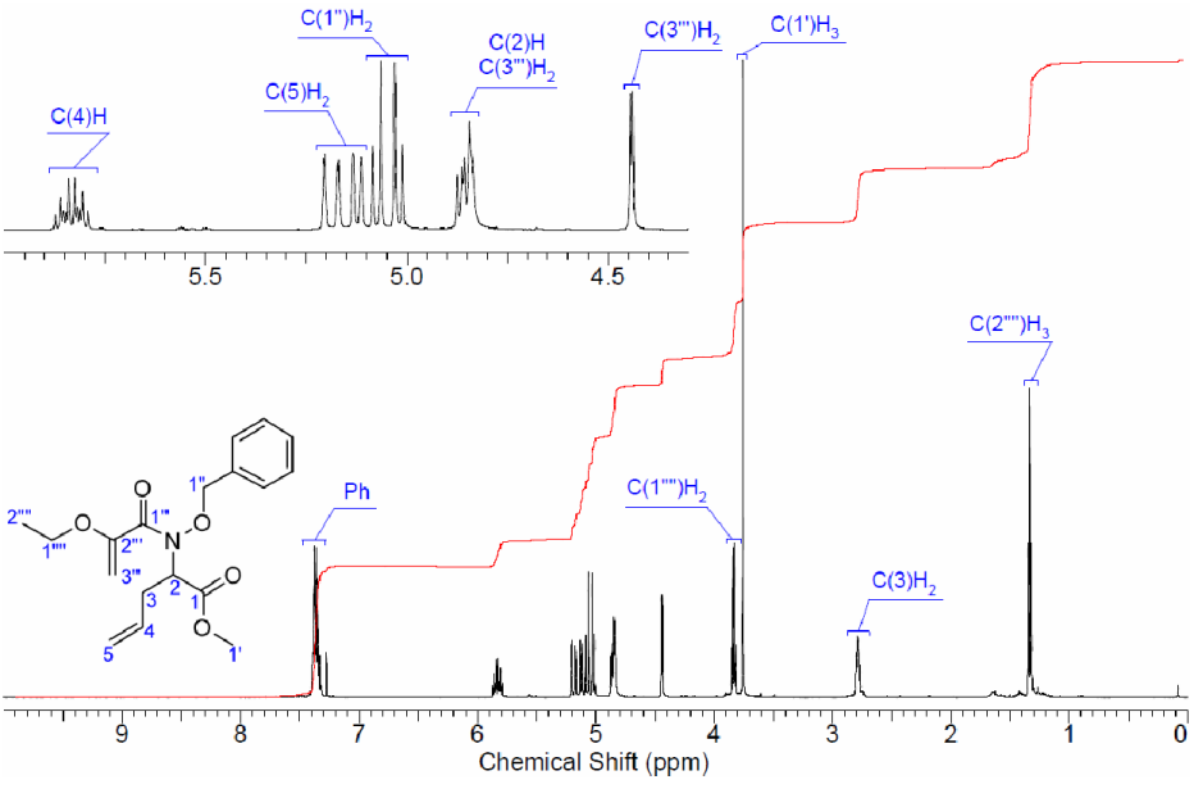
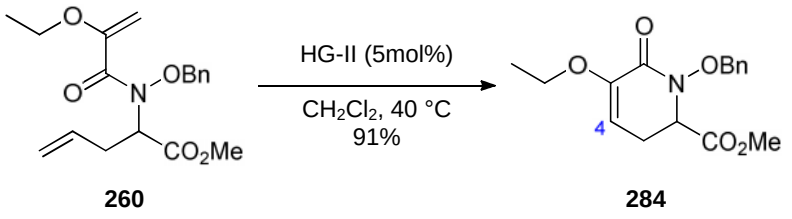


Figure 2.13 *- ^{1}H NMR of diene **260**.*

In addition to the evidence supported by the ^{1}H NMR spectrum, the appearance of a signal in the ^{13}C NMR spectrum at 170.0 which was assigned to (C(1)), and also 167.0 and 154.9 which were assigned to (C(2"')) and (C(1"')) respectively provided conclusive evidence of the formation of diene **260**.

With the diene **260** in hand, the key RCM step was applied using catalyst HG-II to obtain α,β-unsaturated lactam **284** in high yield (Scheme 2.39).[118]

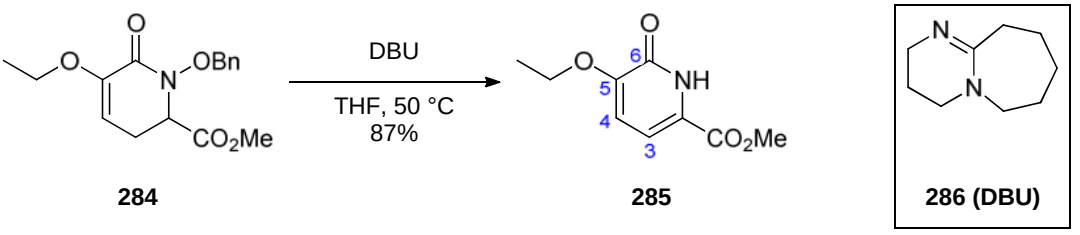


260 **284**

Scheme 2.39 *- Formation of α,β-unsaturated lactam **284** by RCM.*

The formation of α,β-unsaturated lactam **284** was evidenced by the appearance of a lone alkene signals in the ^{1}H NMR spectrum at 5.17 ppm which was assigned to the olefin signal C(4)H.

After the desired α,β-unsaturated lactam **284** was attained, the aromatisation protocol was achieved by a base induced elimination mediated by the electron withdrawing group at the 6-position (i.e. methyl ester). Treatment of α,β-unsaturated lactam **284** with 1,8-diazabicyclo[5.4.0]-undec-7-ene **286** (DBU) afforded the 2-pyridone **285** in good yields (Scheme 2.40).[118]



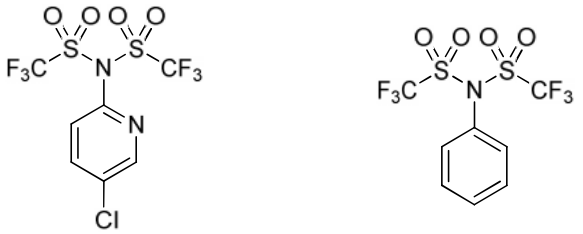
284 **285** **286 (DBU)**

Scheme 2.40 *- Aromatisation of α,β-unsaturated lactam **284**.*

The formation of the 2-pyridone **285** was evidenced by the appearance of signals in the ^{1}H NMR spectrum at 10.46 ppm - assigned to the NH - and at 6.90 and 6.55 ppm which

corresponded to the aromatic signals C(3)H and C(4)H. Furthermore the coupling constant of $J_{3\text{-}4}$ of 7.5 Hz is in agreement with an *ortho* coupling in 2-pyridones.[126] The appearance of the signals in the ^{13}C NMR spectrum at 157.1 ppm and 153.7 ppm, which were assigned to C(5) and C(6), are in agreement with literature reports of the 2-pyridone moiety.[75]

In 1992, Comins and Dehghani published a study into the triflation of ketones using *N*-(5-Chloro-2-pyridyl)bis(trifluoromethanesulfonimide) **287** (Comins' reagent)and showed that this reagent has several advantages over other triflating agents(Figure 2.14).[127]



287 (Comins' reagent) **288 ($PhNTf_2$)**

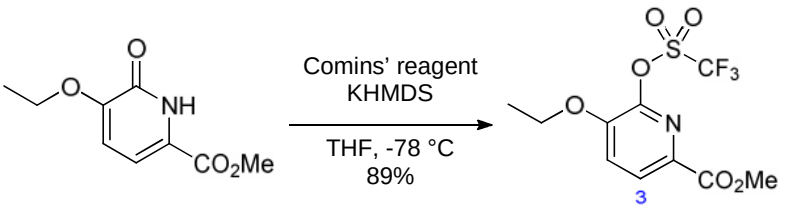
Figure 2.14 *- Triflating agents.*

Comins' reagent is a stable solid, which can be prepared easily from the commercially available 5-chloro-2-aminopyridine and purified by Kugelrohr distillation.[127]

Triflic anhydride is not as stable, and depending on the storage conditions, contains triflic acid which is likely to quench any preformed anion. In addition, Comins' reagent is more reactive than *N*-phenyltriflimide **288** (PhNTf2), which means that the reaction can be carried out at a much lower temperature avoiding possible decomposition.[127]

Finally, the by-products of triflation using Comins' reagent are easy to remove while the by-products of triflation with *N*-phenyltriflimide could be difficult to purify.[127]

The heteroaromatic compound 2-pyridone **285** was converted to pyridine **289** by triflation of the 2-hydroxyl tautomer with Comins' reagent (Scheme 2.41).[118]



285 **289**

Scheme 2.41*-Activation of 2-pyridone* ***285*** *by triflation.*

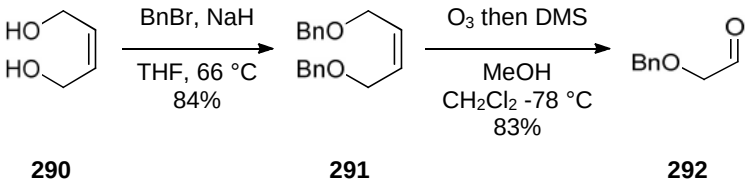
The formation of pyridine **289** was evidenced by the appearance of the signals in the ^{13}C NMR at 118.5 ppm which appears as a *quartet* with a $J_{C\text{-}F}$ of 320 Hz, and was assigned to CF_3. Also the appearance of a signal in the ^{1}H NMR spectrum at 8.17 ppm that corresponds to C(3)H is in accordance with the series of 2-triflated pyridines.[75]

The triflation of hydroxyl groups in aromatic system converts this moiety into a good leaving group for cross-coupling protocols. These reactions are important because it provides access to substitution with aromatic groups (*via* Suzuki-Miyaura cross-coupling or Stille cross-coupling),[118, 128, 129] alkynes (*via* Sonogashira cross-coupling),[118] alkenes (*via* Heck reactions).[130] Other substituents are possible because the triflated group behaves as a pseudohalide and the substitution of 2-halopyridines with nitrogen and oxygen containing derivatives (*via* Buchwald-Hartwig cross coupling or nucleophilic substitution)[131 - 134] are known.

The formation of this substrate readily expands the methodology for the synthesis of 3-alkoxypyridines and it serves as a template for the synthesis of substitution with other heteroatom containing moieties.

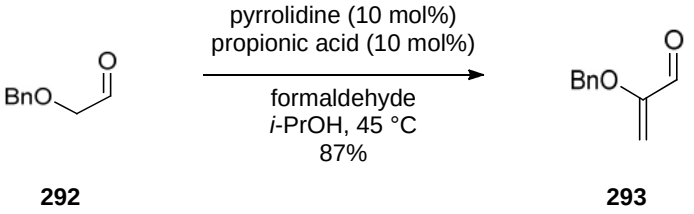
In order to obtain a free hydroxyl substituent at the 3-position, an alkoxy group that can be easily deprotected was sought. In this case, a benzyloxy group would take the place of the ethoxy group in pyridine **289**.

The reaction sequence started from *Z*-1,4-butenediol **290**. Protection of diol **290** with benzyl bromide afforded the *bis*-protected alkene **291**. Reductive ozonolysis of alkene **291** afforded the aldehyde **292** (Scheme 2.42).



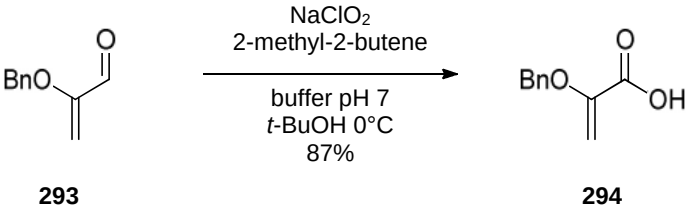
***Scheme 2.42**- Synthesis of aldehyde **292**.*

In 2006, Erkkilä and Pihko presented an improved method for the Mannich reaction between a series of 2-substituted acetaldehydes and formaldehyde using 10% pyrrolidine and 10% propionic acid as catalysts to generate acrylic aldehydes.[135] This protocol was used to convert aldehyde **292** into acrylic aldehyde **293** (Scheme 2.43).



***Scheme 2.43** - α-Methylenation of aldehyde **292**.*

Oxidation of acrylic aldehyde **293** was achieved using sodium chlorite as the oxidant.[136]The pH of this reaction was maintained at 7 so as to preserve the aldehyde **293** or the acid **294** from decomposition. Moreover, sodium chlorite was added while maintaining the reaction in an ice bath and the reaction mixture was warmed up slowly to room temperature (Scheme 2.44).

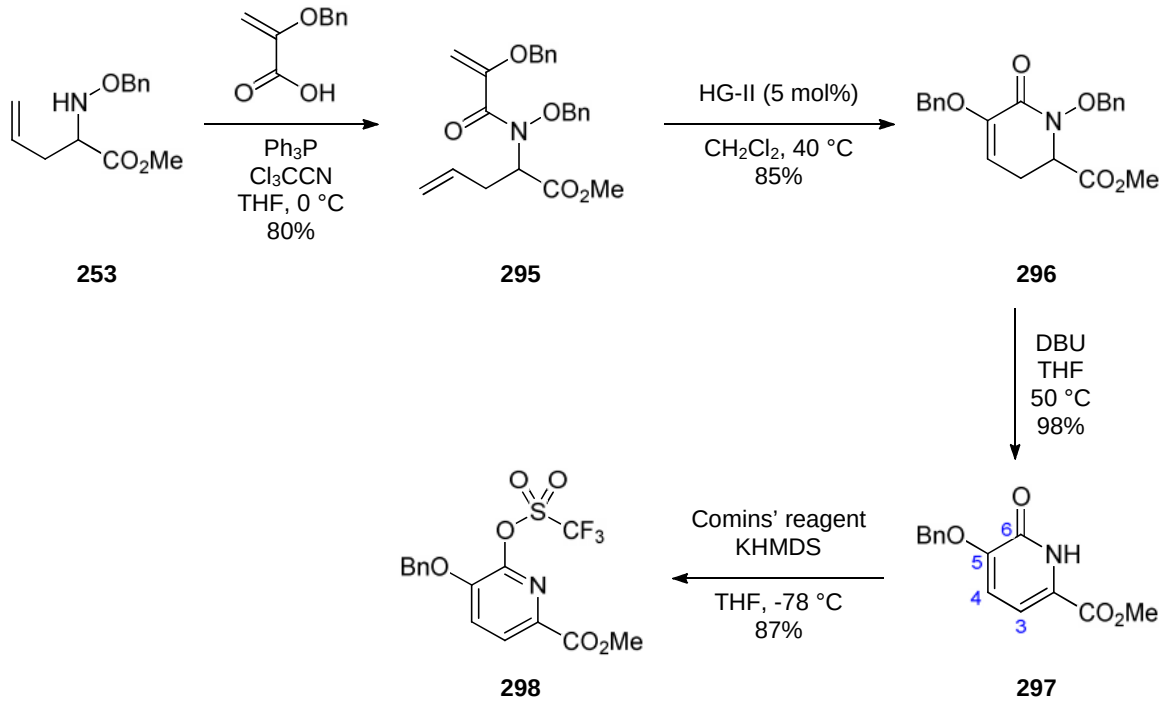


293 **294**

Scheme 2.44- *Synthesis of acid **294**.*

This novel route to the synthesis of acid **294** facilitated the preparation of multi-gram quantities and is superior in many respects to the use of alkylation protocols from pyruvic acid.

With acid **294** in hand, the synthesis of desired 2-pyridone **297** was undertaken. Amide coupling using amine **253** provided the diene **295**. Key RCM of diene **295** provided the α,β-unsaturated lactam **296**. Elimination of the benzyloxy protecting group from α,β-unsaturated lactam **296** afforded the desired 2-pyridone **297** which can be triflated to obtain pyridine **298** in four steps from amine **253**.[118]



253 **295** **296** **298** **297**

Scheme 2.45 *- Synthesis of pyridine **298**.*

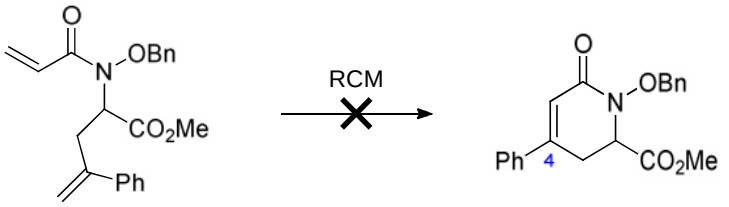
The formation of the 2-pyridone **297** was evidenced by the appearance of signals in the ^{1}H NMR spectrum at 9.54 ppm which was assigned to the NH, also the appearance of the

signals at 6.94 and 6.67 which corresponded to the aromatic signals C(3)H and C(4)H. Furthermore the coupling constant of $J_{3\text{-}4}$ of 7.5 Hz is in agreement with an *ortho* coupling The appearance of the signals in the ^{13}C NMR spectrum at 157.0 ppm and 153.8 ppm which were assigned to C(5) and C(6) are in agreement with the presence of the 2-pyridone moiety

2.3.2 Functionalisation prior to aromatisation

The method discussed above for the synthesis of 2-pyridones used a rapid assembly of different components that produced the desired heteroaromatic moiety. The only limitation arose from the key step, the RCM, as it is difficult to place a substituent at the 4-position.

As an example, Fishlock has synthesized diene **299** and shown that it does not undergo a RCM to afford the desired α,β-unsaturated lactam **300** (Scheme 2.46).[118] This was not a surprising find, given that the metathesis catalyst does not initiate readily in the presence of electron deficient olefins, or 1,1-disubsuituted alkenes.[37]



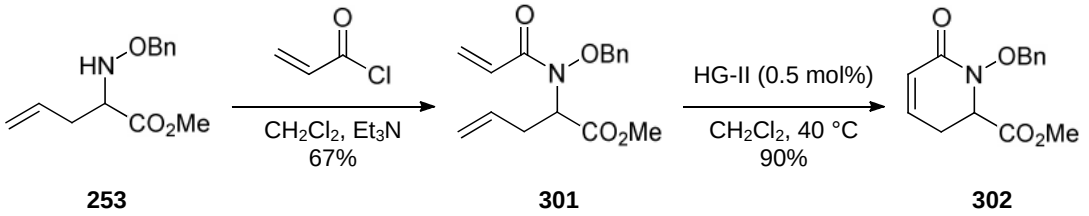
299 **300**

Scheme 2.46 *- Synthesis of 4-substituted α,β-unsaturated lactam **300**.*
Work carried by L. P. Fishlock

To circumvent this limitation, the synthesis of desired α,β-unsaturated lactam **300** can be formed by the use of the RCM approach and then intercepting and functionalizing the non-aromatic heterocycle intermediate prior to subjecting it to the aromatisation protocol. The reactivity of the α,β-unsaturated lactam would be utilized instead of modifying the 2-pyridone moiety.

This is an important concept, because the RCM approach is very effective in producing this α,β-unsaturated lactam in such a short sequence of events.[111, 137 - 140]

In order to test this hypothesis, amine **253** was converted to diene **301** by reaction with acryloyl chloride. RCM of diene **301** afforded the desired α,β-unsaturated lactam **302** in good yields (Scheme 2.47).



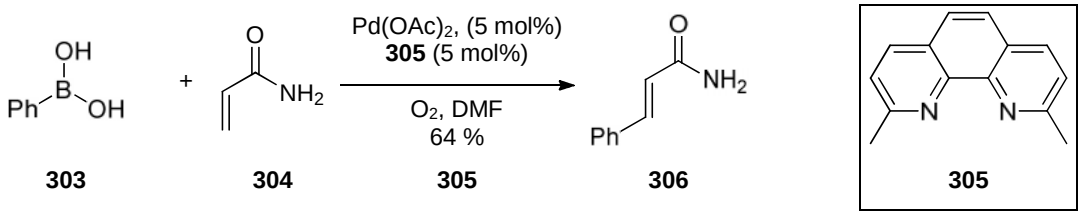
253 **301** **302**

Scheme 2.47 *- Synthesis of α,β-unsaturated lactam **302**.*

The Heck reaction is known to be a good method for the substitution of alkenes, and when an α,β-unsaturated carbonyl is used the regioselectivity increases. It is well established that the new aryl group is coupled to the β-position.[141, 142] To this end, it was decided to test this cross-coupling reaction with lactam **302**.

However, the use of base to promote a Heck reaction may promote the aromatisation of lactam **302**, rendering this substrate inactive for the desired cross-coupling.

In 2006, Jung and co-workers developed an oxidative Heck reaction which is carried out with catalytic amounts of palladium acetate and in the absence of base. In this instance phenylboronic acid **303** and acrylamide **304** are combined in the presence of Pd(II) catalyst and O_2 as a re-oxidant to give the desired Heck product **306** (Scheme 2.48).[143]

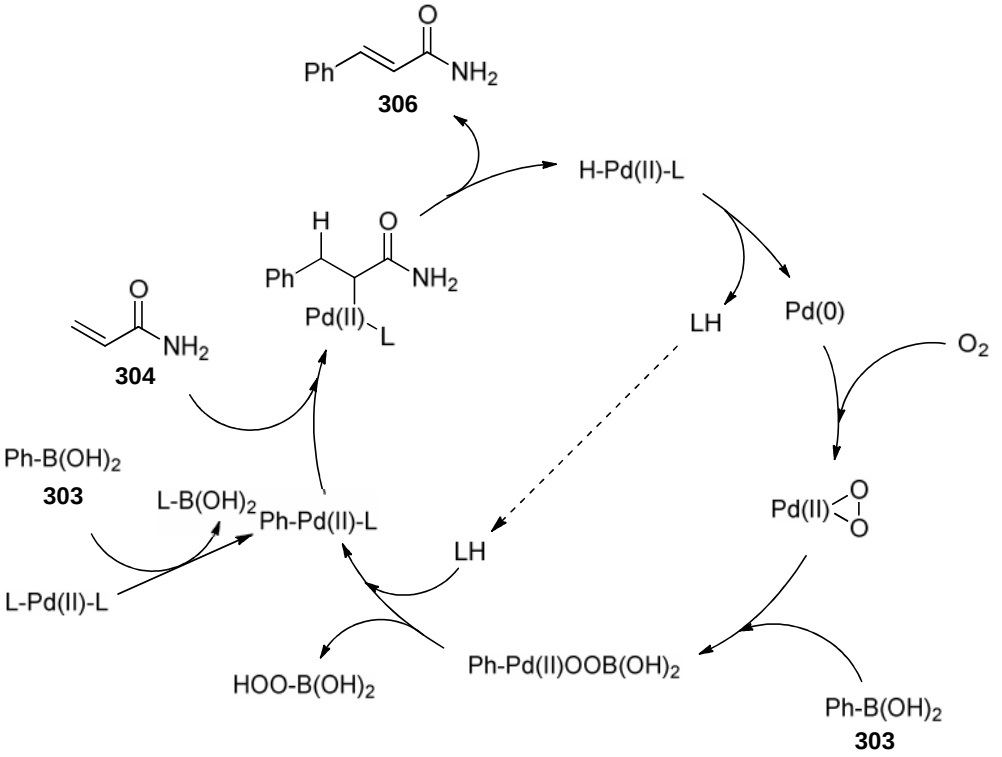


303 **304** **305** **306** **305**

Scheme 2.48 *- Oxidative heck reaction.*

The mechanism of this reaction is described by the authors. They showed a possible transmetallation from a Pd(II) species (L-Pd(II)-L or Pd(II)O_2) to the boronic acid, followed by a migratory insertion that installed the Ph group at the β-position, and finally β-hydride elimination to generate a Pd(II) species. Molecular oxygen then reacts with Pd^0 and forms

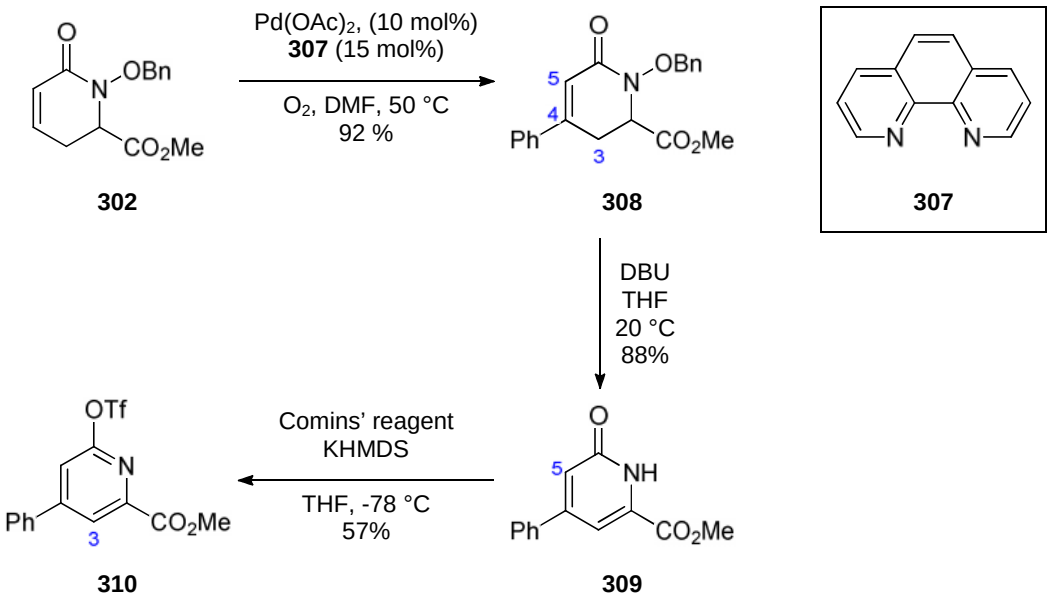
the peroxopalladium complex ($Pd(II)O_2$) that can enter the transmetallation event and continue the catalytic cycle (Scheme 2.49).[143]



Scheme 2.49 *- Plausible mechanism for the base free oxidative Heck reaction.*

The α,β-unsaturated lactam **302** was treated with phenylboronic acid under the conditions described, although 1,10-phenanthroline **307** was used instead of **305**, and the desired product **308** was obtained (Scheme 2.50).

The aromatisation protocol was applied to α,β-unsaturated lactam **308** and the 2-pyridone **309** was obtained. Triflation of the heteroaromatic **309** afforded the desired 4-substituted pyridine **310** (Scheme 2.50).[118]



Scheme 2.50 *- Synthesis of 4-substituted pyridine*

The formation of α,β-unsaturated lactam **308** was evidenced by the appearance of a signal in the ^{1}H NMR spectrum at 6.30 ppm that corresponded to the olefin signal C(5)H with a $J_{5\text{-}3}$ 2.5 Hz that is in accordance with an allylic coupling. Furthermore appearance of six signals in the ^{13}C NMR spectrum at 129.9 ppm, 129.7 ppm, 128.7 ppm, 128.7 ppm, 128.4 ppm and 125.7 ppm that corresponded to six phenyl carbons appeared. Three signals in the ^{13}C NMR spectrum at 147.1 ppm, 136.1 ppm, 135.6 ppm that corresponded to two quaternary Ph carbons and C(4), while the signal at 119.3 ppm corresponded to C(5) as determined by DEPT and HSQC analysis.

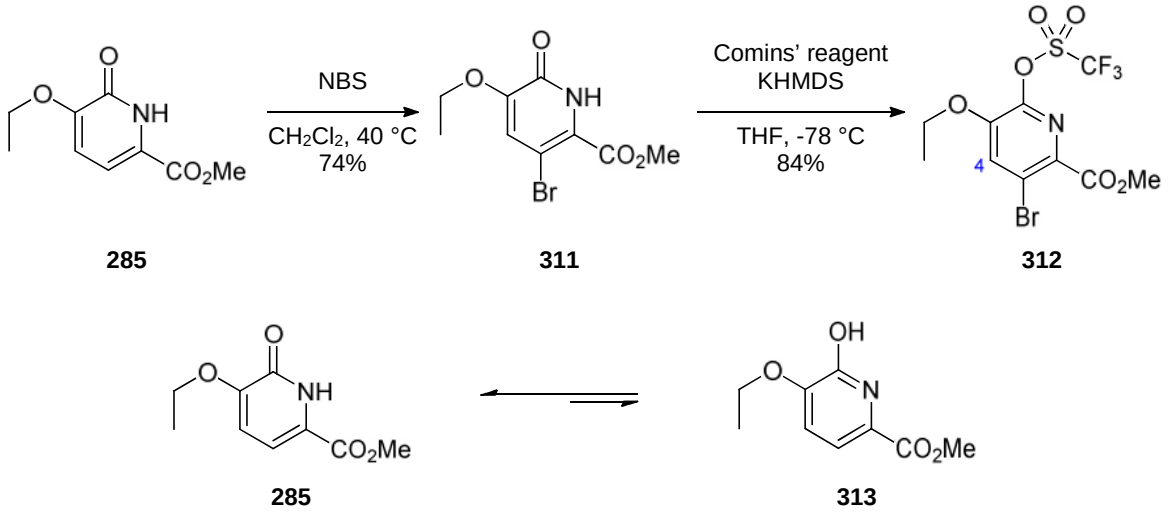
The formation of 2-pyridone **309** was evidenced by the appearance of a signal in the ^{1}H NMR spectrum at 9.60 ppm and 7.00 ppm that corresponded to NH and C(5)H respectively. Furthermore the appearance of a signal in the ^{13}C NMR spectrum at 129.8 ppm, 129.0 ppm and 126.7 ppm that corresponded to only three Ph signals.

The formation of pyridine **310** was evidenced by the appearance of a signal in the ^{1}H NMR spectrum at 8.44 ppm that correspond to C(3)H is in accordance with the series of 2-triflated pyridines. Further evidence is the appearance of the signals in the ^{13}C NMR at 118.6 ppm which appears as a *quartet* with a $J_{C\text{-}F}$ of 320 Hz, and was assigned to CF_3.

The concept of using the α,β-unsaturated lactam intermediates can also be exemplified by the use of another method for functionalisation, such as a halogenation. This would become important, because it would produce a polysubstituted pyridine equipped with a leaving group at the 4-position capable of being used in cross-coupling protocols as the electrophilic component.

During the synthesis of the 3-ethoxy substituted pyridine **289**, we have demonstrated that the α,β-unsaturated lactam **284** was converted to the 2-pyridone **285** (Scheme 2.40).

This 2-pyridone **285** can be selectively brominated at the 5-position to afford bromide **311**; the electrophilic aromatic substitution is possibly due to the effect of the 2-hydroxyl group in tautomer **313**, which directs the bromination *para* with a high level of regioselectivity(Scheme 2.51). Bromide **311** can be converted into a pyridine **312** that is equipped with two leaving groups at the 2- and 5- position for selective cross-coupling.[118]



Scheme 2.51 *- Bromination of 2-pyridone* ***285****.*

The formation of 5-bromopyridone **311** was confirmed by single crystal X-ray data (Figure 2.15, Appendix III)

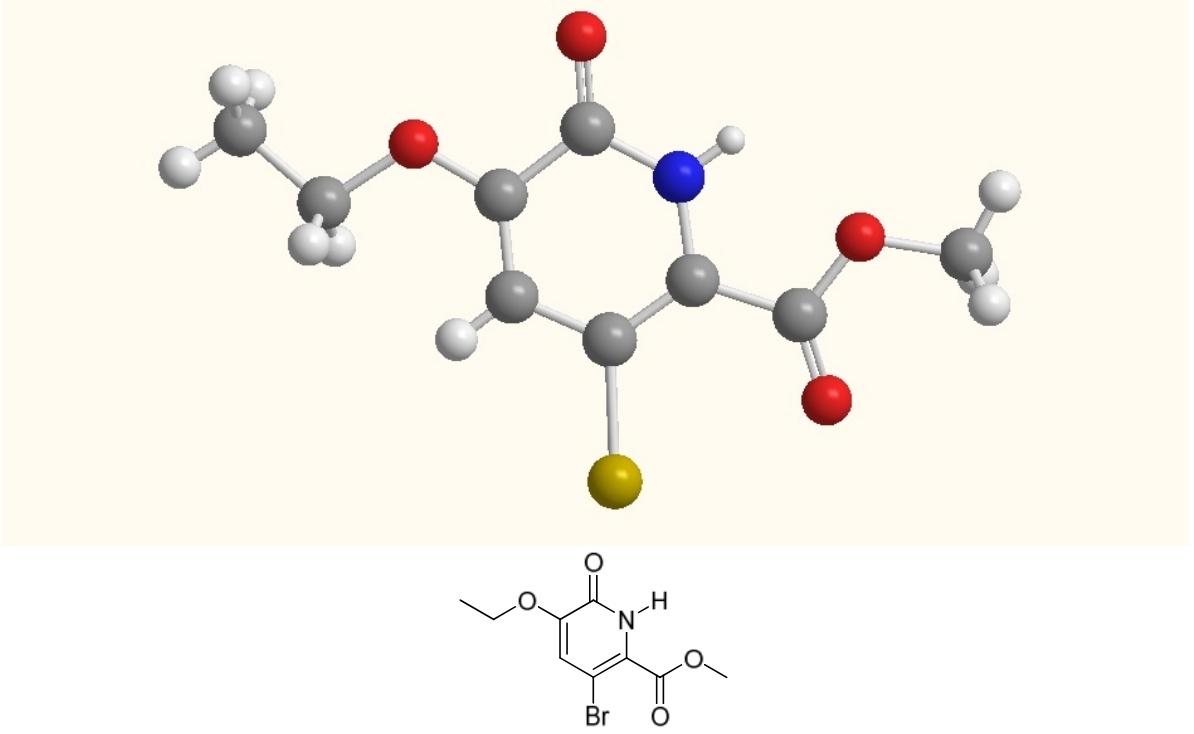


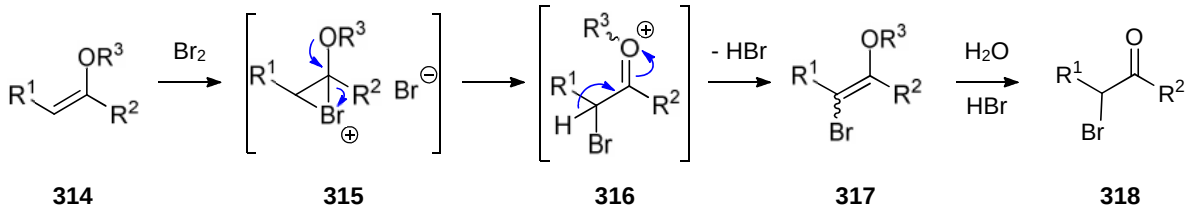
Figure 2.15 *- Single crystal X-ray analysis of 5-bromo-2-pyridone* ***311****.*

The formation of pyridine **312** was evidenced by the appearance of a signal in the ^{1}H NMR spectrum at 7.60 ppm that corresponded to C(4)H. Further evidence was the appearance of the signals in the ^{13}C NMR at 118.5 ppm which appears as a *quartet* with a $J_{C\text{-}F}$of320 Hz, and was assigned to CF_3.

An important avenue of overcoming the limitation of installing a substituent at the 4-position *via* a RCM, is to activate the lactam intermediate prior to aromatisation. Installing, for example, a halogen would afford a pyridine structure equipped with a leaving group at the 4 -position which could be used to install further heteroatoms, *via* Buchwald-Hartwig cross-coupling, or aromatic substituents that are not possible to install using the oxidative Heck reaction. Furthermore, exploring a method for bromination prior to aromatisation would afford the complementary regioisomer to the one obtained above (Scheme 2.51).

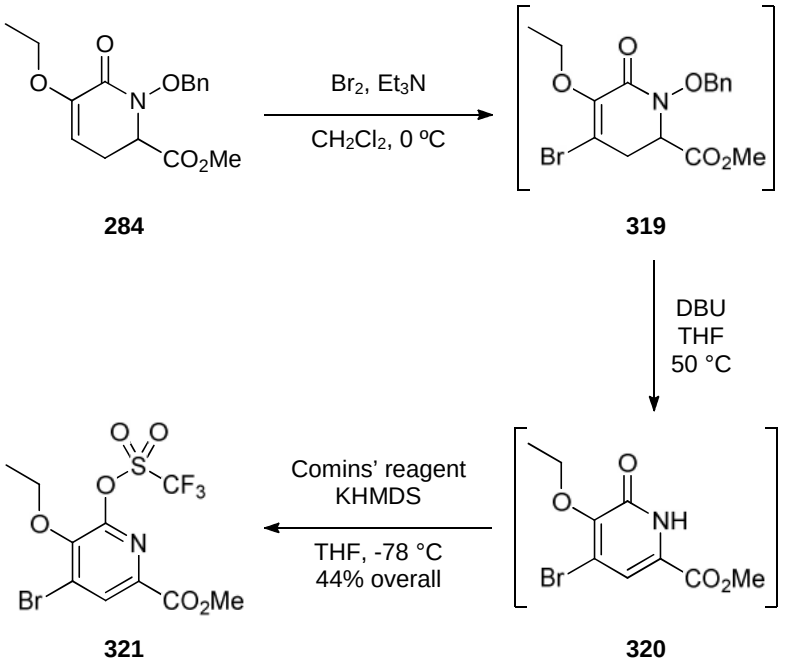
The bromination of enol ether is a known reaction and it can lead to the corresponding alpha brominated ketone product if the intermediate enol ether is hydrolysed during the reaction by

advantageous water. This process is catalyzed by hydrobromic acid, which is a by-product of the bromination event (Scheme 2.52).[144]



Scheme 2.52 *- Alpha bromination of enol ethers.*

In order to obtain the 4-substituted bromide **319**, the α,β-unsaturated lactam **284** was treated with a mixture of triethylamine and bromine. The intermediate **319** was difficult to isolate and therefore once the reaction had gone to completion, it was then converted to the 4-bromo-2-pyridone **320** and then to the pyridine **321** that is equipped with two leaving groups at the 2- and 4-position for selective cross-coupling protocols (Scheme 2.53).[118]



Scheme 2.53 *- Synthesis of polysubstituted pyridine **321**.*

Gratifyingly, sequence control allows for the synthesis of pyridine **312** and pyridine **321** selectively, and these two structures are complementary in their substitution patterns (Figure 2.16).

It is important to emphasise the outcome of this method because a 2,3,5,6-tetrasustituted pyridine **312** was obtained as a single regioisomer by a RCM approach followed by a bromination of the 2-pyridone, and the complementary 2,3,4,6-tetrasubstituted pyridine **321** was also obtained as a single regioisomer utilizing the non-aromatic character of the intermediate unsaturated lactam.

These results also proved the important concept of using a RCM metathesis approach, with a functionalisation of the intermediate non-aromatic heterocyclic, in order to obtain highly substituted targets with the different regiochemical outcome of the heteroaromatic product.

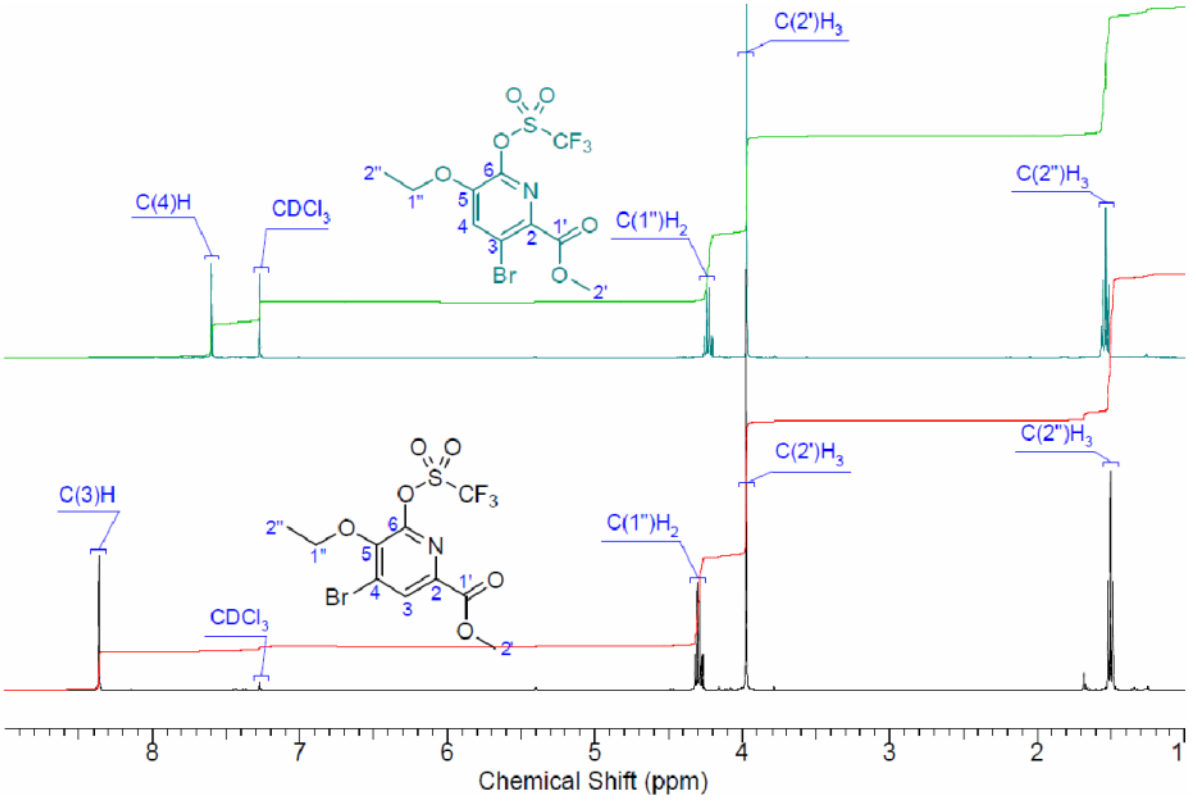


Figure 2.16 *- ^{1}H NMR of bromopyridines **312** and **321**.*

In conclusion, the synthesis of polysubstituted pyridines was achieved *via* a RCM approach in a very short reaction sequence. The incorporation of substituents containing heteroatoms was successful, and key amide coupling was demonstrated. The synthesis of pyridine **289** serves as a platform for the use of this methodology in the total synthesis of a very important pyridine containing natural products.

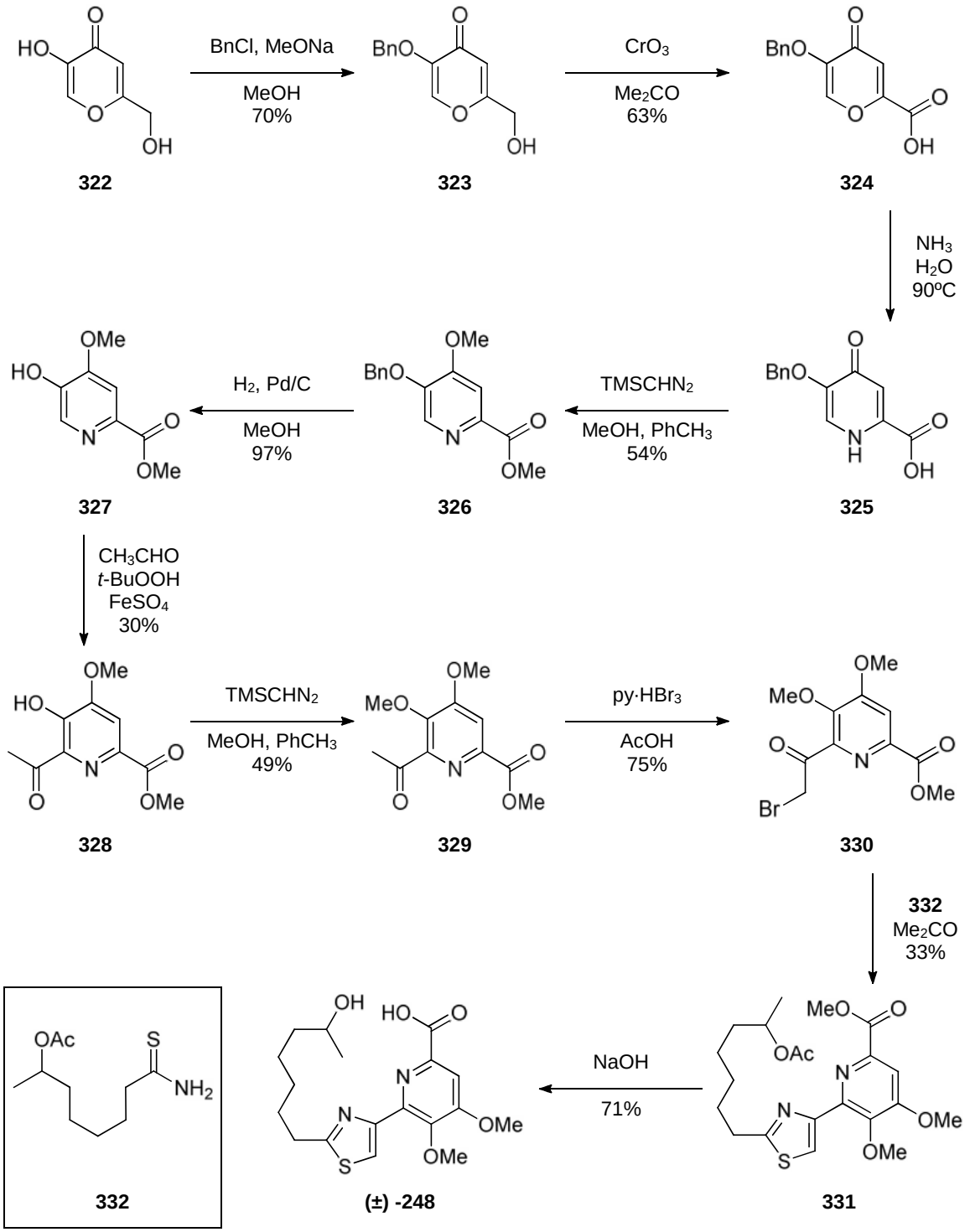
Also, the functionalisation of the heterocyclic intermediates prior to the aromatisation protocol was demonstrated successfully. This important concept of modifying the heterocyclic structure resolves some of the limitation of the metathesis reactions, and is also a source of inspiration for many of the metathesis based methodologies developed later on in the group.

2.4 Synthetic approaches towards WS 75624 A and B

2.4.1 Introduction

The target pyridine WS 75624 A **247** (Figure 2.10) was used as a platform to explore the methodology developed above in the context of total synthesis. This target is of special interest because it is one of the first non-peptide inhibitors of the endothelin converting enzyme that regulates the synthesis of an important vasoconstrictor, Endothelin-1 (ET-l), which plays an important role in diseases such as pulmonary hypertension.[145, 146]

In 1997, Patt and Massa achieved the first total synthesis of WS 75624 B **248**, starting from commercially available kojic acid **322** (Scheme 2.54).[147]

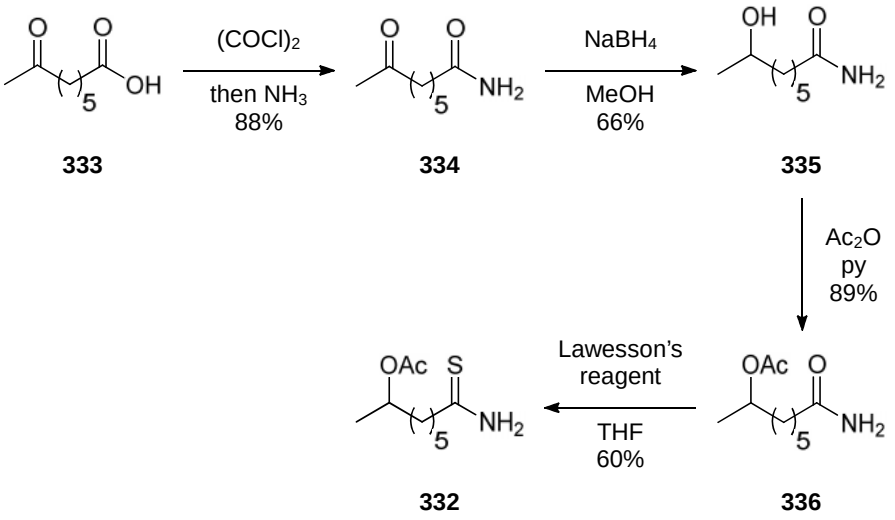


Scheme 2.54 *- Patt's synthesis of WS 75624 B (±) -* ***248****.*

Kojic acid **322** was converted to the 4-pyridone **325** in three steps; first by benzylation to achieve **323**, then Jones' oxidation to afford **324** and finally condensation with ammonia. Pyridone **325** was then methylated to afford the pyridine **326** which was deprotected to give pyridine **327**. To install the last substituent on the pyridine core a radical acylation was

performed to give the desired pyridine **328**. This was converted to the desired target in a further four steps: methylation to afforded pyridine **329**, bromination to generate **330**, condensation with thioamide **332** and then ester hydrolysis to furnish (±) - **248** (Scheme 2.54).[147]

The required thioamide **332** was synthesized from 7-oxooctanoic acid **333** in four steps (Scheme 2.55).[147]

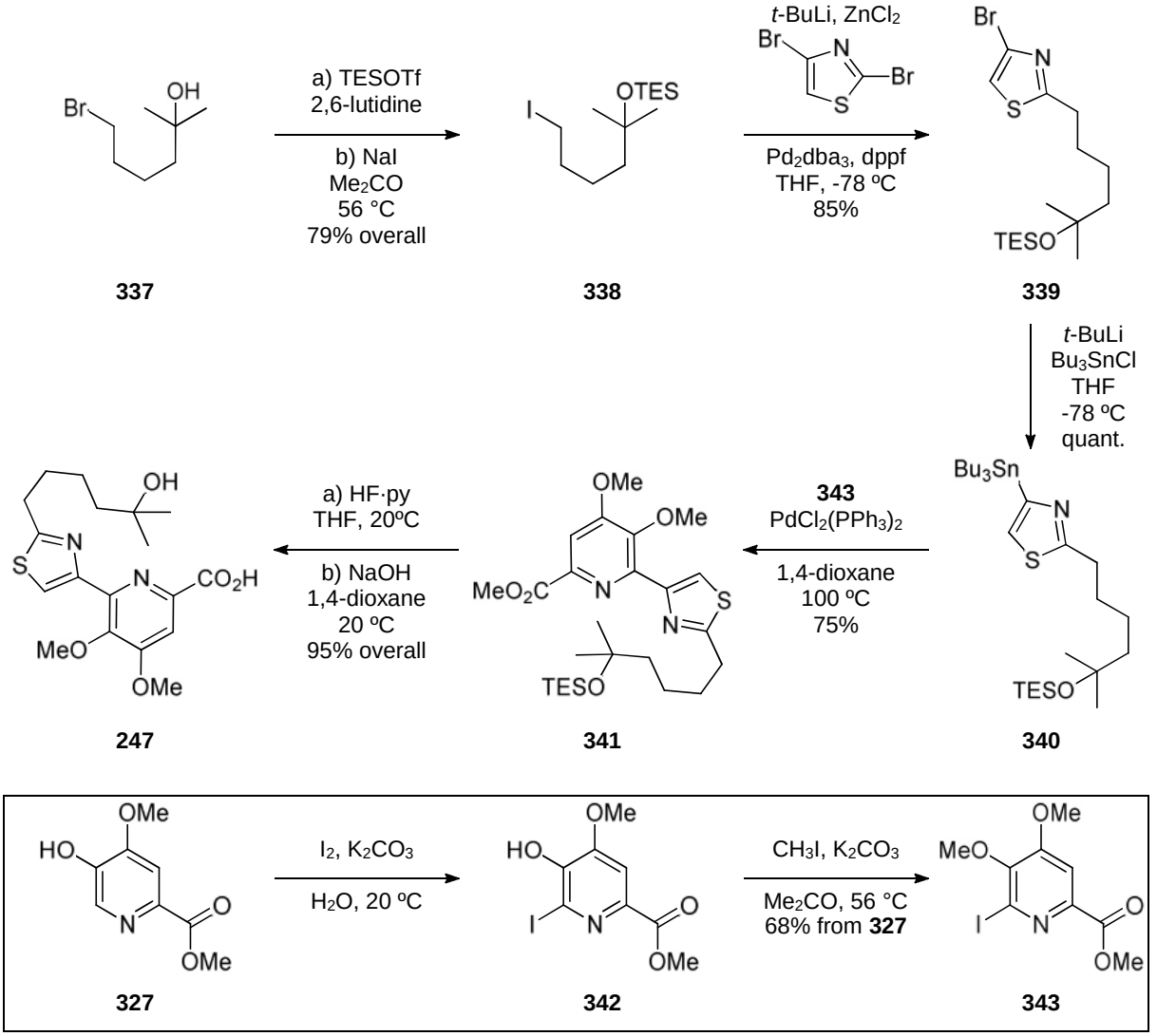


Scheme 2.55 *- Synthesis of thioamide**332**.*

In 2002, Bach and Heuser reported the synthesis of WS 75624 A **247** by preparing a pyridine core and then using a cross-coupling protocol to insert the thiazole moiety.[115]

The synthesis of the pyridine core was also realised from kojic acid **322**, and pyridine **327** obtained from the same sequence of steps as the previous synthesis. Pyridine **327** was converted to iodide **342** and then methylated to give pyridine **343** (Scheme 2.56).[115]

Bromide **337** was transformed to iodide **338** in two steps. Negishi coupling between 2,4-dibromothiazole and iodide **338** gave the bromothiazole **339**, which was converted to the stannylthiazole **340**. Stille cross-coupling between **343** and **340** afforded the protected target **341**. Deprotection furnished the desired target, WS 75624 A **247** (Scheme 2.56).[115]



Scheme 2.56 *- Bach's synthesis of WS 75624 A* ***247****.*

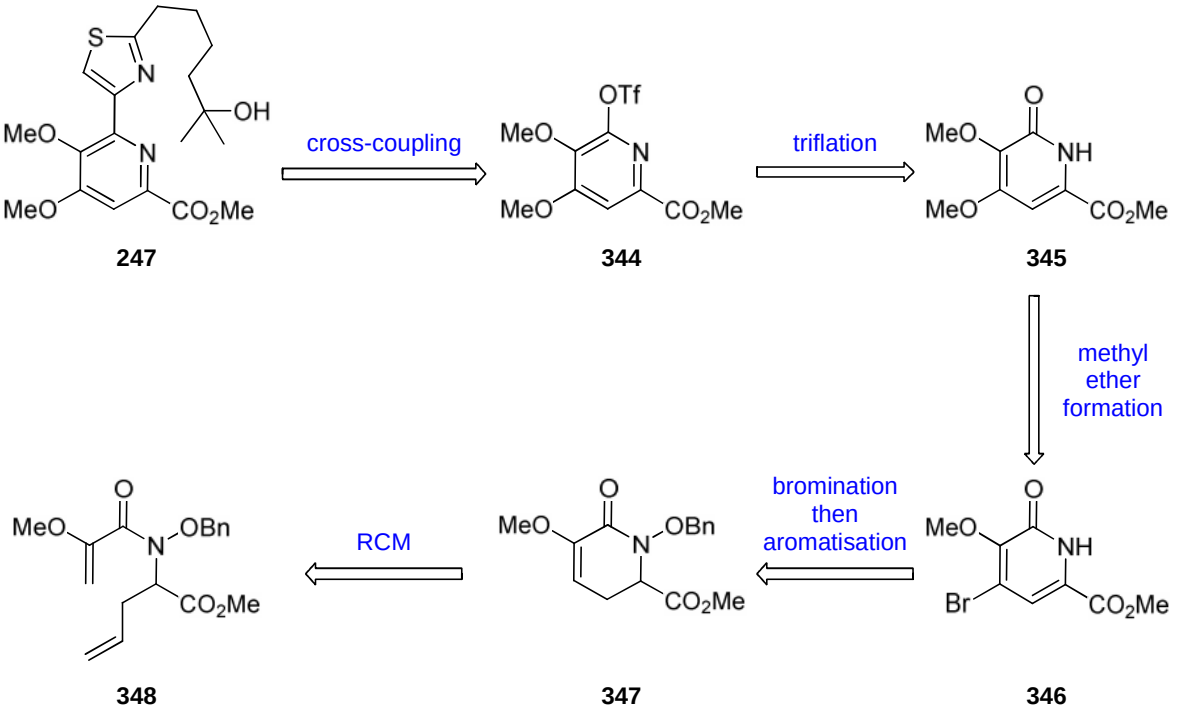
2.4.2 Results and discussion

Using the RCM methodology previously described, a new synthetic approach towards these two natural products was planned. This synthesis would have the advantage of being shorter, with the starting materials readily available, which would significantly reduce the costs associated with producing enough material for a thorough biological evaluation.

The synthesis of WS 75624 A **247** was thought to be achievable by a Stille cross-coupling between stannylthiazole **340** and the triflated pyridine **344** (Scheme 2.57)

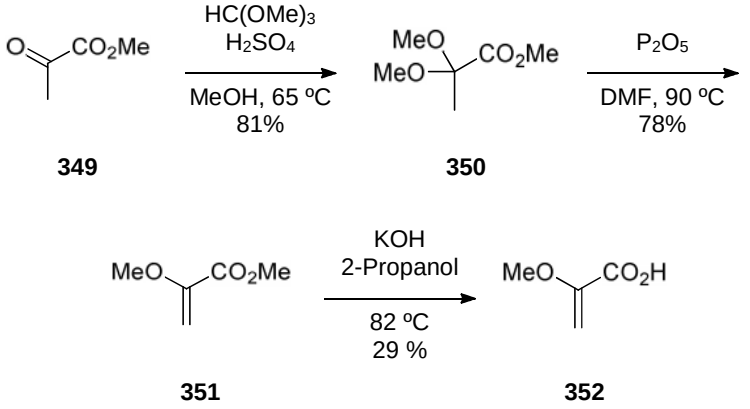
Pyridine **344** could be synthesize from 2-pyridone **345** by a triflation using Comins' reagent. 2-Pyridone **345** could be formed from 2-pyridone **346** by displacement of the bromide by

methanol. Pyridone **346** can be obtained selectively by bromination and then aromatisation of unsaturated lactam **347**, which can be prepared by a RCM of diene **348** (Scheme 2.57).



Scheme 2.57 *- Retrosynthetic analysis of WS 75624 A* ***247****.*

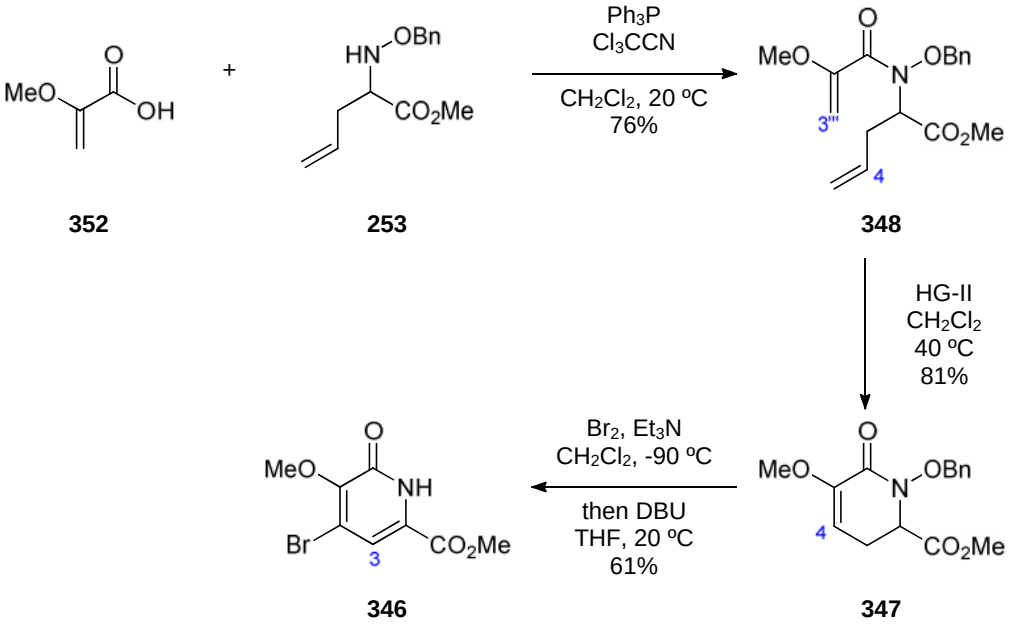
Firstly, acrylic acid **352** was prepared from methyl pyruvate **349** by conversion to the dimethyl acetal **350**. Acetal **350** was transformed to acrylic ester **351** and this ester was hydrolysed to the desired acid **352** (Scheme 2.58).



Scheme 2.58 *- Synthesis of acrylic acid* ***352****.*

Amide coupling of acrylic acid **352** and homoallylic amine **253** afforded the desired product without inconvenience, proving the robustness of this coupling method. Key RCM of diene

348 using catalyst HG-II produced the desired unsaturated lactam **347** in a high 81% yield. Selective bromination of unsaturated lactam **347** was achieved with bromine and triethylamine to generate the desired 4-bromo-2-pyridone **346**.



Scheme 2.59 *- Synthesis of 2-pyridone **346**.*

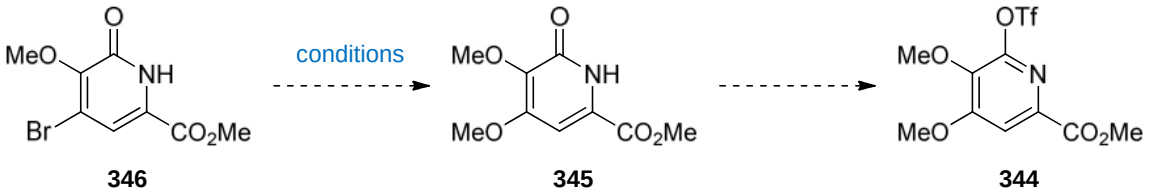
Formation of diene **348** was evidenced by the appearance of a signal in the ^{1}H NMR spectrum at 5.82 ppm which was assigned to the olefinic proton C(4)H, also 4.47 ppm which was assigned to the terminal olefin signals C(3”’)H_2. Furthermore the appearance of the two methyl signals at 3.76 ppm and 3.64 ppm were assigned to C(1’)H_3 and C(1””)H_3 respectively.

Formation of unsaturated lactam **347** was evidenced by the appearance of a signal in the ^{1}H NMR spectrum at 5.28 ppm which was assigned to the single olefinic proton C(4)H with a $J_{4\text{-}3}$ of 2.5 Hz and $J_{4\text{-}3}$6.0 Hz.

Formation of pyridone **346** was evidenced by the appearance of a signal in the ^{1}H NMR spectrum at 9.45 ppm which corresponded to the NH signal. Furthermore the appearance of a signal at 7.18 ppm which was assigned to C(3)H.

Attempts at conversion 4-bromo-2-pyridone **346** to the desired 4,3-dimethoxy-2-pyridone **345** were undertaken (Scheme 2.60).Pyridone **345** would then be converted to pyridine **344**, and this substrate would be ready for a Stille cross-coupling protocol.

However, the formation of pyridone **345** could not be achieved, and nucleophilic displacement with sodium methoxide under a range of conditions was unsuccessful (Table 2.4).

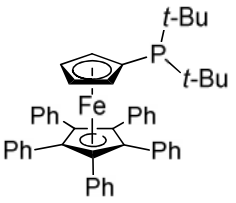


Scheme 2.60 *- Synthetic approach towards pyridine **344**.*

Entry	Conditions	Yield
1	MeONa, MeOH, 65 ºC	starting material
2	KOH, MeOH, 65 ºC	ester hydrolysis
3	MeONa, 1,4-dioxane, 110 ºC	decomposition
4	MeONa, DMF, 110 ºC	decomposition
5	MeONa, MeOH, 110 ºC	ester hydrolysis
6	CuI, Cs_2CO_3, N,N-dimethylglycine hydrochloride, MeOH, 110 ºC	starting material
7	MeONa, Pd_2dba_3 (5 mol%), **353** (20 mol%), $PhCH_3$, 100 ºC	starting material
8	*t*-BuONa, Pd_2dba_3 (5 mol%), **353** (20 mol%), $PhCH_3$, 100 ºC	starting material
9	MeOH, HCl (cat.), 20 ºC	starting material
10	MeOH, HCl (cat.), 70 ºC	starting material

Table 2.4*-Attempted conversion of 4-bromo-2-pyridone **346**to 3,4-dimethoxy-2-pyridone **345**.*

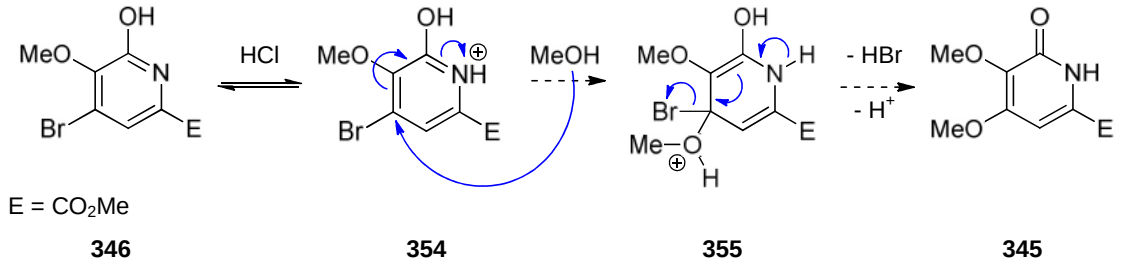
In 2002, Hartwig and co-workers reported the use of an electron rich, sterically hindered, monodentate ligand, QPhos **353**, for the etherification of aryl halides (Figure 2.17).[148] The conditions reported by Hartwig were also screened in this case but without a positive result (entry 7 and 8; Table 2.4).



353

***Figure 2.17**-QPhos: 1,2,3,4,5-Pentaphenyl-1'-(di-tert-butylphosphino)ferrocene.*

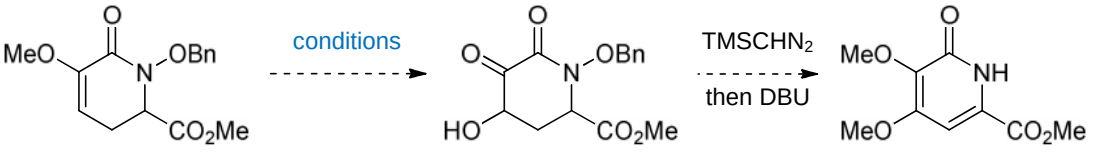
Given that the 2-pyridone **346** is electron-rich, treatment with acid should produce the pyridinium salt **354**, which may be more susceptible to attack of methanol, which would produce the desired product **345** (Scheme 2.61). However, when conditions were attempted to this effect no reaction was observed (Entry 10, 11; Table 2.4).



346 **354** **355** **345**

***Scheme 2.61** - Proposed acid mediated aromatic substitution of pyridone **346**.*

In order to install the required methoxide group, the dihydroxylation of unsaturated lactam **347** was attempted under UpJohn conditions.[149] If successful, this would deliver a keto-hydroxyl group that can be converted to the desired target by methylation of the free hydroxyl tautomer (Scheme 2.62). However, this route was also unsuccessful.



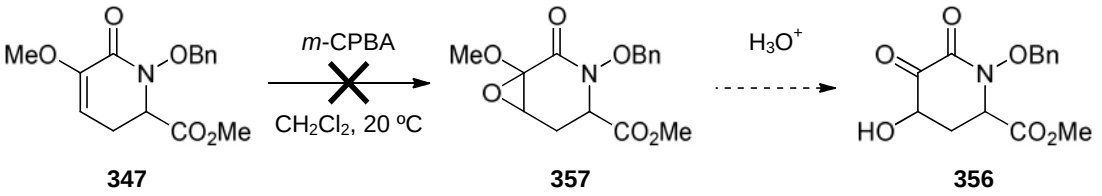
347 **356** **345**

***Scheme 2.62**-Attempted synthesis of pyridone **347** via dihydroxylation.*

Entry	Conditions	Yield
1	OsO_4, NMO, *t*-BuOH, H_2O, Me_2CO, 20 ºC	decomposition
2	OsO_4, NMO, citric acid, *t*-BuOH, H_2O, Me_2CO, 20 ºC	decomposition
3	K_2OsO_4, $K_3Fe(CN)_6$, Quinuclidine, $MeSO_2NH_2$ K_2CO_3, t-BuOH, H_2O, 20 ºC	decomposition

Table 2.5*- Failed dihydroxylation of unsaturated lactam* ***347****.*

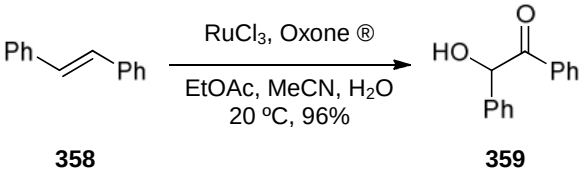
Next, the possibility to oxidize the enol ether **347** *via* an epoxidation was investigated. If successful, the epoxide intermediate could be to the desired product **356**. However, epoxidation of unsaturated lactam **347** did not produce the desire product (Scheme 2.63), and this was not explorer further. Instead a more elegant solution was sought.



Scheme 2.63*- Failed epoxidation of unsaturated lactam* ***347*** *.*

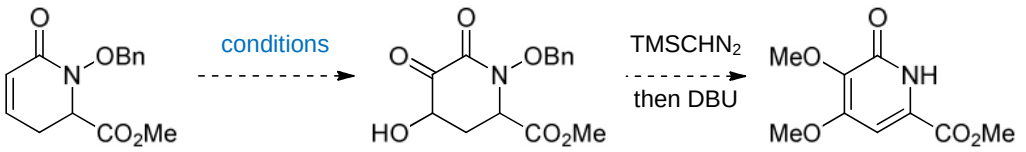
All the efforts of converting unsaturated lactam **347** proved to be futile and a different approach for the preparation of the desired tetrasubstituted pyridone **345** was undertaken.

Attention was focused on a ruthenium mediated keto-hydroxylation reaction developed by Plietker,[150] in which an alkene **358** is oxidized to the acyloin **359** (Scheme 2.64). Using this keto-hydroxylation method, we hoped to be able to prepare the unsaturated lactam **356**.



Scheme 2.64 *- Keto-hydroxylation of alkene* ***358****.*

Using this approach the unsaturated lactam **302** was subjected to a range of conditions, however these efforts also prove to be ineffective (Scheme 2.65).



302 **356** **345**

Scheme 2.65- *Failed keto-hydroxylation of unsaturated lactam* ***302***.

Entry	Conditions	Yield
1	$RuCl_3$, EtOAc, MeCN, H_2O, CH_3CO_3H, 20 ºC	decomposition
2	$RuCl_3$, EtOAc, MeCN, H_2O, Oxone ®, 20 ºC	decomposition
3	$RuCl_3$, EtOAc, MeCN, H_2O, Oxone ®, $NaHCO_3$, 20 ºC	starting material

Table 2.6- *Failed keto-hydroxylation of unsaturated lactam****302***.

The construction of a C-O bond *via* transition metal catalyzed cross-coupling process in heterocyclic compounds remains an important limitation in organic chemistry. The construction of the 3,4-dimethoxy-2-pyridone **345** was abandoned and the focus of the project was turned to finding other methods to prepare polysubstituted pyridines using a RCM as the key event, so as the need for such a transition metal catalyzed etherification can be obviated.

2.5 Summary

The approach to the synthesis of 2-pyridones and 2-trifluorosulfonyl pyridines has been enhanced by the formation of targets that include heteroaromatic substituents. Such targets are the basis of a current project for the total synthesis of streptonigrin in the Donohoe group.

The concept of functionalisation of the RCM heterocyclic products before aromatisation has been introduced and applied to the synthesis of polysubstituted pyridines. This functionalization overcomes the limitation of the RCM in introducing a substituent at the three position.

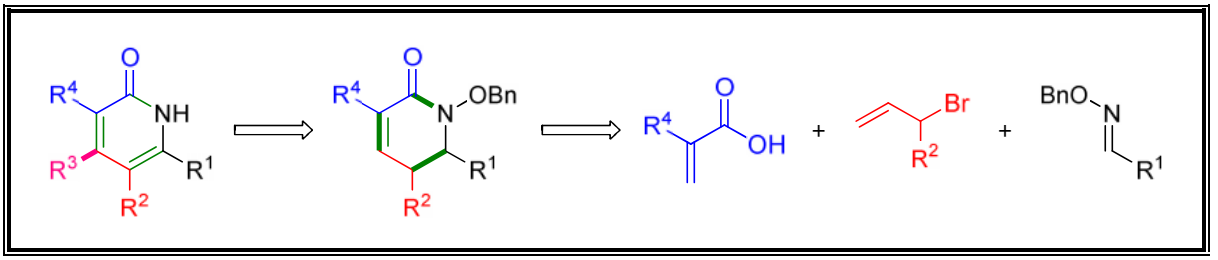


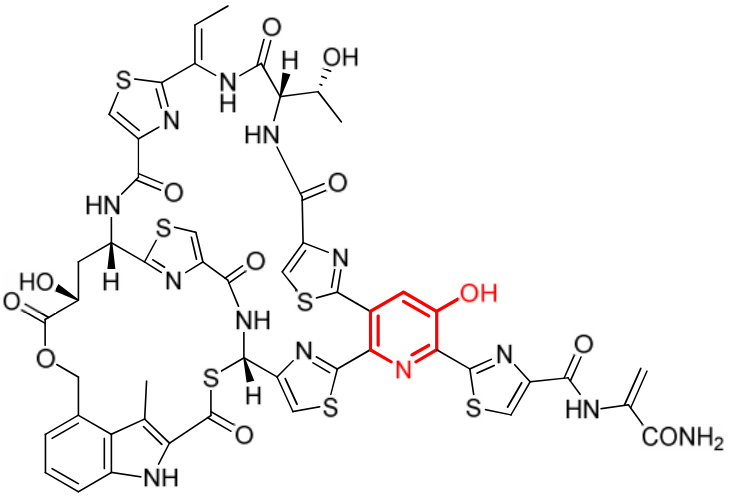
Figure 2.18 *- Improved synthesis of 2-pyridones.*

Chapter three: The synthesis of 3-hydroxypyridines

Chapter three: The synthesis of 3-hydroxypyridines

3.1 Introduction

The 3-hydroxypyridine motif is present in many natural products that have demonstrated important biological activity. As mentioned earlier, the three forms of vitamin B6 (Figure 2.6) are examples of this scaffold in natural products. Another important molecule with the 3-hydroxypyridine motif is nosiheptide **360** (Figure 3.1), a powerful thiopeptide antibiotic, whose total synthesis remains elusive.[151, 152]



360

Figure 3.1- *Nosiheptide.*

The synthesis of the 3-hydroxypyridine moiety has attracted much attention, and a number of methods for their construction have emerged.

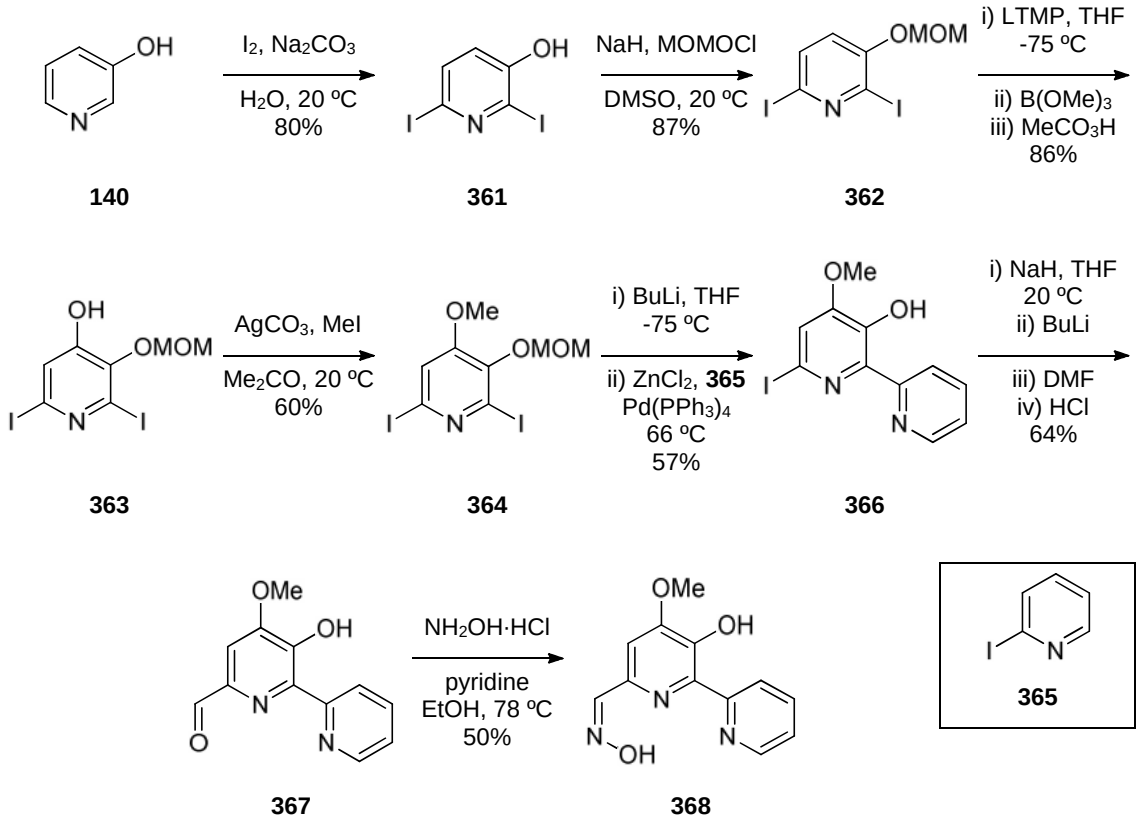
Common strategies for the synthesis of this important class of heterocycles often involves a step-by-step elaboration starting from a simple 3-hydroxypyridine. This approach relies on the use of a directing group to obtain a certain substitution pattern, and although it can be an efficient route for a certain number of 3-hydroxypyridines, is often a tedious and lengthy approach to a variety of targets.

In 2002, Quéguiner and co-workers published a total synthesis of caerulomycin B**368** starting from 3-hydroxypyridine **140** (Scheme 3.1).[153,154]

Key steps in this synthesis involved the conversion of 3-hydroxypyridine **362** to **363** by introduction of the hydroxyl group at the 4-position *via* a selective deprotonation using lithium 2,2,6,6-tetramethylpiperidine as a base and trimethylborate as the electrophile.[153]

Selective metallation at the 2-position of pyridine **364** was used to introduce the 2-pyridyl moiety via a Negishi cross-coupling in whichbipyridine **366** was obtained.[153]

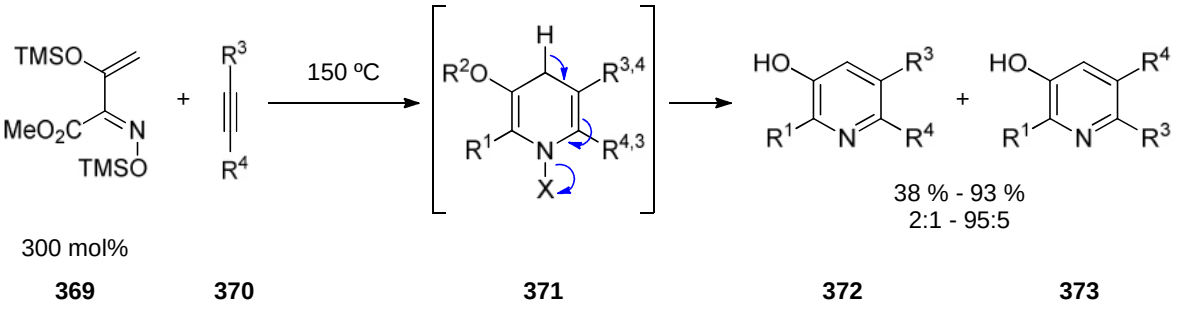
These two steps were achieved with excellent levels of regiocontrol. This is mainly due to the directing effect of the 3-alkoxygroup. Caerulomycin B **368**was prepared in two further steps.[153]



Scheme 3.1 *- Quéguiner's synthesis of caerulomycins B**368**.*

In 2007, Arndt and Lu published a *de novo* method for the synthesis of 3-hydroxypyridines, in which a hetero Diels-Alder reaction between silylated enol oxime **369** and alkyne **370** was

used to prepare the dihydropyridine **371** with spontaneous aromatisation to produce the 3-hydroxypyridine **372** and **373** (Scheme 3.2).[152]

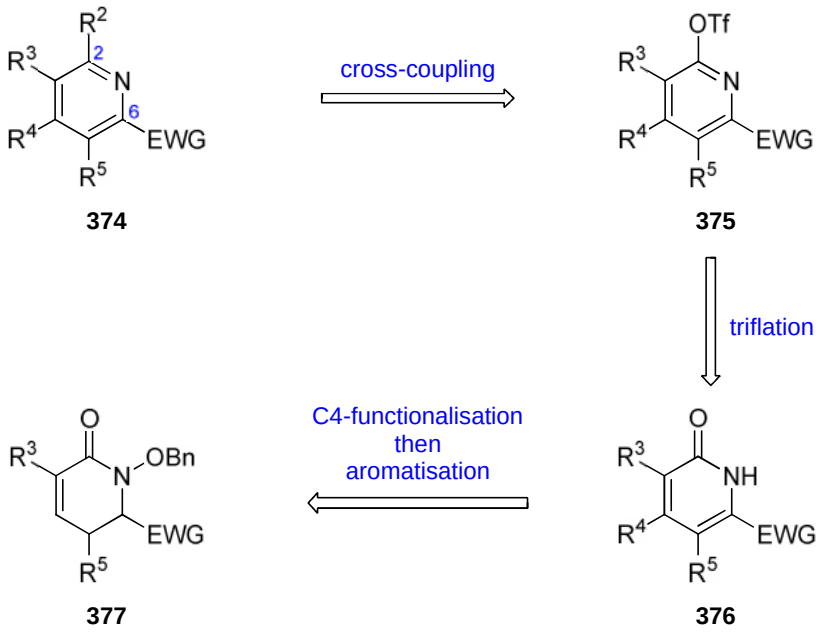


Scheme 3.2*- Hetero Diels-Alder approach to 3-hydroxypyridines.*

3.2 A metathesis approach to the synthesis of 3-hydroxypyridines

Given the success of the RCM approach to the synthesis of 2-pyridones, a new approach to the synthesis of 3-hydroxypyridines was envisioned. This methodology would address some of the limitations that were encountered in the earlier synthetic route developed for the formation of 2-pyridones.

The RCM approach to 2-pyridones had the limitation that an electron withdrawing group at the 6-position was required for the aromatisation protocol, such as target pyridine **374**which can be formed from a transition metal catalyzed cross-coupling of pyridine **375** (Scheme 3.3).

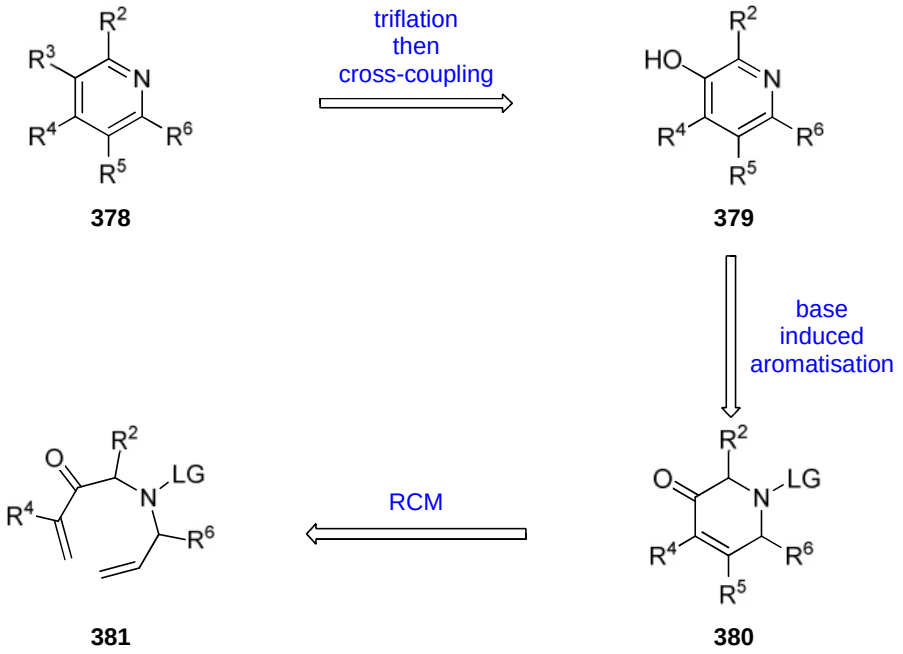


Scheme 3.3*- Retrosynthetic analysis for the formation of substituted pyridine* ***374****.*

Triflate **375** can be formed from the 2-pyridone **376**, which can be obtained from dihydropyridone **377** via a C4-functionalisation and then base induced aromatisation mediated by the electron withdrawing group at the 2-position (Scheme 3.3).

3.2.1 Outline of research

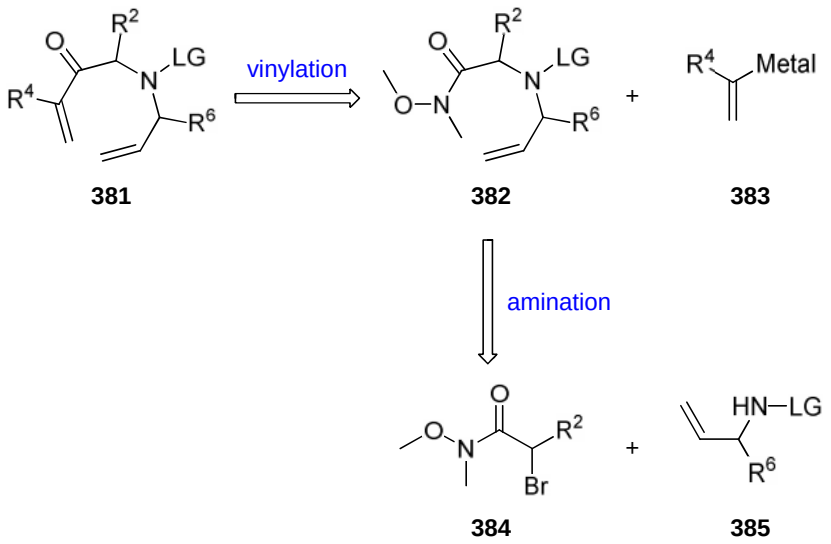
The focus of this investigation lies in the forms of a new method, based on a RCM, to prepare 3-hydroxypyridine **379** (Scheme 3.4). The formation of the desired pyridine **378**can be achieved *via* an activation followed by a transition metal catalyzed cross coupling protocol (Scheme 3.4).



Scheme 3.4 *- Retrosynthetic analysis for the formation of substituted pyridine* ***378****.*

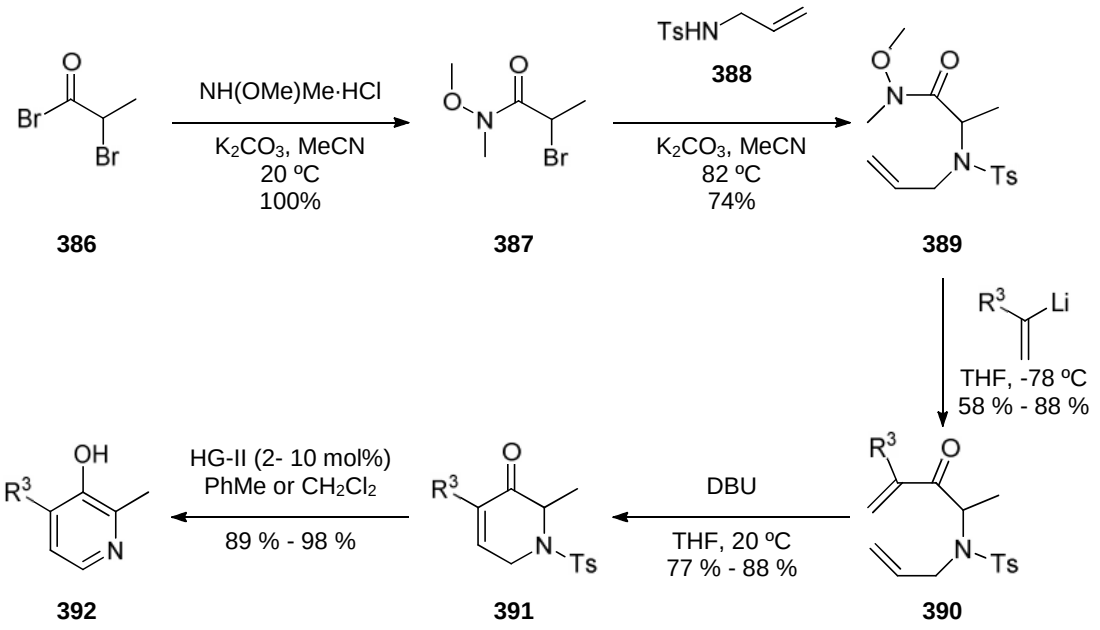
The desired target polysubstituted 3-hydroxypyridine **379** can be obtained from a base-induced elimination of a leaving group, from dihydropyridine **380**, which can be prepared by a RCM of diene **381**. Furthermore, dihydropyridine **380** can be functionalized at the 5-position prior to aromatisation (Scheme 3.4).

Diene **381** can be obtained from vinylation of Weinreb amide **382** with a range of vinyl metal species **383**. Amide **382** can be formed by a substitution of α-bromo amide **384** with an allylic sulfonamide **385** (Scheme 3.5).



Scheme 3.5- *Retrosynthetic analysis for the formation of diene **381**.*

Initial results from the Donohoe group had demonstrated that, by using this approach, a series of 3-hydroxypyridines can be formed. Starting from 2-bromopropionyl bromide **386**, the Weinreb amide **387** was obtained in high yields. Allylic sulfonamide **388** was used to displace the α-bromo leaving group, and amide **389** was obtained (Scheme 3.6).[155]

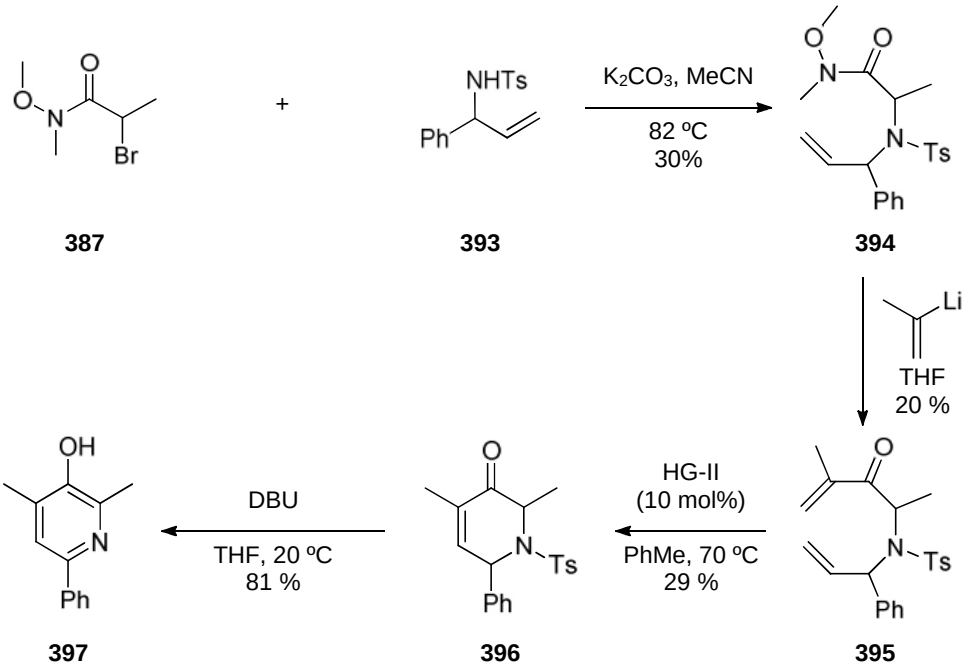


Scheme 3.6 *- Synthesis of 3-hydroxypyridines via a RCM.*

Work carried out by L. P. Fishlock

Amide **389** was converted to diene **390**, which was subjected to a RCM using catalyst HG-II, to afford the dihydropyridine **391**. Base induced elimination of the leaving group produced the desired 3-hydroxypyridine **392**.[155]

An important limitation of this approach was demonstrated by the Donohoe group when the Weinreb amide **387** could be substituted with allylic sulfonamide **393** in low yield (Scheme 3.7).



Scheme 3.7 *- Synthesis of 3-hydroxypyridine **397**.*

Work carried out by I. A. Roslan

Furthermore, the conversion of amide **394** to diene **395** resulted in very low yield of the desired product, and RCM using catalyst HG-II required high catalyst loadings, and afforded the desired dihydropyridine **396** in low yield. Formation of 3-hydroxypyridine **397**, *via* a base induced aromatisation, was achieved in good yield (Scheme 3.7).[123]

3.3 Results and discussion

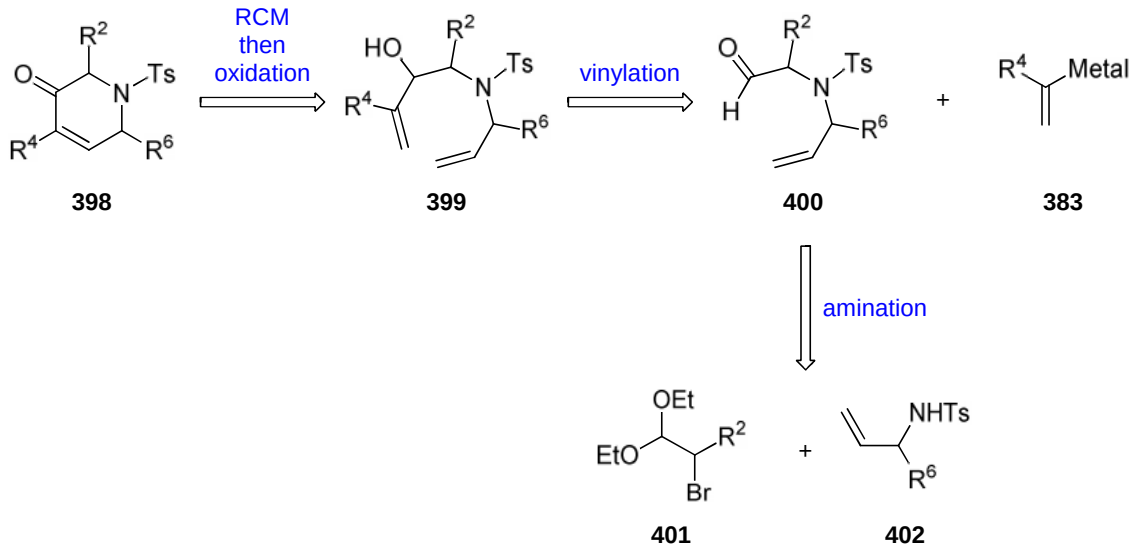
3.3.1 The synthesis of 3-hydroxypyridines

The synthesis of 3-hydroxypyridines was sought in order to extend the early results and establish a method for the formation of a wider series of pyridine motifs with substituents at the 6-position. In order to achieve this goal, a new approach that would address all the limitations that were presented during the synthesis of 3-hydroxypyridine **397** was required (Scheme 3.7).

Addition of a vinyl metal species to the Weinreb amide proved to be a difficult reaction, because of the low reactivity of this functional group to the attack of the metal species. Leaving the reaction for longer or performing it at a higher temperature leads to decomposition of the starting material, presumably because of the acidic α-hydrogens in amide **394** (Scheme 3.7).

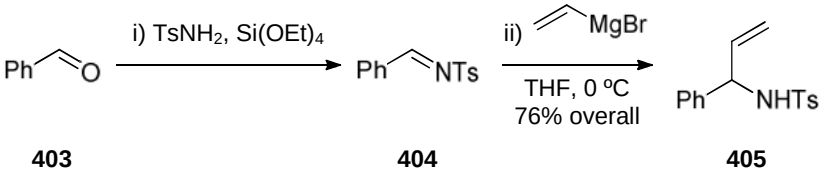
Using aldehyde functionality instead of a Weinreb amide would be an advantage for two reasons. First the aldehyde would be more reactive towards the vinylation steps leading to an allylic alcohol and secondly, the diene obtained would be much more reactive towards the RCM reaction, because this new diene does not contain any olefins with pendant electron deficient groups (which deactivate the alkenes towards metathesis). Furthermore, the allylic alcohol functionality is an excellent substrate for metathesis reactions.[156]

Dihydropyridine **398** can be formed from diene **399** by a RCM followed by an oxidation of the intermediate allylic alcohol. Diene **399** could be prepared by addition of a vinyl metal species **383** to an α-aminoaldehyde **400** and this aldehyde can be formed by an amination of bromide **401** with allylic amine **402** followed by a deprotection step (Scheme 3.8).



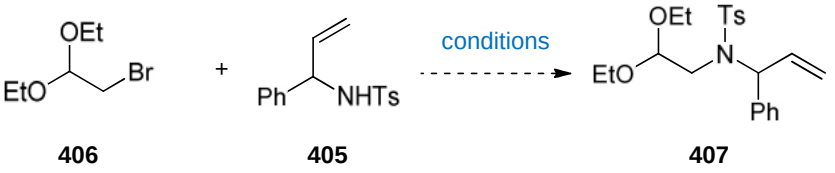
Scheme 3.8- *Retrosynthetic analysis for the formation of diene* ***398****.*

Allylic sulfonamide **405** was prepared from benzaldehyde **403** by first condensation with *p*-toluenesulfonamide and then vinylation of the resulting imine (Scheme 3.9).[157]



Scheme 3.9 *- Preparation of sulfonamide* ***405****.*

Unfortunately, amination of commercially available α-bromo acetal **406** and the sulfonamide **405** could not be achieved (Scheme 3.10).

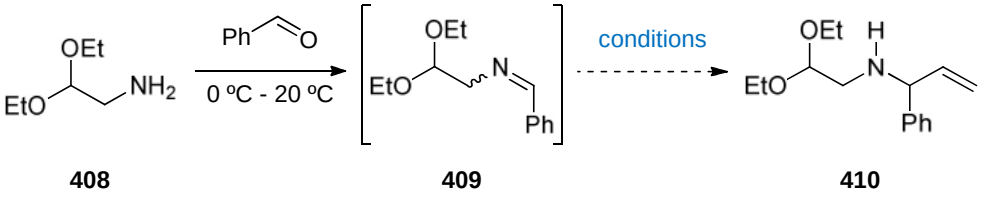


Scheme 3.10 *- Failed amination of α-bromo acetal* ***406****.*

Solvent	Base	Temperature	Yield
DMF	NaH	20 ºC	starting material
DMF	NaH	50 ºC	starting material
MeCN	K_2CO_3	82 ºC	starting material
DMF	K_2CO_3	80 ºC	starting material

Table 3.1*-Attempted amination of α-bromo acetal* ***406****.*

Formation of the sulfonamide was then attempted successfully by a different disconnection. Condensation of commercially available α-amino acetal **408** and benzaldehyde **403** afforded the intermediate imine **409** which was treated with vinylmagnesium bromide, but no product **410** was observed (Scheme 3.11).We suspected that the addition of $BF_3{\cdot}OEt_2$ was required in order to activate the imine for the nucleophilic attack of the vinylmagnesium species, but this led to a complex mixture of products (Entry 4, Table 3.2).



408 **409** **410**

Scheme 3.11*- Failed formation of amine* ***410****.*

Entry	Conditions	Yield
1	MgBr 0 ºC, THF	imine
2	MgBr 20 ºC, THF	imine
3	MgBr -78 ºC, THF, $BF_3{\cdot}OEt_2$	imine
4	MgBr 0 ºC, THF, $BF_3{\cdot}OEt_2$	complex mixture of products

Table 3.2 *- Attempted formation of sulfonamide* ***410****.*

Imine intermediate **409** was not isolated but instead the formation of **409** was monitored by crude ^{1}H NMR analysis evidenced by the shift of the signal at 2.79 ppm, which corresponded to the methylene protons C(1)H_2 of the starting material **408**, to 3.81 ppm which corresponded to the methylene proton C(1)H_2 of the intermediate imine **409** (Figure

3.2). Furthermore we observed the appearance of a signal at 8.30 ppm which corresponded to the imine signal C(1')H of the intermediate product **409**.

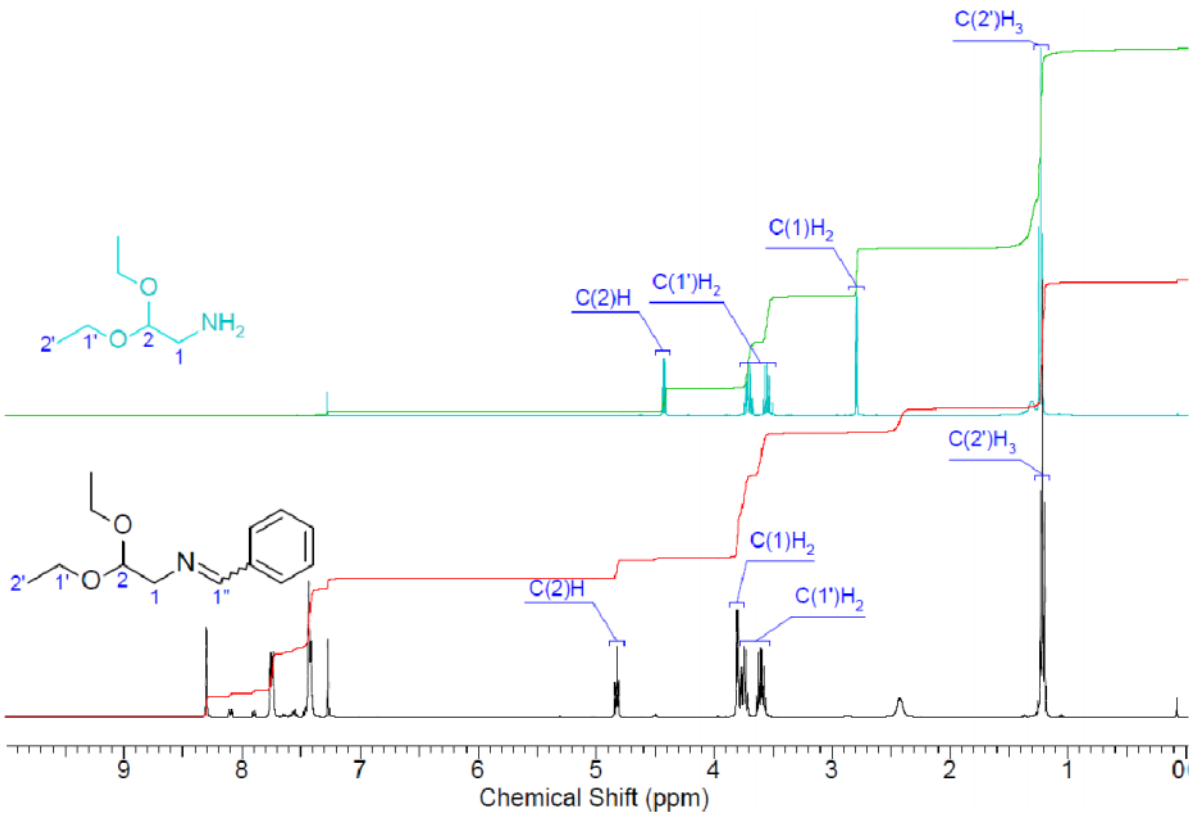
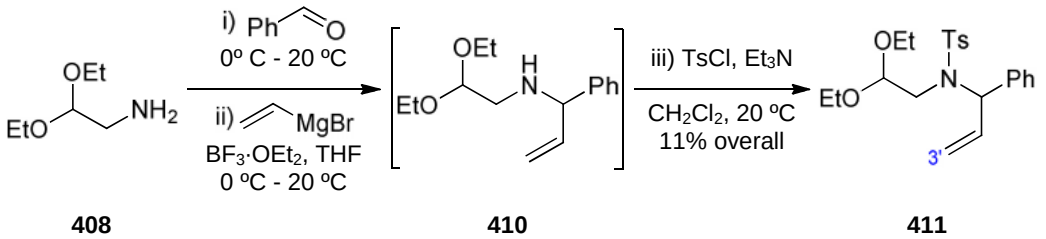


Figure 3.2- *Crude ^{1}H NMR of amine **408** and imine **409**.*

The conditions described in Entry 4 (Table 3.2) were repeated and the crude material was subjected to a tosylation in order to facilitate chromatographic separation and install the required leaving group (Scheme 3.12). The desired sulfonamide **411** was obtained in low yields.



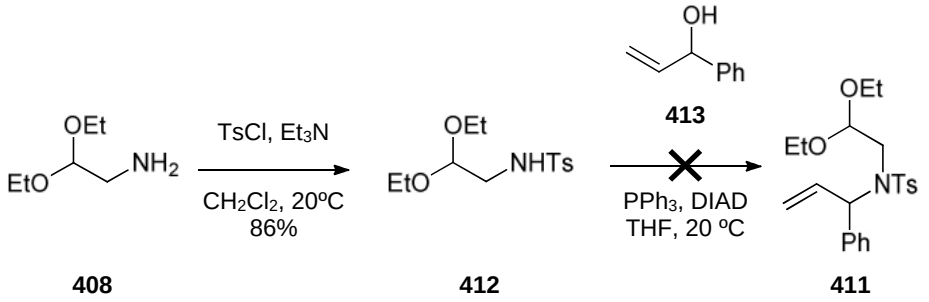
408 **410** **411**

Scheme 3.12- *Formation of sulfonamide **411**.*

The formation of sulfonamide **411** was evidenced by the appearance in the ^{1}H NMR of signals at 5.54 ppm and 5.26 ppm which corresponded to the terminal olefin C(3')H_2,

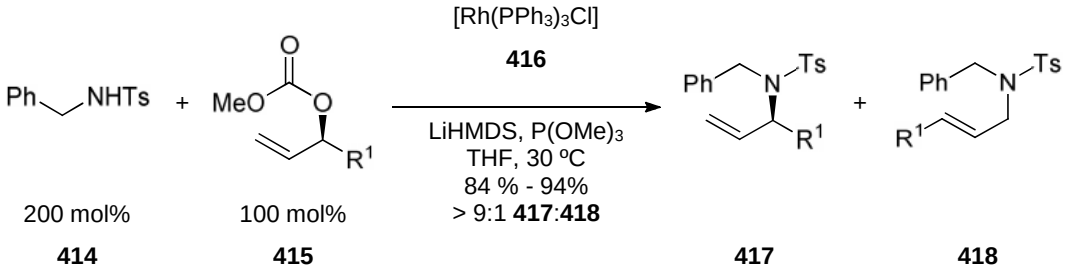
furthermore the appearance of signal at 2.43 ppm corresponded to the methyl signal of the tosyl group $C(1''')H_3$.

Changing the order of events was required in order to obtain the desired sulfonamide **411** more efficiently. Amine **408** was converted to the sulfonamide **412**, but Mitsunobu reaction using ally alcohol **413** yielded a complex mixture of products (Scheme 3.13).



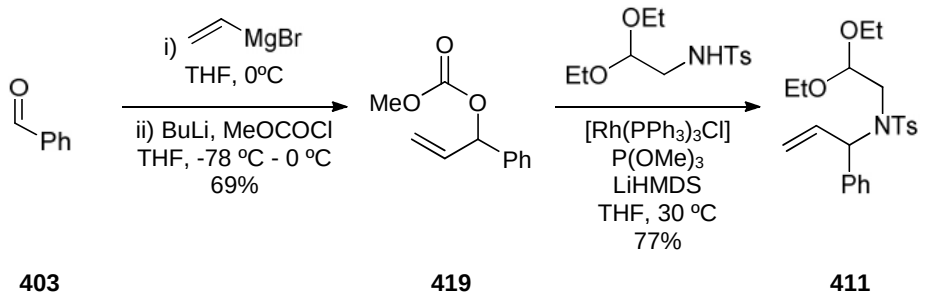
Scheme 3.13 *- Failed synthesis of sulfonamide **411**.*

In 1999, Evans and co-workers developed a rhodium-mediated allylic amination reaction, in which amine **414** can be converted to the desired allylic amine **417** using carbonate **415** (Scheme 3.14).[158] The catalyst is obtained *in situ* from Wilkinson's catalyst **416** and trimethyl phosphite ($P(OMe)_3$). The high levels of regiocontrol towards a branched product **417** made this protocol very attractive for our needs.



Scheme 3.14 *- Rhodium mediated allylic amination.*

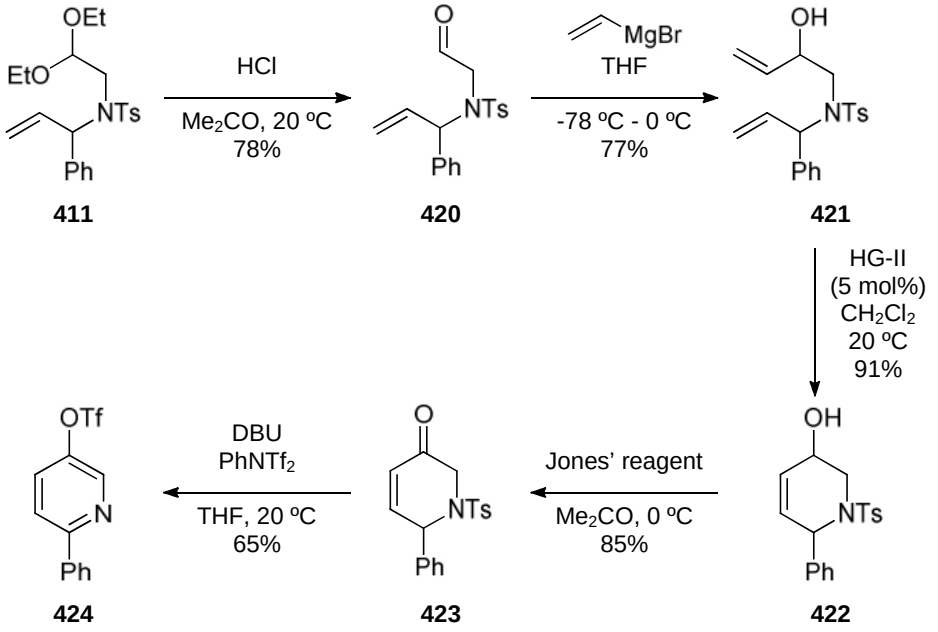
Evans' protocol was successfully applied to the synthesis of the desired sulfonamide **411** using carbonate **419**, which was obtained from benzaldehyde **403** (Scheme 3.15).[155]



Scheme 3.15 *- Synthesis of sulfonamide* ***411****.*

The formation of sulfonamide **411** was evidenced by comparison of the spectroscopic data to the previously obtained material (Scheme 3.12).

Sulfonamide **411** was converted to the desired pyridine **424** in five steps. Deprotection of the acetal group in sulfonamide **411** afforded the aldehyde **420** which was converted to diene **421**(Scheme 3.16).[155]



Scheme 3.16 *- RCM approach to the synthesis of pyridine* ***424****.*

RCM of diene **421**, using catalyst HG-II gave the desired tetrahydropyridine **422**, which was oxidized with Jones' reagent to produce enone **423** (Scheme 3.16).[155]

Enone **423** is in the correct oxidation state for pyridine formation and has the required acidifying functional group to promote the elimination of sulfinic acid and produce a 3-hydroxypyridine. By including a triflating agent, *N*-phenyltriflimide **288**, the aromatisation

and functionalisation was accomplished in one pot to afford the desired pyridine **424** in good yields (Scheme 3.16).[155]

Formation of pyridine **424** was evidenced by single crystal X-ray analysis (Figure 3.3).

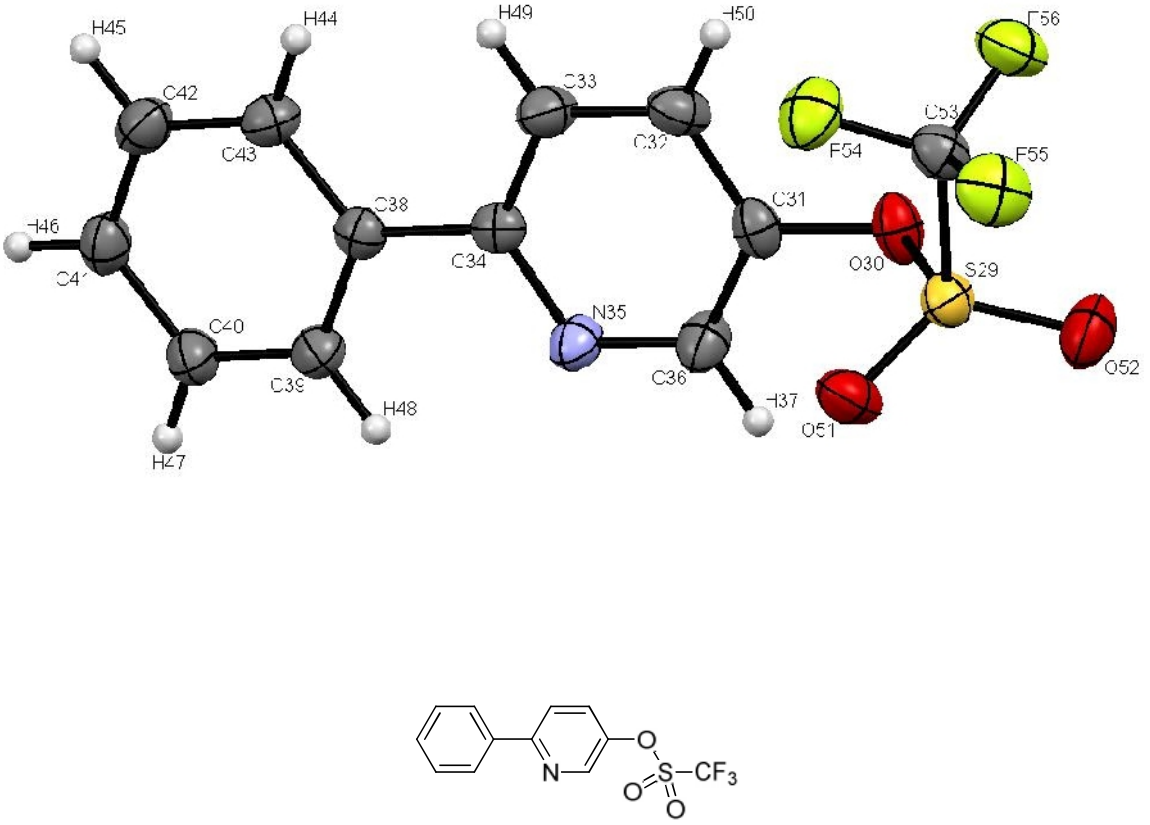
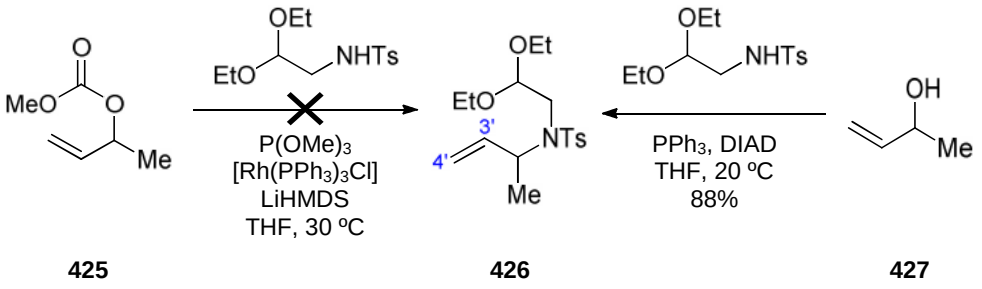


Figure 3.3 *- Single crystal X-ray analysis of pyridine* ***424****.*

The sequence of events previously described formed the basis of the methodology for the synthesis of 6-substituted-3-hydroxy pyridines from readily available starting materials, and with high levels of regiocontrol to afford a series of pyridines with a predictable outcome.

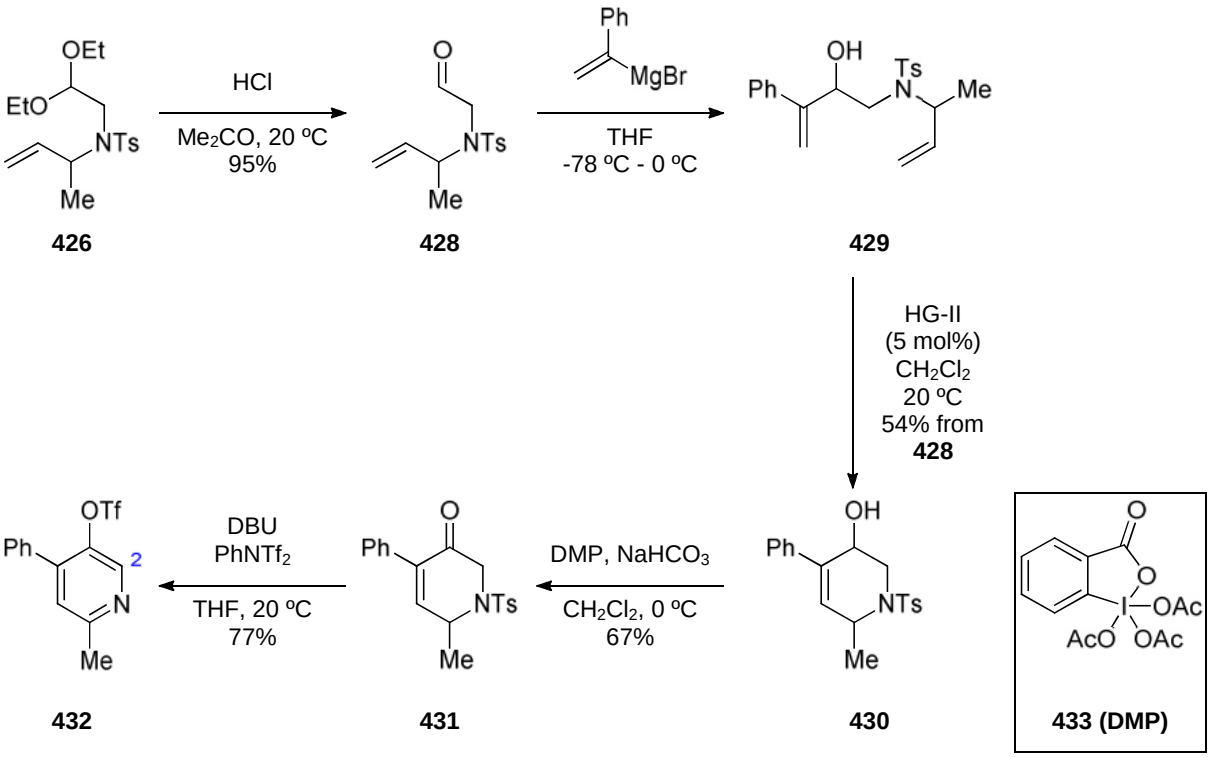
However in order to demonstrate this further, Evans' protocol for the allylic amination reaction using carbonate **425** and sulfonamide **416** was undertaken, but this reaction did not yield any product. Instead a Mitsunobu reaction between alcohol **427** and sulfonamide **416** yielded the desired sulfonamide **426** (Scheme 3.17).[155]



***Scheme 3.17**- Synthesis of sulfonamide **426**.*

Formation of sulfonamide **426** was evidenced by the appearance of the signals in the ^{1}H NMR spectrum at 5.52, 5.04 and 4.80 and corresponded to the three olefinic C(3')H and $C(4')H_2$.

Sulfonamide **426** was subjected to the same sequence of events previously developed to obtain the desired pyridine **432** (Scheme 3.18). Deprotection afforded the aldehyde **428**, which was transformed in diene **429** and carried through to tetrahydropyridine **430** in good overall yields (Scheme 3.18). Diene **429** contained some unreacted starting aldehyde **428** which was difficult to separate, nevertheless the RCM yielded the desired heterocycle without any inconvenience, and the overall yield for the two steps was 54%.[155]

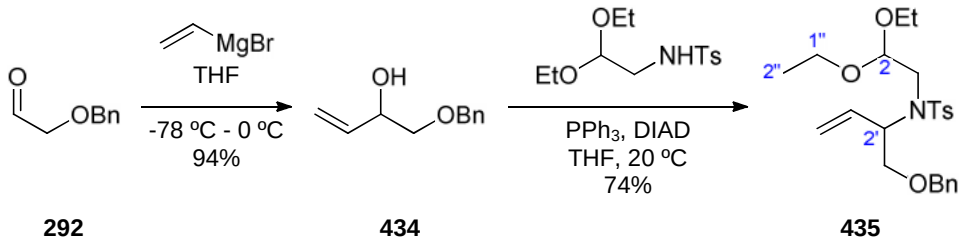


Scheme 3.18*- RCM approach to the synthesis of pyridine* ***432****.*

Dess-Martin periodinane **433** (DMP) was used for the oxidation of tetrahydropyridine **430**, to prove that milder oxidizing agents can be used with these types of substrates, and enone **431** was formed. Enone **431** was then transformed into pyridine **432** which contains a leaving group at the 3-position for further cross-coupling (Scheme 3.18).[155]

Formation of pyridine **432** was evidenced by the appearance of the signals in the ^{1}H NMR spectrum at 8.53 ppm which corresponded to the pyridine signal C(2)H as compared to the C(2)H signal at 8.66 ppm of pyridine **424** (evidenced by single crystal X-ray analysis).

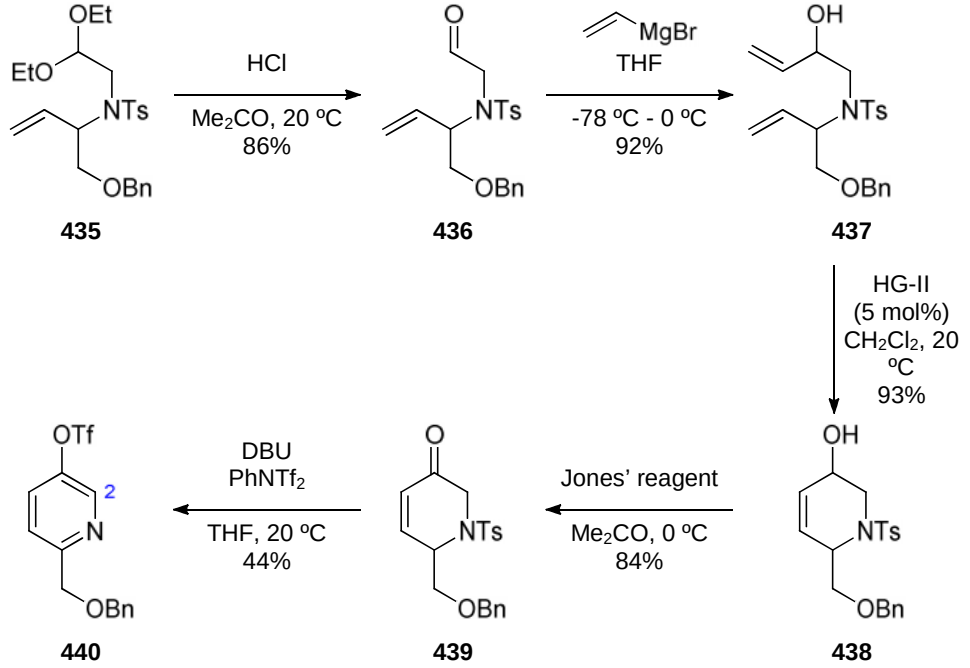
In order to obtain a further functionalized substituent at the 6-position alcohol **434** was prepared from aldehyde **292**(Scheme 3.19).A Mitsunobu reaction between alcohol **434** and sulfonamide **416** produced the desired product **435** in high yields.



Scheme 3.19- *Synthesis of sulfonamide **435**.*

The formation of sulfonamide **435** was demonstrated by the appearance of the signals in the ^{1}H NMR spectrum at 4.70 ppm and 4.53 ppm which corresponded to the CH signals C(2)H and C(2')H. Further evidence is the appearance of the ethyl signals at 3.69 ppm and 1.20 ppm which corresponded to C(1")H_2 and C(2")H_3 respectively.

Sulfonamide **435** was transformed to the desired pyridine **440** using the abovementioned methodology. Acetal deprotection afforded aldehyde **436**, which was converted to diene **437** by vinylation (Scheme 3.20).[155]



Scheme 3.20 *- RCM approach to the synthesis of pyridine **440**.*

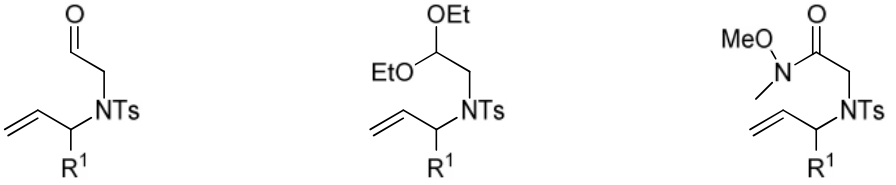
Diene **437** was subjected to RCM to afford the tetrahydropyridine **438** in very high yields, and Jones' oxidation of this intermediate produced enone **439**. This enone supplied the

desired pyridine **440** in moderate yields *via* elimination followed by the *in situ* triflation described earlier (Scheme 3.20).[155]

Formation of pyridine **440** was evidenced by the appearance of the signal in the ^{1}H NMR spectrum at 8.53 ppm corresponded to the pyridine signal C(2)H.

3.3.2 Elaboration at the 4-position *via* Baylis-Hillman reaction

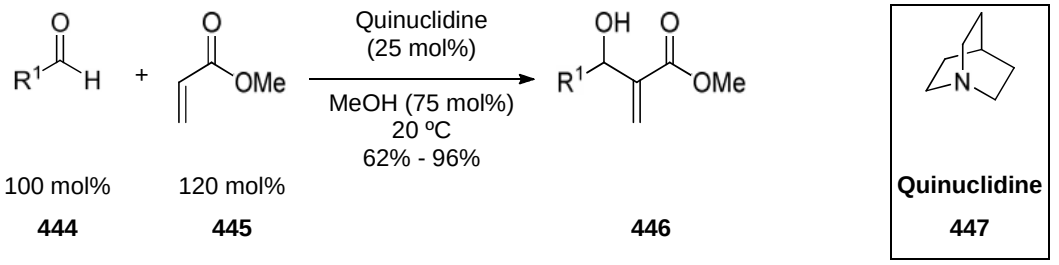
The intermediate aldehyde **441**, obtained from acetal deprotection of sulfonamide **442**, is a more potent electrophile than Weinreb amide **443** obtained *via* other routes (Figure 3.4). In order to elaborate on other substituents at the 4-position, other types of vinylation reactions were sought.



441 **442** **443**

Figure 3.4 *- Intermediates for the synthesis of pyridines.*

In 2003, Aggarwal and co-workers reported an optimized set of conditions for the Baylis-Hillman reaction of methylacrylate **445** and a series of aldehydes **444** (Scheme 3.21).[159] Quinuclidine **447** was found to be the most efficient catalyst for this reaction.

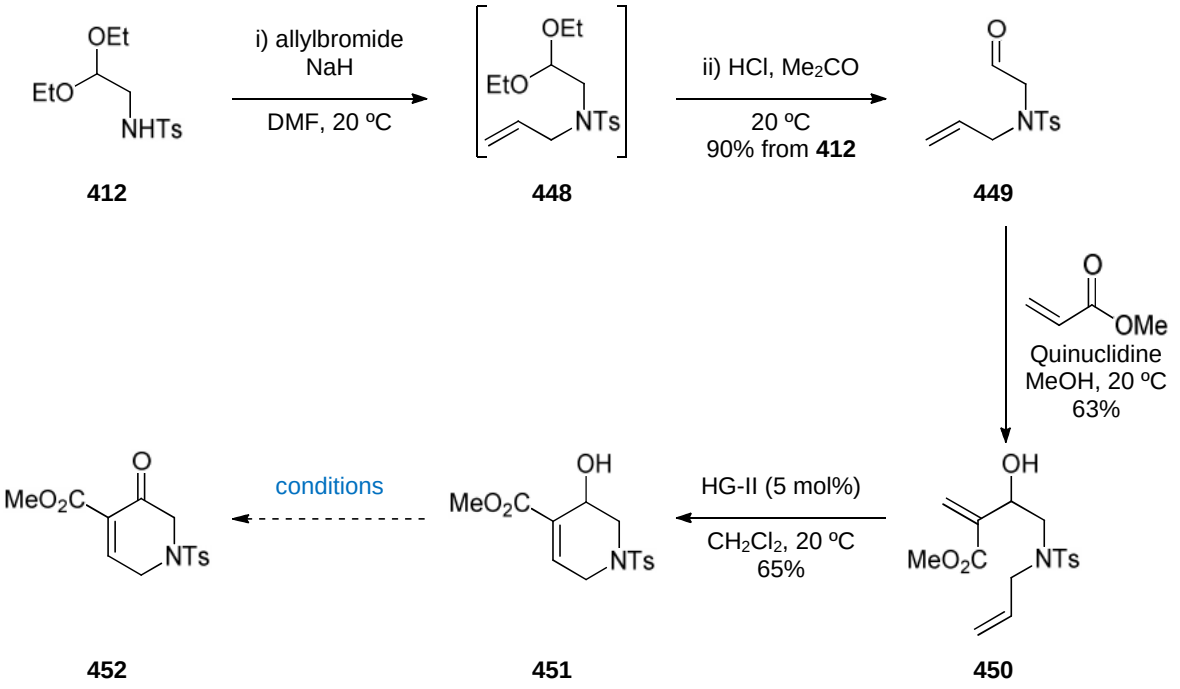


100 mol% 120 mol%

444 **445** **446** **Quinuclidine** **447**

Scheme 3.21 *- Synthesis of 3-hydoxy-2-methylene ester **447**.*

Sulfonamide **448** was prepared from allylbromide and sulfonamide **416**, which was deprotected to afford the desired aldehyde **449** (Scheme 3.22).



Scheme 3.22 *- Failed synthesis of enone* ***452****.*

Conditions	Yield
Jones' reagent, Me_2CO, 0 ºC	decomposition
Jones' reagent, Me_2CO, -10 ºC	decomposition
DMP, CH_2Cl_2, $NaHCO_3$, 0 ºC	decomposition
MnO_2, CH_2Cl_2, 0 ºC	decomposition

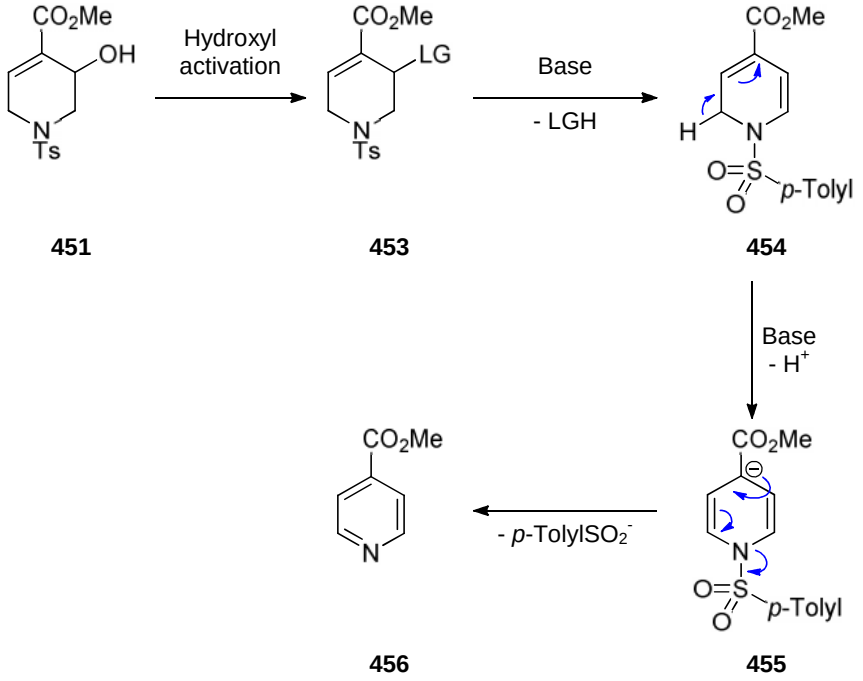
Table 3.3 *- Attempted oxidation of tetrahydropyridine* ***451****.*

Aldehyde **449** was converted to diene **450** using the Baylis-Hillman reaction conditions discussed earlier. RCM of diene **450** using catalyst HG-II produced the tetrahydropyridine **451** in good yields (Scheme 3.22).[118]

Oxidation of tetrahydropyridine **451** towards enone **452** was not achieved under an array of conditions (Table 3.3). Instead it was realized that the carbomethoxy electron-withdrawing group at the 4-position may acidify the 6-position to promote a base induced elimination.

By an activation of the hydroxyl group of allylic alcohol **451**, the intermediate **453** ought to be formed and treatment with excess base should give a dihydropyridine **454**. This

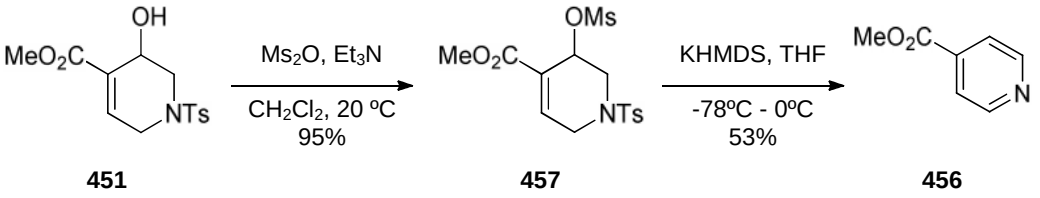
heterocycle has an acidic proton at the 6-position, and could be further eliminated to form the aromatic isonicotinic acid derivative **456** (Scheme 3.23).



Scheme 3.23 *- Proposed formation of methyl isonicotinate* ***456****.*

This approach should give a concise entry to isonicotinic acid derivatives, and these targets are important biologically active molecules.[160]

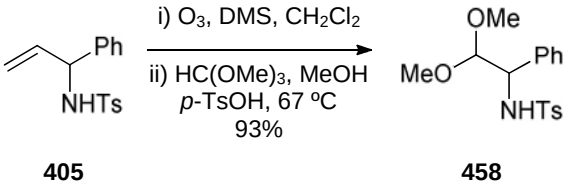
Treatment of allylic alcohol with methanesulfonic anhydride (Ms_2O) afforded the intermediate mesylate **457** that was converted successfully to methyl isonicotinate **456** in good overall yields (Scheme 3.24).[118]



Scheme 3.24 *- Synthesis of methyl isonicotinate* ***456****.*

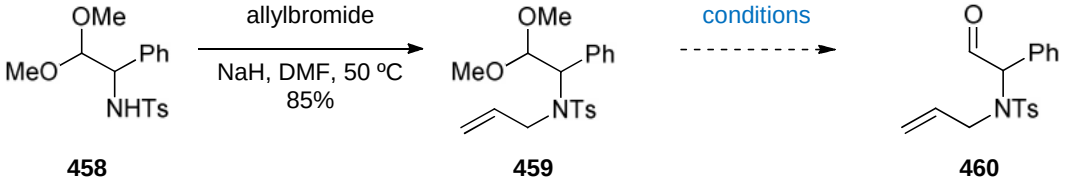
3.3.3 Elaboration at the 2-position

In order to obtain a pyridine core, with a substituent at the 2-position, sulfonamide **458** was prepared from allylic sulfonamide **405** by a reductive ozonolysis and acetal protection of the intermediate aldehyde (Scheme 3.25).



Scheme 3.25 *- Synthesis of sulfonamide* ***458****.*

N-Alkylation of sulfonamide **458** was achieved using allylbromide and the allylic sulfonamide **459** was obtained in high yields. Deprotection of the acetal moiety in sulfonamide **459** proved to be problematic, and aldehyde **460** was not isolated (Scheme 3.25).



Scheme 3.25 *- Failed Synthesis of aldehyde* ***460****.*

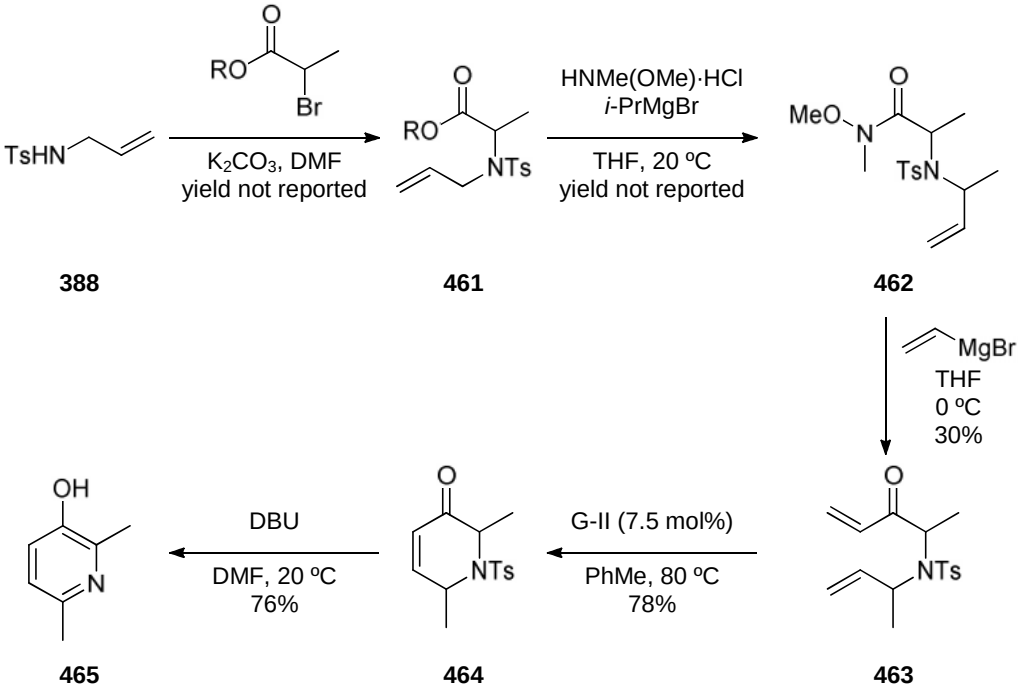
Conditions	Yield
HCl, Me_2CO, H_2O, 20 ºC	decomposition
HCl, Me_2CO, H_2O, 0 ºC	decomposition
HCl, Me_2CO, H_2O, -20 ºC	starting material
TMSCl, NaI, MeCN, 20 ºC	decomposition

Table 3.4 *- Attempted deprotection of sulfonamide* ***459****.*

Formation of acetal **459** was evidenced by the appearance of a signal in the ^{1}H NMR spectrum at 5.52 ppm the internal olefinic signal C(2")H.

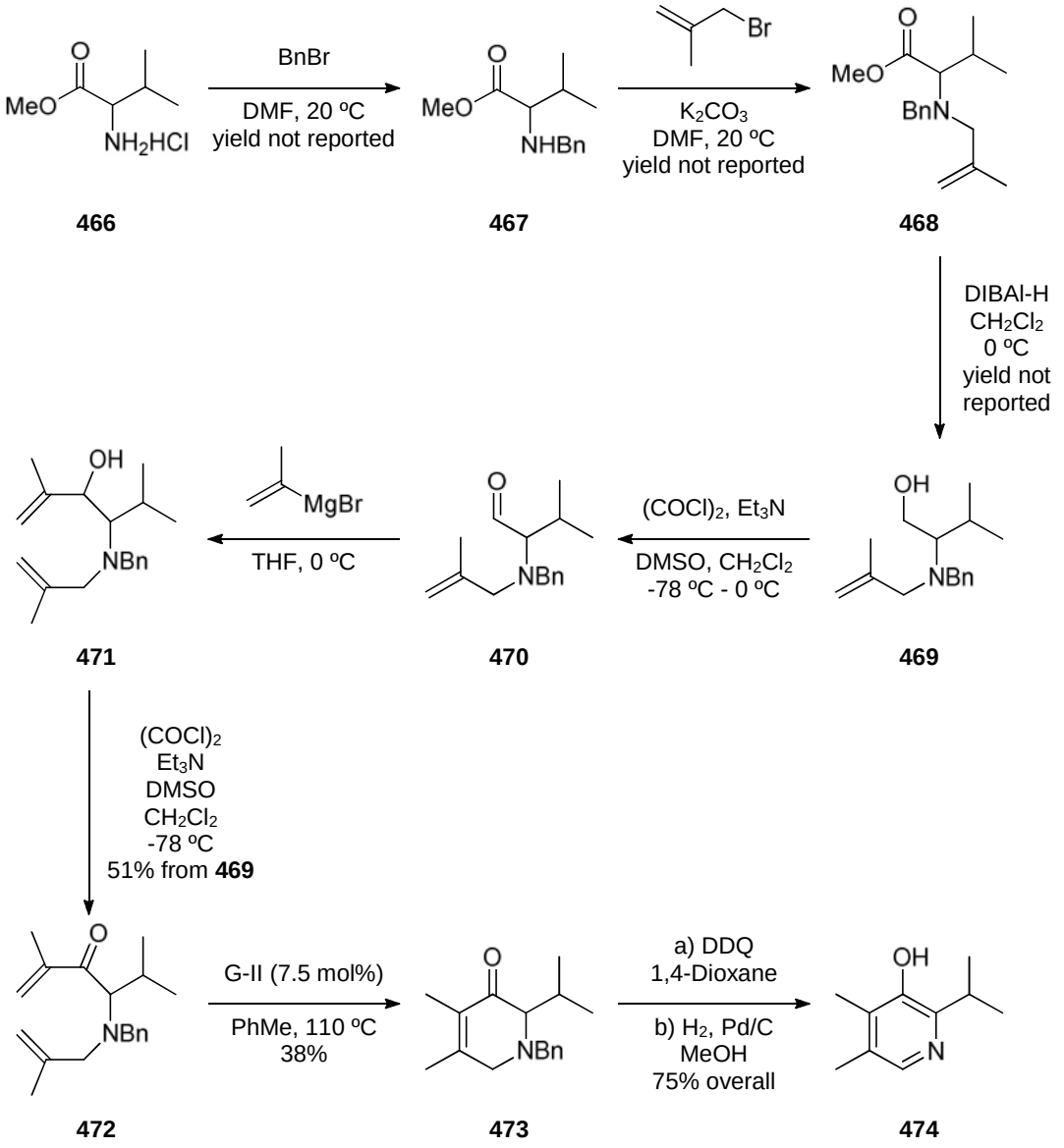
During the course of our investigation, Yoshida and co-workers reported a related route to the synthesis of 3-hydroxypyridines *via* a RCM which complements our results.[161]

For example, allylic sulfonamide **388** was *N*-alkylated to form sulfonamide **461**, which then was converted to the Weinreb amide **462**. Vinylation of this amide afforded the required diene **463** which was subjected to a RCM using catalyst G-II to afford the enone **464**. Base-induced elimination provided the desired 3-hydroxypyridine **465** (Scheme 3.27).[161]



Scheme 3.27 *- Yoshida's approach to the synthesis of 3-hydroxy pyridine **465**.*

A second disconnection was also reported by Yoshida and co-workers in the same publication, in which the α-aminoester **466** was protected as the benzylamine **467** and then *N*-alkylated to afford the allylic amine **468**. This amine was reduced to the alcohol **469** and then oxidized to the aldehyde **470**, which was vinylated to afford diene **471**. Oxidation of diene **471** was executed prior to the RCM step, which produced the desired enone **473** in low yield. Aromatisation of enone **473** was achieved by an oxidation, mediated by DDQ, and then hydrogenolysis of the intermediate pyridinium chloride, to produce the desired pyridine **474** (Scheme 3.28).[161]



466 **467** **468** **469** **470** **471** **472** **473** **474**

Scheme 3.28 *- Yoshida's approach to the synthesis of 3-hydroxy pyridine 474.*

RCM of diene **471** would have been an easier task than the RCM of diene **472**, since this diene has two electron rich olefins on which the catalyst could initiate, and is likely to increase the efficiency of this step.[156]

The method developed by Yoshida has several similarities to the method developed earlier, although our method can achieve the desired target in a shorter number of steps, and the oxidation of the allylic alcohol **471** prior to the RCM event is not discussed by the authors, instead the synthesis of diene **472** is shown only in the supporting information.

3.4 Summary

A method for the synthesis of 3-hydroxypyridines has been achieved in which a key RCM is utilized to form a nitrogen containing heterocycle from a diene precursor.

An important aspect of this method is the simple process of the aromatisation protocol, in which a further functionalisation can be achieved in the same reaction pot.

This competitive area of research is an important aspect of current development in synthetic methodology due to the increasing need for the construction of compound libraries. Our method facilitates medicinal chemist in the construction of pyridine based libraries because it is modular and the transformations required are regiospecific.

Due to the reports by Yoshida and co-workers,[161] further exemplification of this methodology was not undertaken; instead the focus of the project was turned into finding a method that requires fewer steps in the construction of polysubstituted pyridines. As such, we will discuss the use of a cross-metathesis approach.

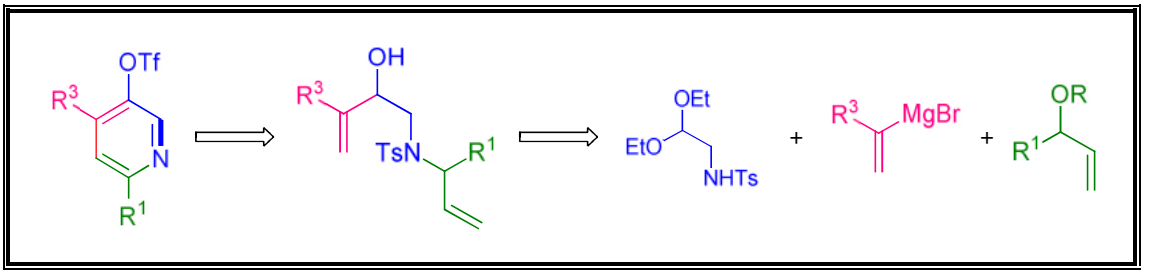


Figure 3.5 *- RCM approach to 3-hydroxypyridines.*

Chapter four: A Cross-Metathesis approach to the synthesis of pyridines

Chapter four: A Cross-Metathesis approach to the synthesis of pyridines

4.1 Introduction

The methodology described in the previous chapter for the synthesis of 3-hydroxypyridines, utilizing a RCM as a key C-C bond forming event, has been the source of several pyridine structures with high levels of regiocontrol. However, the synthesis of the required diene precursors proved to be a challenging task, and although the RCM reaction required little optimisation to produce a cyclic structure in good to excellent yields, the tedious formation of the diene precursor is unappealing to construct a library of compounds for biological studies.

The sequence for the described RCM approach in Chapter Three can be summarized in a series of *linear* events in which a simple starting material, Module 1, was increased in complexity by incorporating Module 2 and Module 3 (Figure 4.1).

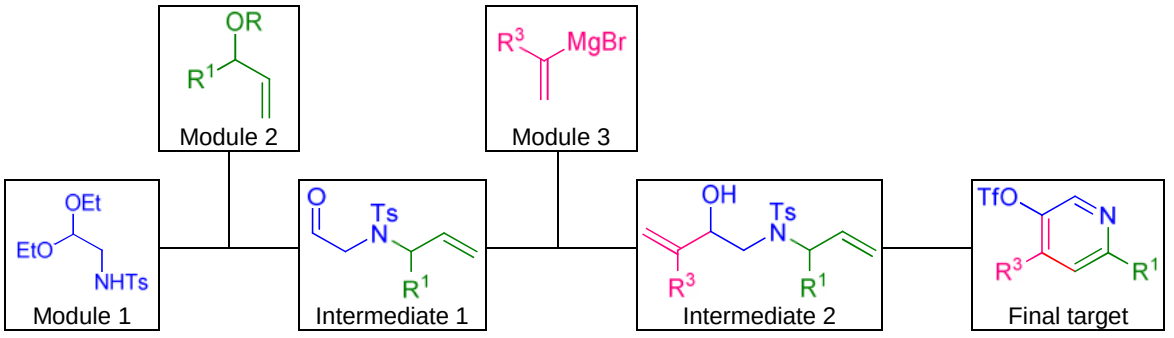


Figure 4.1 *- Description of the RCM approach to pyridines.*

A new methodology that delivers a desired scaffold in a short sequence and with high levels of regiocontrol using a convergent strategy was sought (Figure 4.2).

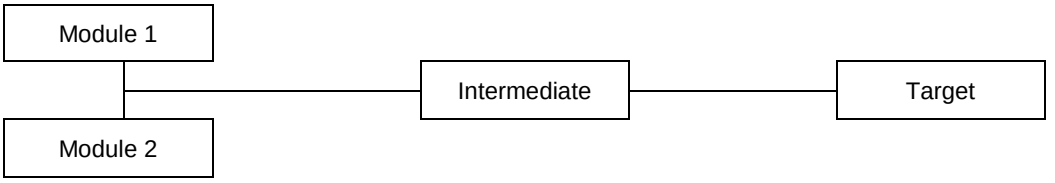
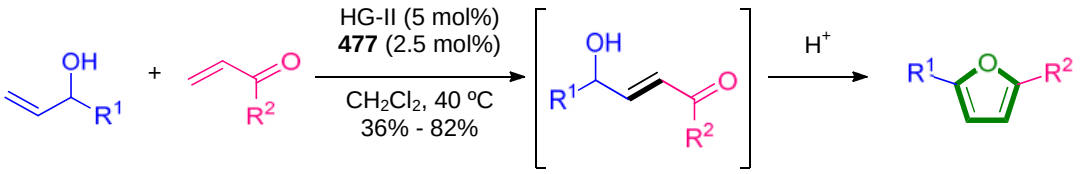


Figure 4.2 *- Convergent methodology for the synthesis of desired target.*

The Donohoe group had started to develop a methodology for the synthesis of furans with the required convergent sequence as described in Figure 4.2.

The key aspect of this method was the use of a cross-metathesis (CM) reaction as the main C-C bond forming event, in which two different olefins were combined to obtain an intermediate that was easily converted to the desired heteroaromatic target. Allylic alcohol **475** and enone **476** participate in a CM reaction mediated by catalyst HG-II and in the presence of pyridinium *p*-toluenesulfonate **477** form 4-hydroxy-ketone **478** that was condensed *in situ* to the desired furan **479**.[162]



Scheme 4.1 *- CM approach to the synthesis of Furans.*

Work carried by J. F. Bower

Given the success of early results from this method, we decided to investigate the possibility of using a CM approach to other heteroaromatic targets. A highly selective CM event would be the key requirement for such method to succeed.

In 2003, Grubbs and co-workers studied the selectivity of the CM reaction and developed a model to predict the outcome of this reaction. During this study it was also demonstrated that the reactivity of an olefin substrate towards a metathesis process depended on the catalyst used.[36]

Most importantly, the reactivity of a series of alkenes were ranked accordingly to their rate of homodimerisation. This was a good indicator to determine if two olefin partners would undergo a selective CM.[36]

Although these studies were not performed utilizing more advanced catalysts, such as catalyst HG-II, Z-1B, amongst others, the main aspects of this model still apply.

Grubbs and co-workers identified four types of olefins: Type I was assigned to those substrates that rapidly homodimerize, and the dimer products are an active species for a CM reaction. Type II was assigned to the range of substrate that undergo slow homodimerisation. Type III was assigned to those substrates that do not form a homodimer but were still active in some metathesis process. Type IV was assigned to those substrate that were inert to a CM, but do not deactivate the catalyst.[36]

Type I fast homodimerisation	Type II slow homodimerisation	Type III no homodimerisation	Type IV spectator to CM
▪ terminal olefins ▪ 1º allylic alcohols ▪ allyl boronate esters ▪ styrenes ▪ allyl phosphonates ▪ allyl silanes ▪ protected allyl amines	▪ acrylates ▪ vinylketones ▪ 2º allylic alcohol ▪ 3º allylic alcohol (unprotected)	▪ 1,1-disubstituted-olefins ▪ 3º allylic alcohol (protected)	▪ vinyl nitro olefins

Table 4.1*- Olefin categories for CM using catalyst G-II.*

Two olefins of type I would undergo a rapid CM and the product would be a statistical mixture. Two olefins of the same type (other than type I) would produce a non-selective CM. A selective CM event is obtained when two substrate of different types are used. The best results are obtained when an olefin of type I is used in conjunction with an excess of an olefin of type II.[36]

It is important to point out that when a type I olefin and a type II olefin are used, it is likely that the type I olefin will undergo a fast homodimerisation. This dimer, however, is also a type I olefin and therefore re-enters the metathesis catalytic cycle. The cross-product

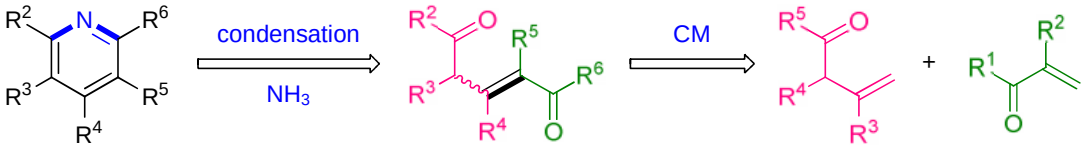
between the type I and type II olefin is another type II olefin which does not enter the catalytic cycle effectively. This is the main reason for the high levels of selectivity.[36]

In terms of stereoselectivity in general, the CM reaction produces *E* olefins as the major product. The reason is because the *E* isomer is less hindered and the metathesis process is very susceptible to steric hindrance effects. The ratio of *E*/*Z* depends vastly on the steric bulk of the olefins used.[36] Clearly this presents a problem for the formation of cyclic, aromatic structures.

4.2 The CM approach to pyridines *via* condensation of 1,5-diketones

Similar to the synthesis of furans *via* a CM approach, new methods for the synthesis of other heteroaromatic compounds can be developed. The use of a CM reaction to establish an intermediate olefin that can be easily converted to the desired pyridine structure in a simple step proved to be an attractive sequence due to its simplicity, the familiarity of the CM and the easy manner the regiochemical outcome of such a method can be predicted.

The condensation of α,β-unsaturated-1,5-diketones into a pyridine motifs a known transformation (Scheme 2.6).[101] Ideally a CM approach to the heteroaromatic **480** will involve the condensation of α,β-unsaturated-1,5-diketone **481** formed from a CM between β,γ-unsaturated ketone **482** and α,β-unsaturated ketone **483** (Scheme 4.2).



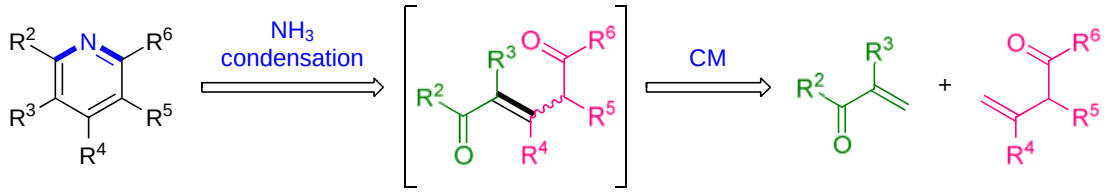
Scheme 4.2 *- Retrosynthetic analysis for the formation of substituted pyridines via CM.*

The relatively small number of methods for the synthesis of α,β-unsaturated-1,5-diketones and the fact that these methods rely on the use of directing groups, makes the CM reaction an attractive solution to the achievement of these targets. Furthermore, since the starting

materials are trivial building blocks, with many being commercially available, this approach seems a striking opportunity to develop a fast and modular methodology.

4.2.1 Outline of research

The initial focus of this investigation is the optimisation of the CM between enone **483** and β,γ-unsaturated ketone **482**. Then the focus will turn to whether this reaction is compatible with a source of nitrogen in other to obtain a one pot protocol, and also to find the limitations of the CM reaction described (Scheme 4.3).

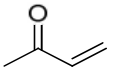


Scheme 4.3- *Retrosynthetic analysis to pyridines via a "one step" CM-condensation approach.*

4.3 Results and discussion

4.3.1 Synthesis of pyridines from β,γ-unsaturated ketones

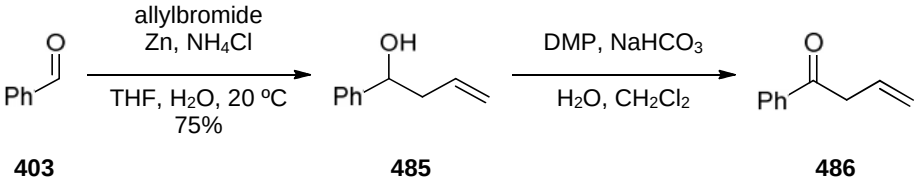
Commercially available methyl vinyl ketone **484** (MVK) was chosen as the enone olefin partner for the preparation of α,β-unsaturated-1,5-diketones and subsequent condensation with ammonia (Figure 4.3).



484 (MVK)

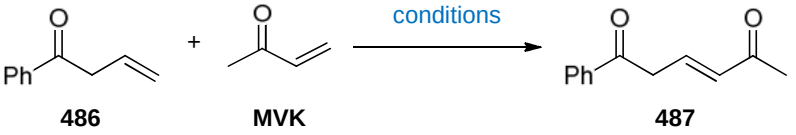
Figure 4.3 - *Methyl vinyl ketone*

The required β,γ-unsaturated ketone **486** was prepared by oxidation of homoallylic alcohol **485**, obtained from benzaldehyde **403**, using DMP in buffered conditions as to avoid acid catalyzed isomerisation (Scheme 4.4).



Scheme 4.4 *- Synthesis of β,γ-unsaturated ketone* ***486****.*

With these two coupling partners in hand, the CM reaction was undertaken (Scheme 4.5). Initial results were encouraging and a series of reaction conditions were tested (Appendix I, Table I.1).Seven parameters were identified as the major source of variability and therefore a simple linear optimisation was attempted, the parameters were: temperature, reaction time, concentration of ketone **486**, MVK equivalents, catalyst, catalyst loading and solvent.



Scheme 4.5 *- Synthesis of α,β-unsaturated-1,5-diketone* ***487****.*

The optimal temperature was found to be between 50 and 60 ºC, and this was achieved by undertaking the reaction in a sealed tube, since this temperature is above the boiling point of dichloromethane (Figure 4.4).

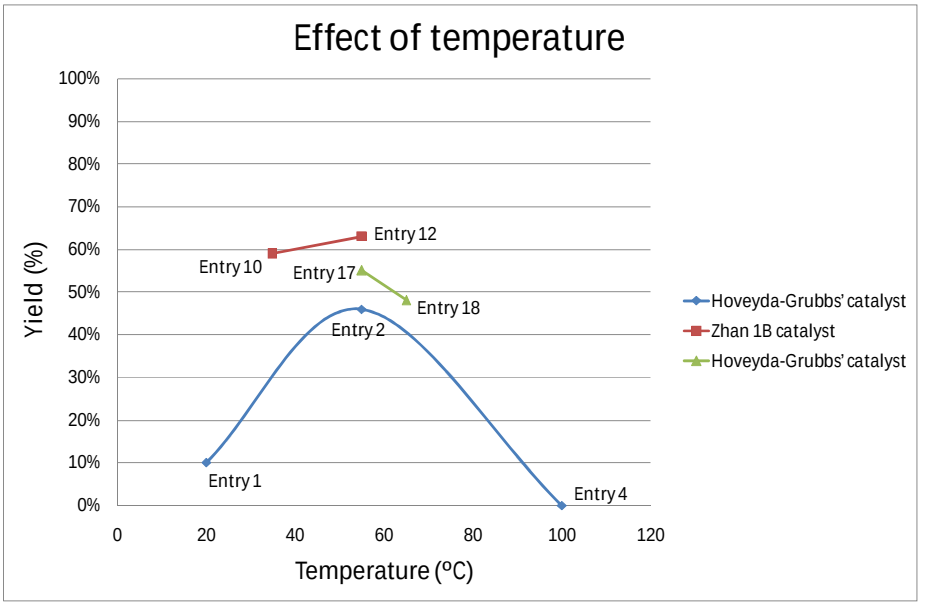


Figure 4.4*- Effect of temperature.*

The reaction time was also investigated, and it was found that for this specific CM after 24 hours, the yield did not improve significantly (Figure 4.5). However, this parameter is expected to change significantly if a more hindered olefin is used.

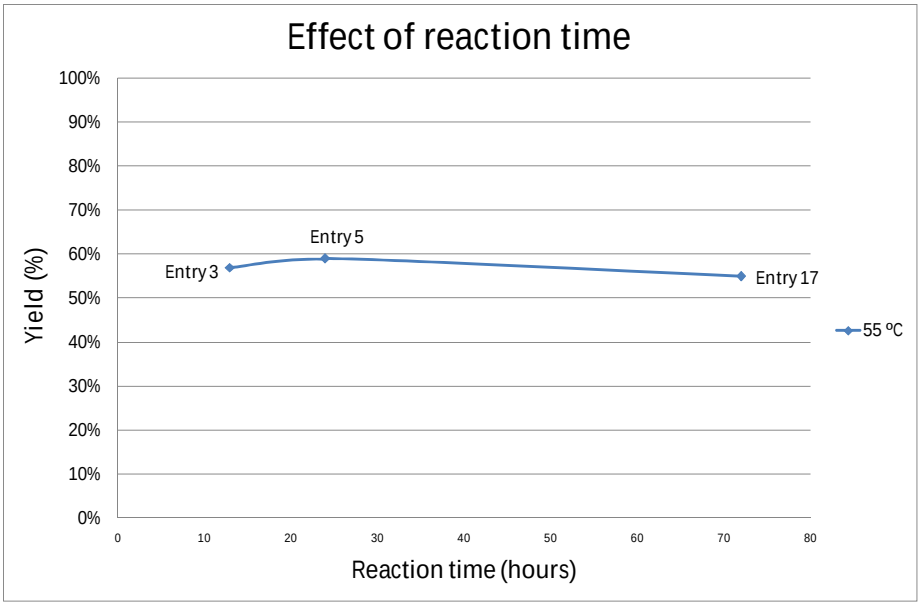


Figure 4.5 *- Effect of reaction time.*

The concentration of the starting material **486** was investigated at 0.05M, 0.10 M and 0.25 M (Figure 4.6). Although an extensive analysis was not performed, for this system the concentration of 0.10 M gave the best results. However, this parameter would also depend on the steric congestion of a particular ketone.

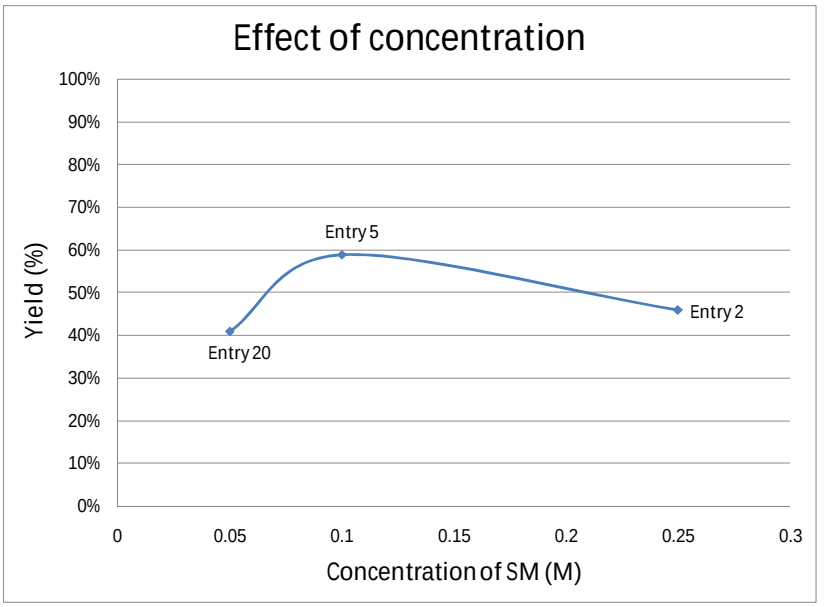


Figure 4.6 *- Effect of concentration of ketone* ***486****.*

The amount of enone reaction partner made a more significant difference than the parameters before. Reducing the amount of this material is important in order to synthesize a large amount of a plausible target. It was found that at least five equivalents of this reaction partner were sufficient to maximize the yield of the CM reaction (Figure 4.7).

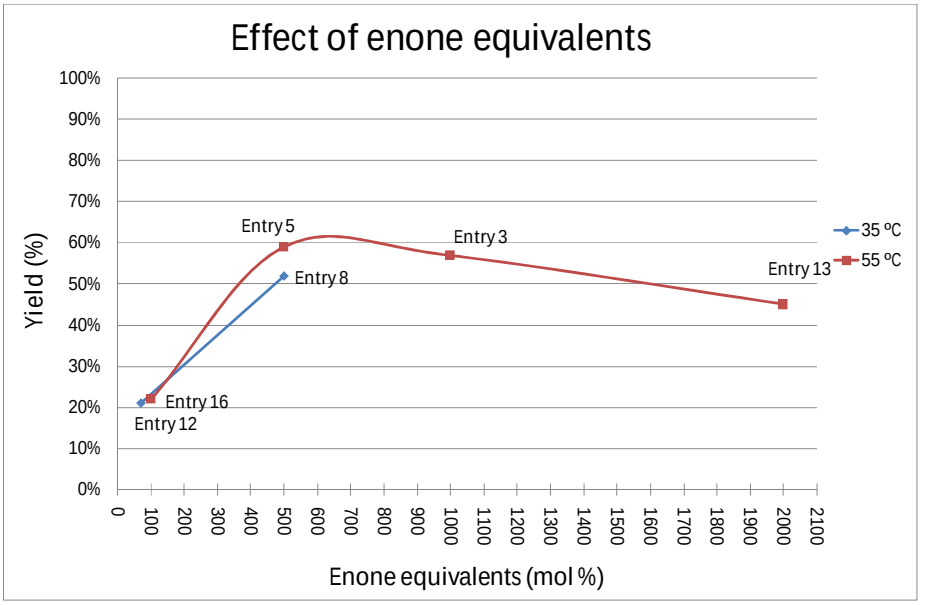


Figure 4.7 *- Effect of the MVK stoichiometry.*

Catalyst HG-II gave lower yields compared to catalyst Z-1B (Figure 4. 8). The fast initiation rate of catalyst Z-1B may improve the yield due to a decrease in the amount of side reaction that this starting material undergoes in the course of the CM reaction.

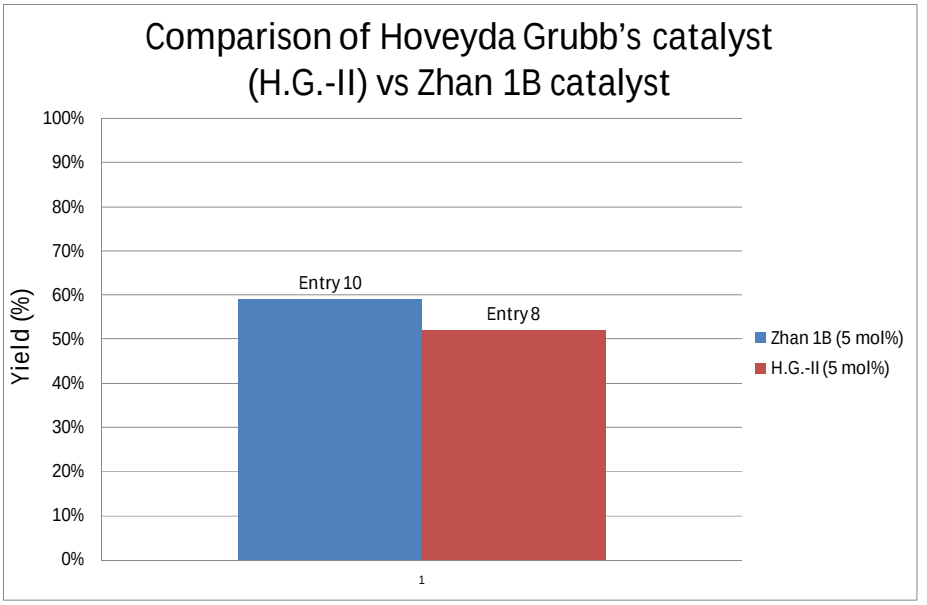


Figure 4. 8 *- Effect of catalyst:* ***HG-II*** *and* ***Z-1B****.*

The catalyst loading of 2.5 mol% for this reaction proved to be sufficient given the fact that higher catalyst loading did not improve the yield (Figure 4.9).

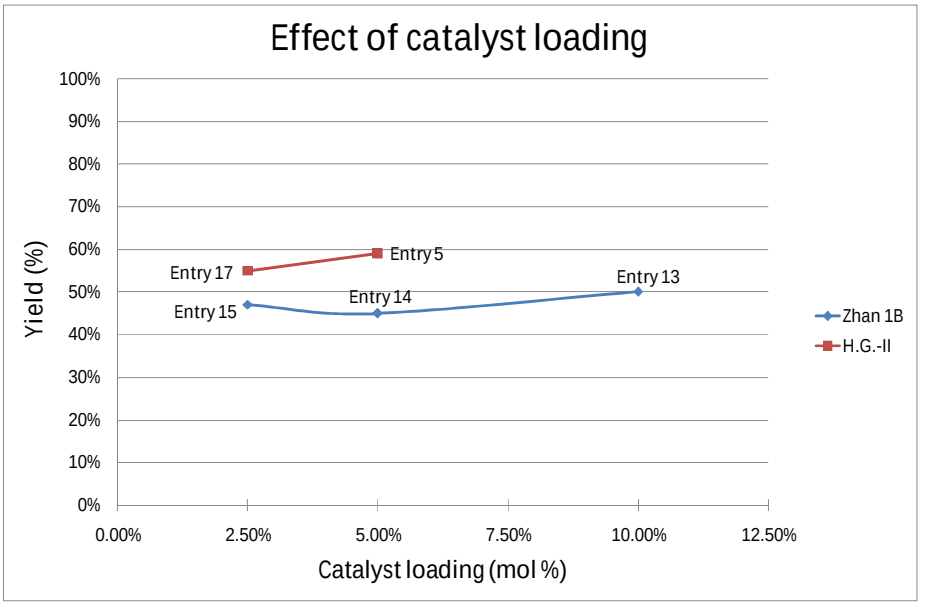


Figure 4.9 *- Effect of catalyst loading.*

The use of chlorinated solvents such as dichloromethane is known to be ideal for the metathesis reaction,[163] nevertheless a reaction in toluene was performed because this solvent is known to be used in a metathesis reaction and since it has a higher boiling point it does facilitate the reaction set up. The reaction was performed in toluene and a very low yield was obtained (Figure 4.10).

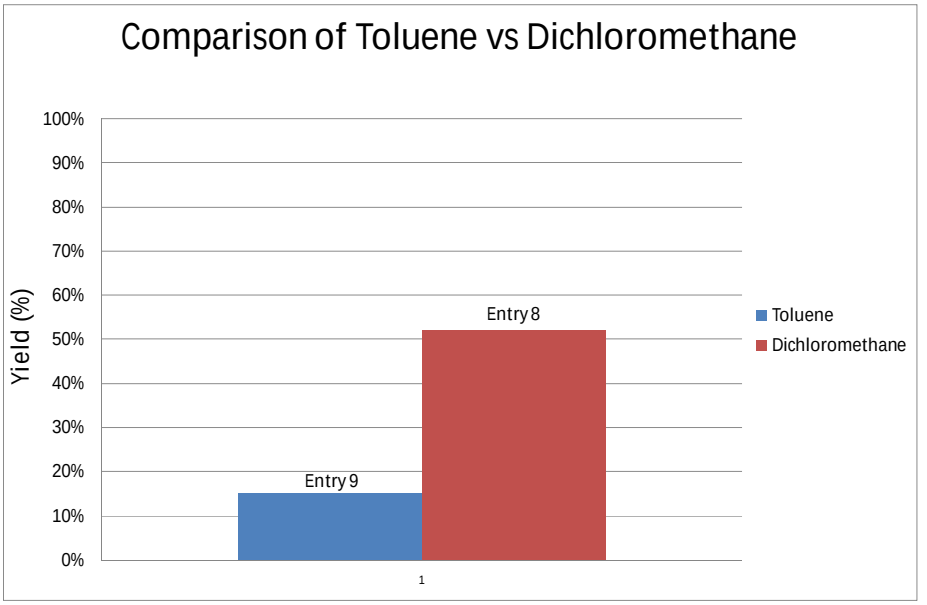
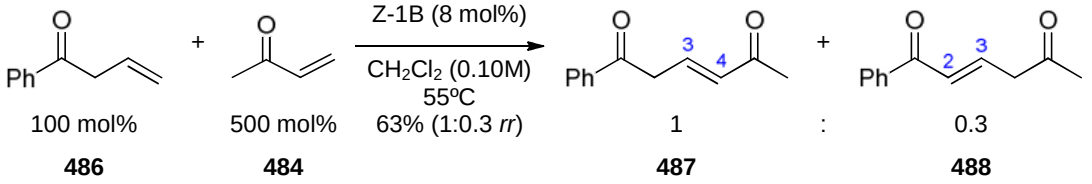


Figure 4.10 *- Comparison of dichloromethane and toluene on the CM reaction.*

In conclusion, the optimized reaction conditions gave a yield of 63% of the CM product, as an inseparable mixture of regioisomers **487** and **488** (Scheme 4.6).



Scheme 4.6 *- Synthesis of α,β-unsaturated-1,5-diketones **487** and **488**.*

The formation of the major regioisomer of unsaturated 1,5-diketone **487** was demonstrated by comparison of its ^{1}H and ^{13}C NMR spectra with the previously reported spectroscopic data for this compound.[164]

The appearance of the minor regioisomer **488** was due to double bond isomerisation that occurred in the overall process. Moreover, from the ^{1}H NMR spectrum a $J_{3\text{-}4}$ of 16.0 Hz for

the major regioisomer **487** and a $J_{2\text{-}3}$ of 15.5 Hz for the minor regioisomer **488** is strong evidence that both regioisomers are *E* configured olefins (Figure 4.11).

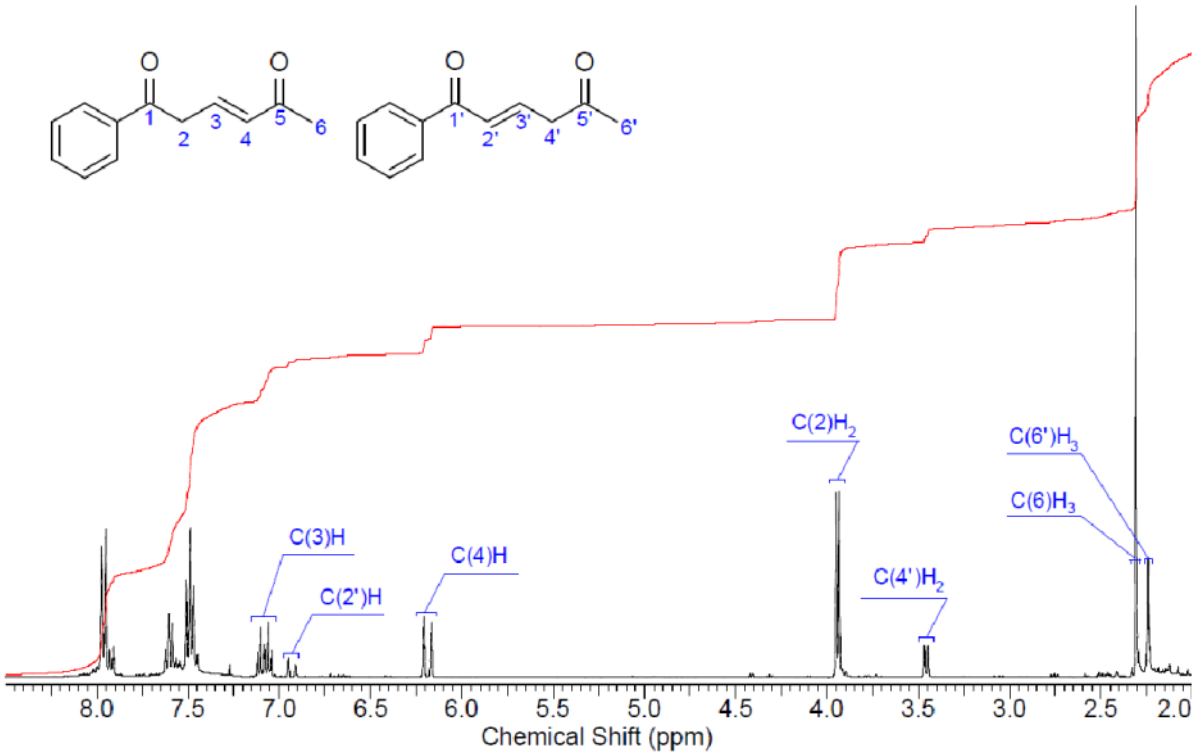
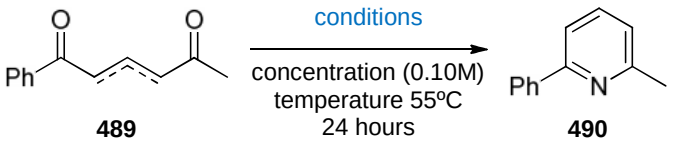


Figure 4.11 *- ^{1}H NMR of unsaturated 1,5-diketones **487**and **488**.*

This double bond isomerisation is likely to occur given the acidity of the internal alpha protons. This double bond isomerisation process may have occurr during the reaction conditions, due to the presence of ruthenium hydride species,[165] or it may occur on silica during purification *via* an acid-mediated process.

The 1,5-diketones **487** and **488** (represented as **489**) obtained were prone to decomposition and they were quickly subjected to the condensation reaction to form the desired 2,6-disubtituted pyridine **490**(Scheme 4.7). A number of conditions were screened in order to establish a highly efficient process (Table 4.2, Entry 7).



489 **490**

Scheme 4.7 *- Synthesis of pyridine **490**.*

Entry	Solvent	NH_3 Source	Additive	Yield
1	CH_2Cl_2	NH_4Cl		57%
2	CH_2Cl_2	NH_4BF_4		0%
3	CH_2Cl_2	NH_4OAc		0%
4	EtOH	NH_4OAc		59%
5	EtOH	NH_4OAc	NaOAc (10 eq.)	0%
6	EtOH	NH_4OAc	I_2 (0.1 eq.)	62%
7	EtOH	NH_4OAc	AcOH (10 eq.)	88%

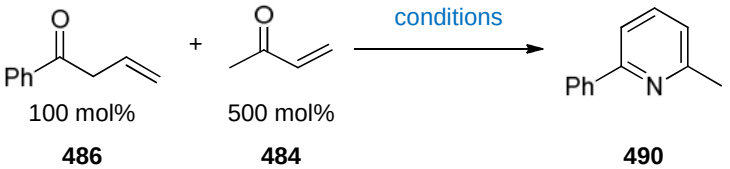
Table 4.2 *- Conditions for the synthesis of pyridine* ***490****.*

The formation of a 2,6-disubtituted pyridine was demonstrated by comparison of the ^{1}H and ^{13}C NMR spectra with the previously reported spectroscopic data for this compound.[166]

A method for the synthesis of 2,6-disubstituted pyridine using the CM-condensation sequence described seem encouraging due to the high yields and the simplicity of the steps involved. The overall yield for this method was 40% when using catalyst HG-II and 55% when using catalyst Z-1B.

A one pot protocol for the CM and the condensation steps would facilitate the synthesis of the desired pyridine. Unfortunately the presence of dichloromethane reduces the efficiency of the condensation step significantly.

However, in order to simplify the handling of the α,β-unsaturated-1,5-diketone intermediates, the metathesis reaction mixture was concentrated *in vacuo* and the crude material was subjected to the condensation conditions optimized before (Scheme 4.8).



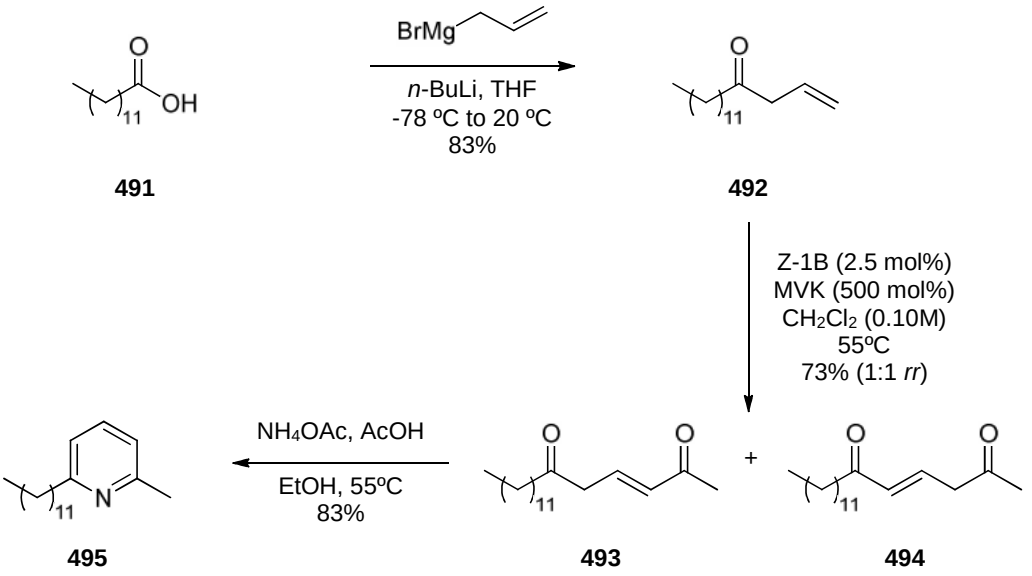
Scheme 4.8 *- One pot synthesis of pyridine* ***490****.*

Entry	Conditions	Yield
1	HG-II (10 mol%), CH_2Cl_2 (0.10M), 55ºC, 48 hours. Solvent remove then NH_4OAc (1000 mol%), AcOH (1000 mol%), EtOH, 55ºC.	28%
2	Z-1B (10 mol%), CH_2Cl_2 (0.10M), 55ºC, 48 hours. Solvent remove then NH_4OAc (1000 mol%), AcOH (1000 mol%), EtOH, 55ºC.	31%

Table 4.3- *Conditions for the synthesis of pyridine* ***490***.

The results for subjecting the crude material to the condensation conditions indicate that the presence of the excess MVK is detrimental to the efficiency of this last step (Table 4.3), and therefore the unsaturated 1,5-dicarbonyl substrates were isolated before aromatisation.

In order to demonstrate that different alkyl substituted pyridines could be obtained with high levels of regiocontrol, the carboxylic acid **491** was converted to the desired target in three steps (Scheme 4.9). Carboxylic acid **491** was converted to β,γ-unsaturated ketone **492** according to a protocol developed by Roemmele and Rapoport.[167] Using the optimized conditions, ketone **492** was converted to the inseparable mixture of 1,5-diketones **493** and **494** which were transformed into the desired pyridine **495**.

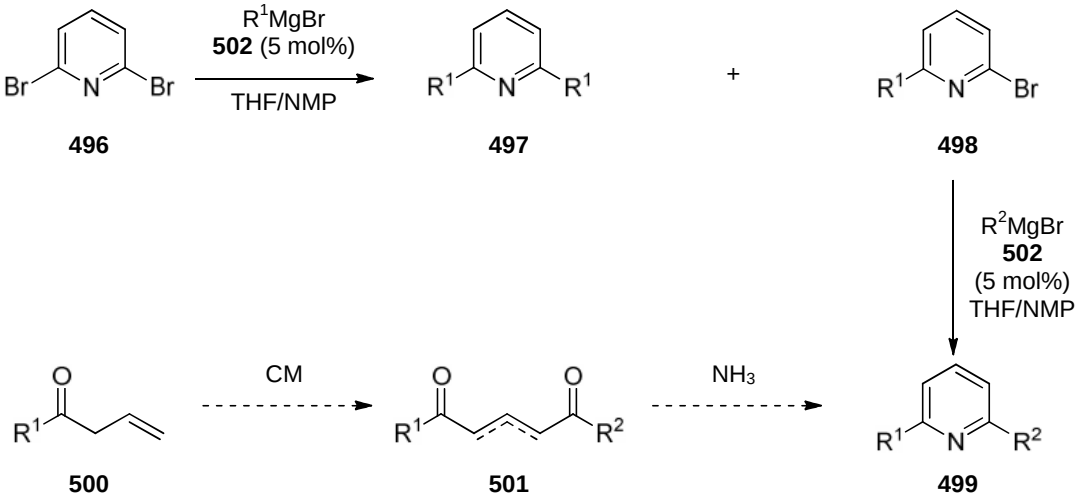


Scheme 4.9 - *Synthesis of pyridine* ***495***.

This reaction sequence proved to be an ideal method for the synthesis of 2,6-disubstitutedpyridines **499** (Scheme 4.10).

The method described represents an important finding because a selective alkylation of a 2,6-dibromopyridine is a difficult reaction that requires organometallic species, anhydrous conditions and normally mixtures of mono- and bi-substituted products are obtained.

For example, Fürstner and Leitner described the use of a Grignard reagent and iron-based catalyst **502** (Figure 4.12) for the alkylation of pyridine **496** and obtained a mixture of dialkylated product **497** and monoalkylated product **498** (Scheme 4.10).[168] A second alkylation was then required in order to obtain the desired disubstituted pyridine **499**.



Scheme 4.10 *- Synthesis of 2,6-disubstituted pyridine* ***499****.*

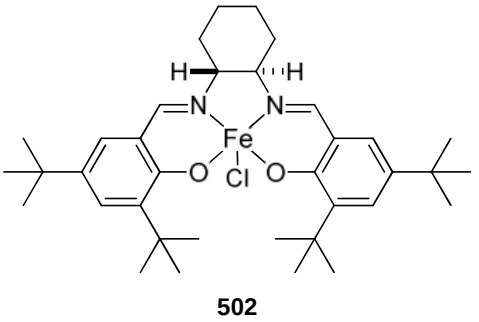
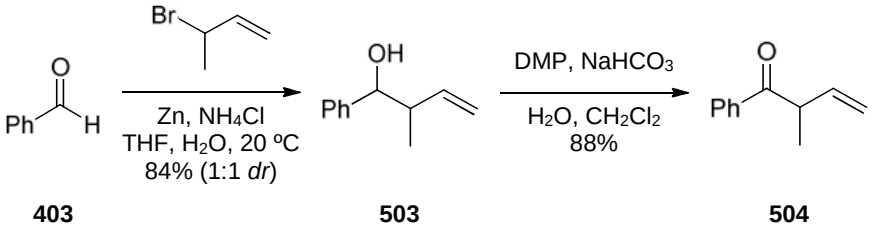


Figure 4.12*- Iron-salen complex* ***502****.*

There are a number of examples in which 2,6-disubstituted pyridines can be obtained very efficiently by using this CM approach, especially if the desired target contains stereogenic centres at the benzylic positions. Although this would be an important aspect of research, the

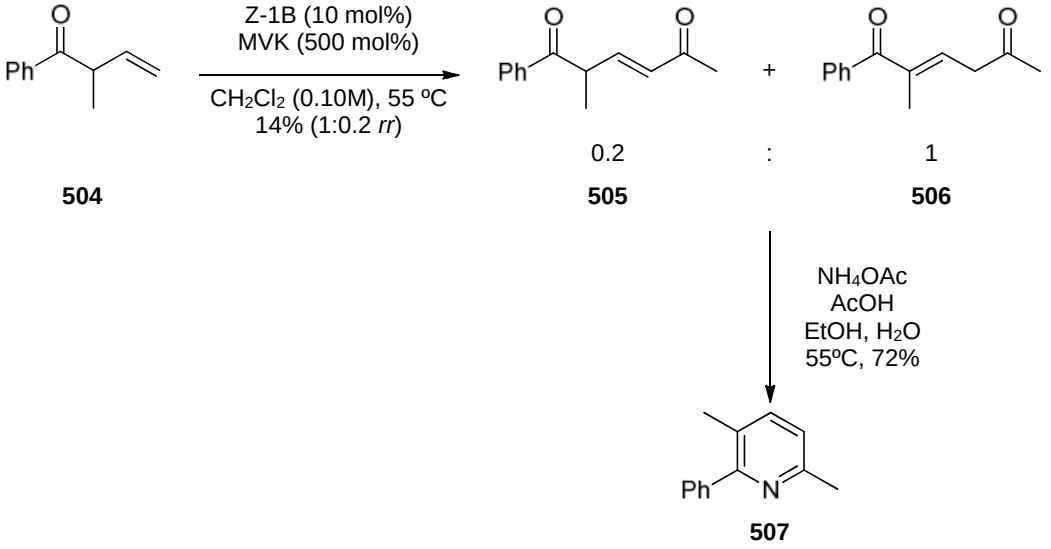
focus of the project turned into demonstrating the use of this method to obtain highly substituted targets, and therefore the synthesis of a 2,3,6-trisubstituted pyridine was next explored.

Benzaldehyde **403** was converted to the β,γ-unsaturated ketone **504** in three simple steps. Homoallylic alcohol **503** was prepared very efficiently by zinc-mediated allylation, and then DMP was used to oxidize this intermediate to the corresponding target **504** (Scheme 4.11).



Scheme 4.11 *- Synthesis of β,γ-unsaturated ketone **504***

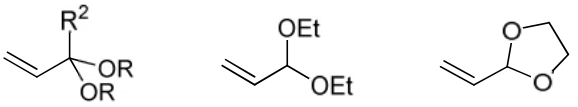
The synthesis of the tri-substituted pyridine **507** was accomplished using the starting β,γ-unsaturated ketone **504** previously prepared (Scheme 4.12). Unfortunately, the CM reaction was not an efficient process and the α,β-unsaturated-1,5-diketones **505** and **506** were obtained in low yield.



Scheme 4.12 *- Synthesis of pyridine **507**.*

The limitation for the synthesis of 2,3,6-trisubstituted pyridines using this method, was thought to be overcome by utilizing the protected carbonyl surrogate **508**, because of the

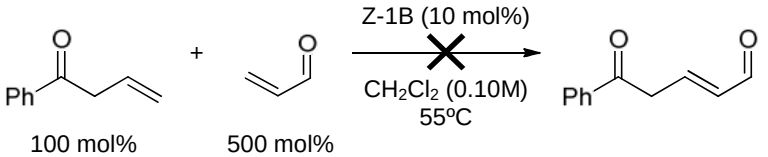
change in the electronic properties of the olefin that should facilitate the cross-metathesis process (Figure 4.13).[169] Some of these protected carbonyls are commercially available, such as diethyl acetal **509** or dioxolane acetal **510**, while others can be made simply *via* a protection step.[170] Furthermore, the acetal moiety in the CM product can be deprotected *in situ* during the condensation step.



508 **509** **510**

Figure 4.13 *- Protected acrylic ketones.*

The CM reaction using acetaldehyde was not successful due to decomposition of the desired product, and the synthesis of pyridines lacking a substitution at the 2-position would benefit from using acetal **509** or **510** (Scheme 4.13).

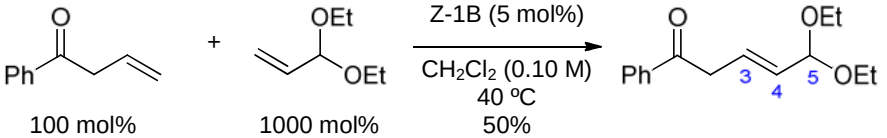


100 mol% 500 mol%

486 **511** **512**

Scheme 4.13*-Failed synthesis of diketone **512**.*

The β,γ-unsaturated ketone **486** was subjected to a CM reaction using acetal **509** and the corresponding product **513** was synthesised (Scheme 4.14).



100 mol% 1000 mol%

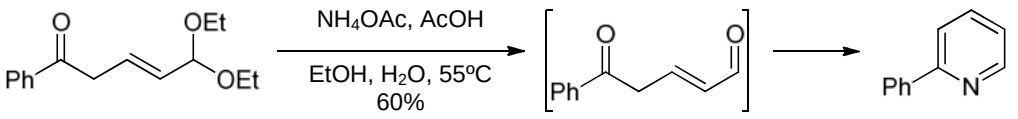
486 **509** **513**

Scheme 4.14 *- Synthesis acetal**513**.*

The formation of acetal **513** was evidenced by the appearance of a signal in the ^{1}H NMR spectrum at 4.90 ppm which corresponded to the ketal signal C(5)H. Further evidence is the appearance of only two olefinic signals at 6.13 ppm and 5.67 ppm, which corresponded to

C(3)H and C(4)H. Coupling constant $J_{3\text{-}4}$ of 16.0Hz is a strong evidence of an *E* configuration, which is the expected outcome of many CM process that deliver disubstituted alkenes.[36]

Deprotection and *in situ* condensation of acetal **513** afforded the desired pyridine **514** in good yield (Scheme 4.15). The conditions used previously (Table 4.2, Entry 7), with the addition of one equivalent of water in order to ensure the hydrolysis of the acetal, have produced the desired target.

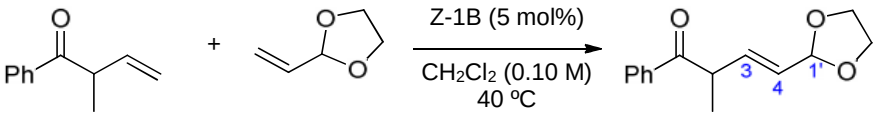


513 **512** **514**

Scheme 4.15 *- Synthesis of 2-subsituted pyridine **514**.*

Utilizing this method an array of 2-substituted pyridines could be synthesized. The simplicity of the steps and mild reaction conditions makes this approach attractive for the synthesis of difficult substrates.

This approach was applied to the synthesis of 2,3-disubstituted pyridines. The β,γ-unsaturated ketone **504** was subjected to the same reaction sequence, using acetal **510**, because the desired CM product **515** was produced in higher yield than the corresponding product using acetal **509** (Scheme 4.16).



100 mol% 1000 mol% 68%

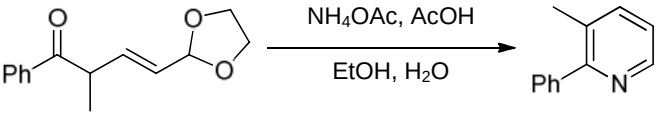
504 **510** **515**

Scheme 4.16 *- Synthesis acetal**515**.*

The formation of acetal **515** was evidenced by the appearance of a signal in the ^{1}H NMR spectrum at 5.22 ppm which corresponded to the ketal signal C(1')H. Further evidence is the appearance of only two olefinic signals at 6.15 ppm and 5.64 ppm, which corresponded to

C(3)H and C(4)H. Coupling constant $J_{3\text{-}4}$ of 15.5 Hz is strong evidence of an *E* configuration.

Conversion of acetal **515** to the desired 2,3-disubstituted pyridine **516** was achieved in good yields (Scheme 4.17). The optimized result was found when the reaction was performed at higher temperature (Table 4.4, Entry 2).



515 **516**

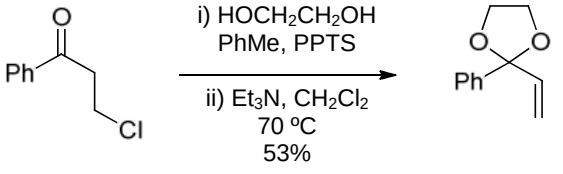
Scheme 4.17 *- Synthesis of pyridine **516**.*

Entry	Temperature	Yield
1	55 ºC	51%
2	90 ºC	87%

Table 4.4 *- Conditions for the synthesis of 2,3-disubstituted pyridine**516**.*

Formation of pyridine **516** was demonstrated by comparison of the ^{1}H and ^{13}C NMR spectra with the previously reported spectroscopic data for this compound.

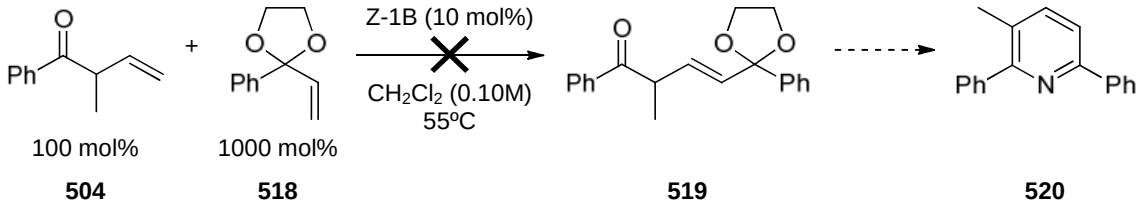
Acetal **518** was prepared from readily available ketone **517** (Scheme 4.18).



517 **518**

Scheme 4.18*- Preparation of acetal **518**.*

The β,γ-unsaturated ketone **504**, in conjunction with acetal **518**, were subjected to the CM reaction conditions, but product **519** was not observed, and it was clear that acetal **518** was too hindered for a CM to occur (Scheme 4.19).



Scheme 4.19 *- Failed synthesis of ketone* ***519****.*

In conclusion, the synthesis of 2,3,6-trisubstituted pyridines would be a difficult task starting from a β,γ-unsaturated ketone. Nevertheless, a method for the synthesis of 2,6-disubstituted pyridines, 2-substituted pyridines and a 2,3-disubstituted pyridine has emerged using a CM approach (Figure 4.14), demonstrated for a small number of examples.

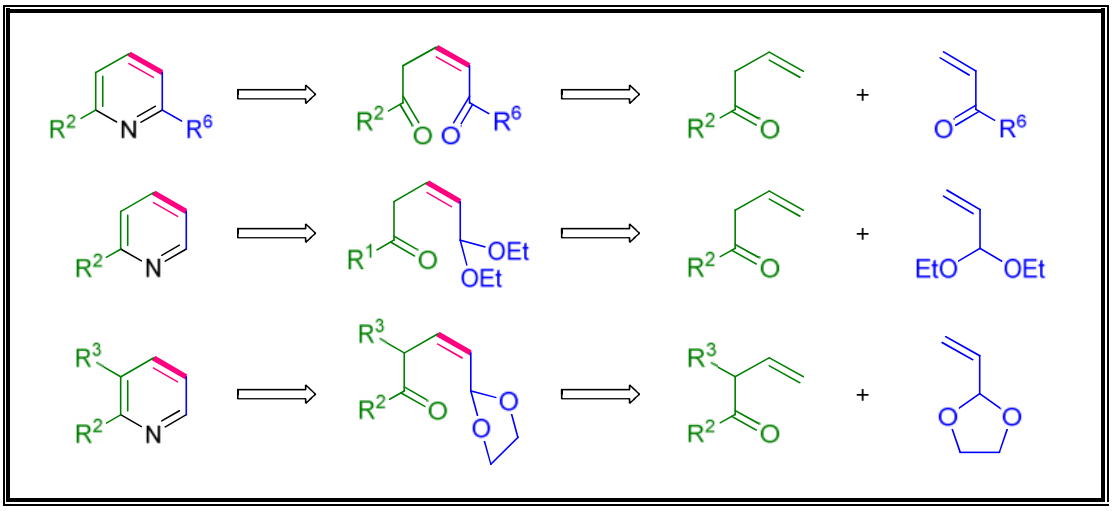


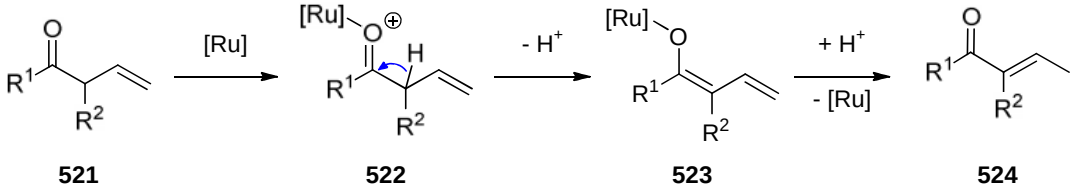
Figure 4.14 *- CM approach to polysubstituted pyridines.*

4.3.2 Synthesis of pyridines from homoallylic alcohols

Given the importance of highly substituted pyridine targets and the limitations on the CM reaction using β,γ-unsaturated ketones, an improved method was required. Our attention was turned to the use of a homoallylic alcohol for the selective CM reaction followed by a protocol that would increase the oxidation level and deliver the pyridine core in one step.

Homoallylic alcohols have the advantage that they do not possess acidic α-protons, which may be the cause of the low efficiency of the metathesis reaction, due to different modes of

deactivation such as isomerisation, mediated by the Lewis acidity of the metal centre (Scheme 4.20).[171]



Scheme 4.20 *- Lewis acid mediated isomerisation of β,γ-unsaturated ketone* ***521****.*

Adding different Lewis acid to the reaction conditions, in order to stop this mode of coordination, was also attempted, but not surprisingly this did not produce any favourable results due to decomposition of the susceptible enone partner.

Allylic alcohols are a special substrate for the CM reaction due to a high affinity with the metathesis catalyst, *via* an intramolecular H-bonding of the hydroxyl group to the chlorine ligand, demonstrated in species **525** (Figure 4.15).[156]

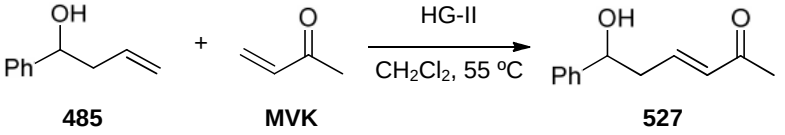


Figure 4.15 *- Formation of hydrogen bonding between a chlorine ligand a tether hydroxyl group.*

Homoallylic alcohols are less likely to have this affinity towards a metathesis catalyst given the required seven membered ring, but nevertheless it was hoped that these substrates would participate in metathesis process effectively and furthermore, they would not require any hydroxyl protective group.

Homoallylic alcohol **485** was subjected to a CM using MVK and the desired α,β-unsaturated-5-hydroxy ketone **527** was obtained (Scheme 4.21). Hydroxy ketone **527** was obtained in quantitative yields, when catalyst HG-II was used, proving that this substrate is a

very good metathesis partner (Entry 2, Table 4.5). Unfortunately, the amount of MVK could not be reduced without a significant loss of efficiency (Entry 4, Table 4.5).



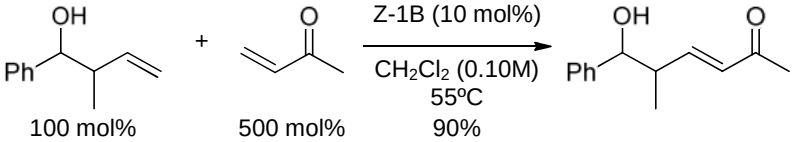
485 **MVK** **527**

Scheme 4.21 *- Synthesis of α,β-unsaturated-5-hydroxyketone **527**.*

Entry	Concentration	Catalyst loading	Enone equivalents	Yield*
1	0.10 M	5%	500 mol%	78%
2	**0.10 M**	**2.5%**	**500 mol%**	**97%**
3	0.25 M	2.5%	500 mol%	71%
4	0.10 M	2.5%	250 mol%	63%

Table 4.5 *- Conditions for the synthesis of α,β-unsaturated-5-hydroxy-ketone **527**.*

Encouraged by these results, the CM reaction between the α-substituted homoallylic alcohol **503** and MVK was also tested (Scheme 4.22). The desired α,β-unsaturated-5-hydroxy ketone **528** was obtained in very high yields and the limitations that were found on the CM of ketone **504** was overcome.



100 mol% 500 mol% 90%

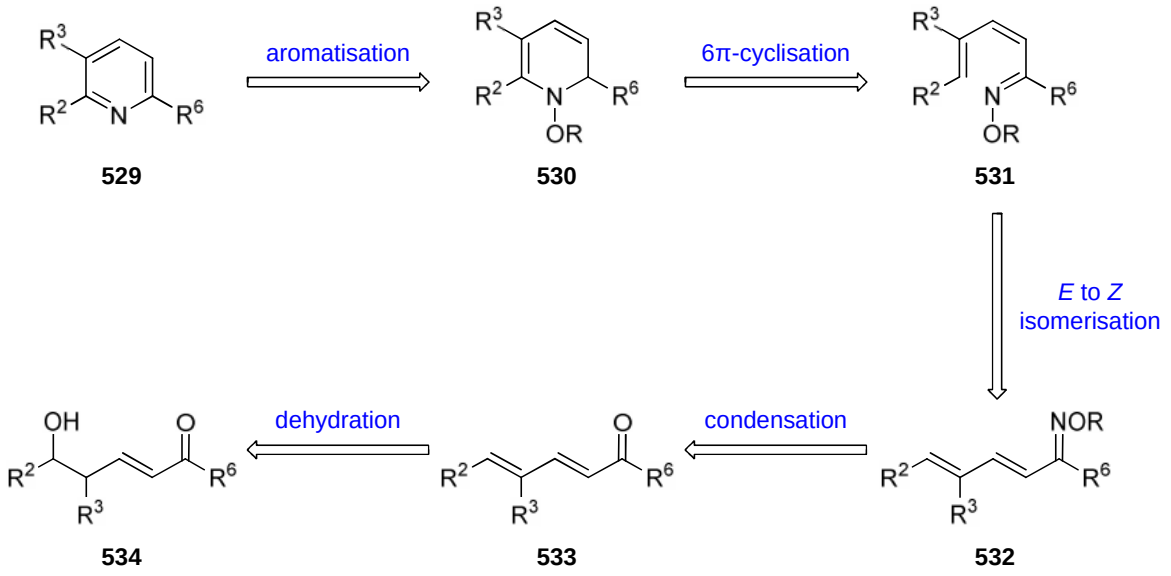
503 **MVK** **528**

Scheme 4.22*- Synthesis of α,β-unsaturated-5-hydroxyketone **528**.*

The formation of α,β-unsaturated-5-hydroxy ketone **528** was evidenced by the appearance of two signals in the ^{1}H NMR spectrum at 6.87 ppm and 6.06 ppm which corresponded to the olefinic signals at C(4)H and C(3)H respectively. A coupling constant $J_{3\text{-}4}$ of 16.0 Hz is a strong evidence for an *E* configuration.

With these results in hand, a method for converting the α,β-unsaturated-5-hydroxy ketone into the desired pyridine was sought. One approach would be to perform an oxidation, similar to the oxidation of the homoallylic alcohol described earlier (Scheme 4.11).

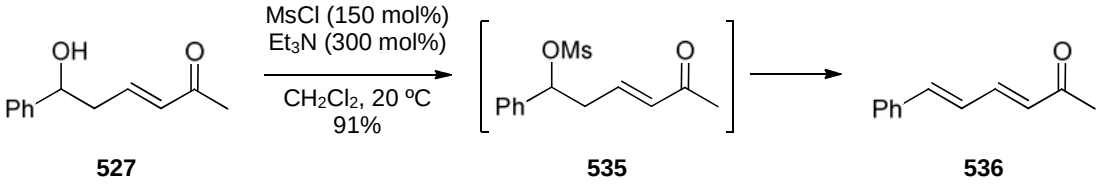
Another approach would involve an introduction of the required oxidation level by utilizing an oxidized form of ammonia, such as hydroxyl amine in the condensation. In this approach the desired pyridine target **529** is formed by acid-mediated elimination of the hydroxyl group from dihydropyridine **530** (Scheme 4.23).[172] This cyclic precursor **530** is obtained from a 6π-electrocyclisation of oxime **531**, which is obtained from *E* to *Z* isomerisation of the corresponding oxime **532**. Condensation of diene **533** with a hydroxylamine source would afford the required oxime **532**. Diene **533** could be obtained from dehydration of the CM product **534**.



Scheme 4.23 *- Retrosynthetic analysis of pyridine **529**.*

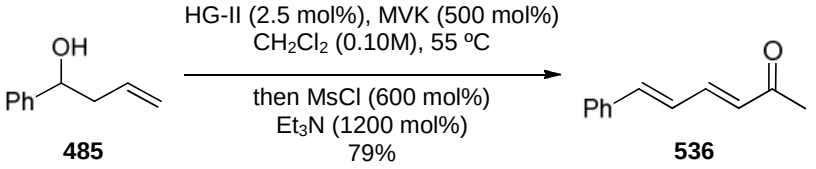
A method based on this process would have the advantage of not requiring an oxidation step, and this would be attractive for a preparative scale.[173] Efforts towards developing a technique to condense this five-step sequence into a single pot reaction would be critical in order to reduce the length of the reaction path and justify this method as a viable source of polysubstituted pyridines.

The 5-hydroxyketone **527** was used to investigate the proposed method. The first step is the formation of the required diene **536** and this was achieved by activation followed by *in situ* elimination using methanesulfonyl chloride in an excess of triethylamine (Scheme 4.24).



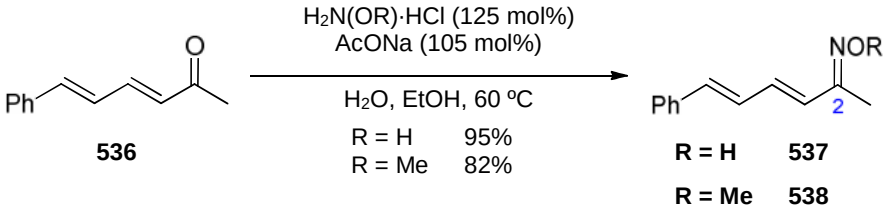
Scheme 4.24 *- Synthesis of diene **536**.*

The synthesis of diene **536** was shortened by using a one pot protocol which involved the CM of homoallylic alcohol **485** and MVK and then subjecting this reaction mixture to the elimination conditions described earlier (Scheme 4.25).



Scheme 4.25 *- Synthesis of diene **536** from homoallylic alcohol **485**.*

With diene **536** in hand the oximes **537** and **538** were prepared by condensation with the corresponding hydroxyl amine source (Scheme 4.26). These two oximes were prepared in order to find out the best leaving group in the aromatisation step.



Scheme 4.26 *- Synthesis of oximes **537** and **538**.*

The formation of oxime **537** was evidenced by the appearance of signal in the ^{1}H NMR spectrum at 9.46 ppm which corresponded to the hydroxyl group. Further evidence is the appearance of two signals in the ^{13}C NMR spectrum at 156.7 ppm and 153.2 ppm which corresponded to C(2) in the two diasteromeric forms.

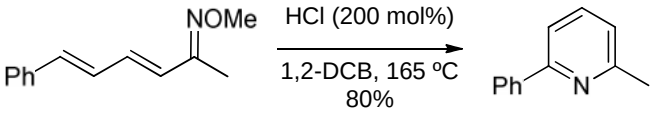
The formation of oxime **538** was evidenced by the appearance of two signals in the ^{1}H NMR spectrum at 3.97 ppm and 3.94 ppm which corresponded to the *O*-methyl group C(1')H_3 in the two diasteromeric forms.

Oxime **538** was used to find the appropriate conditions for which the desired cascade reaction involving the *E* to *Z* isomerisation, 6π-electrocyclization and aromatisation would occur and the desired pyridine could be formed in one step.

It was thought that the *E* to *Z* isomerisation could be achieved by the presence of either a Brønsted acid, a π-acidic Lewis acid or a nucleophilic catalyst that can undergo a reversible 1,4-addition.The 6π-electrocyclasation could be achieved by subjecting the desired intermediate to enough thermal energy, and this reaction should be compatible with the above mentioned aromatisation process.

Finally, the elimination step would be driven by aromatisation and this is likely to occur spontaneously.

Oxime **538** was subjected to a range of reaction conditions, taking into account the previously described requisites (Scheme 4.23). Gratifyingly, after trying many reaction conditions (Table I.2), the desired pyridine **490** was obtained using stoichiometric amounts of a strong acid and at elevated temperatures (Scheme 4.27).



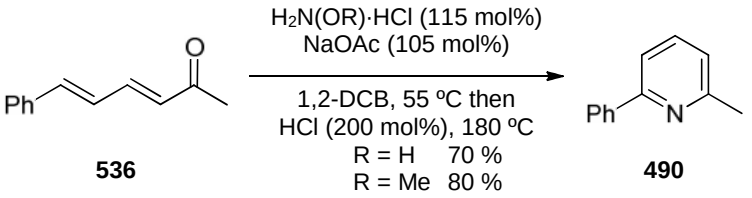
538 **490**

Scheme 4.27 *- 6π-electrocyclisation approach to pyridine* ***490****.*

The use of pyridinium *p*-toluenesulfonate (Entry 7, Table I.2) did not afford any of the desired products, giving an indication that a reasonably strong acid was required to promote this cascade.

Given the fact that any pyridine product formed would be immediately converted to the corresponding pyridinium ion, a stoichiometric amount of a strong acid is required in this reaction.

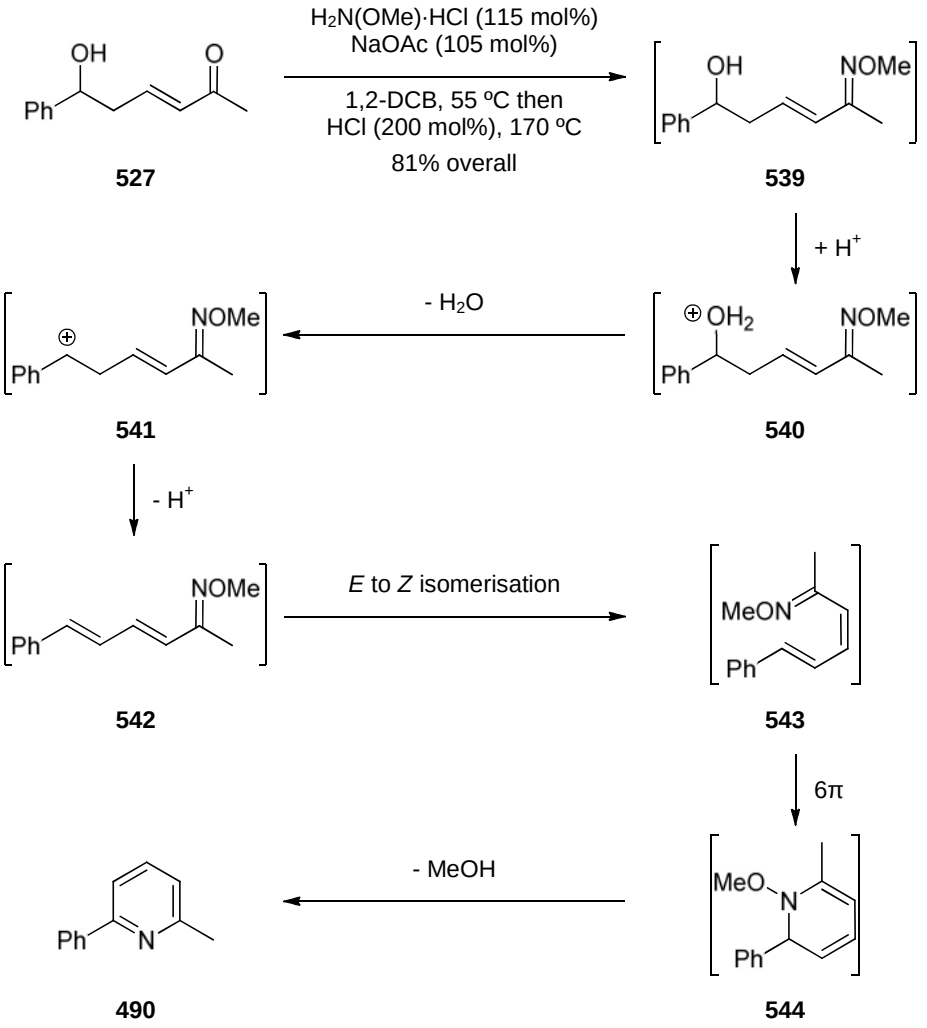
With the optimized conditions uncovered, a one-pot protocol for the formation of the oxime followed by the cascade condensation was successfully achieved (Scheme 4.28). The diene **536** was converted to the desired oxime in 1,2-dichlorobenzene, and when the starting material was consumed, the requisite amount of acid was added and the reaction heated to the correct temperature. The desired pyridine **490** was obtained in very high yields.



Scheme 4.28 *- One pot synthesis of pyridine **490** from diene **536**.*

The results using methoxyamine hydrochloride ($H_2N(OMe)\cdot HCl$) were higher compared to the use of hydroxylamine hydrochloride ($H_2N(OH)\cdot HCl$) and therefore methoxyamine hydrochloride salt was used for other examples.

Formation of the required diene **536** could also be achieved during the reaction conditions by acid-mediated elimination of the hydroxyl group in 5-hydroxy ketone **527** (Scheme 4.29). Therefore homoallylic alcohol **527** was subjected to the one pot protocol developed earlier, and the desired pyridine **490** was obtained after a 7 step cascade event in very high overall yields.



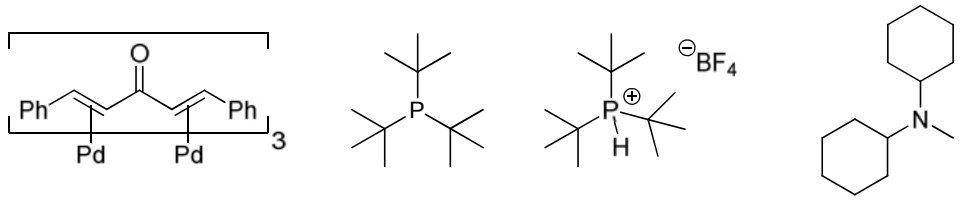
Scheme 4.29 *- One pot synthesis of pyridine* ***490*** *from homoallylic alcohol* ***527****.*

The simplicity of the CM reaction, combined with the high yield of the cascade process made this approach an attractive method for the synthesis of pyridines. Although the reaction conditions are not mild, a number of targets that are not sensitive could be easily prepared in two steps from the homoallylic alcohol starting material.

The synthesis of 2,4,6-trisubstituted pyridines could be achieved by exploiting the 5-hydroxy ketone **527** intermediate obtained so efficiently by a CM reaction and functionalizing this intermediate *via* a Heck reaction.

The Heck reaction is a highly regioselective process in α,β-unsaturated ketones, and it installs an aromatic group at the beta carbon.[141, 142] The conditions developed by Fu and co-workers involves the use **545** (Pd_2dba_3) as the palladium source, **546** (*t*-Bu_3P) as the

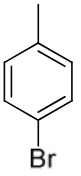
phosphine ligand which is generated in situ by deprotonation of the air stable phosphonium tetrafluoroborate salt **547** (*t*-$Bu_3P{\cdot}HBF_4$), the hindered base **548** (Cy_2NMe) and the corresponding aryl halide (Figure 4.16).[174, 175]



545 (Pd_2dba_3) **546 (*t*-Bu_3P)** **547 (*t*-$Bu_3P{\cdot}HBF_4$)** **548 (Cy_2NMe)**

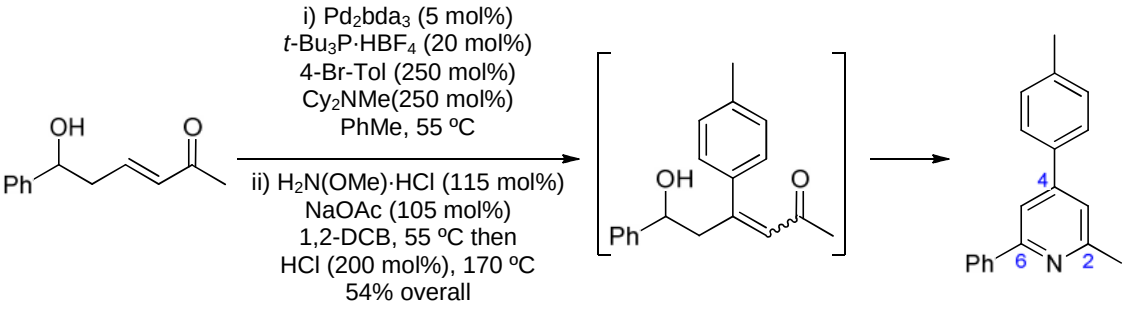
Figure 4.16 *- Reagents for the Heck reaction.*

These reaction conditions were applied successfully to the 5-hydroxy ketone **527** intermediate using 4-bromotoluene **549** (4-Br-Tol) (Figure 4.17), and the crude material was subjected to the cascade conditions to afford the desired 2,4,6-trisubstituted pyridine **551** in good overall yields (Scheme 4.30).



549 (4-Br-Tol)

Figure 4.17*- 4-Bromotoluene **549**.*

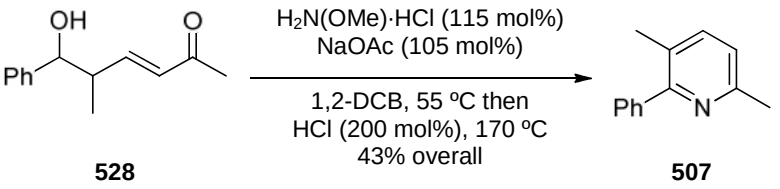


527 **550** **551**

Scheme 4.30*- Synthesis of 2,4,6-trisubstituted pyridine**551**.*

The formation of pyridine **551** was evidenced by the appearance of six signals in the ^{13}C NMR spectrum at 158.8 ppm, 157.6 ppm, 149.3 ppm, 140.0 ppm, 138.9 ppm and 135.9 ppm which corresponded to three quaternary carbons C(6), C(2), C(4) in the pyridine core, two quaternary carbons in the tolyl group and one carbon in the phenyl group. Furthermore the chemical shift of 149.3 ppm corresponds to a carbon at the 4-position as compared with other pyridine structures.[176]

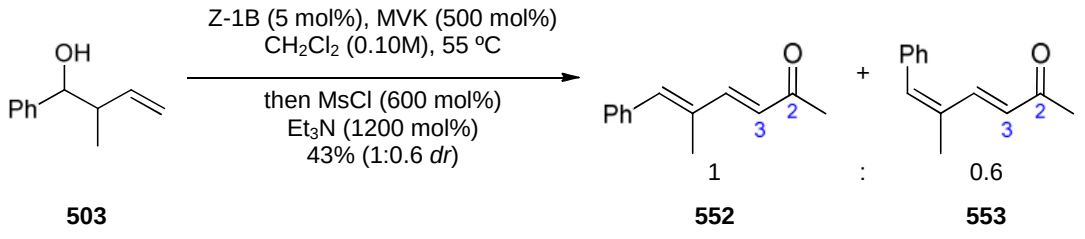
The method for the synthesis of pyridines developed earlier was then applied to the more substituted 5-hydroxy ketone **528** and the desired 2,3,6-trisubstituted pyridine was formed, although a loss of efficiency was observed (Scheme 4.31).



Scheme 4.31 *- Synthesis of pyridine **507**.*

The synthesis of the 2,3,6-trisubstituted pyridine *via* this method gave much higher overall yields, considering the CM step, compared to the use of the corresponding β,γ-unsaturated ketone.

To identify which part of the cascade reaction was not efficient, the diene **552** was prepared in a one-pot protocol from the homoallylic alcohol **503** (Scheme 4.32).

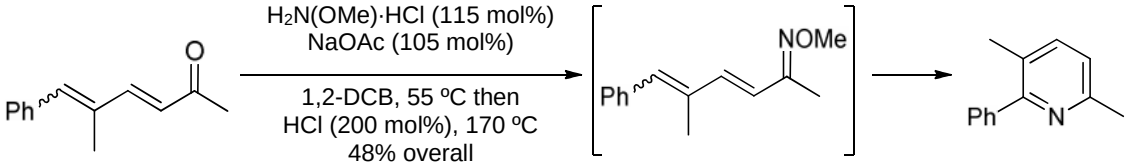


Scheme 4.32 *- Synthesis of dienes **552** and **553** from homoallylic alcohol **485**.*

The formation of dienes **552** and **553** were evidenced by the appearance of two signals in the ^{13}C NMR spectrum at 198.5 ppm and 198.1 ppm which corresponded to the carbonyl C(2) in the two diasteromeric forms. Furthermore the appearance of two signals in the ^{1}H NMR

spectrum at 6.24 ppm and 6.22 ppm which corresponded to the olefinic signal C(3)H, both with a $J_{3\text{-}4}$ of 16.0 Hz which would indicate an *E* configuration of the olefin at the 3-position.

Diene **552** was then subjected to the cascade reaction. The reaction mixture was monitored and formation of oxime intermediate **554**, although not isolated, was observed with complete consumption of starting material **552**. Addition of hydrochloric acid and subjection of the mixture to the appropriate reaction conditions afforded the desired target in moderate yields (Scheme 4.33).

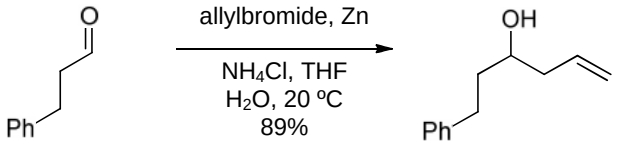


552 **554** **507**

Scheme 4.33 *- Synthesis of pyridine from diene **552**.*

The results previously obtained demonstrate that the loss of efficiency could be in the *E* to *Z* isomerisation step or the 6π-electrocyclisation step.

In order to test the scope of this method by using a different substituent at the 2-position the homoallylic alcohol **556** was prepared using the commercially available aldehyde **555** (Scheme 4.34).



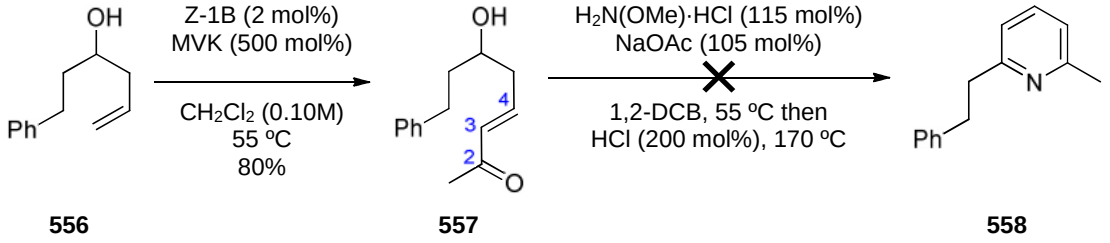
555 **556**

Scheme 4.34 *- Synthesis of homoallylic alcohol **556**.*

Formation of homoallylic alcohol **556** was demonstrated by comparison of the ^{1}H and ^{13}C NMR spectra with the previously reported spectroscopic data for this compound.[177]

The homoallylic alcohol **556** was subjected to the two step method described earlier, in order to obtain a 2,6-dialkyl pyridine. The desired intermediate 5-hydroxy ketone **557** was

obtained in high yields, but this intermediate did not form any of the required pyridine product **558** under the conditions developed earlier (Scheme 4.35).

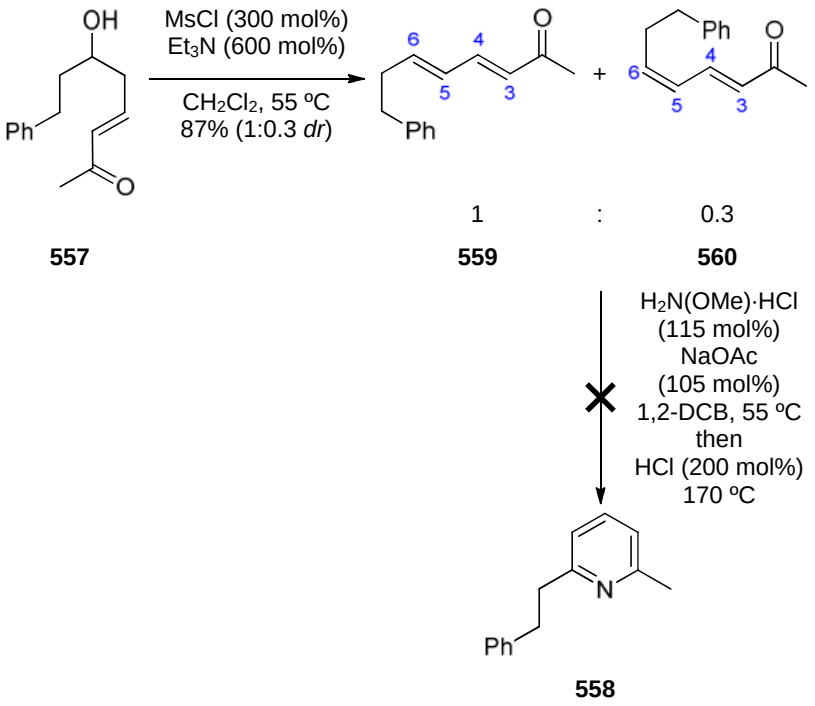


556 **557** **558**

Scheme 4.35 *- Failed synthesis of pyridine **558**.*

The formation of 5-hydroxy ketone **557** was evidenced by the appearance of a signal in the ^{13}C NMR spectrum at 198.6 ppm which corresponded to the carbonyl carbon C(2). Further evidence was the appearance of two signals in the ^{1}H NMR spectrum at 6.84 ppm and 6.14 ppm which corresponded to C(4)H and C(3)H respectively, with a coupling constant of $J_{3\text{-}4}$ 16.0 Hz that is a strong evidence of an *E* configuration.

Not surprisingly the desired pyridine **558** was not formed, since by changing the phenyl substituent for an alkyl group, the dehydration step is slowed down significantly. Therefore the diene **559** was prepared in high yields, and then subjected to the reaction conditions. Formation of the intermediate oxime was observed by TLC analysis, but the desired pyridine **558** was not formed (Scheme 4.36).



Scheme 4.36*- Failed synthesis of pyridine* ***558****.*

The formation of dienes **559** and **560** were evidenced by the appearance of eight signals in the ^{13}C NMR spectrum at 144.0 ppm, 143.55 ppm, 140.6 ppm, 137.5 ppm, 130.5 ppm, 129.3 ppm, 129.0 ppm and 127.5 ppm which corresponded to the four olefinic carbons C(3), C(4), C(5) and C(6) in the two isomeric forms. Further evidence is the appearance of a signal in the ^{1}H NMR spectrum at 6.06 ppm which corresponded to the olefinic signal C(3)H for the major diasteroisomer (**559**). Also, the appearance of a signal at 6.14 ppm which corresponded to the olefinic signal C(5)H for the minor diasteroisomer (**560**) and with a coupling constant of $J_{5\text{-}6}$ of 10.5 Hz that would indicate a *Z* configuration.

Failure to synthesize a dialkyl pyridine **558** *via* this method, the low efficiency for the synthesis of the 2,3,6-trisubstituted pyridine **507** and the harsh reaction conditions reduces significantly the scope of this method.

Regardless of these limitations, the synthesis of pyridines containing an electron-rich group at the 2-position could benefit significantly from this method, given the simplicity of the two steps involved and the high levels of regiocontrol that were obtained. The use of a Heck

reaction makes the synthesis of 2,4,6-trisubstituted pyridines a simple task, that otherwise would require difficult and tedious transformations to achieve these targets by other means (Figure 4.18).

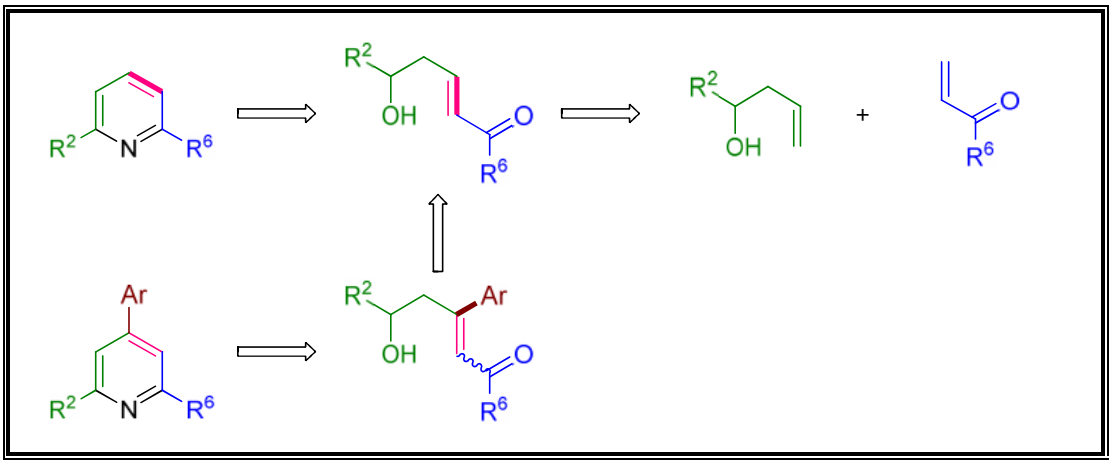
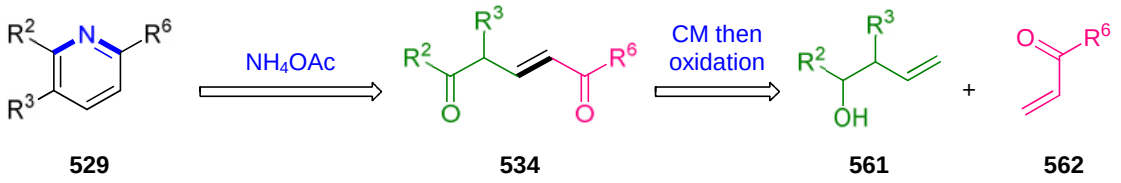


Figure 4.18 *- CM-6π-electrocyclisationapproach to polysubstituted pyridines.*

4.3.3 Synthesis of pyridines *via* CM-oxidation protocol

The partial success of the method described earlier demonstrated that the CM of an homoallylic alcohol and an α,β-unsaturated ketone is a much more efficient process (4.3.2). Furthermore, the condensation with ammonium acetate for the formation of the desired pyridine target from an unsaturated 1,5-diketone demonstrated that it was a reliable process (4.3.1).

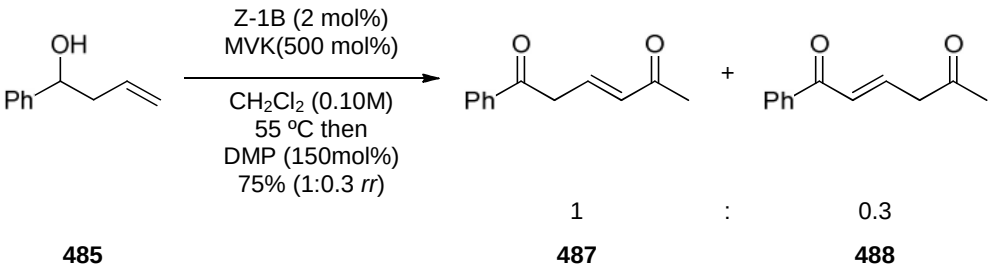
Using these two findings, a method in which the CM product 5-hydroxy ketone could be oxidized to the desired unsaturated 1,5-diketone, after isolation or *in situ*, and then subjected to the condensation conditions to afford the desired pyridine would be desirable (Scheme 4.37).



529 **534** **561** **562**

Scheme 4.37*- Retrosynthetic analysis to pyridines via CM-oxidation approach.*

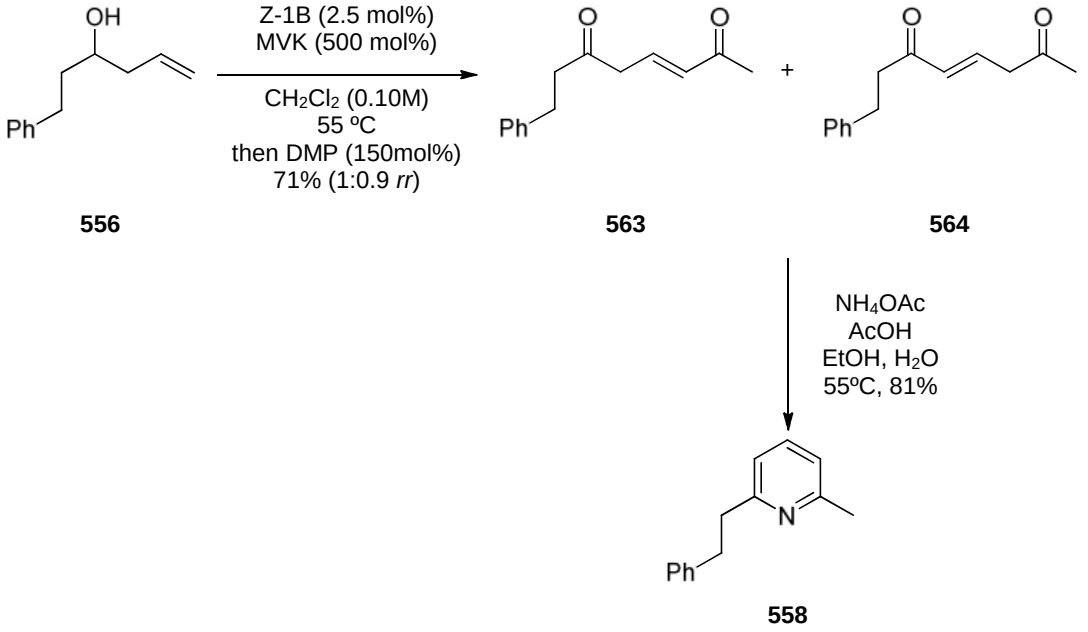
Homoallylic alcohol **485** was subjected to the CM conditions and the consumption of the starting material was monitored by TLC analysis. Once there was no more starting material present, the reaction was cooled down and DMP was added to the reaction mixture and the desired unsaturated 1,5-diketone was obtained in one step (Scheme 4.38). This sequence provided the desired intermediate in a much higher yield, than when using the β,γ-unsaturated ketone as the starting material (Scheme 4.38).[178]



Scheme 4.38 *- Synthesis of 1,5-diketones **487** and **488** from homoallylic alcohol **485**.*

The formation of the desired pyridine from from the mixture of unsaturated 1,5-diketones **487** and **488** was previously demonstrated (Scheme 4.7).[178]

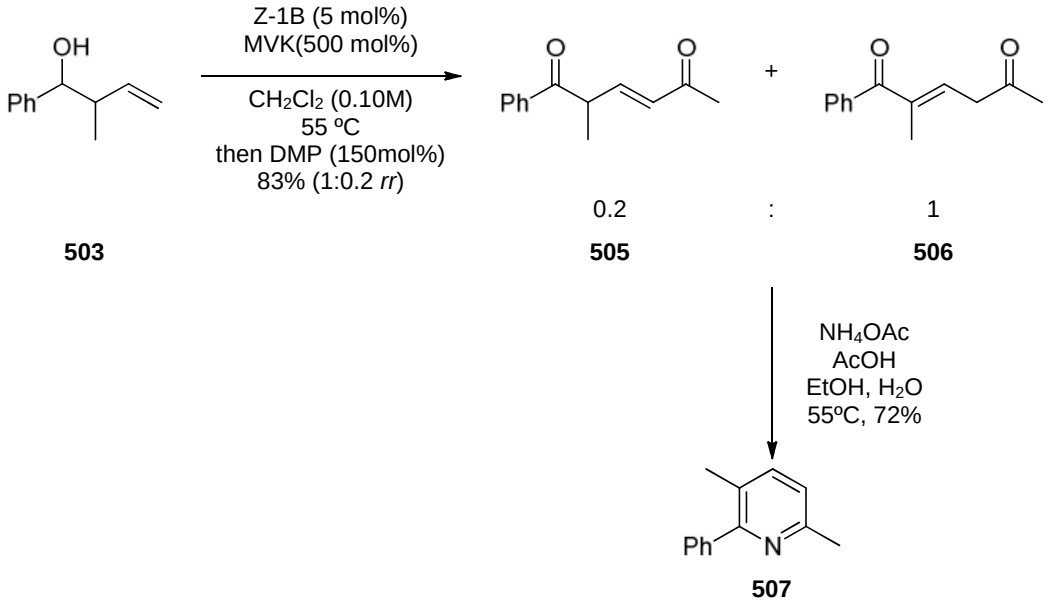
This approach was then applied to the synthesis of a 2,6-dialkyl pyridine, which was not possible using the 6π-electrocyclisation approach. Formation of 1,5-diketones **563** and **564** was observed in high yields by this method. Gratifyingly, the desired pyridine **558** was obtained in very high yields (Scheme 4.39).[178]



Scheme 4.39 *- Synthesis of pyridine **558**.*

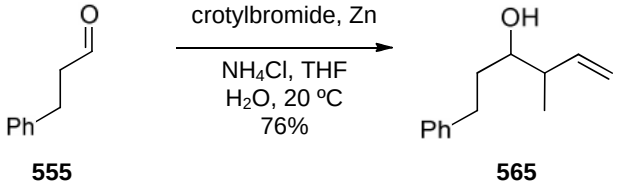
The formation of pyridine **558** was demonstrated by comparison of the ^{1}H and ^{13}C NMR spectra with the previously reported spectroscopic data for this compound.[179]

The method was then applied to the more hindered α-substituted homoallylic alcohol **556** and the desired α,β-unsaturated-1,5-diketone was obtained as the inseparable mixture of ketones diketones **505** and **506** in high yields (Scheme 4.40).[178]



Scheme 4.40 *- Synthesis of pyridine **507**.*

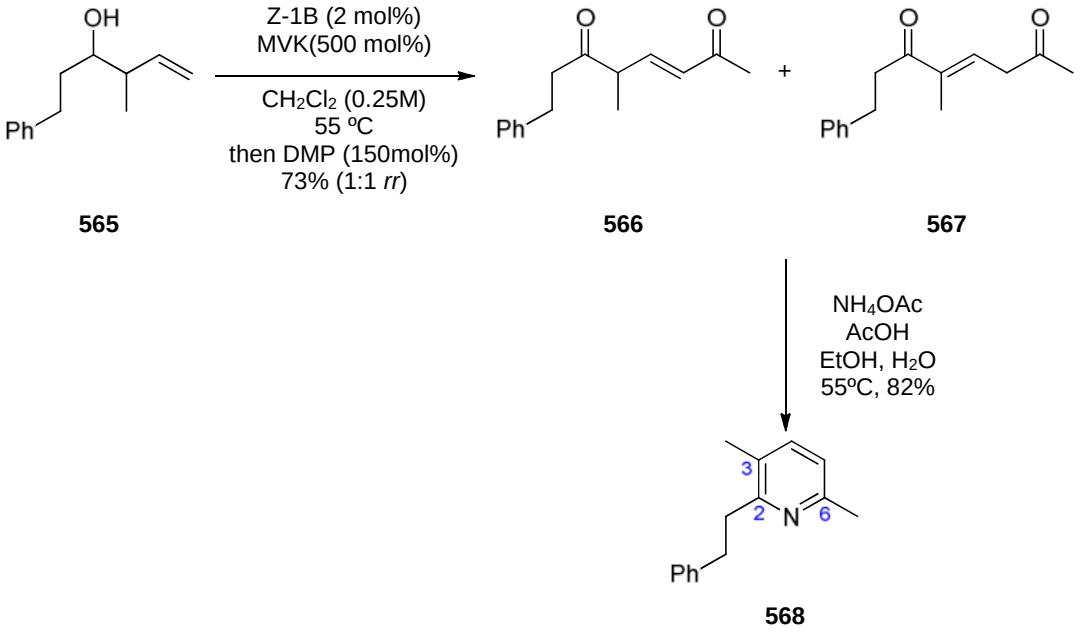
The homoallylic alcohol **565** was prepared in order to be used as the starting point of a pyridine core with three alkyl groups at the 2-, 3- and 6-position(Scheme 4.41).[178]



555 **565**

Scheme 4.41 *- Synthesis of homoallylic alcohol **565**.*

The method was then applied to homoallylic alcohol **565** and the desired pyridine **568** was obtained in high overall yields in two more simple steps (Scheme 4.42). The CM step was carried out at 0.25M, with respect to the homoallylic alcohol **565**, because it gave better yields.[178]

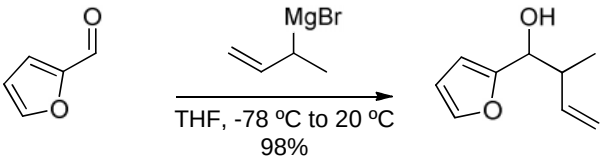


565 **566** **567** **568**

Scheme 4.42 *- Synthesis of pyridine **568**.*

The formation of pyridine **568** was evidenced by the appearance of three signals in the ^{13}C NMR at 158.7 ppm, 155.0 ppm and 127.6 ppm which corresponded to the three quaternary carbons C(6), C(2) and C(3) in the pyridine structure. Furthermore characteristic n.O.e enhancements analysis matched the proposed structure (for n.O.e spectrum see appendix II).

In order to test if a heteroaromatic substituent can be tolerated at the 2-position the homoallylic alcohol **570** was prepared from commercially available aldehyde **569** (Scheme 4.43).[178]

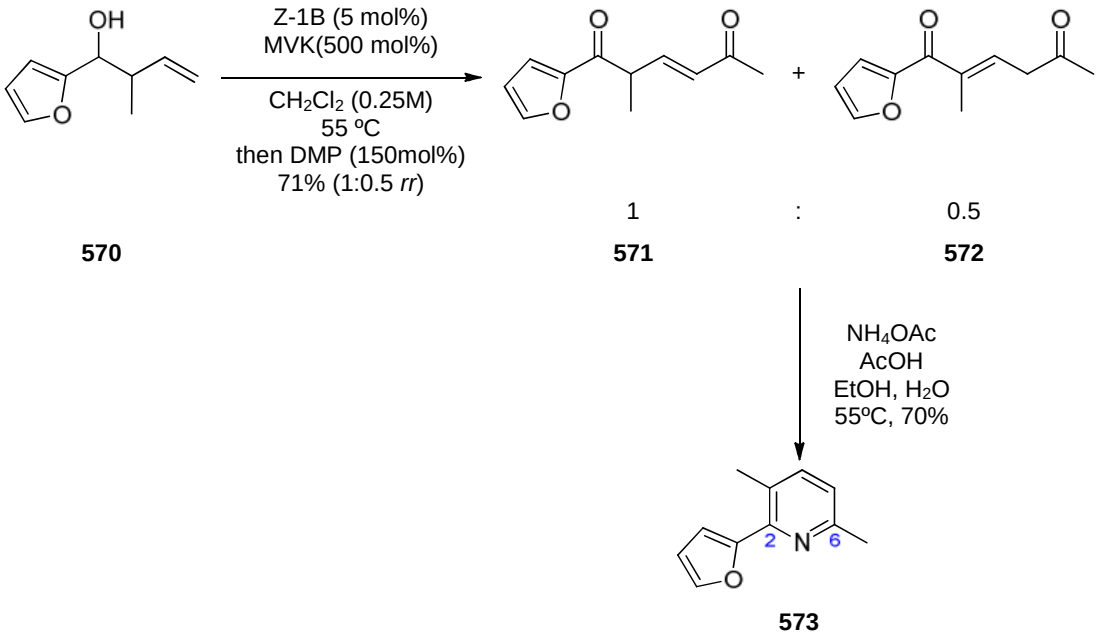


569 **570**

Scheme 4.43- *Synthesis of homoallylic alcohol **570**.*

Formation of homoallylic alcohol **570** was demonstrated by comparison of the ^{1}H and ^{13}C NMR spectra with the previously reported spectroscopic data for this compound.

Homoallylic alcohol **570** was then used and the desired pyridine **573** was obtained without any inconvenience, proving that sensitive substrates can be employed in these two mild steps (Scheme 4.44).[178]

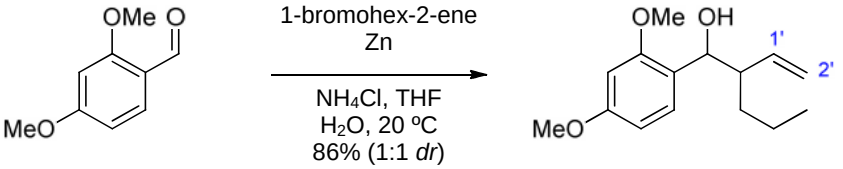


570 **571** **572** **573**

Scheme 4.44 *- Synthesis of pyridine **573**.*

The formation of pyridine **573** was evidenced by the appearance of two signals in the ^{13}C NMR spectrum at 155.5 ppm and 153.5 ppm which corresponded to the two nitrogen attached quaternary carbons C(2) and C(6).

To test whether more bulky groups could be incorporated at the 3-position the homoallylic alcohol **575** was prepared (Scheme 4.45). This alcohol would also incorporate an electron rich aromatic group at the 2-position of the desired pyridine core.

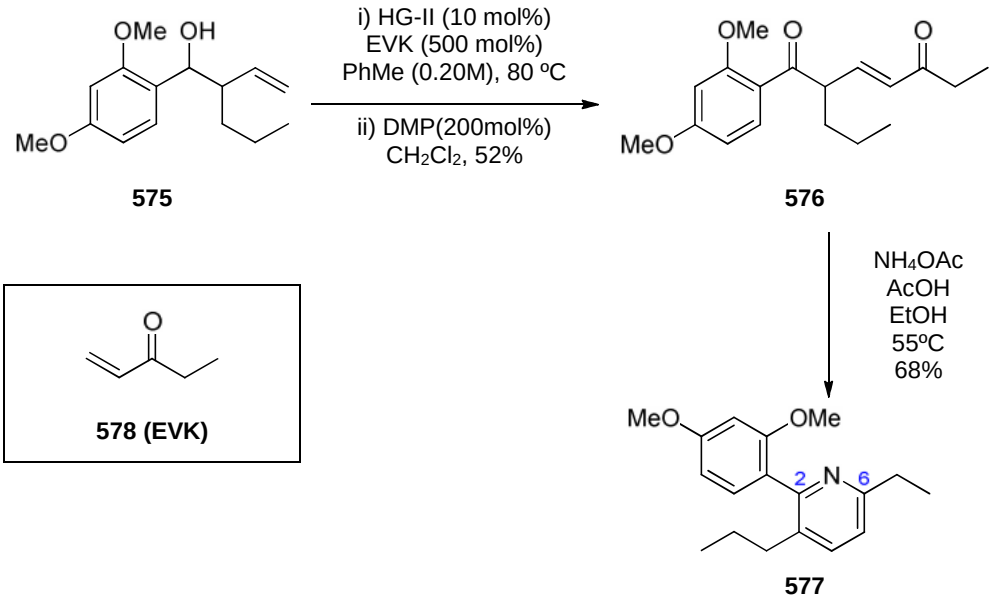


574 **575**

Scheme 4.45*- Synthesis of homoallylic alcohol **575**.*

The formation of homoallylic alcohol **575** was demonstrated by the appearance of six signals in the ^{1}H NMR spectrum at 5.71 ppm, 5.52 ppm, 5.18 ppm, 5.10 ppm, 4.95 ppm, and 4.90 which corresponded to the three olefinic signals C(1')H and C(2')H_2 in both diasteromeric forms.

Homoallylic alcohol **575** was then subjected to the developed CM method using ethyl vinyl ketone **578** (EVK) in order to obtain a different substituent at the 6-position (Scheme 4.46). Gratifyingly after some optimisation, the desired α,β-unsaturated-1,5-diketone **576** was obtained in good yield, and this diketone was then subjected to the condensation conditions and the 2,3,6-trisubstituted pyridine **577** was obtained in high yields.[178]

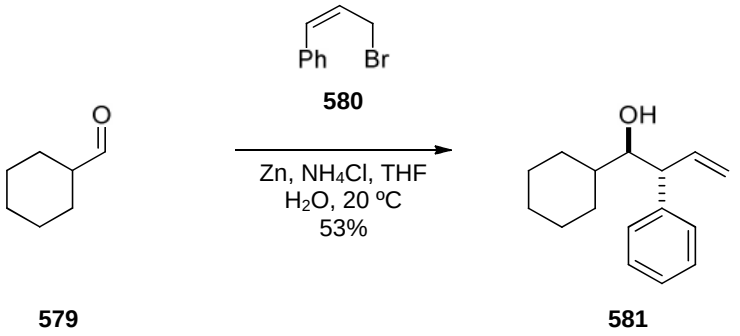


Scheme 4.46- *Synthesis of pyridine **577**.*

The formation of pyridine **577** was evidenced by the appearance of two signals in the ^{13}C NMR spectrum at 155.7 ppm and 155.6 ppm which corresponded to the two nitrogen attached quaternary carbons C(2) and C(6). Furthermore characteristic n.O.e enhancements analysis matched the proposed structure (for n.O.e spectrum see appendix II).

This challenging CM was undertaken using a higher temperature and using catalyst HG-II in toluene. Although a loss of efficiency was observed, a highly substituted target can be prepared in very simple steps and with high levels of regiocontrol.

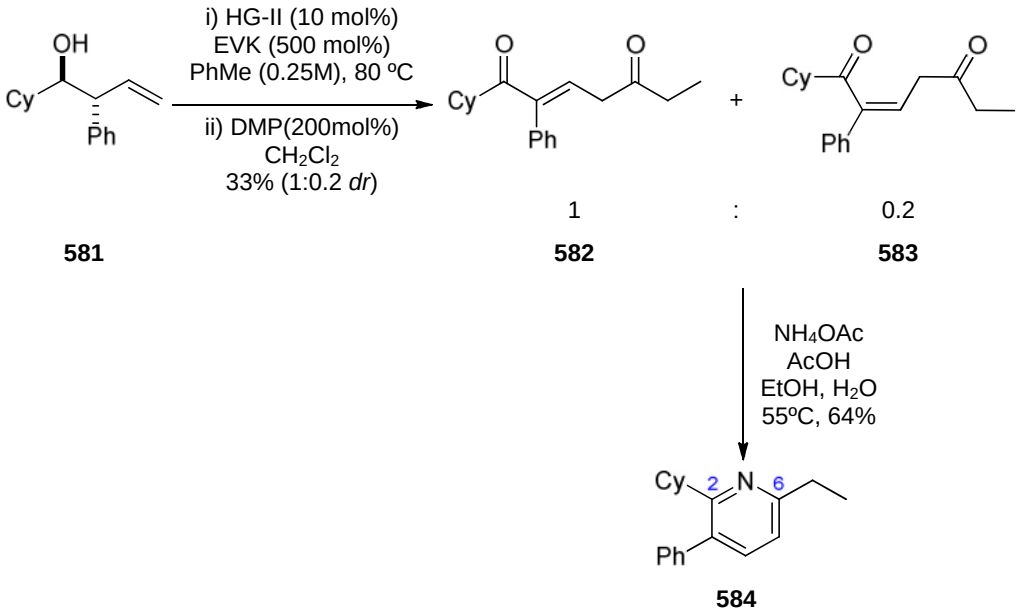
The incorporation of an aromatic group at the 3-position was also sought because (given the importance of this functionality) it will increase the scope of this method. Homoallylic alcohol **581** was prepared in good yields using aldehyde **579** and bromide **580** (Scheme 4.47). The alcohol **581** was obtained as a single diasteroisomer.



Scheme 4.47- *Synthesis of homoallylic alcohol **581**.*

Formation of homoallylic alcohol **581** was demonstrated by comparison of the ^{1}H and ^{13}C NMR spectra with the previously reported spectroscopic data for the *anti* isomer of this compound.[180]

Homoallylic alcohol **581** was then converted to desired 2,3,6-trisubstituted pyridine **584** *via* α,β-unsaturated-1,5-diketones **582** and **583**, obtained as an inseparable mixture of *E* and *Z* diasteroisomers (Scheme 4.48).



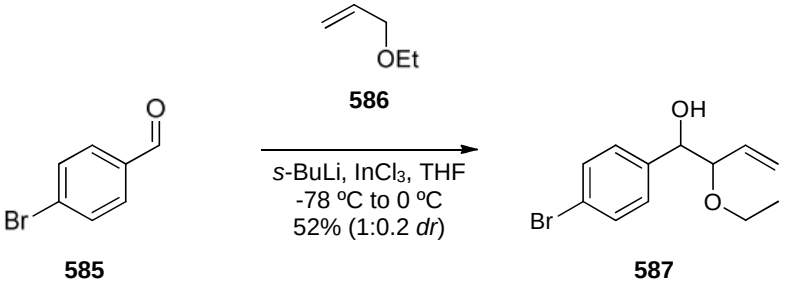
Scheme 4.48 *- Synthesis of pyridine **584**.*

The formation of pyridine **584** was demonstrated by the appearance of two signals in the ^{13}C NMR spectrum at 162.4 ppm and 161.7 ppm which corresponded to the nitrogen attached quaternary carbon signals C(2) and C(6) in the pyridine core. Furthermore, the appearance of

a signal in the ^{1}H NMR spectrum at 7.00 ppm corresponded to the pyridine signal C(5)H, with a coupling constant $J_{5\text{-}4}$ of 8.0 Hz.

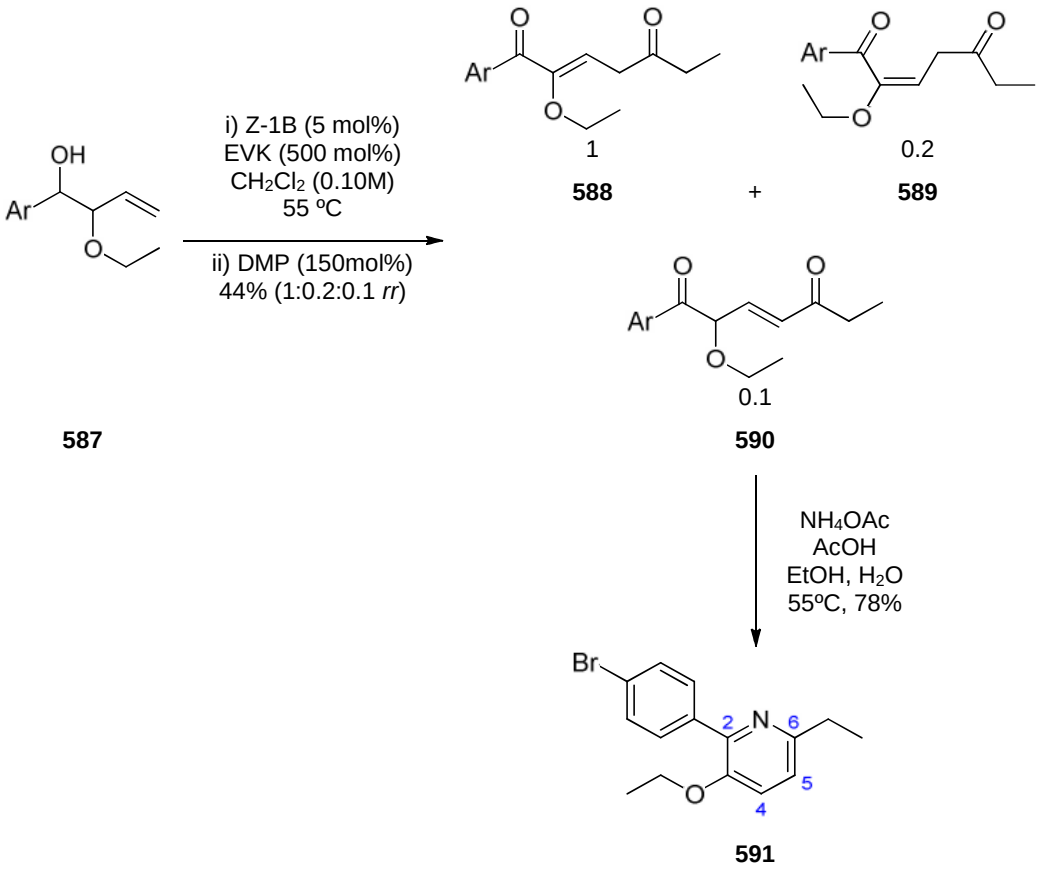
The synthesis of pyridine **584** was achieved in low overall yield, which is expected due to a decrease in efficiency in the CM event given that a more hindered alkene was used. Nevertheless the target obtained includes different alkyl groups at the 2- and 6- positions and an aromatic group at the 3-position and this substitution pattern represents a large number of possible targets that can be easily obtained in two steps. This method allows this substitution without any functionalisation of the pyridine core, or transition metal catalyzed reaction that would require selective functionalisation.

To test if the incorporation of an heteroatom containing substituent, such as an ethoxy group, the homoallylic alcohol **587** was prepared using electron deficient aldehyde **585** and allyl ethyl ether **586** (Scheme 4.49).[178]



Scheme 4.49*- Synthesis of homoallylic alcohol **587**.*

Homoallylic alcohol **587** was subjected to the reaction sequence and the desired pyridine **591** was obtained in a good overall yield (Scheme 4.50).[178]

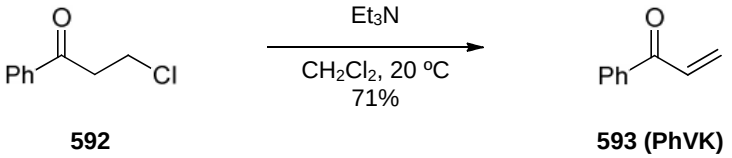


Scheme 4.50 *- Synthesis of pyridine* ***591****.*

The formation of pyridine **591** was demonstrated by appearance of two signals in the ^{13}C NMR spectrum at 154.9 ppm and 150.9 ppm which corresponded to the nitrogen attached quaternary carbons C(2) and C(6) in the pyridine core. Furthermore appearance of two signals in the ^{1}H NMR spectrum at 7.21 ppm and 7.08 ppm which corresponded to the pyridine signals C(4)H and C(5)H with a coupling constant $J_{4\text{-}5}$ of 8.5 Hz.

Gratifyingly the enol ether moiety in the α,β-unsaturated-1,5-diketones **588**, **589** and **590** was not lost under the reaction conditions, presumably because either the condensation step was relatively fast compared with possible hydrolysis or because the final ethyl groups originated from the solvent.

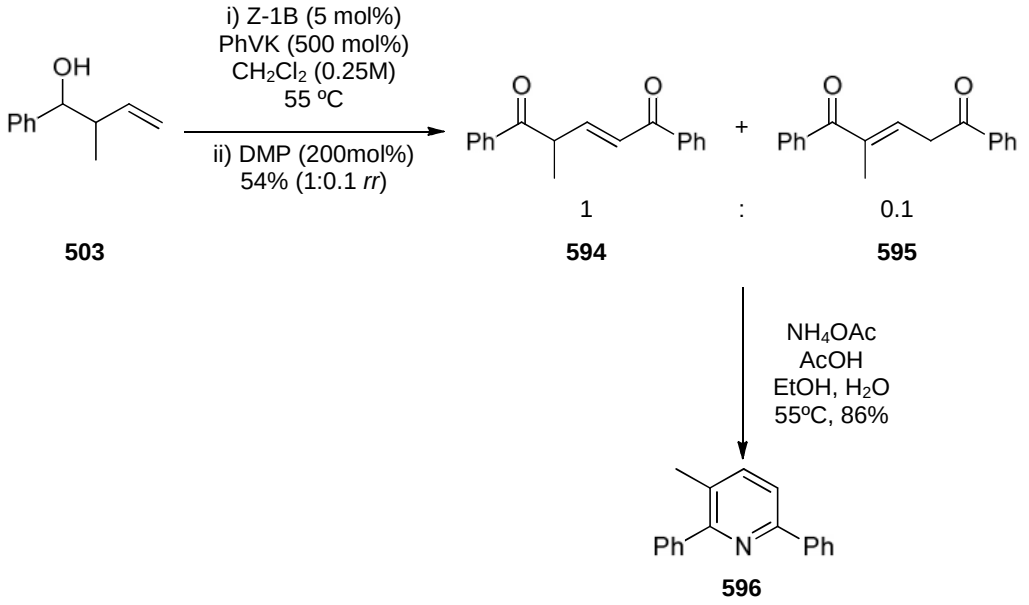
Moreover, to demonstrate that a 2,6-diaryl substituted pyridine could be made *via* this method the α,β-unsaturated ketone **593** (PhVK) was prepared from commercially available chloride **592** (Scheme 4.51).



592 **593 (PhVK)**

Scheme 4.51*- Synthesis of α,β-unsaturated ketone **593**.*

When homoallylic alcohol **503** and PhVK were combined using the CM-oxidation-pyridine formation sequence the desired pyridine **596** was obtained in good overall yield (Scheme 4.52).[178]



503 **594** **595** **596**

Scheme 4.52 *- Synthesis of pyridine **596**.*

The synthesis of 2,6-disubstituted and 2,3,6-trisubsituted pyridines was also achieved using a CM approach. The numbers of targets achieved are a small representation of what this method can produce in very short amount of steps. The level of regiocontrol, the simplicity of the steps involved and the use of simple starting materials are some of the main features of this method. This method represents an important sequence that can be used by organic chemists in order to rapidly prepare a library of compounds of this class (Figure 4.19).

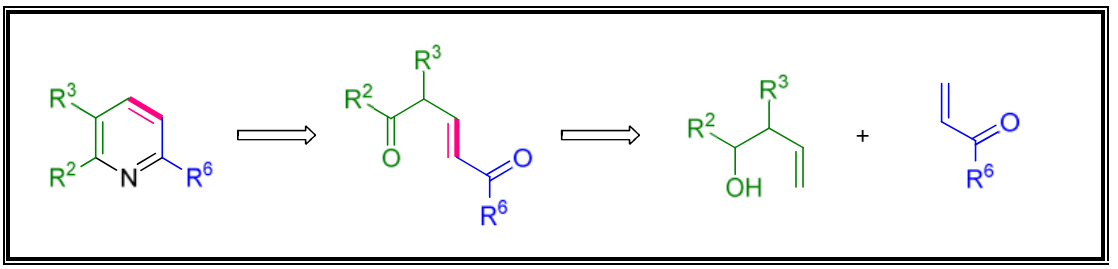
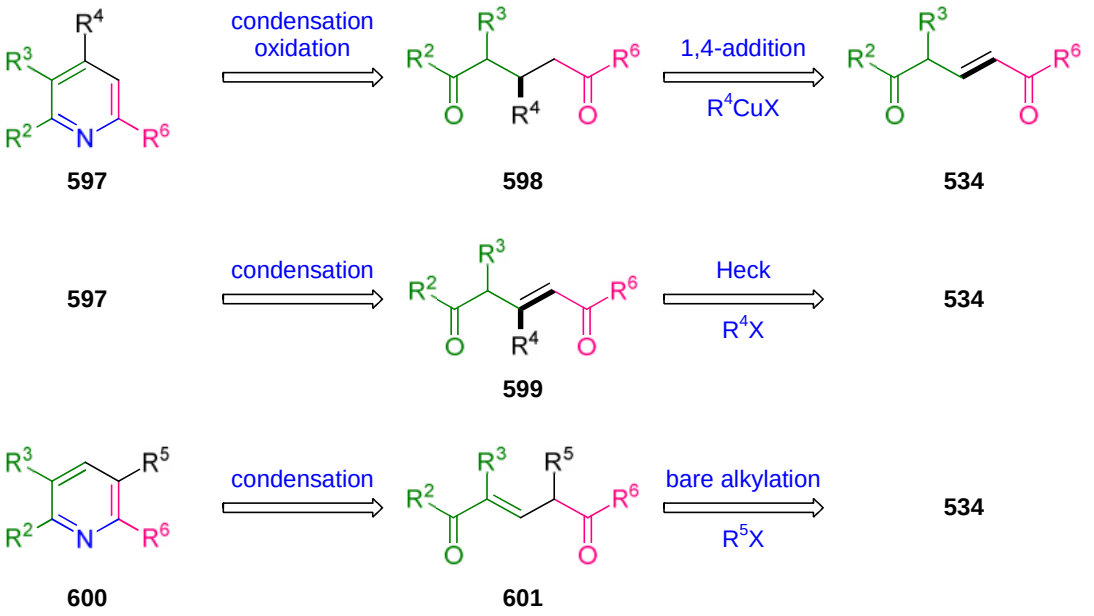


Figure 4.19 *- CM-oxidation approach to polysubstituted pyridines.*

4.3.4 Functionalisation of CM intermediates

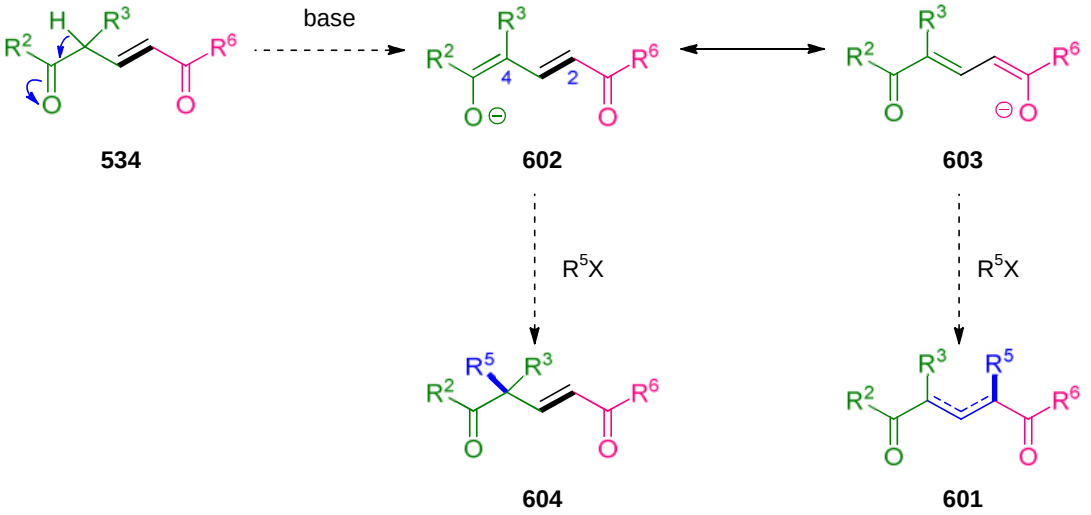
Given the success of the method described in *4.3.3* for the synthesis of α,β-unsaturated-1,5-diketone with good levels of efficiency, a method to further functionalize the intermediates was sought.

The α,β-unsaturated-1,5-diketone would have internal acidic protons at the α-positions, which could act as nucleophile, and also possesses an electrophilic centre at the β-position which could be functionalized by a 1,4-addition. Another possible avenue of functionalisation is to carry out a Heck reaction, which would functionalize this intermediate at the β-position and would not change the oxidation state (Scheme 4.53).



Scheme 4.53 *- Retrosynthetic analysis of tetrasubstituted pyridines **597** and **600**.*

Similar to the alkylation of 1,3-diketones, the acidity of the internal α-protons of intermediate **534** would direct the regiochemical outcome of such an event in the internal α-positions. Furthermore, after the deprotonation event, the formed enolate can be represented by both resonance structures **602** and **603** and therefore the regiochemical outcome would not be affected by the isomeric ratio of the starting material (Scheme 4.54).

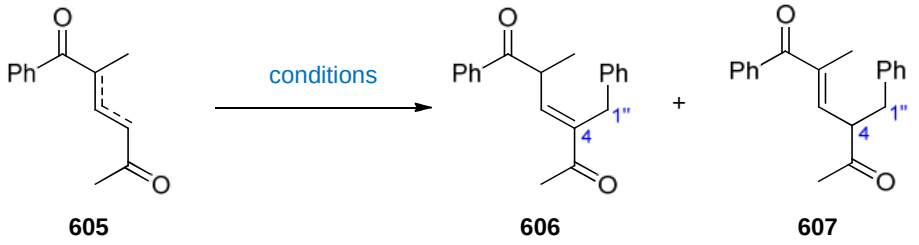


Scheme 4.54 *- Alkylation of intermediate **534**.*

Alkylation at C-2 will be more likely to occur because this position is not hindered by a substituent, while the C-4 position is sterically more crowded (Scheme 4.54).

Given that an internal substituent at the 4-position is easily achieved by the CM reaction, the difficult substitution can be easily overcome and alkylation of intermediate **534** is expected to deliver the intermediate **601** (Scheme 4.54).

Mixture of 1,5-diketones **505** and **506** (represented as **605**) were used in an alkylation reaction under an array of conditions (Scheme 4.55). When the reaction was performed using DBU the alkylation occurred at C(4) with excellent yields and high levels of regioselectivity, giving the diketones **606** and **607** as an inseparable mixture (Table 4.6, Entry 2).[178]



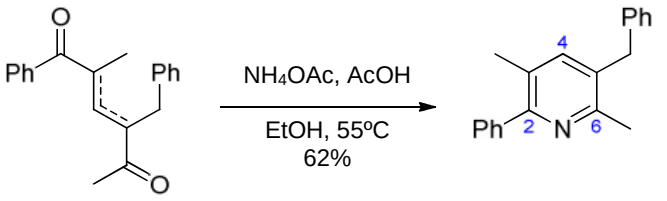
Scheme 4.55 *- Synthesis of unsaturated-1,5-diketones **606** and **607**.*

Entry	Conditions	Yield
1	BnBr, Et_3N, THF, 20 ºC	SM
2	BnBr, DBU, THF, 20 ºC	85% (1:1 *rr*)
3	BnBr, *t*-BuOK, THF, 20 ºC	complex mixture of regioisomers

Table 4.6 *- Conditions for the alkylation of unsaturated-1,5-diketones **605**.*

The formation of 1,5-diketones **606** and **607** were evidenced by the appearance of four signals in the ^1H NMR spectrum at 3.89 ppm, 3.75 ppm, 3.21 ppm and 2.79 ppm which corresponded to the benzylic proton C(1")H_2 in the two diasteromeric forms.

Unsaturated-1,5-diketones **606** and **607** (represented as **608**) were converted to the desired 2,3,5,6-tetrasubstituted pyridine **609** in reasonable yields (Scheme 4.56).[178]



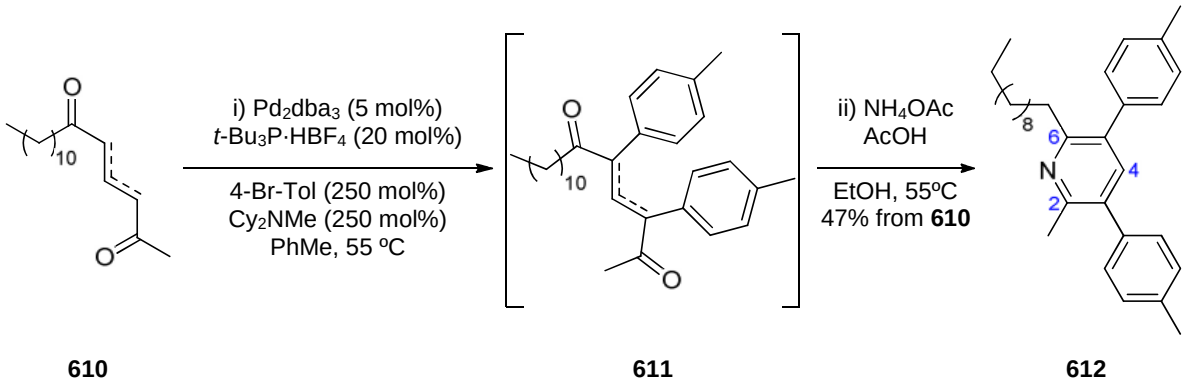
608 **609**

Scheme 4.56 *- Synthesis of 2,3,5,6-tetrasubstituted pyridine* ***609****.*

The formation of pyridine **609** was evidenced by the two signals in the ^{13}C NMR spectrum at 155.9 ppm and 154.1 ppm which corresponded the two nitrogen attached quaternary carbons in the pyridine core C(6) and C(2) respectively. Furthermore, the appearance of a signal at 139.8 ppm corresponded to the pyridine carbon C(4). Characteristic n.O.e enhancements analysis matched the proposed structure (for n.O.e spectrum see appendix II).

The synthesis of tetrasubstituted pyridine **609** proves that this method represents a convenient approach to a regioselective synthesis of pyridine cores with different alkyl groups at the 2-, 3- and 6- position *via* a CM event and another alkyl group at the 5-position by an alkylation step.

The Heck reaction of 1,5-diketones **493** and **494** (represented as **610**) and 4-Br-Tol was also attempted, and the product obtained was subjected to the condensation conditions. The desired Heck product was not isolated; instead the doubly α-arylated product **611** was then converted to the tetrasubstituted pyridine **612** (Scheme 4.57).

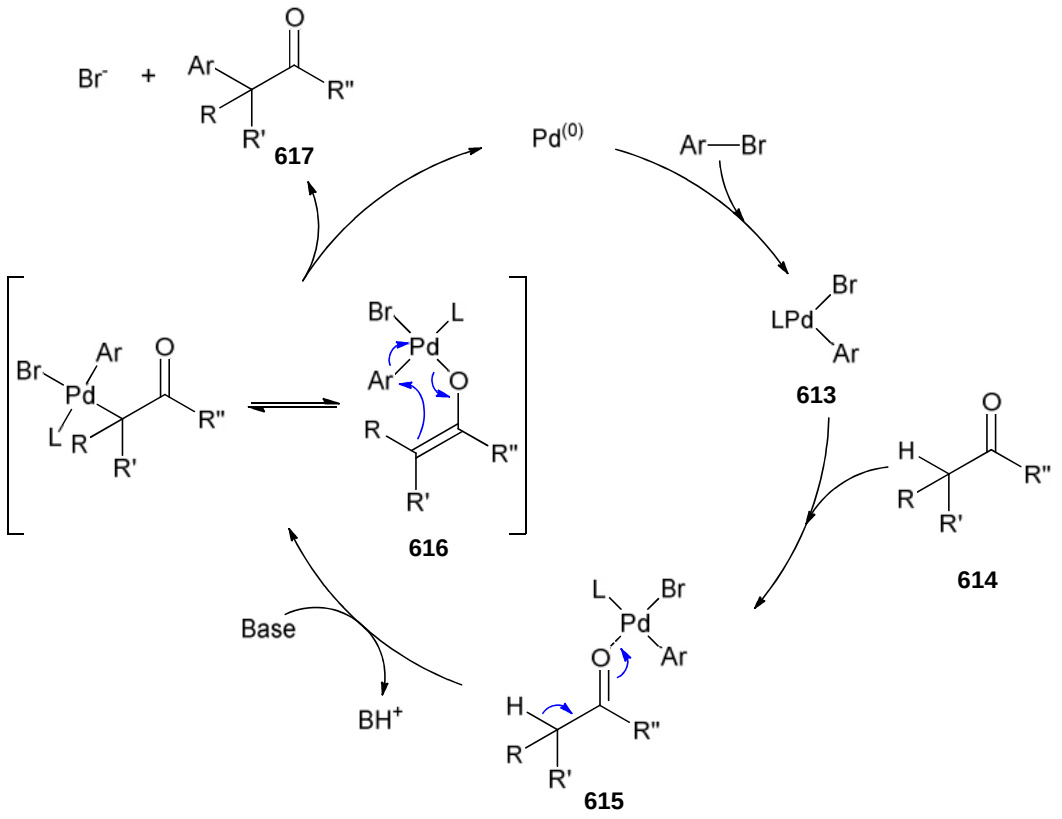


610 **611** **612**

Scheme 4.57 *- Synthesis of pyridine* ***612****.*

The formation of pyridine **612** was evidenced by the appearance of signals two in the ^{13}C NMR spectrum at 158.4 ppm and 154.6 ppm which corresponded to the nitrogen attached quaternary carbons C(6) and C(2) respectively in the pyridine core. Furthermore the appearance of a signal at 139.2 ppm corresponded to the pyridine carbon C(4), and of a signal in the ^{1}H NMR spectrum at 7.40 ppm corresponded to C(4)H with a HSQC correlation with the signal at 139.2 ppm. Characteristic n.O.e enhancements analysis matched the proposed structure (for n.O.e spectrum see appendix II).

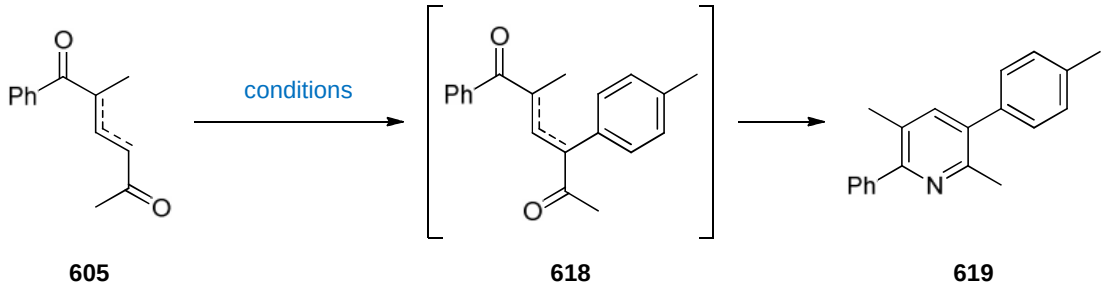
The α-arylation of ketones and aldehydes is an important reaction in organic chemistry and many investigators have endeavoured to produce a reactive system of a transition metal, and an appropriate ligand, that would produce the desired product in high levels of efficiency and stereocontrol.[181, 182] The mechanism of this reaction is speculated to involve the formation of an aryl palladium species **613** which, after coordination to the carbonyl substrate **614**, can form the intermediate species **615**. This species can then be deprotonated by weak bases such as K_3PO_4, and the intermediate enolate **616** is proposed to undergo a C2-arylation to form the desired product **617** and regenerate the catalyst (Scheme 4.58).[183]



Scheme 4.58 *- Mechanism for the palladium mediated α-arylation of ketones.*

The formation of tetrasubstituted pyridine **612** was an important finding, because after the first α-arylation event, the intermediate can undergo a second α-arylation reaction with good overall efficiency. This indicated that a α-arylation reaction would work in a substrate that has a substituent at one of the α-positions.

The intermediates **605** were subjected to a series of conditions to optimize the α-arylation step. The intermediate functionalized products **618** were not isolated, but instead converted to the desired pyridine **619** to simplify the overall process (Scheme 4.59). Other catalyst and ligands system were investigated, but the original conditions suited this process best (Entry 1, Table 4.7).[178]



605 **618** **619**

Scheme 4.59 *- Synthesis of tetrasubstituted pyridine* ***619****.*

Entry	Conditions	Yield
1	(a) Pd_2dba_3 (5 mol%), *t*-$Bu_3P{\cdot}HBF_4$ (20 mol%), 4-Br-Tol (300 mol%), Cy_2NMe (300 mol%), PhMe (0.10 M), 55 ºC 16 hours. (b) NH_4OAc, AcOH, EtOH, 55 ºC.	48%
2	(a) $Pd(OAc)_2$ (10 mol%), *t*-Butyl XPhos (22 mol%), 4-Br-Tol(300 mol%), K_3PO_4 (300 mol%), PhMe (0.10 M), 55 ºC 16 hours. (b) NH_4OAc, AcOH, EtOH, 55 ºC.	32%
3	(a) $Pd(OAc)_2$ (10 mol%), *rac*-BINAP (12 mol%), 4-Br-Tol(300 mol%), K_3PO_4 (300 mol%), PhMe (0.10 M), 55 ºC 16 hours.	SM
4	(a) $Pd(OAc)_2$ (10 mol%), Xantphos (12 mol%), 4-Br-Tol(300 mol%), K_3PO_4 (300 mol%), PhMe (0.10 M), 55 ºC 16 hours. (b) NH_4OAc, AcOH, EtOH, 55 ºC.	25%
5	(a) Pd_2dba_3 (5 mol%), *t*-$Bu_3P{\cdot}HBF_4$ (20 mol%), 4-Br-Tol(300 mol%), K_3PO_4 (300 mol%), PhMe (0.10 M), 55 ºC 16 hours. (b) NH_4OAc, AcOH, EtOH, 55 ºC.	15%
6	Pd_2dba_3 (5 mol%), Xantphos (12 mol%), 4-Br-Tol (300 mol%), *t*-BuOK (130 mol%), PhMe (0.10 M), 55 ºC 16 hours.	dec.

Table 4.7 *- Conditions for the α-arylation of unsaturated-1,5-diketone* ***505****.*

The formation of a single regioisomer was a gratifying finding, given the importance of regioselective processes in this method. The origins of the high levels of regioselectivity are mainly due to steric congestion at the substituted α-position which blocks any α-arylation event that would form a quaternary carbon. Furthermore, competitive Heck reaction is not observed because although the β-position is not substituted it is still in a crowded environment due to the surrounding substituents in both α-positions.

The structure of pyridine **619** was confirmed by single crystal X-ray data (Figure 4.20, Appendix III).

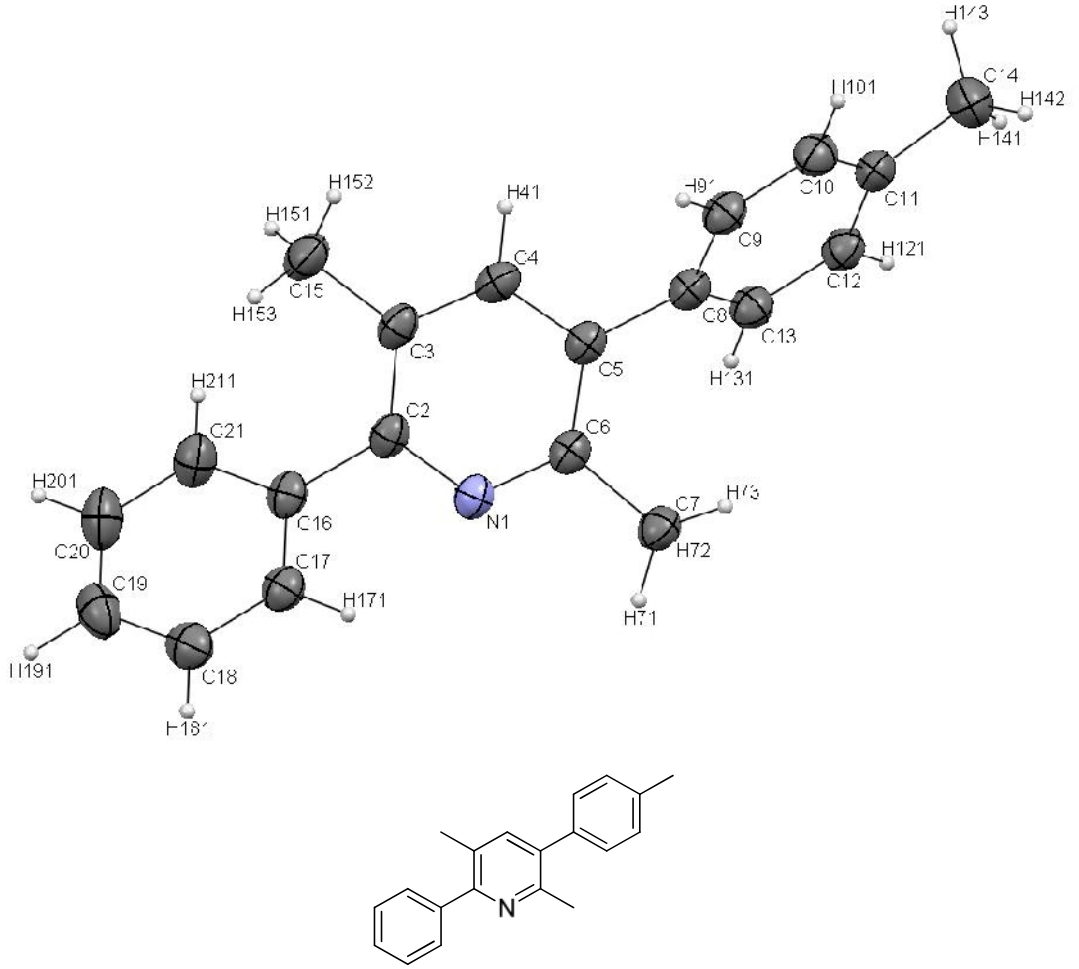
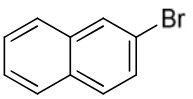


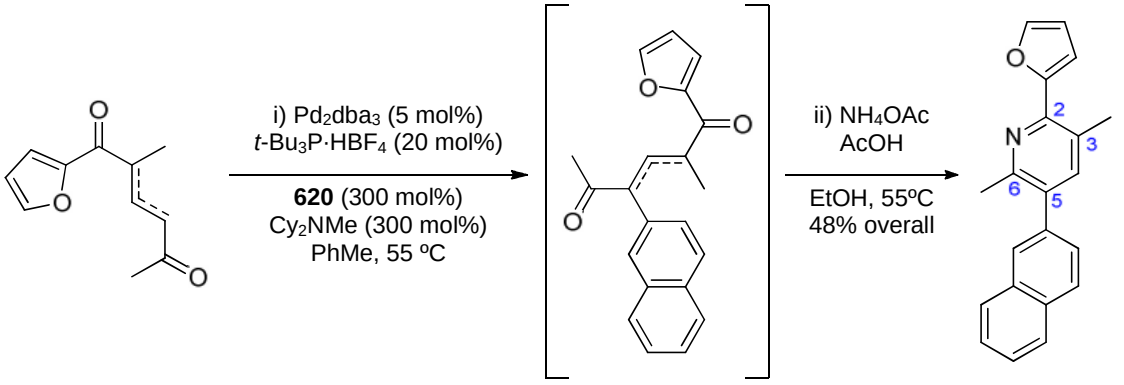
***Figure 4.20**- Single crystal X-ray analysis of pyridine **619**.*

In order to test the scope of this functionalisation, using 2-bromonaphthalene **620** (Figure 4.21) in the α-arylation reaction, the unsaturated-1,5-diketones **571** and **572** (represented as **621**) were converted to the desired tetrasubstituted pyridine **623** which was prepared in good overall yield (Scheme 4.60).[178]



620

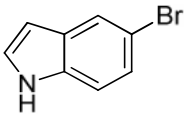
***Figure 4.21**- 2-Bromonaphthalene **620**.*



Scheme 4.60 *- Synthesis of tetrasubstituted pyridine* ***623****.*

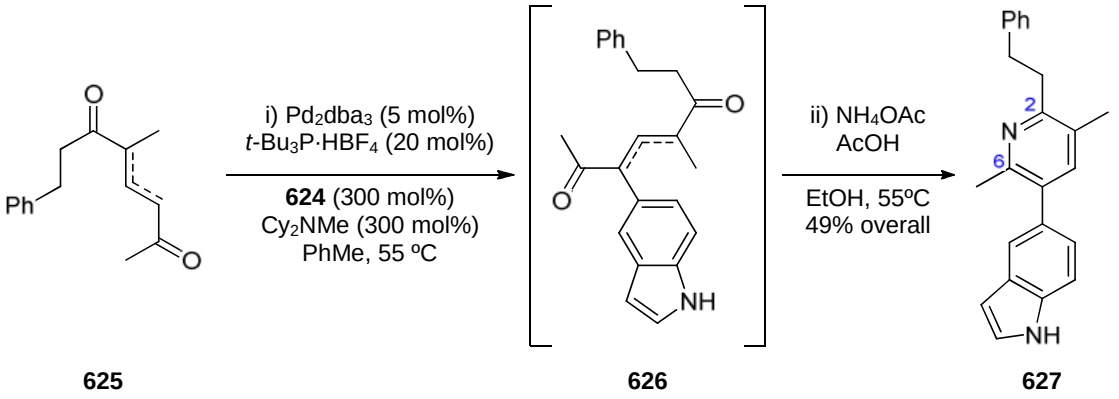
The formation of pyridine **623** was evidenced by the appearance of two signals in the ^{13}C NMR spectrum at 153.4 ppm and 153.1 ppm which corresponded to the two nitrogen attached quaternary carbons C(6) and C(2) in the pyridine core. Furthermore, the appearance of five signals at 137.2 ppm, 135.2 ppm, 133.2 ppm, 132.4 ppm and 111.4 ppm corresponded to two quaternary carbon C(3) and C(5) in the pyridine core and three quaternary carbon in the naphthyl group.

In order to incorporate an heteroaryl group as one of the substituents, the unsaturated-1,5-diketones **566** and **567** (represented as **625**) were subjected to this arylation-condensation sequence, using 5-bromoindole **624** (Figure 4.22), and the desired tetrasubstituted pyridine **627** was obtained in good overall yield (Scheme 4.61).[178]



624

Figure 4.22 *- 5-Bromoindole* ***624****.*

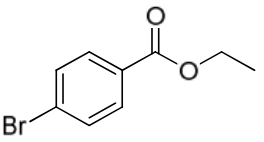


Scheme 4.61- *Synthesis of tetrasubstituted pyridine **627**.*

The formation of pyridine **627** was evidenced by the appearance of two signals in the ^{13}C NMR spectrum at 157.0 ppm and 152.7 ppm which corresponded to the two nitrogen attached quaternary carbons C(6) and C(2) in the pyridine core. Furthermore, characteristic n.O.e enhancements analysis matched the proposed structure (for n.O.e spectrum see appendix II).

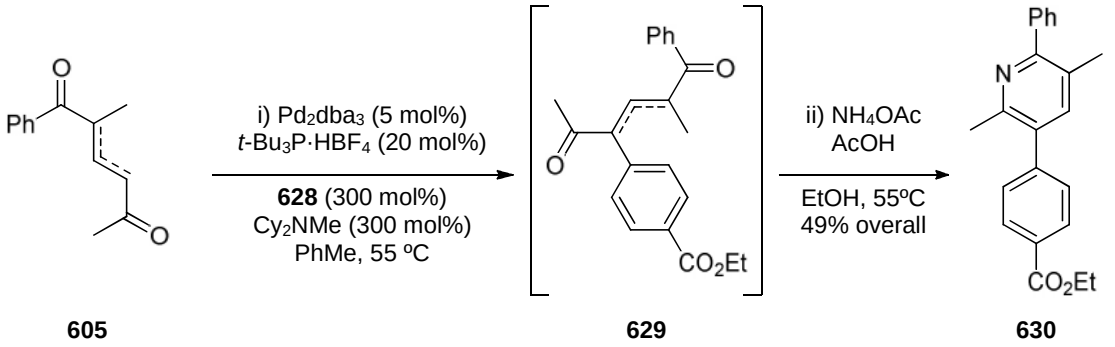
It is important to point out the high levels of regioselectivity in this method, since unsaturated-1,5-diketones **625** could form four different regioisomers and only once is observed. The use of weak base Cy_2NMe seems to be an important element in the high levels of regiocontrol, because it only allows for the formation of the internal enolate which is more easily formed due to the contributing resonance structures across five atoms.

The use of ethyl 4-bromobenzoate **628** (Figure 4.23), as an electron deficient aryl halide was tested, and the unsaturated-1,5-diketones **605** were successfully converted to the desired pyridine **630** in good overall yield (Scheme 4.62).[178]



628

Figure 4.23 *- Ethyl 4-bromobenzoate **628**.*



Scheme 4.62 *- Synthesis of tetrasubstituted pyridine* ***630****.*

The formation of pyridine **630** was confirmed by single crystal X-ray data (Figure 4.24, Appendix III).

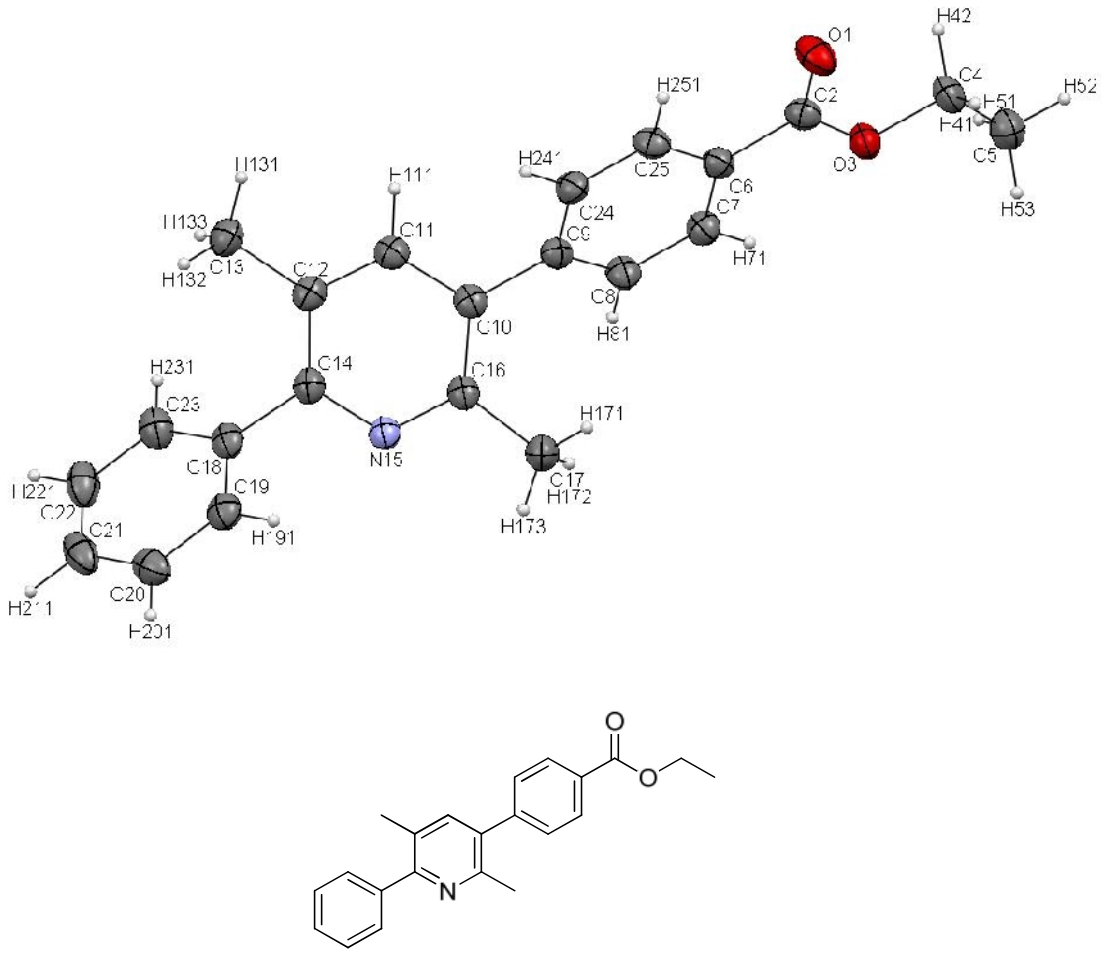


Figure 4.24 *- Single crystal X-ray analysis of pyridine* ***630****.*

The synthesis of 2,3,5,6-tetrasubstituted pyridines was achieved in three steps from a simple homoallylic alcohol, *via* a CM approach and using the nucleophilic character of the unsaturated-1,5-diketone intermediates.

The functionalisation described, either by a simple alkylation or Pd-catalyzed arylation protocol, is a powerful transformation given the high levels of regiocontrol, and introducing a new substituent at the 5-position did not require any previous functionalisation of the pyridine core. The targets obtained process electron rich group, often alkyl groups, and aryl groups in the predetermined position, which would be very difficult to obtain by other means (Figure 4.25).

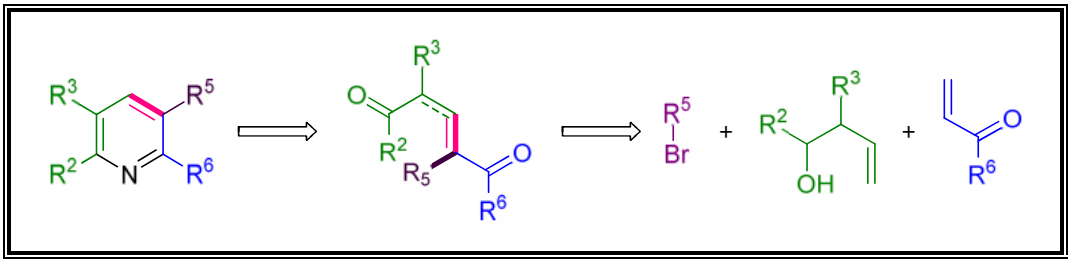


Figure 4.25- *CM-oxidation approach to tetrasubstituted pyridines.*

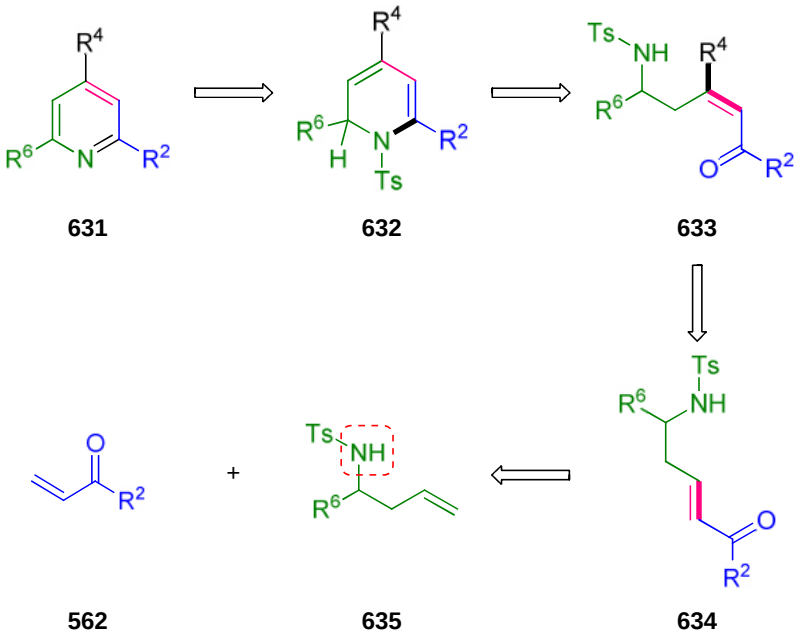
4.3.5 Synthesis of pyridines from allylic sulfonamides

So far, we have established an excellent method for the construction of pyridines using a CM reaction/oxidation protocol. Moreover, the synthesis of tetrasubstituted pyridines was achieved by further functionalisation of the unsaturated 1,5-dicarbonyl compounds. In this method, the use of an exogenous form of ammonia provided the source of nitrogen required to form the desired target.

Another possibility would be the incorporation of an endogenous nitrogen form, that is, using a protected homoallylic amine as the starting material.

The Donohoe group has developed a method for which the desired target **631** is formed from a based induced elimination from dihydropyridine **632**, which does not require any acidifying group (Scheme 4.63). Dihydropyridine **632** is formed by an acid mediated

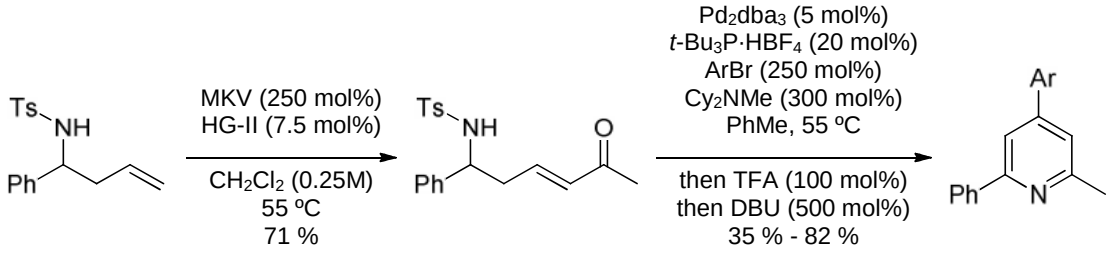
condensation of intermediate **633**, which is obtained from a Heck reaction of 5-amino-enone **634**. Enone **634** is obtained from a CM between homoallylic sulfonamide **635** and α,β-unsaturated ketone **562** (Scheme 4.63).



Scheme 4.63 *- Synthesis of pyridines from homoallylic sulfonamides.*

This method was utilized in the Donohoe group to synthesize an array of 2,4,6-trisubstituted pyridines **638**, giving a rapid approach to this particular substitution pattern (Scheme 4.64).

A one pot protocol for the conversion of 5-amino-enone **637** into pyridine **638** was achieved. A Heck reaction is performed on 5-amino-enone **637** using different arylbromides, then the mixture is subjected to an acid mediated condensation and then an excess of base is added to the same reaction pot, which neutralizes any excess of acid and performs the aromatisation step *via* the elimination of sulfinic acid (Scheme 4.64).



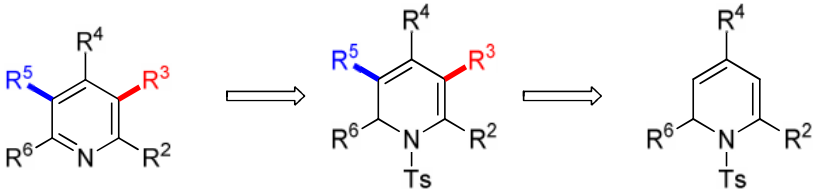
636 **637** **638**

Scheme 4.64 *- Synthesis of 2,4,6-trisubstituted pyridines.*
Work carried by J. F. Bower

An important element of the Heck reaction is that it inverts the olefin geometry allowing for a *Z* configured alkene that participates in the required condensation reaction.[174]

Giving the success of functionalisation of the heterocyclic intermediates prior to the aromatisation protocol in previous methods, we have envisioned a similar process applied to this particular method.

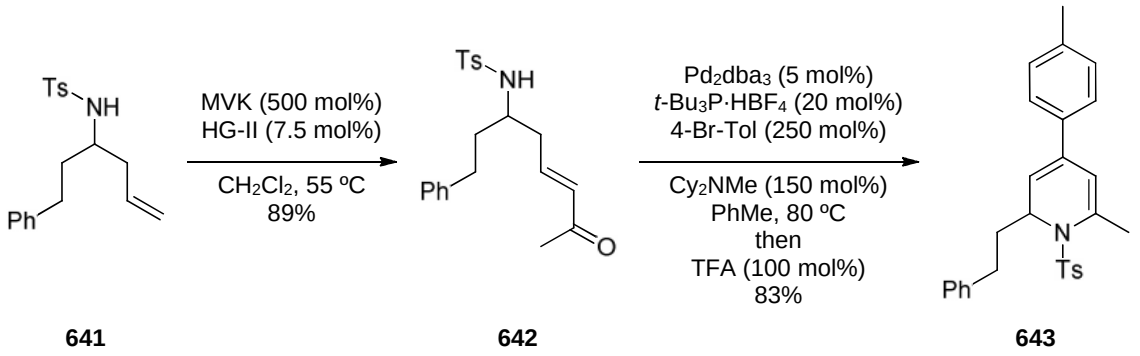
Intermediate **632** could be subjected to a series of reaction conditions, in which an electrophile (X^+ or RCO^+) could be added at either the 3- or 5-position, and then apply the aromatisation protocol to obtain a polysubstituted pyridine **639** (Scheme 4.65).



639 **640** **632**

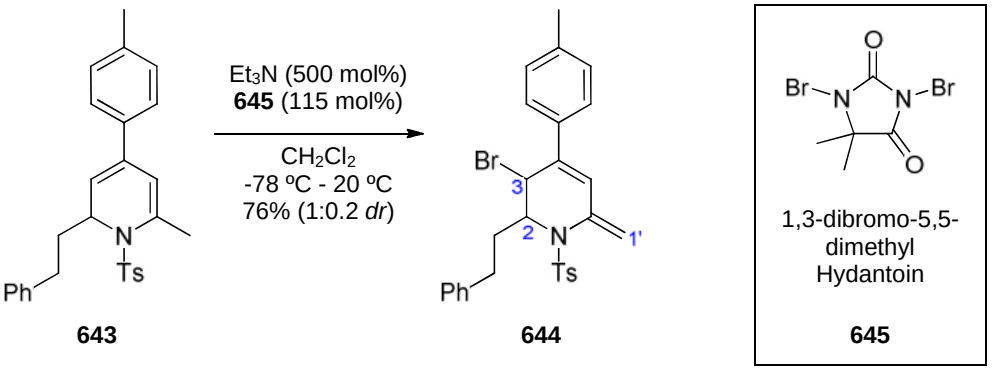
Scheme 4.65 *- Proposed retrosynthesis of polysubstituted pyridine **639**.*

In order to test the idea of functionalizing the diene intermediate, desired 5-hydroxy enone **643** was prepared according to the protocol developed by the Donohoe group (Scheme 4.66). Sulfonamide **641** was converted to the 5-amino enone **642**, which was subjected to a Heck-condensation protocol, using 4-Br-Tol, to give the desired dihydropyridine **643** (Scheme 4.66).



Scheme 4.66- *Synthesis of dihydropyridine **643**.*

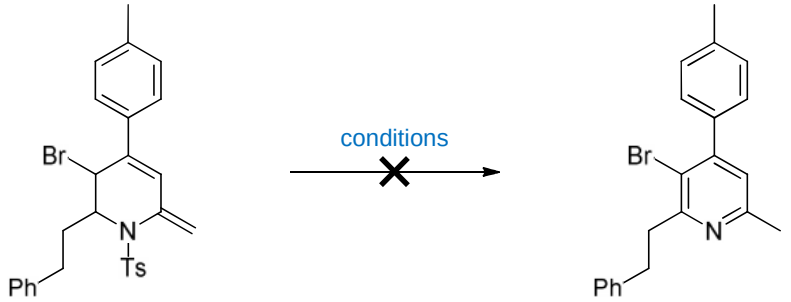
Dihydropyridine **643** was subjected to a bromination protocol using 1,3-dibromo-5,5-dimethyl hydantoin **645** as the brominating agent. Unexpectedly, the exocyclic enamine **644** was obtained in good yields (Scheme 4.67).



Scheme 4.67 *- Bromination of dihydropyridine **643.***

The formation of bromide **644** was evidenced by the appearance of a signal in the ^{1}H NMR spectrum at 6.35 ppm which corresponded to the endocyclic olefinic signal C(5)H. Furthermore, the appearance of signals at 5.26 ppm (C(2)H) and 5.12 ppm (C(3)H) which were correlated to signals in the ^{13}C NMR spectrum at 61.1 (C(2)) ppm and 47.4 (C(2)), and indicates the lack of an olefin at the 2-position. The appearance of signals at 5.67 ppm and 4.90 ppm account for the exocyclic olefin signals C(1')H_2.

The aromatisation of bromide **644** was attempted under an array of conditions, but the endocyclic product that would undergo the required base-induced aromatisation remained elusive, and all efforts towards the desired product **646** were futile (Scheme 4.68).



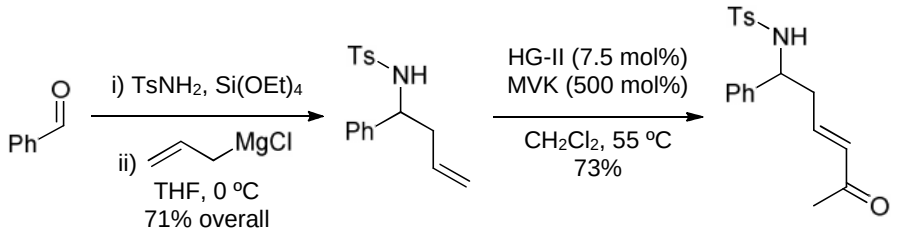
644 **646**

Scheme 4.68 *- Failed aromatisation of bromide* ***644****.*

Entry	Conditions	Yield
1	KHMDS, PhMe, 0 ºC.	dec.
2	KHMDS, PhMe, -40 ºC	SM
3	DBU, 0 ºC	SM
4	*t*-BuOK, t-BuOH, 20 ºC	dec.
5	$AlCl_3$, CH_2Cl_2	dec.

Table 4.8 *- Conditions for the failed aromatisation of bromide* ***644****.*

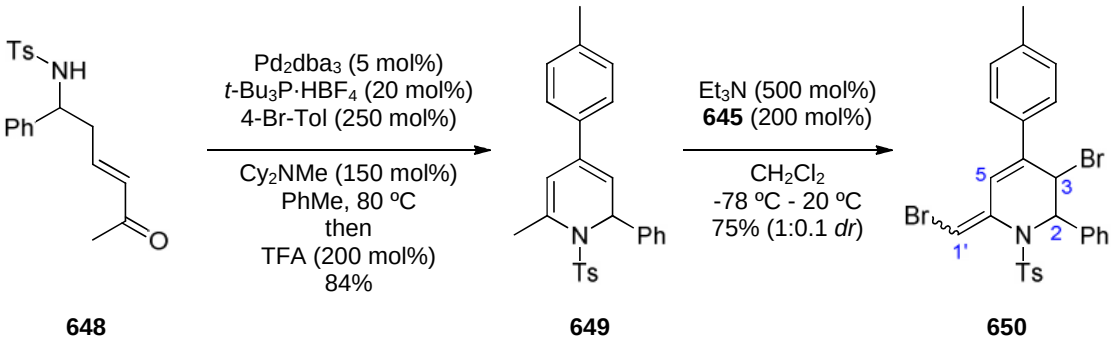
Next, in order to obtain a substrate easier to aromatize by increasing the acidity of the α-hydrogen, benzaldehyde was converted to homoallylic sulfonamide **647** and this substrate was subjected to the CM reaction to afford 5-amino enone **648** in good yields (Scheme 4.69).



403 **647** **648**

Scheme 4.69*-Synthesis of 5-amino enone* ***648****.*

Heck reaction of 5-amino enone **648** and 4-Br-Tol followed by condensation of this enone afforded the desired dihydropyridine **649**, which was subjected to a bromination protocol to obtain the dibromide **650** (Scheme 4.70).

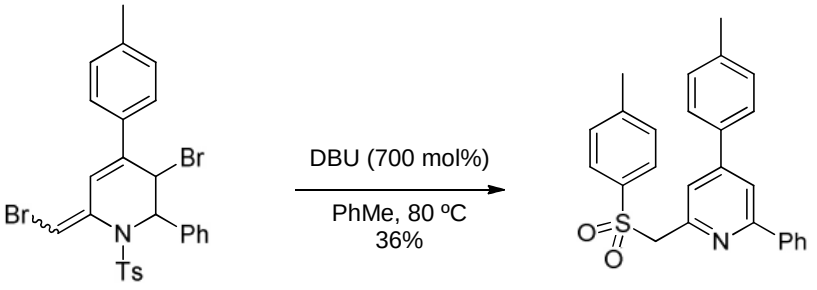


648 **649** **650**

Scheme 4.70*-Formation of exocyclic dibromide **650**.*

The formation of exocyclic dibromide **650** was evidenced by the appearance of two signals in the ^{1}H NMR spectrum at 7.04 ppm and 6.86 ppm which corresponded to two olefinic signals C(5)H and C(1')H. Furthermore appearance of signals at 6.23 ppm and 5.52 ppm corresponded to the endocyclic signals C(2)H and C(3)H respectively. Appearance of two signals in the ^{13}C NMR spectrum at 63.8 and 46.5 corresponded to C(2)and C(3) respectively is in accordance with the proposed structure. Also high resolution mass spectrometry, conducted in a positive electrospray ionisation mode, is in accordance with a dibrominated species.

When dibromide **650** was subjected to a based induced elimination, the resulting product was the unexpected rearrangement product **651** (Scheme 4.71).



650 **651**

Scheme 4.71 *- Unexpected formation of pyridine **651**.*

The formation of pyridine **651** was confirmed by single crystal X-ray data (Figure 4.26**).**

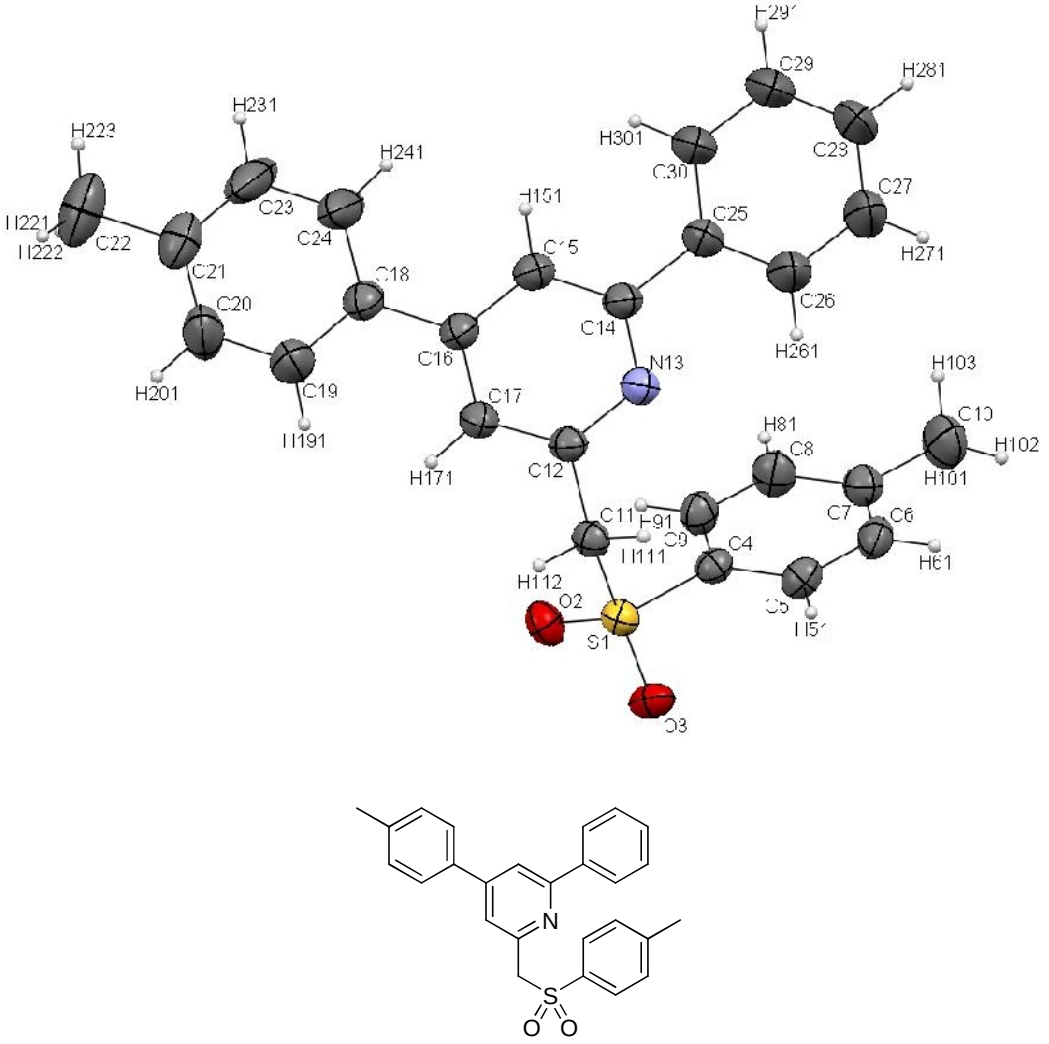
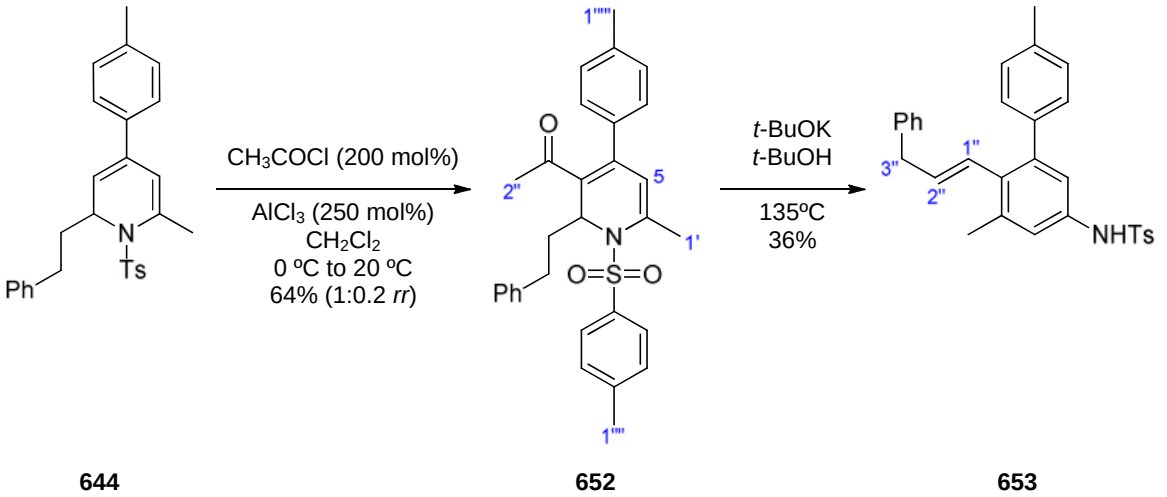


Figure 4.26 *- Single crystal X-ray analysis of pyridine* ***651****.*

In an attempt to vary the electrophile, a Friedel-craft type alkylation was attempted on 5-amino enone **644** giving the desired dihydropyridine **652** in good yields (Scheme 4.72).A small amount of an exocyclic enamine regioisomer was also found in the ^{1}H NMR spectrum. An attempt to convert this heterocycle using a range of bases only led to starting material, and when this substrate was subjected to higher temperature, the rearranged product **653** was isolated (Scheme 4.72).

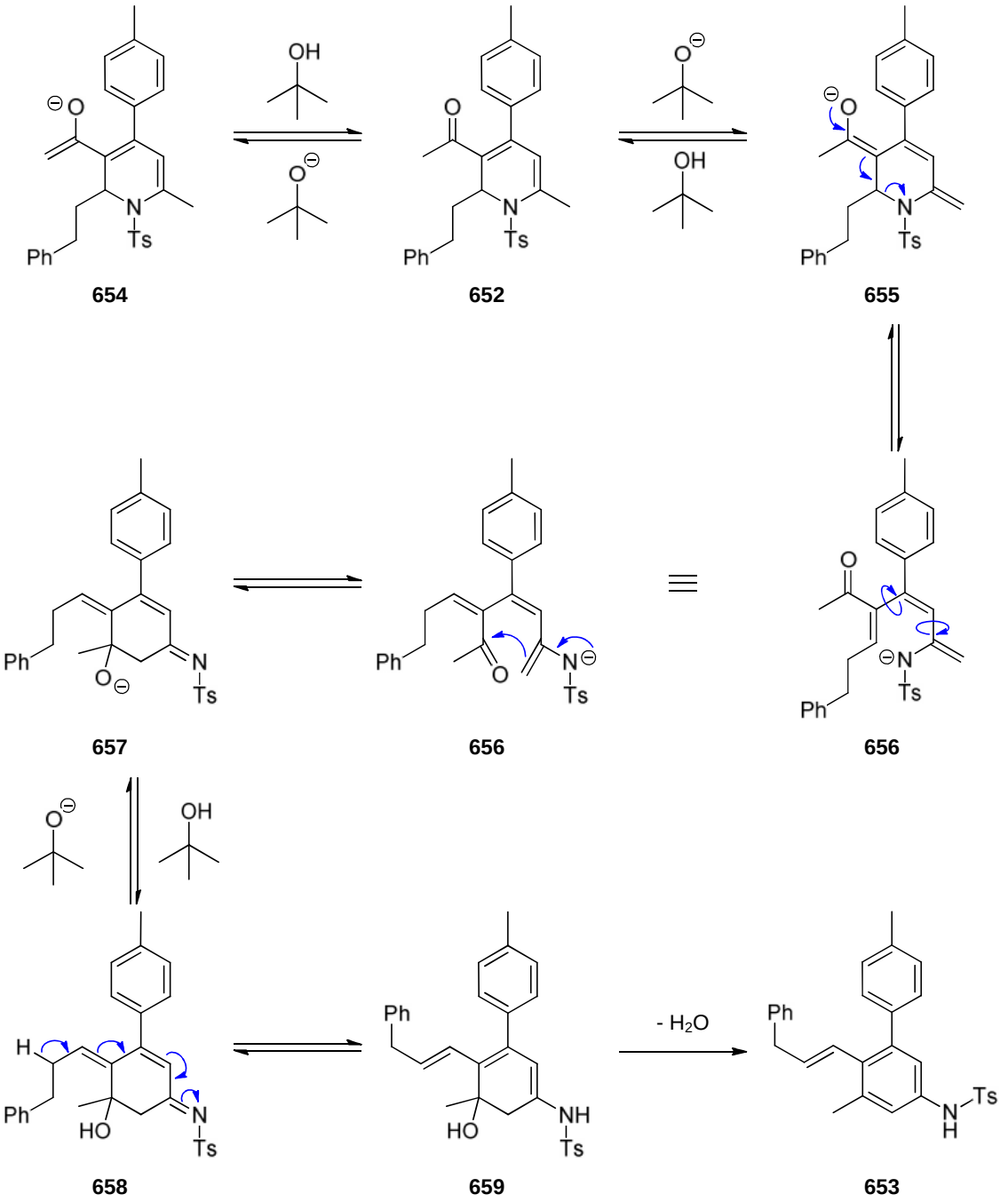


Scheme 4.72 *-Formation of undesired aniline derivative* ***653****.*

The formation of dihydropyridine **652** was evidenced by the appearance of four signals in the ^{13}C NMR spectrum at 29.9 ppm, 23.1 ppm, 21.4 ppm and 21.2 ppm which corresponded to the acetyl methyl C(2”), dihydropyridine methyl C(1’) and tolyl methyl C(1””) and C(1””’). Furthermore the appearance of signal in the ^{1}H NMR spectrum at 5.76 ppm which corresponded to the olefinic signal C(5)H.

The formation of aniline derivative **653** was evidenced by the appearance of a signal in the ^{1}H NMR spectrum at 3.37 ppm which corresponded to the benzylic signal C(3”)H_2. Furthermore, the appearance of two signals at 6.22 ppm and 5.55 ppm corresponded to the olefinic signals at C(1”)H and C(2”)H respectively. A coupling constant $J_{1”\text{-}2”}$ of 16.0 Hz is strong evidence of an *E* configuration. Moreover, characteristic n.O.e enhancements analysis matched the proposed structure (for n.O.e spectrum see appendix II).

A plausible mechanism for the formation of aniline **653** would involve the sulfonamide cleavage of intermediate **655**. Deprotonation of the starting material **652** is more likely to form the enolate **654** and this is a reversible process. The low yields obtained may be attributed to aldol condensation process that enolate **654** could undergo, but such products could not be isolated during the chromatography purification (Scheme 4.73).



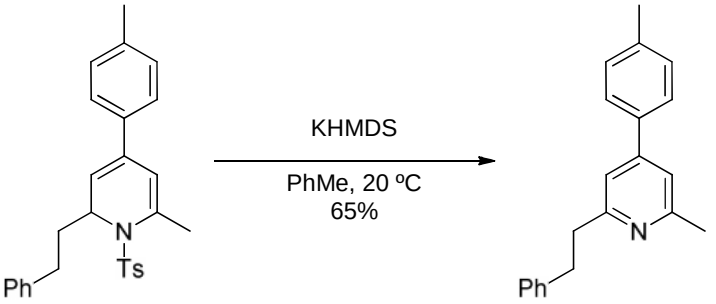
Scheme 4.73 *- Proposed mechanism for the formation of by product* ***653****.*

Deprotonated sulfonamide **656** would then attack the carbonyl functional group *via* the α-carbon to produce intermediate **657**, which forms the carbocycle **658** via proton exchange with the solvent. Tautomerisation of **658** would form the dihydrobenzene **659** that would readily be dehydrated to form the observed by product **653** (Scheme 4.73).

Formation of the heterocyclic substructure **632** was achieved very efficiently via this method, but the functionalisation of this moiety proved to be a difficult task, and efforts towards this aim were abandoned.

Instead, the formation of a pyridine core with a leaving group at the 2-position using this particular CM approach was investigated. A leaving group at the 2-position would give access to an array of 2,4,6-trisubstituted pyridines using transition metal catalyzed process, and the target in question can be generated very rapidly *via* this CM approach.

Formation of such a pyridine by this method would be complementary to the RCM approach discussed in Chapter Two, because it may not require an acidifying group at the 6-position as demonstrated by earlier results where a dihydropyridone **643** can be converted to the desired target **660** by a base induced aromatisation (Scheme 4.74).

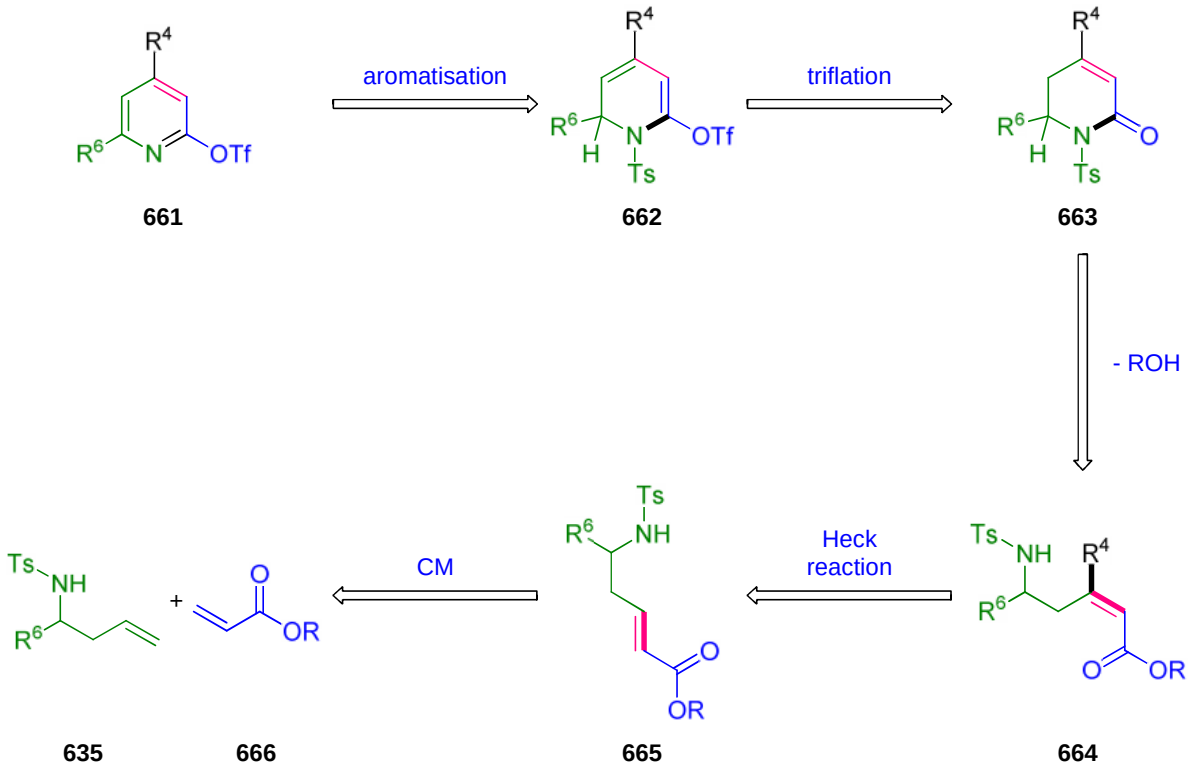


643 **660**

Scheme 4.74 *- Synthesis of pyridine **660**.*

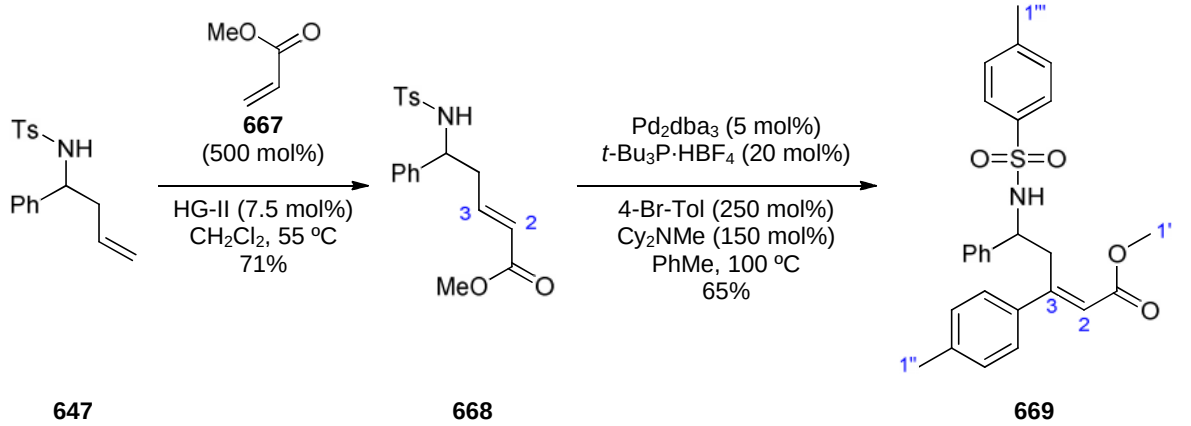
Work carried by J. F. Bower

The synthesis of trisubstituted pyridine **661**, equipped with a leaving group at the 2-position, can be formed by a base induced elimination of heterocycle **662**, that can be generated from a condensation, and trapping of the enolate intermediate with a triflating agent, of enone **664** (Scheme 4.75).



Scheme 4.75 *- Retrosynthetic analysis of 2,4,6-trusibstituted pyridine* ***661****.*

Enone **664** would be formed from a Heck reaction using enone **665**, that would be produced from a CM reaction of homoallylic sulfonamide **635** and acrylic ester **666** (Scheme 4.75). Homoallylic sulfonamide **647** was subjected to a CM reaction using methyl acrylate **667**, and the desired 5-amino acrylate **668** was obtained in good yields (Scheme 4.76).



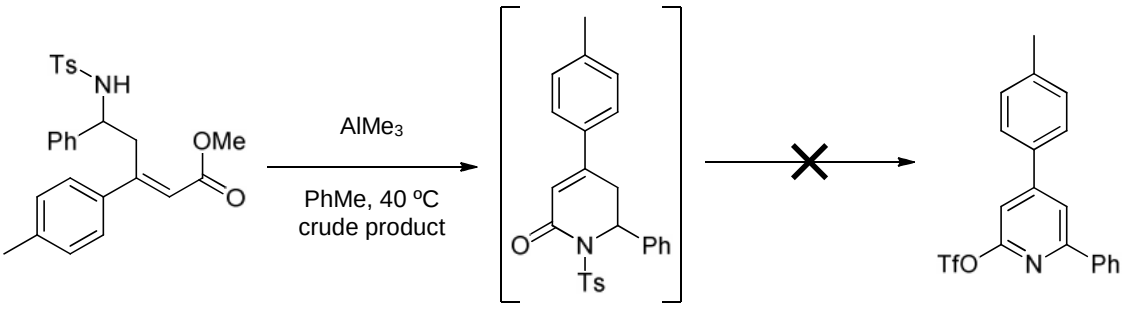
Scheme 4.76*-Synthesis of acrylate* ***669****.*

Acrylate **668** was then subjected to a Heck reaction, using 4-Br-Tol, and the desired trisubstituted olefin **669** was obtained in good yields (Scheme 4.76).

The formation of sulfonamide **668** was evidenced by the appearance of two signals in the ^{1}H NMR spectrum at 6.68 ppm and 5.76 ppm which corresponded to the two olefinic signals C(3)H and C(2)H. A coupling constant of $J_{2\text{-}3}$ 16.0 Hz indicated an *E* configuration.

The formation of methyl acrylate **669** was evidenced by the appearance of a signal in the ^{1}H NMR spectrum at 6.08 ppm which corresponded to the olefinic signal C(2)H. Furthermore the appearance of three signals at 3.76 ppm, 2.40 ppm and 2.35 ppm corresponded to the methoxy signal C(1')H_3 and two tolyl signals C(1")H_3 and C(1"')H_3. Also, the appearance of signal in the ^{13}C NMR spectrum at 155.6 ppm corresponded to the quaternary carbon at C(3).

The olefin **669** was then subjected to an array of conditions in order to form the desired intermediate heterocyclic **670** (Scheme 4.77).



669 **670** **671**

Scheme 4.77 *-Formation of dihydropyridone* ***670****.*

When the reaction was performed using trimethyl aluminium the desired intermediate **670** was observed by ^{1}H NMR of the crude reaction mixture (Figure 4.27).

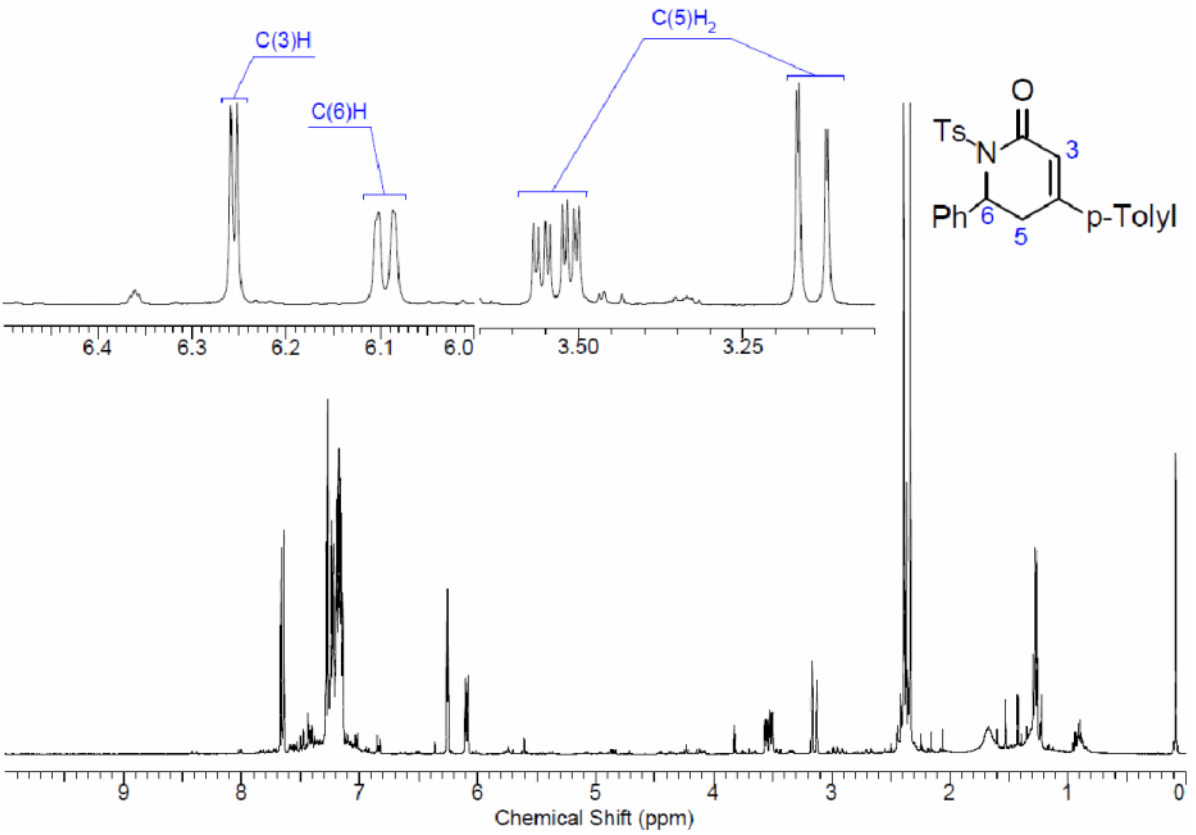


*Figure 4.27 - ^{1}H NMR of crude dihydropyridone **670**.*

However, formation of the desired 2-pyridone **671** was not achieved using an excess of KHMDS in the presence of Comins' reagent and currently more extensive work developing a method to effect this conversion is being undertaken by the Donohoe group.

4.4 Summary

The synthesis of polysubstituted pyridines using a CM approach was a challenging effort given the requirements for a rapid and modular approach to these important heterocyclic structures. Nevertheless, the methods accomplished represent a novel approach to the preparation of this substructure which would serve many chemists in order to obtain a high number of pyridine analogues. The CM reaction between a homoallylic alcohol and an enone gave a predictable outcome, and although only three substituents can be incorporated in this step, the functionalisation prior to oxidation also proved to be a great improvement due to the simplicity of the route and high levels of regiocontrol.

Pyridines, with alkyl, aryl, heteroaryl and heteroatom based substituents can be achieved at the 2-, 3-, 5-, and 6- position with high levels of regiocontrol in only a three step sequence, demonstrating the achievements of employing the metathesis reaction and justifying all the investigations described herein.

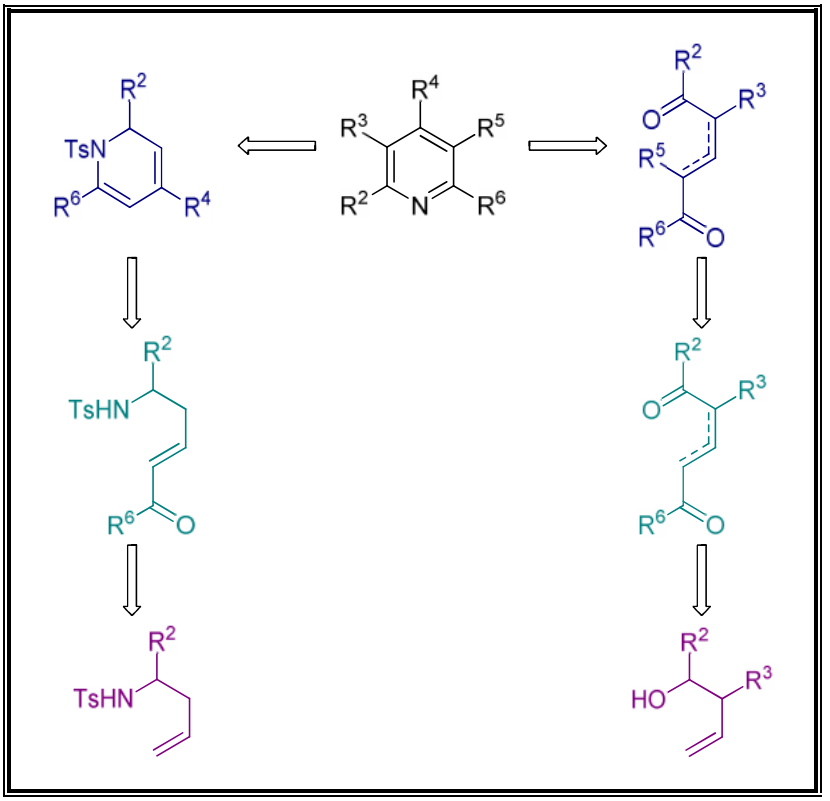
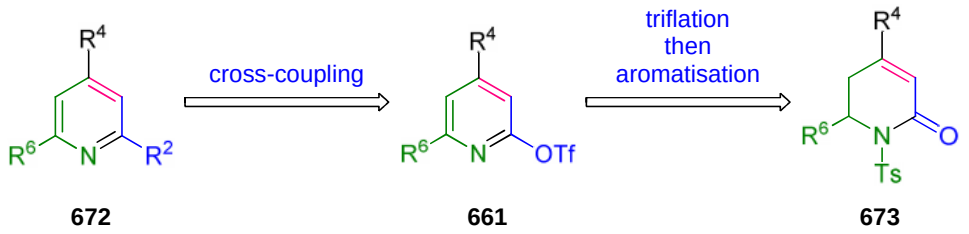


Figure 4.28 *-Summary of CM approach to pyridines.*

4.5 Future work

The CM of allylic sulfonamides have provided some important results for the formation of 2,4,6-trisubstituted pyridines bearing an alkyl group at the 2-position.

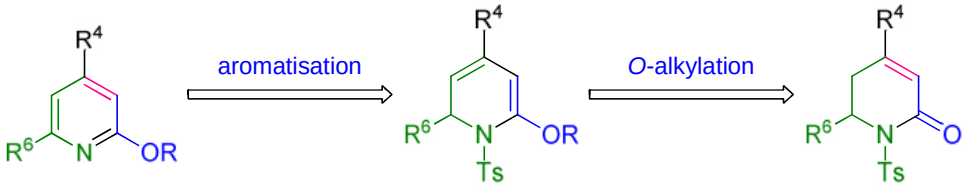
The use of more specialized vinyl ketones as the metathesis partner is required for the synthesis of these pyridines bearing an aryl group at the 2-position. The use of these specialized vinyl ketones, can be overcome by the synthesis of a pyridine core that would include a leaving group at the 2-position such as **661** and to use a transition metal cross-coupling protocol. It is in this area that future investigations will be focused (Scheme 4.78).



672 **661** **673**

Scheme 4.78 *- Retrosynthetic analysis of 2,4,6-trusibstituted pyridine* ***672****.*

Furthermore, the *O*-alkylation of 2-pyridones can be problematic due to competing *N*-alkylation. In order to increase the selectivity for *O*-alkylation this transformation requires the use of non-polar solvents, such as benzene, that do not dissolve the starting material significantly and makes this reaction very slow. Using the CM approach the pyridone core can be formed and the *O*-alkylation product **674** can be produced selectively, because of the protecting group present in the heterocyclic precursor **673** (Scheme 4.79).



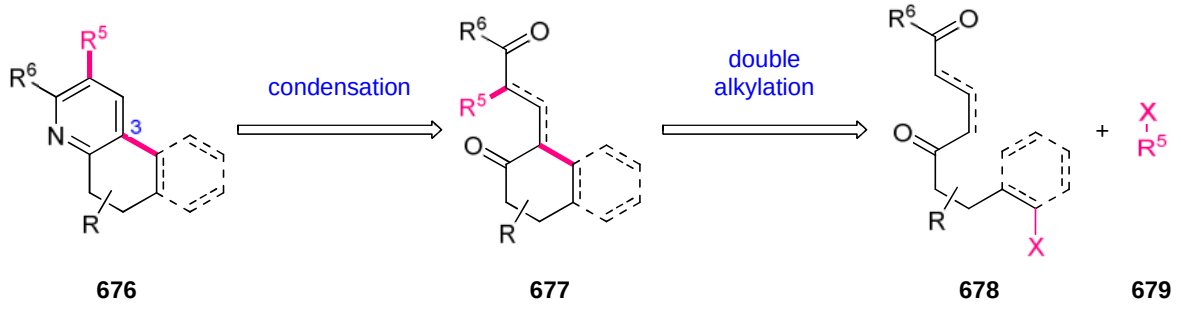
674 **675** **673**

Scheme 4.79*- Retrosynthetic analysis of 2,4,6-trusibstituted pyridine* ***674****.*

The use of unsaturated 1,5-diketones intermediates as nuclephiles for further functionalisation prior to aromatisation, proved to be an excellent avenue of research, delivering routes to tetrasubstituted pyridines. However, the selective alkylation when no substituents are present in the starting unsaturated 1,5-diketones would be a difficult task. Perhaps using an internal electrophile would overcome this limitation and could be a source of tetrahydroquinolines.

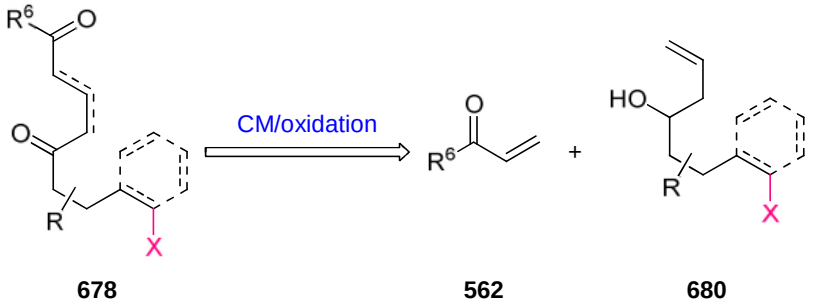
For example, tetrahydroquinoline **676** can be formed from a condensation of unsaturated 1,5-diketone **677**. Alkylation at the 3-position, *via* an internal electrophile, followed by an intermolecular alkylation at the 5-position, *via* external electrophile **679**, would convert the

dikeotne **678** to the diketone **677** (Scheme 4.80). This alkylation could also include an α-arylation protocol, which would prepare a third fused ring.



Scheme 4.80 *- Synthesis of fused pyridine* ***676****.*

A CM approach would be a fast and reliable route to diketone **678** from homoallylic alcohol **680** (Scheme 4.81).



Scheme 4.81 *- Synthesis of unsaturated 1,5-diketone* ***678****.*

Chapter five: Experimental