A Metathesis Based Approach
to the Synthesis of
Heteroaromatic Compounds

A thesis submitted to the
Board of the Faculty of Physical Sciences
in partial fulfilment of the requirements for the degree of

Doctor of Philosophy
in the
University of Oxford

by

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Balliol College
and
The Chemistry Research Laboratory

Trinity Term 2011
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

José A. Basutto  Balliol College  DPhil  Trinity Term 2011

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.
Acknowledgments

I would like to thank Professor Tim Donohoe for giving me the opportunity to undertake a research program in his group. I am extremely grateful for this unique opportunity and for all his efforts in providing me with a great research environment. Also for being so dedicated in encouraging me and ensuring a good learning experience.

I would also like to thank the Clarendon Fund, for providing me with the funding to undertake my DPhil in this prestigious institution. I am very grateful for the opportunities given.

Dr Chris Jones is also appreciated for his helpful comments and proof reading.

The CRL technical staff are also thanked, particularly Dr Barbara Odell for n.O.e data. Dr Amber Thompson, Cedric Callens and Akshat Rathi are thanked for their provision of the single crystal X-ray diffraction data.

I would like to thank Dr. John F. Bower for his significant input into my research career and for providing me with inspiration and trust over the years. I’d also like to thank Dr. Neil Kershaw for his help during the beginning.

In addition, I would like to thank the Donohoe group members for providing such a fun atmosphere, enjoyable Christmas parties and their attempts at playing football.

I like to thank Prof. Rafael Althaus for leading me into this magnificent science and for giving me his time and dedication without asking anything in return.

I’d like to thank Gabriel Turlea for being such an important friend and listening to my struggles.

I’d also like to thank Elsa, Karina and Hugo Almirón for their role in helping me to undertake this degree, and for giving me the gift of a place in their hearts. In addition I like to thank my mother Libia Famularo, my siblings Alfonsina, Adolfo, Maria Esperanza, Luis
and Emanuel Basutto for being part of my beginnings and their efforts at the end of this doctorate. I’d also like to thank their partners, and my nephews and nieces.

I’d especially like to thank my sister Mercedes Basutto for giving us refuge and being a witness to this effort.

Finally, I would like to thank the most important person in my life Ms Michelle Almirón for her constant belief and support and especially for waiting for me to come back. I’d also like to thank her for her role in obtaining this opportunity, her planning and proof reading, and for bringing light into the darkness:

*Of all the bonds I have made, ours is the strongest*
<table>
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<tr>
<td>PMB</td>
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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 by the 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

![Figure 1.1 - Well defined olefin metathesis catalysts.](image_url)
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.

\[ R^1\text{CH}=\text{CH}_2 + R^2\text{CH}=\text{CH}_2 \rightarrow R^1\text{CH}R^2 + \text{H}_2\text{C}=\text{CH}_2 \]

**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.](image)

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.\textsuperscript{6} These catalysts were derived from the Ziegler catalyst system (TiCl\textsubscript{4}/Al(C\textsubscript{2}H\textsubscript{5})\textsubscript{2}Cl) 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.\textsuperscript{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.\textsuperscript{6}

\begin{equation*}
2 \times \text{Mo(CO)\textsubscript{6}/Al\textsubscript{2}O\textsubscript{3}} \xrightarrow{90 - 315^\circ C} \text{H}_2\text{C} = \text{CH}_2 + \\
\text{8} \quad 42\% \quad 7 \quad 55\% \\
\text{9}
\end{equation*}

\textit{Scheme 1.3-Disproportionation reaction of linear olefins.}

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

\begin{center}
\begin{center}
\textbf{10} \xrightarrow{\text{MoCl\textsubscript{5}/Al\textsubscript{2}Et\textsubscript{3}}} \textbf{11}
\textbf{10} \xrightarrow{\text{WCl\textsubscript{6}/Al\textsubscript{2}Et\textsubscript{3}}} \textbf{12}
\end{center}
\end{center}

\textit{Scheme 1.4 - Ring-opening polymerisation.}

\subsection*{1.2.2 Fisher carbenes}

An important development was the isolation of a new type of organometallic compound \textbf{1}, which was later termed a Fisher metal carbene (Figure 1.2). These complexes contained a divalent organic ligand coordinated to the metal centre.\textsuperscript{8}
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 $\text{13}$ was combined with alkene $\text{14}$, a new metal carbene $\text{1}$ and olefin $\text{15}$ was obtained.$^9$ This alkylidene exchange is a key step in Chauvin’s proposed mechanism for the olefin metathesis reaction (Scheme 1.5).$^6$

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 $\text{16}$ (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.$^{15}$
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).\(^{19}\)

![Figure 1.3 - Schrock's catalysts.](image)

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).\(^{21}\)

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.\(^{22}\)
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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{24}

\begin{equation}
\begin{array}{c}
\text{Cy} \quad \text{Cy} \\
\text{Cl} \quad \text{Ru} \quad \text{Ph} \\
\end{array}
\end{equation}

\begin{equation}
\begin{array}{c}
\text{Cy} \quad \text{Cy} \\
\text{Cl} \quad \text{Ru} \quad \text{Ph} \\
\end{array}
\end{equation}

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.\textsuperscript{24}

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

\begin{equation}
\begin{array}{c}
\text{Cy} \quad \text{Cy} \\
\text{Cl} \quad \text{Ru} \quad \text{Ph} \\
\end{array}
\end{equation}

\begin{equation}
\begin{array}{c}
\text{Cy} \quad \text{Cy} \\
\text{Cl} \quad \text{Ru} \quad \text{Ph} \\
\end{array}
\end{equation}

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.\textsuperscript{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).\(^{32}\)

\begin{align*}
\text{G-II} & \xrightarrow{PCy_3} \text{30} & \xrightarrow{R^1\longrightarrow\text{Ph}} \text{31} & \xrightarrow{R^2\longrightarrow\text{R'}} \text{32} \\
\end{align*}

\text{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.\textsuperscript{33}

![Figure 1.6-Hoveyda-Grubbs’ 1\textsuperscript{st} and 2\textsuperscript{nd} generation catalysts.]

Hoveyda also prepared a second generation system \textbf{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).\textsuperscript{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).\textsuperscript{35}
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.\textsuperscript{34}

\subsection*{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 \textit{via} RCM and in some cases \textit{via} CM. Catalyst HG-II can be used for the synthesis of di-substituted and in some cases tri-substituted olefins.\textsuperscript{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 \textit{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 \textit{37} (Figure 1.7).\textsuperscript{37}

\textbf{Figure 1.7-Grubbs' catalyst for 1,1-disubstituted olefin.}

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

\textbf{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 \textit{40}, which would lead to the formation of a 1,3-disubstituted metallacyclobutane, and the transition state \textit{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 \textit{42} and \textit{43} obtained from catalyst HG-II (Figure 1.8).\textsuperscript{23}
Chapter one  

Introduction

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).\textsuperscript{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).\textsuperscript{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.  

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

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).\textsuperscript{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).\textsuperscript{39}

![Scheme 1.13 - RCM of diene 51.](image)

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Yield after 2 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>49 (1.0 mol%)</td>
<td>100%</td>
</tr>
<tr>
<td>G-II (1.0 mol%)</td>
<td>100%</td>
</tr>
<tr>
<td>HG-II (2.5 mol%)</td>
<td>15%</td>
</tr>
</tbody>
</table>

*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).\textsuperscript{39,40} These experiments demonstrate the higher catalytic activity of catalyst 49 and 50 over second generation catalyst G-II and HG-II.

![Scheme 1.14 - Catalyst comparison using different substrate.](image)
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). They subsequently demonstrated that similar heterocycles, plus some new oxygen-containing heterocycles, could be catalyst G-0.

\[
\begin{array}{cc}
\text{O} & \text{Ph} \\
\text{C}_6\text{H}_{12}, 20^\circ\text{C} & 92\% \\
\text{S-I (5 mol\%)} & \\
57 & 58 \\
\hline
\text{O} & \text{Ph} \\
\text{C}_6\text{H}_{12}, 20^\circ\text{C} & 84\% \\
\text{G-0 (4 mol\%)} & \\
59 & 58 \\
\hline
\text{O} & \text{Ph} \\
\text{C}_6\text{H}_{12}, 20^\circ\text{C} & 87\% \\
\text{G-0 (4 mol\%)} & \\
60 & 61 \\
\hline
\text{O} & \text{Ph} \\
\text{C}_6\text{H}_{12}, 20^\circ\text{C} & 86\% \\
\text{G-0 (4 mol\%)} & \\
62 & 63 \\
\end{array}
\]

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.

The synthesis of 3,6-dihydropyran 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).\textsuperscript{44}

![Scheme 1.16 - Synthesis of 3,4-dihydropyran 66.](image)

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 \textit{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.\textsuperscript{45} Hydroxyalkene 67 was converted to a mixture of tetrahydrofuran 68 and tetrahydropyran 69 (Scheme 1.17).

![Scheme 1.17 - Hydroalkoxylation of alkenes.](image)

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).  

\[
\text{Allyliodide} \quad \text{NaHMDS} \quad 71\% \\
\text{70} \quad \text{71} \\
\text{G-I (5 mol\%)} \quad \text{CH₂Cl₂} \quad 40 \degree C, 95\% \\
\text{73} \quad \text{72}
\]

**Scheme 1.18 - Crimmins’ synthesis of (+)-laurencin73.**

The synthesis of five- and six-membered lactones as well as macrolactones has also been achieved by a RCM approach. 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). 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.
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.\(^{55-57}\)

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

**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.](image)

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).\(^{59}\)
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). 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 1.22- Synthesis of cyclic enamides.**

![Scheme 1.22](image_url)

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

![Scheme 1.23](image_url)
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).\(^6\) 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,\(^6\) 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).\(^6\)
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.

Scheme 1.24 - RCM approach to the synthesis of phenols.
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 billion US dollars on sales in 2009), contains a polyfunctionalized pyrrole.

\[ \text{Figure 1.12 - Atorvastatin.} \]

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).

\[ \text{Scheme 1.25 - RCM of diene 102.} \]

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.\textsuperscript{66}

\begin{center}
\textbf{Scheme 1.26-Stevens’ synthesis of pyrroles.}
\end{center}

A more general approach to the synthesis of pyrroles was introduced in 2005 by Donohoe and co-workers (Scheme 1.27).\textsuperscript{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).
In 2006, Lamaty and co-workers developed a synthesis of pyrroles via a RCM in which a 2-trimethylsilylthanesulfonyl (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).\(^\text{69}\)

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.
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). The method consists of the formation of a mixed acetal from allylic alcohol under palladium catalyzed conditions. RCM of the mixed acetal, using catalyst G-II, afforded the dihydrofuran intermediate, which is converted in situ to the desired furan by an acid catalyzed elimination of methanol. This elimination is driven by aromatisation by a very simple and efficient process.

Scheme 1.28- Lamaty’s synthesis of pyrroles.

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). 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.](image)

It is well established that deprotonation of allylic ether 129 in the presence of InCl₃ forms a γ-alkoxy allyllindium reagent that gives high levels of regiocontrol when coupled with an aldehyde. 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{76,77}

Pyridine\textsuperscript{135} is a six-membered heteroaromatic compound with a molecular formula of C\textsubscript{5}H\textsubscript{3}N which corresponds to three double bonds in a ring structure (Figure 2.1).

![Pyridine](image_url)

\textit{Figure 2.1- Pyridine.}

This molecule is planar and has a slightly distorted hexagonal shape, where all the carbons are sp\textsuperscript{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 $\pi$-electrons in this molecule is six, which according to H"{u}ckel’s rule there would be a strong indication that this molecule is aromatic. Important evidence is seen in that the $^1$H 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.\textsuperscript{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
Chapter two The synthesis of 2-pyridones

Pyridine can be considered as a stable imine, which means that it is weakly basic, the pKa of its conjugated acid is 5.25,\(^7\) and it is reasonably nucleophilic.\(^8\)

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 \(\text{136}\) almost exclusively exists in the carbonyl tautomeric form \(\text{137}\) and this structure is called 2-pyridone (Scheme 2.1).\(^8\)

\[
\begin{align*}
\text{136} & \quad \text{\(\leftrightarrow\)} \quad \text{137} \\
\text{138} & \quad \text{OH} \quad \text{\(\leftrightarrow\)} \quad \text{139} \\
\text{140} & \quad \text{OH} \quad \text{\(\leftrightarrow\)} \quad \text{141}
\end{align*}
\]

\text{Scheme 2.1 - 2-Pyridone, 4-Pyridone and 3-Hydroxypyridine.}

This is also true when the hydroxyl group is located at the 4-position \(\text{138}\), as the keto is still the prevalent tautomeric form \(\text{139}\) (Scheme 2.1).\(^8\) Traces of the hydroxyl tautomeric forms \(\text{138}\) and \(\text{136}\) could be seen in diluted solutions using non-polar solvents.\(^8\)

However, the 3-hydroxypyridine \(\text{140}\) is observed in many non-polar solvents, like CDCl\(_3\) and CCl\(_4\). In aqueous solutions it has been demonstrated that the zwitterionic species \(\text{141}\) is observed in comparable proportion to neutral species \(\text{140}\).\(^8\)\(^-\)\(^8\)

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. This reaction was later extended to the use of acid chlorides for the esterification of alcohols in carbohydrate chemistry.

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

\[
\begin{align*}
\text{R}^1\text{CO} & \quad + \quad \text{N} \quad \rightarrow \quad \text{R}^1\text{N}^+ \quad \rightarrow \quad \text{R}^1\text{N}^+\text{CO} \quad \rightarrow \quad \text{R}^1\text{CO} - \text{H}^+ + \text{N} \quad \rightarrow \quad \text{R}^1\text{N}^+\text{CO} \quad + \quad \text{H} - \text{N} \quad \rightarrow \quad \text{R}^1\text{N}^+\text{CO} \quad + \quad \text{H} - \text{N} \quad \rightarrow \quad \text{R}^1\text{N}^+\text{CO} \quad + \quad \text{H} - \text{N} \\
143 & \quad + \quad 135 & \quad \rightarrow \quad 144 & \quad \rightarrow \quad 145 & \quad + \quad 146
\end{align*}
\]

\textit{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 \textit{m}-chloroaniline by replacing pyridine with 4-dimethylaminopyridine (DMAP) (Figure 2.2). Sieglich and Höfle independently discovered that the use of DMAP had a dramatic influence on the rate of acylation reactions.

\[
\begin{align*}
147
\end{align*}
\]

\textit{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.

The electron rich dialkylamine group increases the nucleophilicity of the nitrogen in DMAP, and also it stabilizes the intermediate 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.](image)

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.](image)

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
Chapter two  The synthesis of 2-pyridones

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.
Chapter two

The synthesis of 2-pyridones

Niacin 160, also known as vitamin B₃, 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

Figure 2.4 - NAD⁺ and NADH.

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.

Figure 2.5 - Vitamin B₃ Niacin.

Figure 2.6 - Vitamins B₆.

Due to the occurrence of 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 as acrivastine 166, loratadine 167 and doxylamine 168 (Figure 2.7) amongst others.96, 97

![Figure 2.7 - Histamine and pyridine based histamine antagonists.](image)

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

![Figure 2.8 - 2-Pyridone derivative cofactor.](image)

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).

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 notwithstanding), obviating the need for an oxidation procedure (Scheme 2.6).

Tschitschibabin (Chichibabin) describe the synthesis of pyridines from the condensation of an aldehyde in liquid ammonia. 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).
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).\(^{103}\)

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).\(^{104}\)

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).

\[
\text{BF}_3 \cdot \text{OEt}_2 + \text{CH}_2\text{Cl}_2, -78 \, ^\circ\text{C}
\]

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).

\[
\begin{align*}
\text{EtOH, 40 \, ^\circ\text{C}} & \quad 90\% \\
\end{align*}
\]

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).

\[
\text{NH}_4\text{OAc} + \text{EtOH, 78 \, ^\circ\text{C}}
\]

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
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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-cyanoacetamide 200 reacts selectively with the most electron-deficient carbonyl to generate the pyridine 201 (Scheme 2.13).\(^8\)

![Scheme 2.13 - Guareschi synthesis of pyridines.](image)

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.\(^8\)

### 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.\textsuperscript{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).\textsuperscript{109}

\[
\text{Scheme 2.14 - 6π-Cycloaddition approach to pyridines.}
\]

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 of pyrrolidine 211 to afford the desired pyridine 210 (Scheme 2.15).\textsuperscript{110}
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).\textsuperscript{111}
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).\textsuperscript{112}

Ketone 219 is treated with hydroxylamine hydrochloride (NH$_2$OH·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).\textsuperscript{112}
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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 cyclopentany1 cobalt species 223 (Scheme 2.18).\(^\text{113}\)

\[
\begin{align*}
\text{C}_{6}H_{6}, 70 ^\circ C & \quad \text{L-Co-PPh}_{3} & \quad R^1\equiv N & \quad \text{C}_{6}H_{6}, 70 ^\circ C & \quad \text{N}^+ \quad \text{L-Co-PPh}_{3} \\
223 & \quad 224 & \quad 225 & \quad 226 \\
\end{align*}
\]

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).\(^\text{114}\) 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.\textsuperscript{114}

![Scheme 2.19 - Rhodium mediated synthesis of pyridines.](image)

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).\textsuperscript{114}

![Scheme 2.20 - 6π-Electrocyclisation for the formation of dihydropyridine 234.](image)
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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).\(^7\)

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.

\[ \begin{align*}
\text{triflation then} & \quad \text{cross-coupling} \\
\text{based} & \quad \text{induced} \\
\text{elimination} & \\
\text{RCM} & \\
\text{allylation} & \\
imine formation & \\
\text{imine} & \\
\text{formation} & \\
\end{align*} \]

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 \( X = \text{OR, NR}_2 \) 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 \textit{via} a transition metal catalyzed coupling (Scheme 2.24).

\[
\begin{array}{c}
\text{Scheme 2.24: Retrosynthetic analysis for the formation of substituted pyridines.}
\end{array}
\]

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).

\[
\begin{array}{c}
\text{Figure 2.10 - WS 75624 A} 247 \text{ and WS 75624 B} 248 .
\end{array}
\]

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)\(^{116}\).

![Figure 2.11 - Streptonigrin.](image)

### 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).

![Scheme 2.25 - Synthesis of oxime 252.](image)

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

![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

![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.\textsuperscript{122}

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

\begin{center}
\includegraphics[width=0.8\textwidth]{scheme228.png}
\end{center}

\textit{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 \textsuperscript{261} (Figure 1.13) was used as a more reactive amide coupling agent, there was no evidence of product formation (Table 2.1).

\begin{center}
\includegraphics[width=0.8\textwidth]{scheme229.png}
\end{center}

\textit{Scheme 2.29 - Amide coupling of acid \textsuperscript{256} and amine \textsuperscript{253}.}
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<table>
<thead>
<tr>
<th>Coupling agent</th>
<th>Additive</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDCI</td>
<td>none</td>
<td>CH₂Cl₂</td>
<td>-40 °C</td>
<td>None</td>
</tr>
<tr>
<td>EDCI</td>
<td>none</td>
<td>CH₂Cl₂</td>
<td>0 °C</td>
<td>None</td>
</tr>
<tr>
<td>EDCI</td>
<td>none</td>
<td>CH₂Cl₂</td>
<td>20 °C</td>
<td>None</td>
</tr>
<tr>
<td>EDCI</td>
<td>HOBt</td>
<td>DMF</td>
<td>60 °C</td>
<td>None</td>
</tr>
<tr>
<td>EDCI</td>
<td>HOBt</td>
<td>THF</td>
<td>20 °C</td>
<td>None</td>
</tr>
<tr>
<td>EDCI</td>
<td>4-DMAP, Et₃N</td>
<td>CH₂Cl₂</td>
<td>20 °C</td>
<td>None</td>
</tr>
<tr>
<td>EDCI</td>
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<td>CH₂Cl₂</td>
<td>40 °C</td>
<td>None</td>
</tr>
<tr>
<td>EDCI</td>
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<td>80 °C</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>TBTU</td>
<td>Et₃N</td>
<td>DMF</td>
<td>20 °C</td>
<td>None</td>
</tr>
<tr>
<td>DCC</td>
<td></td>
<td>CH₂Cl₂</td>
<td>40 °C</td>
<td>&lt;85%</td>
</tr>
</tbody>
</table>

Table 2.1 - Conditions for amide coupling.

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.

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).
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.
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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$_2$O$_5$) 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$_2$O$_5$ to form the ester 270 (Scheme 2.32).

\[
\text{HC(OEt)}_3 \xrightarrow{\text{EtOH, H$_2$SO$_4$}} \text{P$_2$O$_5$} \xrightarrow{\text{DMF, 100 ºC}} \text{CO}_2\text{Et}
\]

Scheme 2.32 - Synthesis of ester 270.

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

<table>
<thead>
<tr>
<th>Base</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Yield of 260</th>
</tr>
</thead>
<tbody>
<tr>
<td>none</td>
<td>MeOH</td>
<td>20 ºC to 65 ºC</td>
<td>none</td>
</tr>
<tr>
<td>none</td>
<td>none</td>
<td>20 ºC to 110 ºC</td>
<td>none</td>
</tr>
<tr>
<td>isopropyl magnesium bromide</td>
<td>THF</td>
<td>20 ºC</td>
<td>none</td>
</tr>
<tr>
<td>AlMe$_3$</td>
<td>CH$_2$Cl$_2$</td>
<td>20 ºC</td>
<td>none</td>
</tr>
</tbody>
</table>

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).
The enol ether functionality in acrylic acid 270 is acid labile and therefore it was thought that this acid would be difficult to 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).

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 (Ph3P) in conjunction with trichloroacetonitrile 274 (Cl3CCN), the acid chloride 275 is produced, under neutral conditions, and this can be converted to the desired amide 276 (Scheme 2.36).125
The mechanism of this reaction was not described, but the products formed initially are the acid chloride 275, triphenylphosphine oxide 283 (Ph$_3$PO) 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$_3$PO and acid chloride 275 (Scheme 2.37).

\[
\begin{align*}
\text{Ph$_3$P} & \quad + \quad \text{ClC} \quad \rightarrow \quad \text{ClP($\text{Ph}$)$_3$} & \quad + \quad \text{ClCN} \\
\text{273} & \quad \quad \quad 274 & \quad \quad \quad 277 & \quad \quad \quad 278
\end{align*}
\]

\[
\begin{align*}
\text{ClC} & \quad + \quad \text{H$_2$O} & \quad \rightarrow \quad \text{ClCHCN} & \quad + \quad \text{RCO}^{-} \\
\text{278} & \quad \quad \quad 272 & \quad \quad \quad 279 & \quad \quad \quad 280
\end{align*}
\]

\[
\begin{align*}
\text{RCO}^{-} & \quad + \quad \text{Ph$_3$P} & \quad \rightarrow \quad \text{RCO}^{-} & \quad + \quad \text{Cl}^{-} \\
\text{280} & \quad \quad \quad 277 & \quad \quad \quad 281 & \quad \quad \quad 282
\end{align*}
\]

\[
\begin{align*}
\text{Cl}^{-} & \quad + \quad \text{Ph$_3$P} & \quad \rightarrow \quad \text{Ph$_3$PO} & \quad + \quad \text{RCO}^{-} \\
\text{282} & \quad \quad \quad 281 & \quad \quad \quad 283 & \quad \quad \quad 275
\end{align*}
\]
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

\[
\text{Formation of diene } 260 \text{ was evidenced by the appearance of a signal in the } ^1\text{H NMR spectrum at 5.83 ppm which was assigned to the olefinic signal C(4)H. Further evidence is seen in the appearance of four signals at 5.18 ppm, 5.12 ppm, 5.07 ppm and 5.02 ppm which were assigned to the terminal olefin signals C(5)H}^2 \text{ and the benzylidene signals C(1"')H}_2 \text{ (Figure 2.13).}
\]

![Scheme 2.38 - Amide coupling under neutral conditions.](image.png)

![Figure 2.13 - $^1$H NMR of diene 260.](image.png)
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 $\alpha,\beta$-unsaturated lactam 284 in high yield (Scheme 2.39).

![Scheme 2.39 - Formation of $\alpha,\beta$-unsaturated lactam 284 by RCM.](image)

The formation of $\alpha,\beta$-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 $\alpha,\beta$-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 $\alpha,\beta$-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).

![Scheme 2.40 - Aromatisation of $\alpha,\beta$-unsaturated lactam 284.](image)

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 $J_{3-4}$ of 7.5 Hz is in agreement with an ortho coupling in 2-pyridones.\textsuperscript{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.\textsuperscript{75}

In 1992, Comins and Dehghani published a study into the triflation of ketones using $N$-(5-Chloro-2-pyridyl)bis(trifluoromethanesulfonimide) \textbf{287} (Comins’ reagent) and showed that this reagent has several advantages over other triflating agents(Figure 2.14).\textsuperscript{127}

\begin{center}
\includegraphics[width=0.5\textwidth]{comins-reagent.png}
\end{center}

\textit{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.\textsuperscript{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 \textbf{288} (PhNTf$_2$), which means that the reaction can be carried out at a much lower temperature avoiding possible decomposition.\textsuperscript{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.\textsuperscript{127}

The heteroaromatic compound 2-pyridone \textbf{285} was converted to pyridine \textbf{289} by triflation of the 2-hydroxyl tautomer with Comins’ reagent (Scheme 2.41).\textsuperscript{118}
The formation of pyridine \(289\) was evidenced by the appearance of the signals in the \(^{13}\text{C}\) 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 \(^1\text{H}\) 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-alkoxyypyridines 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).

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. This protocol was used to convert aldehyde 292 into acrylic aldehyde 293 (Scheme 2.43).

Oxidation of acrylic aldehyde 293 was achieved using sodium chlorite as the oxidant. 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).
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

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 $J_{3-4}$ 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 $\alpha,\beta$-unsaturated lactam 300 (Scheme 2.46). 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-disubsitutued alkenes.37

![Scheme 2.46 - Synthesis of 4-substituted $\alpha,\beta$-unsaturated lactam 300.](image)

To circumvent this limitation, the synthesis of desired $\alpha,\beta$-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 $\alpha,\beta$-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 $\alpha,\beta$-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).

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).\(^{143}\)

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)O₂) 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
The formation of $\alpha,\beta$-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 $J_{5-3}$ of 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 $J_{C-F}$ of 320 Hz, and was assigned to CF$_3$. 

Scheme 2.50 - Synthesis of 4-substituted pyridine
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)
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 $J_{C\text{-}F}$ of 320 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). \(^{144}\)

\[
\begin{align*}
\text{Scheme 2.52 - Alpha bromination of enol ethers.}
\end{align*}
\]

In order to obtain the 4-substituted bromide 319, the \(\alpha,\beta\)-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). \(^{118}\)

\[
\begin{align*}
\text{Scheme 2.53 - Synthesis of polysubstituted pyridine 321.}
\end{align*}
\]

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-tetrasubstituted 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.

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-1), 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
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

\[ \text{Scheme 2.55 - Synthesis of thioamide 332.} \]

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
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**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 synthesized 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
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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 $J_{4,3}$ of 2.5 Hz and $J_{4,3'}$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).

\[
\begin{align*}
\text{Scheme 2.60 - Synthetic approach towards pyridine 344.}
\end{align*}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeONa, MeOH, 65 °C</td>
<td>starting material</td>
</tr>
<tr>
<td>2</td>
<td>KOH, MeOH, 65 °C</td>
<td>ester hydrolysis</td>
</tr>
<tr>
<td>3</td>
<td>MeONa, 1,4-dioxane, 110 °C</td>
<td>decomposition</td>
</tr>
<tr>
<td>4</td>
<td>MeONa, DMF, 110 °C</td>
<td>decomposition</td>
</tr>
<tr>
<td>5</td>
<td>MeONa, MeOH, 110 °C</td>
<td>ester hydrolysis</td>
</tr>
<tr>
<td>6</td>
<td>CuI, Cs₂CO₃, N,N-dimethylglycine hydrochloride, MeOH, 110 °C</td>
<td>starting material</td>
</tr>
<tr>
<td>7</td>
<td>MeONa, Pd₃dba (5 mol%), 353 (20 mol%), PhCH₃, 100 °C</td>
<td>starting material</td>
</tr>
<tr>
<td>8</td>
<td>t-BuONa, Pd₃dba (5 mol%), 353 (20 mol%), PhCH₃, 100 °C</td>
<td>starting material</td>
</tr>
<tr>
<td>9</td>
<td>MeOH, HCl (cat.), 20 °C</td>
<td>starting material</td>
</tr>
<tr>
<td>10</td>
<td>MeOH, HCl (cat.), 70 °C</td>
<td>starting material</td>
</tr>
</tbody>
</table>

*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). The conditions reported by Hartwig were also screened in this case but without a positive result (entry 7 and 8; Table 2.4).
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).

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.

Scheme 2.62-Attempted synthesis of pyridone 347 via dihydroxylation.
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 explored further. Instead a more elegant solution was sought.

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,\textsuperscript{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.

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>RuCl₃, EtOAc, MeCN, H₂O, CH₃CO₂H, 20 ºC</td>
<td>decomposition</td>
</tr>
<tr>
<td>2</td>
<td>RuCl₃, EtOAc, MeCN, H₂O, Oxone ®, 20 ºC</td>
<td>decomposition</td>
</tr>
<tr>
<td>3</td>
<td>RuCl₃, EtOAc, MeCN, H₂O, Oxone ®, NaHCO₃, 20 ºC</td>
<td>starting material</td>
</tr>
</tbody>
</table>

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

![Figure 3.1 - Nosiheptide.](image)

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, Quégüiner and co-workers published a total synthesis of caerulomycin B starting from 3-hydroxypyridine (Scheme 3.1). Key steps in this synthesis involved the conversion of 3-hydroxypyridine to by introduction of the hydroxyl group at the 4-position via a selective deprotonation using lithium 2,2,6,6-tetramethylpiperidide as a base and trimethylborate as the electrophile. Selective metallation at the 2-position of pyridine was used to introduce the 2-pyridyl moiety via a Negishi cross-coupling in which bipyridine was obtained. These two steps were achieved with excellent levels of regiocontrol. This is mainly due to the directing effect of the 3-alkoxygroup. Caerulomycin B was prepared in two further steps.

![Scheme 3.1 - Quégüiner’s synthesis of caerulomycins B368.](image)

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 and alkyne was
used to prepare the dihydropyridine $371$ with spontaneous aromatisation to produce the 3-hydroxypyridine $372$ and $373$ (Scheme 3.2).\textsuperscript{152}

\begin{center}
\begin{tikzpicture}
    \node at (0,0) {$\text{Scheme 3.2- Hetero Diels-Alder approach to 3-hydroxypyridines.}$};
    \node at (0,0) {$\text{3.2 A metathesis approach to the synthesis of 3-hydroxypyridines}$};
\end{tikzpicture}
\end{center}

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).
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 3.3- 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).
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).
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).

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

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.\textsuperscript{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).

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).\textsuperscript{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).
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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.
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$_3$·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).

![Scheme 3.11](image)

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Yield</th>
</tr>
</thead>
</table>
| 1     | $\text{MgBr}$  
0 ºC, THF           | imine          |
| 2     | $\text{MgBr}$  
20 ºC, THF           | imine          |
| 3     | $\text{MgBr}$  
-78 ºC, THF, BF$_3$·OEt$_2$ | imine          |
| 4     | $\text{MgBr}$  
0 ºC, THF, BF$_3$·OEt$_2$ | complex mixture of products |

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.](image)

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.

![Scheme 3.12: Formation of sulfonamide 411.](image)

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')H₂,
furthermore the appearance of signal at 2.43 ppm corresponded to the methyl signal of the tosyl group C(1")H₃.

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.](image)

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). 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.](image)

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).
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).\(^{155}\)

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).\textsuperscript{155}

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

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure33.png}
\caption{Single crystal X-ray analysis of pyridine 424.}
\end{figure}

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

Formation of pyridine \( \text{432} \) 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 \( \text{424} \) (evidenced by single crystal X-ray analysis).

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

*Scheme 3.18- RCM approach to the synthesis of pyridine 432.*
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).$^{155}$

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).\textsuperscript{155}

Formation of pyridine 440 was evidenced by the appearance of the signal in the \( ^1H \) 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.

![Figure 3.4 - Intermediates for the synthesis of pyridines.](image)

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).\textsuperscript{159}

Quinuclidine 447 was found to be the most efficient catalyst for this reaction.

![Scheme 3.21 - Synthesis of 3-hydroxy-2-methylene ester 447.](image)

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

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).

![Chemical structures](image)

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\(_2\)O) afforded the intermediate mesylate 457 that was converted successfully to methyl isonicotinate 456 in good overall yields (Scheme 3.24).\(^{118}\)

![Chemical reactions](image)

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).

\[
\begin{align*}
\text{Ph} & \quad \text{O} \\
\text{NHTs} & \quad \text{MeO} \\
\text{MeO} & \quad \text{Ph} \\
405 & \quad \text{ii)} \quad \text{HC(OMe)}_3, \text{MeOH} \\
\rho-\text{TsOH}, 67^\circ \text{C} & \quad 93\%
\end{align*}
\]

\[405 \rightarrow 458\]

Scheme 3.25 - Synthesis of sulfonamide 458.

\[\begin{align*}
458 & \quad \text{MeO} \\
\text{Ph} & \quad \text{NHTs} \\
\text{MeO} & \quad \text{Ph} \\
\text{NaH, DMF, 50}^\circ \text{C} & \quad 85\%
\end{align*}\]

\[458 \rightarrow 459 \rightarrow 460\]

Scheme 3.25 - Failed Synthesis of aldehyde 460.

\begin{tabular}{|c|c|}
\hline
Conditions & Yield \\
\hline
HCl, Me₂CO, H₂O, 20 °C & decomposition \\
HCl, Me₂CO, H₂O, 0 °C & decomposition \\
HCl, Me₂CO, H₂O, -20 °C & starting material \\
TMSCl, NaI, MeCN, 20 °C & decomposition \\
\hline
\end{tabular}

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).

\[ \text{Scheme 3.27} - 
\text{Yoshida's approach to the synthesis of 3-hydroxy pyridine 465.} \]

A second disconnection was also reported by Yoshida and co-workers in the same publication, in which the \( \alpha \)-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).
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.\(^\text{156}\)

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, 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).

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).
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

\[
\begin{align*}
\text{HG-II (5 mol\%)} & \quad 477 (2.5 \text{ mol\%}) \\
\text{CH}_2\text{Cl}_2, 40 ^\circ\text{C} & \quad 36\% - 82\%
\end{align*}
\]

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.\(^{36}\)

<table>
<thead>
<tr>
<th>Type I</th>
<th>Type II</th>
<th>Type III</th>
<th>Type IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>fast homodimerisation</td>
<td>slow homodimerisation</td>
<td>no homodimerisation</td>
<td>spectator to CM</td>
</tr>
<tr>
<td>▪ terminal olefins</td>
<td>▪ acrylates</td>
<td>▪ 1,1-disubstituted-olefins</td>
<td></td>
</tr>
<tr>
<td>▪ 1º allylic alcohols</td>
<td>▪ vinylketones</td>
<td>▪ 3º allylic alcohol</td>
<td></td>
</tr>
<tr>
<td>▪ allyl boronate esters</td>
<td>▪ 2º allylic alcohol</td>
<td>(protected)</td>
<td></td>
</tr>
<tr>
<td>▪ styrenes</td>
<td>▪ 3º allylic alcohol (unprotected)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ allyl phosphonates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ allyl silanes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ protected allyl amines</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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.\textsuperscript{36}

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

\section*{4.2 The CM approach to pyridines via condensation of 1,5-diketones}

Similar to the synthesis of furans \textit{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 \(\alpha,\beta\)-unsaturated-1,5-diketones into a pyridine motifs a known transformation (Scheme 2.6).\textsuperscript{101} Ideally a CM approach to the heteroaromatic \(480\) will involve the condensation of \(\alpha,\beta\)-unsaturated-1,5-diketone \(481\) formed from a CM between \(\beta,\gamma\)-unsaturated ketone \(482\) and \(\alpha,\beta\)-unsaturated ketone \(483\) (Scheme 4.2).

\begin{center}
\begin{tikzpicture}
  \node [draw] (a) at (0,0) {\textbf{480}}; \\
  \node [draw] (b) at (1.5,0) {\textbf{481}}; \\
  \node [draw] (c) at (3,0) {\textbf{482}}; \\
  \node [draw] (d) at (4.5,0) {\textbf{483}}; \\

  \draw [->] (a) -- (b) node [midway, right] {condensation \textit{NH}_3} ;
  \draw [->] (b) -- (c) node [midway, right] {CM} ;
  \draw [->] (c) -- (d) node [midway, right] {+} ;
\end{tikzpicture}
\end{center}

\textit{Scheme 4.2 - Retrosynthetic analysis for the formation of substituted pyridines via CM.}

The relatively small number of methods for the synthesis of \(\alpha,\beta\)-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 order to obtain a one pot protocol, and also to find the limitations of the CM reaction described (Scheme 4.3).

\[
\begin{align*}
\text{R}^2 & \quad \text{N} \quad \text{R}^6 \\
\text{R}^3 & \quad \text{R}^4 \\
\text{R}^5 \\
\text{NH}_3 \text{ condensation} & \quad \text{CM} \\
\text{R}^2 & \quad \text{R}^3 & \quad \text{R}^4 & \quad \text{R}^5 \\
\text{R}^6 & \quad \text{O} \quad \text{R}^4 \\
\text{O} & \quad \text{R}^6 \\
\end{align*}
\]

*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).

\[
\text{484 (MVK)}
\]

*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).
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A Cross-Metathesis approach to the synthesis of pyridines

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.

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).

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

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

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.

![Effect of reaction time](image)

**Figure 4.5 - Effect of reaction time.**

The concentration of the starting material 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.
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).
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.

![Comparison of Hoveyda Grubb's catalyst (H.G.-II) vs Zhan 1B catalyst](image)

**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).

![Effect of catalyst loading](image)

**Figure 4.9 - Effect of catalyst loading.**
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The use of chlorinated solvents such as dichloromethane is known to be ideal for the metathesis reaction, 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).

![Comparison of Toluene vs Dichloromethane](image)

*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](image)

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.

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 $J_{3,4}$ of 16.0 Hz for
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the major regioisomer 487 and a $J_{2,3}$ 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.](image)

This double bond isomerisation is likely to occur given the acidity of the internal alpha protons. This double bond isomerisation process may have occurred during the reaction conditions, due to the presence of ruthenium hydride species, 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-disubstituted pyridine 490 (Scheme 4.7). A number of conditions were screened in order to establish a highly efficient process (Table 4.2, Entry 7).

![Scheme 4.7 - Synthesis of pyridine 490.](image)
<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>NH₃ Source</th>
<th>Additive</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₂Cl₂</td>
<td>NH₃Cl</td>
<td></td>
<td>57%</td>
</tr>
<tr>
<td>2</td>
<td>CH₂Cl₂</td>
<td>NH₄BF₄</td>
<td></td>
<td>0%</td>
</tr>
<tr>
<td>3</td>
<td>CH₂Cl₂</td>
<td>NH₄OAc</td>
<td></td>
<td>0%</td>
</tr>
<tr>
<td>4</td>
<td>EtOH</td>
<td>NH₄OAc</td>
<td></td>
<td>59%</td>
</tr>
<tr>
<td>5</td>
<td>EtOH</td>
<td>NH₄OAc</td>
<td>NaOAc (10 eq.)</td>
<td>0%</td>
</tr>
<tr>
<td>6</td>
<td>EtOH</td>
<td>NH₄OAc</td>
<td>I₂ (0.1 eq.)</td>
<td>62%</td>
</tr>
<tr>
<td>7</td>
<td>EtOH</td>
<td>NH₄OAc</td>
<td>AcOH (10 eq.)</td>
<td>88%</td>
</tr>
</tbody>
</table>

Table 4.2 - Conditions for the synthesis of pyridine 490.

The formation of a 2,6-disubstituted 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 \(\alpha,\beta\)-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.](image)
Chapter four A Cross-Metathesis approach to the synthesis of pyridines

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HG-II (10 mol%), CH(_2)Cl(_2) (0.10M), 55(^\circ)C, 48 hours. Solvent remove then NH(_4)OAc (1000 mol%), AcOH (1000 mol%), EtOH, 55(^\circ)C.</td>
<td>28%</td>
</tr>
<tr>
<td>2</td>
<td>Z-1B (10 mol%), CH(_2)Cl(_2) (0.10M), 55(^\circ)C, 48 hours. Solvent remove then NH(_4)OAc (1000 mol%), AcOH (1000 mol%), EtOH, 55(^\circ)C.</td>
<td>31%</td>
</tr>
</tbody>
</table>

*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.](image)

This reaction sequence proved to be an ideal method for the synthesis of 2,6-disubstitutedpyridines 499 (Scheme 4.10).
Chapter four A Cross-Metathesis approach to the synthesis of pyridines

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). 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 $\beta,\gamma$-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 $\beta,\gamma$-unsaturated ketone 504](image)

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

![Scheme 4.12 - Synthesis of pyridine 507.](image)

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). 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. Furthermore, the acetal moiety in the CM product can be deprotected in situ during the condensation step.

![Figure 4.13 - Protected acrylic ketones.](image)

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).

![Scheme 4.13-Failed synthesis of diketone 512.](image)

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

![Scheme 4.14 - Synthesis acetal513.](image)

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 $J_{3-4}$ of 16.0Hz is a strong evidence of an $E$ configuration, which is the expected outcome of many CM process that deliver disubstituted alkenes.\textsuperscript{56}

Deprotection and \textit{in situ} condensation of acetal 513 afforded the desired pyidine 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.

![Scheme 4.15 - Synthesis of 2-substituted pyridine 514.](image)

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 $\beta,\gamma$-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).

![Scheme 4.16 - Synthesis acetal 515.](image)

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 $J_{3-4}$ 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).

\[
\begin{align*}
\text{NH}_4\text{OAc}, \text{AcOH} & \quad \text{EtOH, H}_2\text{O} \\
\end{align*}
\]

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>55 ºC</td>
<td>51%</td>
</tr>
<tr>
<td>2</td>
<td>90 ºC</td>
<td>87%</td>
</tr>
</tbody>
</table>

**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).

\[
\begin{align*}
\text{i) HOCH}_2\text{CH}_2\text{OH} & \quad \text{PhMe, PPTS} \quad \text{ii) Et}_3\text{N, CH}_2\text{Cl}_2 \\
\end{align*}
\]

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

The $\beta,\gamma$-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).
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.

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).\textsuperscript{171}

![Scheme 4.20 - Lewis acid mediated isomerisation of $\beta,\gamma$-unsaturated ketone 521.](image)

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).\textsuperscript{156}

![Figure 4.15 - Formation of hydrogen bonding between a chlorine ligand a tether hydroxyl group.](image)

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 $\alpha,\beta$-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).

\[
\begin{align*}
\text{Entry} & \quad \text{Concentration} & \quad \text{Catalyst loading} & \quad \text{Enone equivalents} & \quad \text{Yield*} \\
1 & 0.10 \text{ M} & 5\% & 500 \text{ mol}\% & 78\% \\
2 & \textbf{0.10 M} & \textbf{2.5}\% & 500 \text{ mol}\% & \textbf{97}\% \\
3 & 0.25 \text{ M} & 2.5\% & 500 \text{ mol}\% & 71\% \\
4 & 0.10 \text{ M} & 2.5\% & 250 \text{ mol}\% & 63\% \\
\end{align*}
\]

*Table 4.5 - Conditions for the synthesis of α,β-unsaturated-5-hydroxyketone 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.

\[
\begin{align*}
\text{Scheme 4.22} & \quad \text{Synthesis of α,β-unsaturated-5-hydroxyketone 528.}
\end{align*}
\]

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 $J_{3,4}$ of 16.0 Hz is a strong evidence for an E configuration.
With these results in hand, a method for converting the $\alpha$,$\beta$-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).

\[
\begin{align*}
\text{527} & \xrightarrow{\text{MsCl (150 mol%), Et$_3$N (300 mol%), CH$_2$Cl$_2$, 20 ºC}} \text{535} \\
\text{535} & \xrightarrow{\text{Et$_3$N (1200 mol%), CH$_2$Cl$_2$, 20 ºC}} \text{536}
\end{align*}
\]

*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).

\[
\begin{align*}
\text{485} & \xrightarrow{\text{HG-II (2.5 mol%), MVK (500 mol%), CH$_2$Cl$_2$ (0.10M), 55 ºC}} \text{536}
\end{align*}
\]

*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.

\[
\begin{align*}
\text{536} & \xrightarrow{\text{H$_2$N(OR)$\cdot$HCl (125 mol%), AcONa (105 mol%), H$_2$O, EtOH, 60 ºC}} \text{537, 538}
\end{align*}
\]

*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 diastereomeric 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 diastereomeric 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-electrocyclisation 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).

```
**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.
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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.

\[
\begin{array}{c}
\text{H}_2\text{N(OR)HCl (115 mol\%)} \\
\text{NaOAc (105 mol\%)} \\
1,2\text{-DCB, 55 }^\circ\text{C then} \\
\text{HCl (200 mol\%), 180 }^\circ\text{C} \\
\end{array}
\]

\[
\begin{array}{c}
\text{R = H} \\
\text{R = Me} \\
70 \% \\
80 \%
\end{array}
\]

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

The results using methoxyamine hydrochloride (H\textsubscript{2}N(OMe)HCl) were higher compared to the use of hydroxylamine hydrochloride (H\textsubscript{2}N(OH)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.
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 \(\alpha,\beta\)-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\(\text{dpba}\)) as the palladium source, \(546\) (t-Bu\(\text{P}\)) as the
phosphine ligand which is generated in situ by deprotonation of the air stable phosphonium tetrafluoroborate salt \(547\) (\(t\)-Bu\(_3\)P HBF\(_4\)), the hindered base \(548\) (Cy\(_2\)NMe) and the corresponding aryl halide (Figure 4.16).\(^{174,175}\)

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).

![Figure 4.16 - Reagents for the Heck reaction.](image)

![Figure 4.17 - 4-Bromotoluene 549.](image)

![Scheme 4.30 - Synthesis of 2,4,6-trisubstituted pyridine 551.](image)
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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.\textsuperscript{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).

\begin{center}
\includegraphics[width=0.5\textwidth]{scheme4.31.png}
\end{center}

\textit{Scheme 4.31 - Synthesis of pyridine 507.}

The synthesis of the 2,3,6-trisubstituted pyridine \textit{via} this method gave much higher overall yields, considering the CM step, compared to the use of the corresponding $\beta,\gamma$-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).

\begin{center}
\includegraphics[width=0.5\textwidth]{scheme4.32.png}
\end{center}

\textit{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 diastereomeric 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 $J_{3-4}$ 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).

![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).

![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.\textsuperscript{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).

**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 $J_{3-4}$ 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).
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 diastereoisomer (559). Also, the appearance of a signal at 6.14 ppm which corresponded to the olefinic signal C(5)H for the minor diastereoisomer (560) and with a coupling constant of $J_{5,6}$ 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).

![Diagram of CM-6π-electrocyclisation approach to polysubstituted pyridines.](image)

**Figure 4.18 - CM-6π-electrocyclisation approach 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).

![Scheme 4.37- Retrosynthetic analysis to pyridines via CM-oxidation approach.](image)

**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

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
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.\textsuperscript{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).\textsuperscript{178}
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).\(^\text{178}\)

![Scheme 4.41 - Synthesis of homoallylic alcohol 565.](image)

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.\(^\text{178}\)

![Scheme 4.42 - Synthesis of pyridine 568.](image)

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).\(^{178}\)

![Scheme 4.43 - Synthesis of homoallylic alcohol 570.](image)

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).\(^{178}\)

![Scheme 4.44 - Synthesis of pyridine 573.](image)

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.

\[
\begin{align*}
\text{Scheme 4.45} & \quad \text{Synthesis of homoallylic alcohol 575.}
\end{align*}
\]

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 ppm which corresponded to the three olefinic signals C(1’)H and C(2’)H$_2$ in both diastereomeric 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 $\alpha,\beta$-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.\textsuperscript{178}
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A Cross-Metathesis approach to the synthesis of pyridines

**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 diastereoisomer.
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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.\(^\text{180}\)

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

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

**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 $J_{5-4}$ 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).\textsuperscript{178}

\begin{center}
\includegraphics[width=\textwidth]{Scheme_4.49.png}
\end{center}

\textit{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).\textsuperscript{178}
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 $J_{4,5}$ of 8.5 Hz.

Gratifyingly, the enol ether moiety in the $\alpha,\beta$-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-diphenyl substituted pyridine could be made via this method the $\alpha,\beta$-unsaturated ketone 593 (PhVK) was prepared from commercially available chloride 592 (Scheme 4.51).
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).\textsuperscript{178}
The synthesis of 2,6-disubstituted and 2,3,6-trisubstituted 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).

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).
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![Diagram of pyridine synthesis](image)

**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).

![Diagram of alkylation](image)

**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).\footnote{178}

![Scheme 4.55 - Synthesis of unsaturated-1,5-diketones 606 and 607.](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BnBr, Et₃N, THF, 20 °C</td>
<td>SM</td>
</tr>
<tr>
<td>2</td>
<td>BnBr, DBU, THF, 20 °C</td>
<td>85% (1:1 rr)</td>
</tr>
<tr>
<td>3</td>
<td>BnBr, t-BuOK, THF, 20 °C</td>
<td>complex mixture of regioisomers</td>
</tr>
</tbody>
</table>

\textit{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 \(^1\)H NMR spectrum at 3.89 ppm, 3.75 ppm, 3.21 ppm and 2.79 ppm which corresponded to the benzylic proton C(1")H₂ in the two diastereomeric 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).\footnote{178}
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 $\alpha$-arylated product 611 was then converted to the tetrasubstituted pyridine 612 (Scheme 4.57).
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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 $\alpha$-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.\textsuperscript{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$_3$PO$_4$, 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).\textsuperscript{183}
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).\textsuperscript{178}
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).
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).\textsuperscript{178}

\begin{center}
\includegraphics[width=0.5\textwidth]{figure420.png}
\end{center}

\textit{Figure 4.20- Single crystal X-ray analysis of pyridine 619.}

\begin{center}
\includegraphics[width=0.2\textwidth]{figure421.png}
\end{center}

\textit{Figure 4.21- 2-Bromonaphthalene 620.}
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).

**Figure 4.22 - 5-Bromoindole 624.**
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$_2$NMe 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).
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.](image)

### 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.](image)

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).
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![Scheme 4.64](image)

**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.\(^\text{174}\)

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).

![Scheme 4.65](image)

**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).
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).

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).
Table 4.8 - Conditions for the failed aromatisation of bromide 644.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>KHMDS, PhMe, 0 ºC.</td>
<td>dec.</td>
</tr>
<tr>
<td>2</td>
<td>KHMDS, PhMe, -40 ºC</td>
<td>SM</td>
</tr>
<tr>
<td>3</td>
<td>DBU, 0 ºC</td>
<td>SM</td>
</tr>
<tr>
<td>4</td>
<td>t-BuOK, t-BuOH, 20 ºC</td>
<td>dec.</td>
</tr>
<tr>
<td>5</td>
<td>AlCl₃, CH₂Cl₂</td>
<td>dec.</td>
</tr>
</tbody>
</table>

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).

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).
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).

The formation of pyridine 651 was confirmed by single crystal X-ray data (Figure 4.26).
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).
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 $J_{1''-2''}$ 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).
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).

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).
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).

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 $J_{2,3}$ 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).

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).
However, formation of the desired 2-pyridone \textbf{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.

\section*{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.](image)

**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).
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).

The use of unsaturated 1,5-diketones intermediates as nucleophiles 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