PALLADIUM-CATALYZED [1,3] O→C REARRANGEMENT OF PYRANS TOWARDS FUNCTIONALIZED CYCLOHEXANONES

The University Of Sheffield.

A thesis submitted in partial fulfilment of the degree of Doctor of Philosophy

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Department of Chemistry

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"Time spent wishing is time wasted"

"When you do things right, people won't be sure you've done anything at all"

"Nothing in this world that's worth having comes easy"
I ABSTRACT

Functionalised cyclohexanones are prepared from cyclic enol ethers via a Pd-catalysed [1,3] O→C rearrangement reaction. A variety of α-arylketones are generated with excellent diastereocontrol and yield when basic phosphine ligands are used. In contrast, a Lewis acid is required to promote rearrangement of alkyl-substituted enol ether systems. These reactions proceed in excellent yield, but exhibit poor diastereocontrol.

Attempts towards an asymmetric [1,3] O→C rearrangement reaction through the use of chiral phosphine ligands are also described. After screening a wide range of ligands only 1Bu-Phox has provided reasonable levels of enantiocontrol (84% yield, 49% ee).

The preparation of enantiomerically enriched enol ethers is also described. Unfortunately, when applied to the rearrangement chemistry, two enantiopure enol ethers have each provided racemic cyclic ketones.

Aspects of the reaction mechanism are described, which resulted in the development of a kinetic resolution protocol. This led to the preparation of enantiopure enol ethers (>95% ee) and cyclic ketones.

Finally, initial chemistry into the development of a new rearrangement paradigm utilizing a cyclobutadieneiron tricarbonyl motif is discussed. Although late stage intermediates are prepared, the desired enol ethers could not be prepared, potentially due to the lability of the substrates.
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### IV ABBREVIATIONS

<table>
<thead>
<tr>
<th>Ac</th>
<th>Acetyl</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIBN</td>
<td>Azobisisobutyronitrile</td>
</tr>
<tr>
<td>Ar</td>
<td>Aryl</td>
</tr>
<tr>
<td>Aq.</td>
<td>Aqueous</td>
</tr>
<tr>
<td>BBN</td>
<td>Borabicyclo[3.3.1]nonane</td>
</tr>
<tr>
<td>BINAP</td>
<td>2,2’-Bis(diphenylphosphino)-1,1’-binaphthalene</td>
</tr>
<tr>
<td>Boc</td>
<td>Di-tert-butyl dicarbonate</td>
</tr>
<tr>
<td>Bn</td>
<td>Benzyl</td>
</tr>
<tr>
<td>Bu</td>
<td>Butyl</td>
</tr>
<tr>
<td>Bz</td>
<td>Benzoyl</td>
</tr>
<tr>
<td>CAN</td>
<td>Ceric ammonium nitrate</td>
</tr>
<tr>
<td>cat</td>
<td>Catalyst</td>
</tr>
<tr>
<td>CBS</td>
<td>Corey-Bakshi-Shibata</td>
</tr>
<tr>
<td>Cbz</td>
<td>Carboxybenzyl</td>
</tr>
<tr>
<td>CSA</td>
<td>Camphorsulfonic acid</td>
</tr>
<tr>
<td>d</td>
<td>Day</td>
</tr>
<tr>
<td>DACH</td>
<td>1,2-Diaminocyclohexane-$N,N'$-bis(2-diphenylphosphinobenzoyl)</td>
</tr>
<tr>
<td>DavePhos</td>
<td>2-Dicyclohexylphosphino-2’-(N,N’-dimethylamino)biphenyl</td>
</tr>
<tr>
<td>dba</td>
<td>Dibenzylideneacetone</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-Diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DCC</td>
<td>Dicyclohexylcarbodiimide</td>
</tr>
<tr>
<td>de</td>
<td>Diastereomeric excess</td>
</tr>
<tr>
<td>DIBAL</td>
<td>Diisobutylaluminium hydride</td>
</tr>
<tr>
<td>DIOP</td>
<td>2,3-O-Isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane</td>
</tr>
<tr>
<td>DiPhos</td>
<td>1,2-Bis(methylphenylphosphino)benzene</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-Dimethylaminopyridine</td>
</tr>
<tr>
<td>DMPU</td>
<td>1,3-Dimethyltetrahydropyrimidin-2(1H)-one</td>
</tr>
<tr>
<td>DMS</td>
<td>Dimethylsulfide</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Ms</td>
<td>Mesyl</td>
</tr>
<tr>
<td>n</td>
<td>Normal/Nano</td>
</tr>
<tr>
<td>NHC</td>
<td>N-Heterocyclic carbene</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear magnetic resonance</td>
</tr>
<tr>
<td>Nu</td>
<td>Nucleophile</td>
</tr>
<tr>
<td>p</td>
<td>Para</td>
</tr>
<tr>
<td>PCC</td>
<td>Pyridinium chlorochromate</td>
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<td>PDC</td>
<td>Pyridinium dichromate</td>
</tr>
<tr>
<td>Ph</td>
<td>Phenyl</td>
</tr>
<tr>
<td>PPTS</td>
<td>Pyridinium toluene-4-sulfonate</td>
</tr>
<tr>
<td>Pr</td>
<td>Propyl</td>
</tr>
<tr>
<td>psi</td>
<td>Pounds per square inch</td>
</tr>
<tr>
<td>PTSA</td>
<td>p-Toluenesulfonic acid monohydrate</td>
</tr>
<tr>
<td>“R”-Phox</td>
<td>2-[2-(Diphenylphosphino)phenyl]-4-“R”-2-oxazoline</td>
</tr>
<tr>
<td>rt</td>
<td>Room temperature</td>
</tr>
<tr>
<td>s/sec</td>
<td>Secondary</td>
</tr>
<tr>
<td>T/Temp</td>
<td>Temperature</td>
</tr>
<tr>
<td>t/tert</td>
<td>Tertiary</td>
</tr>
<tr>
<td>TBAF</td>
<td>Tetrabutylammonium fluoride</td>
</tr>
<tr>
<td>TBAT</td>
<td>Tetrabutylammonium triphenyldifluorosilicate</td>
</tr>
<tr>
<td>TBDPS</td>
<td>tert-Butyldiphenylsilyl</td>
</tr>
<tr>
<td>TBS</td>
<td>tert-Butyldimethylsilyl</td>
</tr>
<tr>
<td>TMEDA</td>
<td>N,N,N',N'-Tetramethyl-ethane-1,2-diamine</td>
</tr>
<tr>
<td>TMS</td>
<td>Trimethylsilyl</td>
</tr>
<tr>
<td>Tf</td>
<td>Triflyl</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin layer chromatography</td>
</tr>
<tr>
<td>TMAO</td>
<td>Trimethylamine N-oxide</td>
</tr>
<tr>
<td>Ts</td>
<td>Tosyl</td>
</tr>
<tr>
<td>uv</td>
<td>Ultraviolet</td>
</tr>
</tbody>
</table>
1 INTRODUCTION

1.1 OVERVIEW

O→C rearrangements, whether [1,3] or [3,3], have been widely studied. In particular, the rearrangement of vinyl ethers to carbonyl containing compounds has received worldwide interest. In recent years, there has been a significant effort to accomplish such transformations catalytically and stereoselectively. **Scheme 1** summarises three main general methods by which O→C rearrangements have been employed in organic chemistry.

**Transition Metal Catalysis**

**Nucleophilic Catalysis**

**Lewis Acid Catalysis**

Scheme 1
1.2 TRANSITION METAL CATALYSIS

1.2.1 FERRIER TYPE II REARRANGEMENTS

The Ferrier type II rearrangement reaction was first reported by Ferrier in 1979.\textsuperscript{3} It is a mercury-mediated synthetic route to carbocycles or carbosugars \textit{2} using a common sugar enol ether \textit{1} as the starting material (\textbf{Scheme 2}).

\begin{equation}
\begin{array}{cccc}
\text{BzO} & \text{O} & \text{TsO} & \text{OMe} \\
\text{HgCl} & \text{(1 eq)} & \text{aq. acetone} & \text{HgCl} \\
\text{BzO} & \text{O} & \text{TsO} & \text{OH} \\
\end{array}
\end{equation}

\textbf{Scheme 2}

The mechanism that is proposed involves oxymercuration followed by ring closure on to the \textit{in situ} generated aldehyde \textit{3}.

Aside from mercury(II) chloride, other mercury salts have been used in such transformations. Studies have shown that one equivalent of mercury(II) trifluoroacetate at room temperature proved more effective.\textsuperscript{4} Catalytic transformations have also been developed including the use of mercury(II) sulphate in dioxane with aqueous sulphuric acid at 50-60 °C.\textsuperscript{5}
Similar to Ferrier’s chemistry, Adam reported that palladium(II) chloride and palladium(II) acetate salts also led to the rearrangement of enol ether containing carbohydrates 4 (Scheme 3).\(^6\)

![Scheme 3](image)

Applying the above chemistry with the use of mercury(II) salts (2 mol%) led to similar results, albeit, over a longer reaction time. The main difference is in the stereochemistry of the isolated products. The palladium(II) system gives a diastereomeric ratio of 3 : 2 whilst the mercury(II) system gave a 7 : 1 mixture of diastereomers (Scheme 4).\(^7,8\)

![Scheme 4](image)
Further development of the palladium(II) rearrangement was undertaken by Ikegami, where several sugar units underwent transformation to the corresponding ketone in high yields and with excellent stereoselectivities (Scheme 5).\(^9\)

\[
\text{PdCl}_2 (5 \text{ mol%})
\]
\[
\begin{align*}
\text{dioxane}:\text{H}_2\text{O} & \quad 60 ^\circ \text{C} \\
\text{R} = \text{Bz} & \quad 68\% ; \quad (\alpha:\beta = >99:1) \\
\text{R} = \text{Bn} & \quad 81\% ; \quad (\alpha:\beta = 3:1)
\end{align*}
\]

\[
\text{PdCl}_2 (5 \text{ mol%})
\]
\[
\begin{align*}
\text{dioxane}:\text{H}_2\text{O} & \quad 60 ^\circ \text{C} \\
\text{R} = \text{Bz} & \quad 68\% ; \quad (\alpha:\beta = >99:1) \\
\text{R} = \text{Bn} & \quad 94\% ; \quad (\alpha:\beta = 9:1)
\end{align*}
\]

\[
\text{PdCl}_2 (5 \text{ mol%})
\]
\[
\begin{align*}
\text{dioxane}:\text{H}_2\text{O} & \quad 60 ^\circ \text{C} \\
\text{R} = \text{Bz} & \quad 95\% ; \quad (\alpha:\beta = >99:1) \\
\text{R} = \text{Bn} & \quad 90\% ; \quad (\alpha:\beta = >99:1)
\end{align*}
\]

**Scheme 5**

The use of palladium(II) acetate and palladium(II) sulfate salts produced significantly lower yields (<10%). A rationale for the observed stereocontrol is highlighted in Figure 1 (OR groups omitted for clarity).

![Figure 1](image)

In a similar fashion, sugar units can also undergo rearrangements with the use of a titanium(IV) complex as shown in Scheme 6.\(^{10}\)

\[
\text{BnO}_2 \text{O}_2 \text{O}_2 \text{OMe} \quad \text{Ti(O^{Pr})Cl}_3 (1.5 \text{ eq})
\]
\[
\begin{align*}
\text{CH}_2\text{Cl}_2, -78 ^\circ \text{C} & \quad 98\%
\end{align*}
\]

**Scheme 6**
Titanium(IV) chloride, a stronger Lewis acid than Ti(O\textsuperscript{t}Pr)Cl\textsubscript{3}, was initially used in this transformation however this gave a poorer yield of ~50%. Several similar sugar units can undergo this rearrangement, all with yields >80% and which exhibit a high degree of stereoselectivity. Stereocontrol is proposed to originate from an analogous intermediate to that in Figure 1.

Chemistry of a similar manner has been used to obtain cyclopentenones. Grée has demonstrated that vinylic furanoses 5 undergo skeletal rearrangement with the use of an iron catalyst under \textit{uv} irradiation (Scheme 7).\textsuperscript{11} The reaction appears to involve isomerisation of the allylic acetal to the corresponding enol ether.

![Scheme 7](image_url)

Aside from the 5-vinyl furan derivatives (R = H), various functional groups have been shown to undergo this transformation under identical conditions including aryls (R = Ph, 42% yield) and esters (R = CO\textsubscript{2}Me, 52%). Further examples expanded to 3-alkoxy-substituted derivatives, precursors to prostaglandins. These rearrangements on vinyl sugars 6 gave aldol products from which cyclopentenone 7 can be accessed via elimination (Scheme 8).

![Scheme 8](image_url)
Further examples have been recently reported where cyclohexenones can be obtained from vinyl lactols, again using the [Fe(CO)₅] catalyst (Scheme 9).\textsuperscript{12}

\[
\begin{align*}
\text{R} & \quad \text{(10 mol\%)} \quad h\nu \\
\text{[Fe(CO)₅]} & \quad \text{MsCl, Et₃N} \\
\text{[R]} & \quad \text{42-55\%} \\
\text{R} = \text{H, Me, Ph, CO₂Me} \\
\end{align*}
\]

**Scheme 9**

Compared to the cyclopentenone examples, the yields are lower. However, when applied to a vinyl pyranose 8, an excellent yield was obtained (Scheme 10).

```
\[
\begin{align*}
\text{BnO} & \quad \text{[Fe(CO)₅] (10 mol\%)} \quad h\nu \\
\text{[BnO]} & \quad \text{MsCl, NEt₃} \\
\text{[BnO]} & \quad \text{65\%} \\
\text{BnO} & \quad \text{(2 steps)} \\
\end{align*}
\]
```

**Scheme 10**
1.2.2 TSUJI-TROST REARRANGEMENT

The Tsuji-Trost reaction is the widely used palladium catalysed substitution of allylic- or propargylic-compounds with carbon nucleophiles such as enolates. In the first example reported by Tsuji, the reaction of allylpalladium chloride dimer 9 with diethyl malonate and ethyl acetoacetate with sodium at room temperature provided mono- and di-allylated products 10 and 11 (Scheme 11).\(^{13}\)

\[
\begin{align*}
\text{Pd} \quad \text{Cl} \quad \text{Pd} \quad \text{Cl} \quad + \quad R \quad \text{C} \quad \text{O} \quad \text{Et} & \quad \text{Na} \quad \rightarrow \quad \text{C} \quad \text{O} \quad \text{Et} \quad + \quad \text{C} \quad \text{O} \quad \text{Et} \\
9 & \quad R = \text{CO}_2\text{Et}, \text{COMe} \\
10 & \quad 11
\end{align*}
\]

Scheme 11

Trost’s initial investigations also concentrated on the use of allylpalladium complexes,\(^{14}\) which were made directly from olefins with palladium(II) chloride and a base. Using such complexes (12) in the presence of the anion derived from diethyl malonate 13, and triphenylphosphine, led to immediate allylation at room temperature (Scheme 12).

\[
\begin{align*}
\text{nPr} \quad \text{Pd} \quad \text{Cl} \quad \text{Pd} \quad \text{Cl} \quad \text{nPr} \quad + \quad \text{EtO}_2\text{C} \quad \text{CO}_2\text{Et} & \quad \text{PPh}_3 \quad \rightarrow \quad \text{nPr} \quad \text{Et} \quad \text{CO}_2\text{Et} \\
12 & \quad 13 \quad 14 \quad 54\% \\
15 & \quad 16 \quad 12\% \quad 34\%
\end{align*}
\]

Scheme 12
This reaction provides a mixture of three isomers; the major products were derived from nucleophilic addition at the least hindered position (14 and 15; 88%; -3 : 2; Z : E). Further studies with dimethylsulfonylacetate 17 using the same catalyst yielded a single product 18 (Scheme 13). In this case, the reaction proceeds with high regio- and stereoselectively. From this investigation, Trost made the surprising conclusion that the alkylation species can affect the regio- and stereo-selectivity.

![Scheme 13](image)

Although the exact mechanisms of these transformations were unknown at the time, Trost proposed the intermediacy of an ionic complex 19, as shown in Figure 2. This proposal was based on the observation that four equivalents of phosphine per dimer were required in order for the reaction to proceed.

![Figure 2](image)
1.2.3 O→C MIGRATIONS

Attempts to promote intramolecular trapping of \( \pi \)-allyl palladium complexes by Tsuji and co-workers showed that octenoates 20 can undergo various reactions to give a variety of products with the use a palladium catalyst, as shown in Table 1.\(^{15}\)

![Chemical Structure](image_url)

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Solvent</th>
<th>Time / h</th>
<th>% 21</th>
<th>% 22</th>
<th>% 23</th>
</tr>
</thead>
<tbody>
<tr>
<td>P(OPh)(_3)</td>
<td>MeCN</td>
<td>8</td>
<td>0</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>PBu(_3)</td>
<td>MeCN</td>
<td>1</td>
<td>85</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>PPh(_3)</td>
<td>MeCN</td>
<td>1</td>
<td>87</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>PPh(_3)</td>
<td>THF</td>
<td>8</td>
<td>37</td>
<td>57</td>
<td>0</td>
</tr>
</tbody>
</table>

**Table 1**

When the allyl enol ether 23 was subjected to the Pd(OAc)\(_2\)/PPh\(_3\) conditions in acetonitrile, the same ratio of cyclopentanone 21 and cycloheptanone 22 was obtained (87 : 13). This showed that the phosphite ligand could not catalyse the O→C rearrangement of the enol ether 23 whilst triphenyl- and tributylphosphine could.

From the results obtained, Tsuji proposed that the vinyl allyl ether 23 was an intermediate, leading onto various rearranged products. **Scheme 14** summarises these findings.
Trost has further developed methodology for the catalytic rearrangement of alkylidenetetrahydrofuran derivatives 24 to form carbocycles 25, as shown in Scheme 15.\(^\text{16}\)

When alkylidenetetrahydrofuran 24 is exposed to heat only, the cycloheptanone 26 product is formed \((\text{cf} \ \text{Claisen rearrangement})\).\(^\text{17}\) In all cases, the cyclopentanone 25 was the sole product when a palladium catalyst was employed, with no trace of cycloheptanone 26 observed. At the same time, Tsuji found that the terminal alkene 23 would undergo rearrangements to the cyclopentanone 21 and cycloheptanone 22 when palladium(II) acetate/triphenylphosphine was utilised.\(^\text{15}\)
In principle, the zwitterionic intermediate 27 could undergo competing cyclisation reactions. The influence of catalyst system, solvent and additives on the regio- and stereochemistry of the rearrangements has been studied by Trost. A summary of these investigations is shown in Table 2.\(^\text{18}\)

\[
\begin{array}{ccccccc}
X & R & \text{Catalyst} & \text{Solvent} & \text{Yield / %} & \% 29 & \% 30 & \% 31 \\
\hline
\text{O}^\text{t} \text{Bu} & \text{H} & \text{Pd(PPh}_3\text{)}_4 & \text{DMSO} & 85 & 0 & 59 & 41 \\
\text{O}^\text{t} \text{Bu} & \text{H} & \text{Pd(dppe)}_2 & \text{DMSO} & 64 & 0 & 0 & 100 \\
\text{O}^\text{t} \text{Bu} & \text{H} & \text{Pd(polymer)}^a & \text{PhMe} & 100 & 98 & 0 & 2 \\
\text{N(Et)}_2 & \text{Me} & \text{Pd(dppe)}_2 & \text{DMSO} & 62 & 56 & 0 & 44 \\
\text{N(Et)}_2 & \text{Me} & \text{Pd(dppe)}_2 & \text{Dioxane} & 93 & 100 & 0 & 0 \\
\hline
\end{array}
\]

\text{Table 2}

\(^a\) \text{Pd(polymer): derived from phosphinylated polystyrene}^\text{19}

Using tetrakis(triphenylphosphine)palladium, a mixture of cycloheptanone 31 and decarboxylated cyclopentanone 30 was obtained. This was the first time that cycloheptanones had been observed in a palladium catalysed rearrangement reaction (Table 1, \textit{vide supra}). The use of a less sterically demanding catalyst, \text{Pd(dppe)}_2, yielded cycloheptanone 31 only. However, a polymer-bound catalyst (which can be viewed as been sterically hindered) gave mainly cyclopentanone 29. Replacing the ester group with an amide, using the dppe system, gave approximately equal ratios of cyclopentanone 29 and cycloheptanone 31. Changing the solvent to dioxane yielded cyclopentanone 29 exclusively.
With respect to the intermediate palladium-π-allyl complex, the use of dimethyl sulfoxide\textsuperscript{20} and pyridine\textsuperscript{21} are known to favour syn-anti interconversion. Therefore a wide range of solvents were screened in this reaction, however there was not a significant change in the product \( E : Z \) ratios.

The structural dependence of the starting alkylidenetetrahydrofuran \( \text{24} \) on the stereochemistry of the resulting cyclopentanone was next studied.\textsuperscript{22} Specifically, both \( E \) and \( Z \) isomers of the starting material were subjected to \( O\rightarrow C \) rearrangements, using similar conditions. The use of a sterically unhindered palladium catalyst, such as \( \text{Pd(dppe)}_2 \), yielded little of the desired cyclopentanone \( \text{25} \), instead the Claisen product was obtained. However, the use of a polymer bound palladium catalyst gave ratios in excess of 17 : 1 in favour of the cyclopentanone \( \text{25} \).

Tsuji undertook related studies on the palladium-catalysed reaction of allyl acetoactates \( \text{32} \) and \( \text{33} \). In the presence of palladium, these substrates undergo a rearrangement to give allyl ketones \( \text{34} \), with the loss of carbon dioxide. Regardless of stereochemistry of the starting allyl ester, only one product was obtained, as outlined in Scheme 16.\textsuperscript{23}

\begin{center}
\includegraphics[width=\textwidth]{Scheme_16.png}
\end{center}

Scheme 16
A key step in the Tsuji-Trost chemistry is the C-C bond forming alkylation step. This type of reaction is quite general. For example, silyl enol ethers 35 can undergo allylation with a π-allyl palladium complex. Here, the π-allyl palladium complex was accessed from an allyl carbonate 36, as shown in Scheme 17.\(^{23}\)

![Scheme 17](image)

These allylations occur regiospecifically, and are dependent on the regiochemistry of the starting silyl enol ether 37 (Scheme 18).

![Scheme 18](image)

In a similar fashion, intramolecular allylations have been performed with vinyl allyl carbonates 38 and 39, and have been shown to proceed regioselectively (Scheme 19).

![Scheme 19](image)
Recently, asymmetric allylation reactions have been developed by analogy to Tsuji’s chemistry. Firstly, a phosphinoxazoline ligand 42 has been found to allylate enol silyl ethers 40 and 41 enantioselectively, as shown by Stoltz and Paquin respectively (Scheme 20).\(^{24,25}\)

\[
\begin{align*}
\text{OTMS} & \quad \text{TBAT, diallyl carbonate} & \quad [\text{Pd}_2(\text{dba})_3].\text{CH}_2\text{Cl}_2 (2.5 \text{ mol%}) & \quad \xrightarrow{42 (6.25 \text{ mol%}), \text{THF}, 25 ^\circ\text{C}} \quad 95\%; \quad 87\% \text{ ee} \\
\text{40} & \quad \text{OTMS} & \quad \text{TBAT, ethyl allyl carbonate} & \quad [(\text{Pd}(\pi-\text{C}_3\text{H}_5))\text{Cl}_2] (1.25 \text{ mol%}) & \quad \xrightarrow{42 (3.1 \text{ mol%}), \text{PhMe}, 40 ^\circ\text{C}} \quad 52-93\%; \quad 83-95\% \text{ ee} \\
\text{41} & & & & \\
\end{align*}
\]

**Scheme 20**

Likewise, the vinyl allyl carbonate decarboxylative alkylations can be performed enantioselectively. Trost has shown that the use of a bisiminoferrocene ligand 43 affords the rearranged product in excellent yields and enantioselectivity, an example is shown in Scheme 21.\(^{26}\)

\[
\begin{align*}
\text{O} & \quad \text{[Pd}_2(\text{dba})_3].\text{CH}_2\text{Cl}_2 (2.5 \text{ mol%}) & \quad \xrightarrow{43 (5.5 \text{ mol%})} & \quad \xrightarrow{\text{dioxane, 23 ^\circ\text{C}, } 2 \text{ h}} & \quad 94\%; \quad 97\% \text{ ee} \\
\text{43} & & & & \\
\end{align*}
\]

**Scheme 21**
Yields are somewhat lower with carbonates 44. However, when applied to dienyl carbonates 45, quantitative yields and excellent enantioselectivities can be obtained (Scheme 22).²⁷

Scheme 22

![Scheme 22](image-url)
1.3 NUCLEOPHILIC CATALYSTS

The rearrangement of vinyl ethers can also be accomplished by the use of a nucleophilic molecule or organocatalyst as described by Steglich and Höfle. Their examples involve the rearrangement of oxazoles 47 with pyridine to obtain oxazolinones 48 (Scheme 23).\(^{28,29}\)

\[
\begin{align*}
\text{Scheme 23}
\end{align*}
\]

Black also reported similar chemistry where 4-dimethylaminopyridine was used in the rearrangement of enol carbonates 49, via a proposed enolate intermediate 50 (Scheme 24).\(^{30}\)

\[
\begin{align*}
\text{Scheme 24}
\end{align*}
\]

Further development of this type of rearrangement has been described by Fu where a chiral nucleophilic catalyst can be used to promote an enantioselective rearrangement (Scheme 25).\(^{31}\)

\[
\begin{align*}
\text{Scheme 25}
\end{align*}
\]
A similar system has also been developed by Richards, using a cobalt metallocene rather than iron. This catalyst can be used at lower loadings but gives similar enantioselectivities (Scheme 26).\textsuperscript{32}

\begin{center}
\begin{align*}
\text{BnO} & \text{O} \\
\text{N} & \text{=O} \\
\text{Ar} & \\
\end{align*}
\end{center}

\begin{center}
\text{52 (3 mol\%)} \\
\text{PhMe, -20 °C} \\
\text{75\% ee} \\
\text{Ar} = \text{p-MeOC}_6\text{H}_4 \\
\end{center}

\begin{center}
\text{Scheme 26}
\end{center}

Other 4-dimethylaminopyridine based metal free catalysts have been used for rearrangements of similar substrates, such as in the examples by Vedejs (Scheme 27).\textsuperscript{33}

\begin{center}
\begin{align*}
\text{MeO} & \text{O} \\
\text{Ph} & \text{N} \text{=O} \\
\text{R} & \\
\end{align*}
\end{center}

\begin{center}
\text{53 (1 mol\%)} \\
\text{\textsuperscript{t}amyl alcohol, 0 °C} \\
\text{95\%, 91\% ee} \\
\text{R} = \text{p-MeOC}_6\text{H}_4 \\
\end{center}

\begin{center}
\text{Scheme 27}
\end{center}

Similar catalyst can also be used in rearrangements in other systems, such as indoles to oxindoles (Scheme 28).\textsuperscript{34,35}

\begin{center}
\begin{align*}
\text{Ph} & \text{O} \text{CO}_2\text{Ph} \\
\text{R} & \\
\end{align*}
\end{center}

\begin{center}
\text{51a or 53} \\
\text{CH}_2\text{Cl}_2, 35 °C \\
\text{PhCO}_2\text{Ph} \\
\end{center}

\begin{center}
\text{51a: 91\%, 99\% ee (R = Me)} \\
\text{53 : 93\%, 86\% ee (R = CO}_2\text{Ph)} \\
\end{center}

\begin{center}
\text{Scheme 28}
\end{center}
Carbene ligands have also been utilised not only in the rearrangements of oxazoles and indoles, but also in the case of benzofurans. The examples in Scheme 29 show how these heterocycles can be rearranged using the same NHC catalyst 54 generated in situ from a triazolium salt.\(^{36,37}\)

![Scheme 29](image)

Recently, a cascade reaction has been developed whereby oxazolinones can be obtained from amino acid derivatives 55 via \(N,N'\)-dicyclohexylcarbodiimide coupling, carbonate formation, followed by O→C rearrangement, as shown in Scheme 30.\(^{38}\)

![Scheme 30](image)

Aside from \(N\)-p-anisoyl alanine, other amino acid derivatives that have undergone this chemistry include phenylalanine (71%), leucine (70%), norleucine (73%) and tyrosine (84%).
Furthermore, Smith has shown that the exact same transformations can be performed with amidines (for example 56), as illustrated in Scheme 31. Other amidines are able to catalyse the oxazole rearrangement, albeit in lower yields.

Scheme 31
1.4 ACID CATALYSTS

1.4.1 BRØNSTED ACIDS

Ring opening of pyranyl ethers followed by cyclisation can be accomplished with Brønsted acids as reported by Ley and co-workers. Examples reported utilise triflic acid for these rearrangements, which can either be used in stoichiometric or substoichiometric amounts (Scheme 32).  

\[
\text{Scheme 32}
\]

With the cyclohexenyl ether 57, stoichiometric triflic acid was required and gave an excellent yield of rearranged product with excellent stereocontrol, although two alkene isomers were formed. However, only one product was obtained with the cyclopentenyl ether 58, which used 0.5 equivalents of acid, albeit with a lower yield.

A recent report by Terada described the synthesis of β-amino aldehydes from a hemiaminal vinyl ether 59 via a Petasis-Ferrier rearrangement. To accomplish these transformations, a chiral phosphoric acid catalyst 60 is utilised, as outlined in Table 3.
As results in the table show, higher temperatures gave better enantioselectivities. This chemistry has also been used in the synthesis of aliphatic $\beta$-amino aldehydes. Examples include replacing the benzyl group with methyl, pentyl or hexyl groups under the same conditions to give up to 86% yield of the anti-product with ee’s greater than 97%.

<table>
<thead>
<tr>
<th>$E/Z$</th>
<th>Solvent</th>
<th>Temp / °C</th>
<th>Time / h</th>
<th>Yield / %</th>
<th>ee / %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(anti : syn)</td>
<td>(anti / syn)</td>
</tr>
<tr>
<td>$Z$</td>
<td>AcOEt</td>
<td>0</td>
<td>18</td>
<td>89 (99 : 1)</td>
<td>89 / 65</td>
</tr>
<tr>
<td>$Z$</td>
<td>AcOEt</td>
<td>40</td>
<td>1.5</td>
<td>93 (97 : 3)</td>
<td>95 / 6</td>
</tr>
<tr>
<td>$Z$</td>
<td>Acetone</td>
<td>40</td>
<td>6</td>
<td>82 (99 : 1)</td>
<td>95 / 13</td>
</tr>
<tr>
<td>$E$</td>
<td>AcOEt</td>
<td>40</td>
<td>1.5</td>
<td>94 (23 : 77)</td>
<td>17 / 88</td>
</tr>
<tr>
<td>$E$</td>
<td>Acetone</td>
<td>40</td>
<td>6</td>
<td>69 (8 : 92)</td>
<td>38 / 88</td>
</tr>
</tbody>
</table>

Table 3
1.4.2 LEWIS ACIDS

Ley and co-workers have shown that pyranyl vinyl acetals with an attached nucleophilic component on the anomeric oxygen (for example 61) can undergo O→C rearrangements by the use of a Lewis acid. These processes are postulated to proceed via an oxocarbenium intermediate 62 (Scheme 33).

Scheme 33

2,6-Di-substituted pyrans 63 can undergo diastereoselective transformations in the presence of a Lewis acid. The stereochemistry is rationalised by a half-chair, oxocarbenium intermediate 64 (Scheme 34).

Scheme 34

Aside from pyran formation, substituted tetrahydrofurans can also be accessed and this approach has been employed in the synthesis of muricatetrocin C.
Further development has led to a catalytic Lewis acid system for the rearrangement of the vinyl acetals 65 to obtain trans-pyrans 66. However, using a stoichiometric amount of Lewis acid at a higher temperature leads to the cis-pyran 67 (Scheme 35).45

![Scheme 35](image)

Lewis acid catalysed stereoretentive rearrangements of pyranyl vinyl acetal 68 has also been developed recently by Rovis. The use of a mixture of Lewis acids influences the product diastereomeric ratio, as shown in Scheme 36.46

![Scheme 36](image)

The use of boron trifluoride and trimethylaluminium provides the cis product via a tight ion pair. The use of boron trifluoride only gives the trans product. From this, it was deduced that two ionic species were involved. In the case of boron trifluoride, the solvent-equilibrated ion pair equates to an intermolecular nucleophilic addition to an oxocarbenium intermediate 69 (Figure 3).
Rovis has also utilised a Lewis acid in the [1,3] rearrangement of allyl vinyl ethers 70. Although stoichiometric quantities of the Lewis acids are generally required in such rearrangements, a small number are effective at lower loadings (Table 4).

**Table 4**

<table>
<thead>
<tr>
<th>Lewis Acid</th>
<th>Yield / %</th>
<th>Ratio [1,3] : [3,3]</th>
</tr>
</thead>
<tbody>
<tr>
<td>SnCl$_4$</td>
<td>40</td>
<td>80 : 20</td>
</tr>
<tr>
<td>TiCl$_4$</td>
<td>44</td>
<td>&gt;95 : 5</td>
</tr>
<tr>
<td>EtAlCl$_2$</td>
<td>55</td>
<td>&gt;95 : 5</td>
</tr>
<tr>
<td>Me$_2$AlCl</td>
<td>73</td>
<td>&gt;95 : 5</td>
</tr>
<tr>
<td>Cu(OTf)$_2$ (10 mol%)</td>
<td>81</td>
<td>&gt;95 : 5</td>
</tr>
</tbody>
</table>

Recent chemistry in the Harrity group on O→C rearrangements have focused on the synthesis of cyclohexanones 72 from enol ethers 71, as shown in Scheme 37.
Initial chemistry focused on a Lewis acid mediated rearrangement reaction of a pyran bearing a cobalt-alkyne cluster 73 with titanium(IV) chloride (Scheme 38).\(^{49}\)

![Reagent](73.png)

Scheme 38

Aside from titanium(IV) chloride, boron trifluoride can also be used to perform such transformations in yields varying from 86-98%. Moreover, \(\text{nBu}_2\text{BOTf} \) can be used in the rearrangement of pyrans 74 with a tri-substituted enol ether bearing a butenyl moiety to give a single diastereomeric of cyclohexanone 75 (Scheme 39).\(^{50}\)

![Reagent](74.png)

Scheme 39

The use of diethylaluminium chloride promoted rearrangements of enol ethers not only gives the desired cyclohexanone, but proceeds with high degrees of stereochemical control. The diastereoselectivity of these rearrangements was rationalised by invoking a chair-like transition state 76 (Scheme 40).
Aside from cyclohexanones, similar conditions can be used in the synthesis of cyclopentanones and cycloheptanones. However, the former transformation requires three equivalents of Lewis acid and results in poorer yields (Scheme 41). \(^{51}\)

This chemistry can also be applied to the rearrangement of endo enol ethers 77 to gain disubstituted cyclobutanes 78 in high yields (Scheme 42). \(^{52}\)
2 PROJECT PLAN

2.1 BACKGROUND

Although the Lewis acid mediated O→C rearrangement chemistry of pyran-based enol ethers bearing cobalt-alkyne clusters is a very robust and an excellent method to access functionalised cyclic ketones, the fact that stoichiometric quantities of a cobalt carbonyl are required for these transformations limits its appeal.

As discussed earlier in Scheme 15, Trost has shown that vinyl allyl ethers can undergo rearrangement in the presence of a palladium catalyst to provide cyclic ketones. This chemistry seemed limited in scope as the only examples involved 5-membered ring systems in which the enolate intermediate 27 is stabilised by an electron withdrawing functional group. However using this chemistry as a basis, similar substrates to those employed in the cobalt-mediated rearrangement were subject to conditions analogous to those reports by Trost (Table 5).53

![Chemical structures](image)

**Table 5**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>% 80</th>
<th>% 81</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(PPh₃)₄ (15%), Et₂AlCl, PhMe, 50 °C</td>
<td>40</td>
<td>&lt;5</td>
</tr>
<tr>
<td>2</td>
<td>Et₂AlCl, PhMe, 50 °C</td>
<td>&lt;5</td>
<td>50</td>
</tr>
<tr>
<td>3</td>
<td>PhNO₂, 185 °C</td>
<td>&lt;5</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>Pd(PPh₃)₄ (10%), MeCN, 55 °C, 48 h</td>
<td>70</td>
<td>&lt;5</td>
</tr>
<tr>
<td>5</td>
<td>Pd(OAc)₂ (10%), P₃Bu₃ (60%), MeCN, 55 °C, 24 h</td>
<td>82</td>
<td>&lt;5</td>
</tr>
</tbody>
</table>

Subjecting enol ether 79 to palladium catalysis in the presence of a Lewis acid provided the desired cyclic ketone 80 in moderate yield (Table 5, Entry 1). Subjecting 79 to the Lewis acid alone did not generate 80, however cyclooctenone 81 was isolated (Entry 2), the result of a Claisen rearrangement of 79. This showed that Lewis
acid alone could not lead to an O→C rearrangement as reported by Rovis (Scheme 36). In a similar vein, just refluxing 79 in nitrobenzene gave 81 in excellent yields (Entry 3). Removal of the Lewis acid and using a polar solvent solely provided 80 in good yield (Entry 4). Replacing Pd(PPh₃)₄ with a more electron-rich palladium-phosphine system gave an excellent yield of 80 (Entry 5).

With a suitable catalyst system in hand, various aspects of the rearrangement were investigated. Firstly, the effect of E- and Z-allyl ether moieties on the stereoselectivity of the rearrangement was studied (Scheme 43).

Regardless of the alkene configuration of the enol ethers, the product was generated bearing an E-alkene exclusively in both cases. A rationale for this observation can be invoked upon examination of the intermediate palladium-π-allyl complex (Scheme 44).

When either enol ether 79 or 82 is exposed to palladium, intermediates 83 and 84 can be formed in both cases. These isomers can interconvert via π-σ-π process such that both are in equilibrium. The so-called syn-syn isomer 83 is favoured over 84 as an unfavourable A¹,³ interaction is present in the latter intermediate. Assuming that the
enolate collapse is irreversible, this equilibrium must be faster than cyclisation of 84 as only trace amounts of the Z-cyclic ketone 85 are observed over 80.

![Scheme 44](image)

Secondly, the effect of the enol ether substituent was examined. As summarised in **Table 6**, the catalyst system provided different results for aryl and alkyl substituents.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Conditions</th>
<th>Yield</th>
<th>cis : trans</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph 79</td>
<td>Pd(OAc)&lt;sub&gt;2&lt;/sub&gt; (10%), P&lt;sup&gt;np&lt;/sup&gt;Bu&lt;sub&gt;3&lt;/sub&gt; (60%), MeCN, 55 °C</td>
<td>80; 82%</td>
<td>&gt;5 : 95</td>
</tr>
<tr>
<td>2</td>
<td>Et 86</td>
<td>Pd(OAc)&lt;sub&gt;2&lt;/sub&gt; (10%), P&lt;sup&gt;np&lt;/sup&gt;Bu&lt;sub&gt;3&lt;/sub&gt; (40%), MeCN, 70 °C</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>Et 86</td>
<td>Pd(OAc)&lt;sub&gt;2&lt;/sub&gt; (10%), DavePhos&lt;sup&gt;b&lt;/sup&gt; (40%), Et&lt;sub&gt;2&lt;/sub&gt;AlCl&lt;sub&gt;3&lt;/sub&gt; (50%), PhMe, 55 °C</td>
<td>87; 71%</td>
<td>1 : 1.5</td>
</tr>
</tbody>
</table>

**Table 6**

<sup>a</sup>9 : 1 E : Z enol ratio in all cases

<sup>b</sup>DavePhos: 2-Dicyclohexylphosphino-2'-{N,N-dimethylamino)biphenyl. See Figure 4 for structure
Using the phenyl enol ether 79, the cyclic ketone 80 was isolated in an 82% yield, with a cis : trans ratio of <5 : 95 (Table 6, Entry 1). When identical conditions were applied to the ethyl enol ether 86, none of the desired product was observed (Entry 2). However, varying the catalyst conditions, 87 was obtained in a 71% yield, with a cis : trans ratio of 1 : 1.5 (Entry 3). In this case, the addition of a Lewis acid presumably promotes ionisation and the formation of the enolate intermediate.

The observed differences in the product diastereoselectivities could be explained by a combination of the pKₐ of the α-proton and the basicity of the phosphine. As outlined in Scheme 45, the O→C rearrangement can give either cis or trans cyclic ketones. In the case of the phenyl derivatives (80 and 88) the α-protons are relatively acidic (pKₐ ~ 17), whereas in the ethyl-substituted product 87 and 89, the acidity is less pronounced (pKₐ ~ 25). Since n-tributylphosphine is more electron rich than DavePhos (Figure 4), it is more basic, hence more likely to deprotonate the product. Upon reprotonation, the more stable configuration of the cyclic ketones will be formed.
Table 7 summarises the rearrangement chemistry of the various enol ethers that have previously been studied. Electron donating and withdrawing enol ethers can undergo rearrangement in good yields (Table 7, Entries 1 and 2). Additionally, the terminal alkene rearranges smoothly in an excellent yield (Entry 3). In line with results highlighted earlier, Z-alkene gave E-alkene cyclic ketone 93 in an 87% yield (Entry 4). Alkyl enol ether bearing a terminal alkene also gave a good yield under DavePhos conditions (Entry 5). Lastly, the ethyl enol ether with a Z-alkene substituent provides the E-alkene cyclic ketone 95 in a high yield (Entry 6).

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>R&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Method&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Yield (cis : trans)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>E-&lt;sup&gt;1&lt;/sup&gt;Bu</td>
<td>p-MeOC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>A</td>
<td>90; 66% (&gt;5 : 95)</td>
</tr>
<tr>
<td>2</td>
<td>E-&lt;sup&gt;1&lt;/sup&gt;Bu</td>
<td>p-NO&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>A</td>
<td>91; 73% (&gt;5 : 95)</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>Ph</td>
<td>A</td>
<td>92; 84% (&gt;5 : 95)</td>
</tr>
<tr>
<td>4</td>
<td>Z-(CH&lt;sub&gt;2&lt;/sub&gt;)OTBDPS</td>
<td>Ph</td>
<td>A</td>
<td>93; 87% (&gt;5 : 95)</td>
</tr>
<tr>
<td>5</td>
<td>H</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;OBn</td>
<td>B</td>
<td>94; 64% (1 : 2.5)</td>
</tr>
<tr>
<td>6</td>
<td>Z-&lt;sup&gt;1&lt;/sup&gt;Bu</td>
<td>Et</td>
<td>B</td>
<td>95; 74% (−)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Method A: Pd(OAc)<sub>2</sub> (10%), P<sup>3</sup>Bu<sub>3</sub> (60%), MeCN, 55 °C, 24 h

Method B: Pd(OAc)<sub>2</sub> (10%), DavePhos (40%), Et<sub>2</sub>AlCl (50%), PhMe, 55 °C, 24 h

<sup>b</sup> Ratio not determined
2.2 AIMS

The palladium catalyzed O→C rearrangement reactions of aryl enol ethers studied to-date have all been carbocyclic. To expand to scope of this chemistry, we wished to extend this process to include heteroaromatic substituents (Scheme 46).

Additionally, the development of an asymmetric catalyst system would have the exciting potential to generate enantioenriched cyclic ketones, which could have an important impact in the enantioselective synthesis of functionalised carbocycles (Scheme 47).
3 RESULTS AND DISCUSSION

3.1 STUDIES TOWARDS α-HETERAROMATIC CYCLOHEXANONES

Before any rearrangement chemistry could be attempted, the necessary enol ethers had to be prepared. The synthesis of the requisite enol ethers had previously been optimised within the group,\textsuperscript{50,53} and this method provided significant flexibility with respect to incorporation of the substituents at the allyl and enol ether moieties. The retrosynthetic analysis is highlighted in Scheme 49.

The enol ether substituents were to be installed by a Wittig olefination from phosphonium salt 97. The insertion of various R\textsuperscript{2} groups late in the synthesis is appealing, provided that the required aldehyde is readily available. The phosphonium salts would be obtained by treating pyranyl ethers 98 with triphenylphosphine tetrafluoroborate. Compound 98 would be prepared by the addition of vinyl metal reagents to cyclic sulfone 99.\textsuperscript{55}

The synthesis started by preparing cyclic sulfone 99 following the method of Ley and co-workers.\textsuperscript{56} Specifically, benzenesulfinic acid was added to 3,4-dihydro-2-methoxy-2H-pyran 100 to generate the desired product in 70% yield. The cyclic sulfone 99 can be synthesised on a 40 gram scale in good yield. Although the two diastereoisomers of 99 could be separated via column chromatography, the mixture was carried on through subsequent transformations as they ultimately converge to a single compound during enol ether formation (Scheme 50).
Cyclic sulfone 99 is a very versatile intermediate as various aryl and vinyl zinc reagents can be used to substitute the sulfone group. Although Ley’s studies focused on aryl and vinyl zinc reagents (some via the Grignard reagent), it was hoped that vinyl aluminium reagents would perform equally well. The reason for choosing the aluminium reagent was the relative ease of accessing the required organometallic intermediate 101 from terminal alkynes (Scheme 51).\(^5\)

In the event, alkenyl aluminium 101 was prepared via the diisobutyaluminium hydride reduction of 1-hexyne, and employed directly in situ. Pleasingly, 101 displaced the sulfone of 99 to give pyranyl ether 102 in excellent yield. Notably, 102 can be synthesised on a reasonably large scale (>5 grams).
Using chemistry that had already been developed within the laboratory, phosphonium salt 103 was readily synthesised from pyranyl ether 102 and hydrogen triphenylphosphonium tetrafluoroborate. Hydrogen triphenylphosphonium tetrafluoroborate itself can be easily made by heating triphenylphosphine at reflux with aqueous tetrafluoroboric acid, and is accessible on a multigram scale (Scheme 52).

![Scheme 52](image)

The Wittig olefination to provide the target enol ethers was also optimised within the group. The use of potassium bis(trimethylsilyl)amide was found to be the most suitable base for this transformation. It was found that the enol ethers are sensitive to both extremely basic and acid environments where isomerisation could occur to give 104 (Figure 5). Additionally, the use potassium tert-butoxide leads to the oxidation of the phosphonium salt to give 105.

![Figure 5](image)

With regard to the olefin isomerisation problem, the best method of purification of the enol ethers was found to be flash chromatography on Florisil®, which minimised isomerisation but provided the products with small traces of triphenylphosphine oxide still present. Nonetheless, using the optimised conditions, analytically pure enol ether 106 was obtained by reaction with pyridine-3-carboxaldehyde in a good yield of 76%
The yield of this reaction is dependent on the age of the potassium bis(trimethylsilyl)amide solution; if this was stored for more than one week, the olefination yields dropped significantly (40%).

With the enol ether 106 in hand, the rearrangement chemistry was attempted. Unfortunately, using the standard conditions, no cyclohexanone 107 was observed after numerous attempts (Scheme 54).

Due to the disappointment of enol ether 106 not undergoing successful rearrangement, it was decided to attempt to replicate the conditions with enol ether 79. This was synthesised using the optimised Wittig olefination conditions in good yield (Scheme 55).
The exact conditions that had provided cyclic ketone 80 in good yield previously (Scheme 43), failed to afford 80 after numerous attempts (Scheme 56).

![Scheme 56]

At this point, attempts were made to find conditions that would promote the rearrangement of 79. This included varying the solvent, palladium and phosphine ligand aspects. The findings are summarised in Table 8.

<table>
<thead>
<tr>
<th>Entry</th>
<th>P\textsuperscript{n}Bu\textsubscript{3} loading / x mol%\textsuperscript{a}</th>
<th>Yield / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>60\textsuperscript{b}</td>
<td>&lt;5\textsuperscript{c}</td>
</tr>
<tr>
<td>2</td>
<td>60\textsuperscript{d}</td>
<td>&lt;5\textsuperscript{c}</td>
</tr>
<tr>
<td>3</td>
<td>60\textsuperscript{e}</td>
<td>&lt;5\textsuperscript{c}</td>
</tr>
<tr>
<td>4</td>
<td>60\textsuperscript{f}</td>
<td>&lt;5\textsuperscript{c}</td>
</tr>
<tr>
<td>5</td>
<td>40\textsuperscript{f}</td>
<td>&lt;5\textsuperscript{c}</td>
</tr>
<tr>
<td>6</td>
<td>80\textsuperscript{f}</td>
<td>&lt;30</td>
</tr>
<tr>
<td>7</td>
<td>100\textsuperscript{f}</td>
<td>78</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Pd(OAc)\textsubscript{2} and P\textsuperscript{n}Bu\textsubscript{3} are pre-treated at 80 °C for 20 minutes prior to cooling to 55 °C then the addition of substrate 79
\textsuperscript{b}Using freshly distilled MeCN
\textsuperscript{c}Starting material recovered (>80%)
\textsuperscript{d}Using degassed MeCN (Freeze-Pump-Thaw)
\textsuperscript{e}Using an alternate Pd(OAc)\textsubscript{2} batch
\textsuperscript{f}Using freshly distilled P\textsuperscript{n}Bu\textsubscript{3}
Unfortunately, additional purification of the solvent failed to provide cyclic ketone 80. Using freshly distilled acetonitrile (Table 8, Entry 1) and thoroughly degassed acetonitrile, via the Freeze-Pump-Thaw method (Entry 2) returned starting material in both cases. An alternate batch of palladium(II) acetate was also used, an attempt to rule out the possibility of batch contamination. The rearrangement was unsuccessful in this case (Entry 3).

Our attention was then turned to the quality of the phosphine sample. $^{31}$P NMR analysis showed that phosphine contained a considerably amount of phosphine oxide. When present in the reaction, this could inhibit the catalyst, leading to low conversion. Although the phosphine was successfully purified via vacuum distillation, applying this in the rearrangement was ineffective (Entry 4). Changing the loading of the phosphine ligand was next examined; a lower loading was found to be inadequate (Entry 5), however, increasing the loading was more promising. Indeed, using 80 mol% of the phosphine gave a 30% yield (Entry 6), whilst 100 mol% gave an excellent yield of 78% after an extended reaction time (Entry 7).

Applying these conditions to enol ether 106 smoothly provided cyclic ketone 107 in an excellent yield of 73%, albeit after an extended reaction time (Scheme 57).

![Scheme 57](image)

It appears that phosphine loading is critical for the rearrangements to proceed. To examine this observation further, a detailed survey of catalyst conditions were undertaken, including varying the palladium and phosphine loading, temperature and time of both the catalyst synthesis and rearrangement. Under the optimal conditions, the palladium and phosphine were heated at reflux for 20 minutes, before cooling and then adding the enol ether. Table 9 summarises the major findings.
Adjusting the phosphine loading had a significant effect on the rearrangement. Using 20 mol% of palladium with both 80 and 120 mol% of phosphine failed to promote the rearrangement (Table 9, Entries 1 and 2). Pleasingly, a loading of 160 mol% provided cyclic ketone 80 in an excellent yield of 87%. This was however conducted at room temperature and required extensive reaction times; 64 hours for catalyst preparation and 48 hours for the rearrangement to reach completion. Increasing the temperature dramatically reduced reaction times. At 40 °C, the catalyst was prepared in 90 minutes and, after addition of the enol ether, the rearrangement was complete within 16 hours with an excellent yield of 93% (Entry 4).

Table 9

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd source, (x mol%)</th>
<th>P^3Bu / x mol%</th>
<th>Catalyst preparation temperature, time</th>
<th>Rearrangement temperature, time</th>
<th>Yield / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(OAc)_2 (20)</td>
<td>80</td>
<td>rt, 64 h</td>
<td>rt, 48 h</td>
<td>&lt;5</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OAc)_2 (20)</td>
<td>120</td>
<td>rt, 64 h</td>
<td>rt, 48 h</td>
<td>&lt;5</td>
</tr>
<tr>
<td>3</td>
<td>Pd(OAc)_2 (20)</td>
<td>160</td>
<td>rt, 64 h</td>
<td>rt, 48 h</td>
<td>87</td>
</tr>
<tr>
<td>4</td>
<td>Pd(OAc)_2 (20)</td>
<td>160</td>
<td>40 °C, 1.5 h</td>
<td>40 °C, 16 h</td>
<td>93</td>
</tr>
<tr>
<td>5</td>
<td>Pd(OAc)_2 (10)</td>
<td>40</td>
<td>40 °C, 1.5 h</td>
<td>40 °C, 16 h</td>
<td>&lt;5</td>
</tr>
<tr>
<td>6</td>
<td>Pd(OAc)_2 (10)</td>
<td>60</td>
<td>40 °C, 1.5 h</td>
<td>40 °C, 16 h</td>
<td>&lt;5</td>
</tr>
<tr>
<td>7</td>
<td>Pd(OAc)_2 (10)</td>
<td>80</td>
<td>40 °C, 1.5 h</td>
<td>40 °C, 16 h</td>
<td>59</td>
</tr>
<tr>
<td>8</td>
<td>[(allyl)PdCl]_2 (5)</td>
<td>40</td>
<td>rt, 16 h</td>
<td>40 °C, 16 h</td>
<td>&lt;5</td>
</tr>
<tr>
<td>9</td>
<td>[(allyl)PdCl]_2 (10)</td>
<td>80</td>
<td>rt, 16 h</td>
<td>40 °C, 16 h</td>
<td>70</td>
</tr>
<tr>
<td>10</td>
<td>None</td>
<td>160</td>
<td>-</td>
<td>rt, 5 days</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>None</td>
<td>160</td>
<td>-</td>
<td>40 °C, 16 h</td>
<td>0</td>
</tr>
</tbody>
</table>
The effect of the palladium loading was next examined. Using 10 mol% of the catalyst, 40 and 60 mol% of the phosphine failed to mediate the rearrangement (Entries 5 and 6). However, using 80 mol% (the same palladium-phosphine ratio as entry 4) gave the cyclic ketone in a modest 59% yield (Entry 7). When a dipalladium catalyst source was employed at 5 mol% with 40 mol% phosphine, the same palladium-phosphine ratio to entries 1 and 5, only starting material was returned (Entry 8). However, using 10 mol% dipalladium and 80 mol% phosphine afford ketone 80 in a good yield of 70% (Entry 9).

It appears that having a high phosphine loading is key for the rearrangement to proceed, and this raised the possibility that the phosphine might be promoting the rearrangement itself. To test this hypothesis, the rearrangements were conducted in the absence of palladium. Using 160 mol% of phosphine, under thermal conditions and extended reaction times, no trace of the cyclic ketone was observed (Entries 10 and 11). This confirmed that the rearrangements are palladium catalysed.

Based on these studies, the scope of the palladium catalyzed O—C rearrangement reactions have been expanded to include a heteroaromatic substituent. Although unsuccessful using previously optimised conditions, the rearrangement occurs smoothly with a higher phosphine loading. Consistent results are obtained using this method provided that the phosphine is free of major impurities.
3.2 STUDIES TOWARDS AN ENANTIOSELECTIVE REARRANGEMENT REACTION

The palladium-catalysed rearrangement with an electron rich phosphine provides the ketone product as a single diastereomer, favouring trans stereochemistry. We envisaged that a chiral phosphine ligand would provide the opportunity for enantiocontrol, and decided to explore a series of chiral phosphines towards this end. The first ligand screened was BINAP 108. Initial chemistry was conducted with the racemic form of the ligand due to the high expense of the enantiopure sample. If suitable conditions could be uncovered, enantiopure ligands would then be used in the rearrangement (Table 10).

Disappointingly, replacing n-tributylphosphine directly with BINAP under the optimised conditions, failed to afford the cyclic ketone 80 (Table 10, Entry 1). A possible reason for this catalyst system’s apparent inactivity likely lies in the fact that BINAP is insoluble in acetonitrile, therefore the active catalyst may not have formed. Unfortunately, using the same conditions but with toluene as the solvent also returned starting material (Entry 2). Although a homogeneous solution was present throughout, the low polarity of the solvent may have prevented the formation of the enolate intermediate 83 (Scheme 44, page 29).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Yield / %</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeCN, 55 °C, 48 h</td>
<td>&lt;5</td>
<td>Heterogeneous</td>
</tr>
<tr>
<td>2</td>
<td>PhMe, 55 °C, 48 h</td>
<td>&lt;5</td>
<td>Homogeneous</td>
</tr>
<tr>
<td>3</td>
<td>PhMe, Et₂AlCl (0.5 eq), 55 °C, 48 h</td>
<td>&lt;5</td>
<td>72% 81 (page 27)</td>
</tr>
<tr>
<td>4</td>
<td>MeCN:PhMe (1:1), 55 °C, 16 h</td>
<td>&lt;5</td>
<td>Homogeneous</td>
</tr>
<tr>
<td>5</td>
<td>MeCN:PhMe (2:1), 55 °C, 16 h</td>
<td>&lt;5</td>
<td>Homogeneous</td>
</tr>
</tbody>
</table>

Table 10

*a Starting material (>80%) recovered in all cases*
Upon addition of a Lewis acid, which promotes rearrangements in toluene, full conversion of the enol ether was obtained. Unfortunately, the material isolated was not that of cyclic ketone 80, but cyclooctanone 81 (Table 5, page 27). The use of Lewis acids has already been shown to promote this Claisen rearrangement (Entry 3).

The use of a mixed toluene-acetonitrile solvent system was also attempted. It was hoped that toluene would aid in the solubility of the BINAP ligand and acetonitrile would promote the rearrangement. Unfortunately, using both a 1 : 1 mixture (Entry 4) and 2 : 1 ratio (acetonitrile/toluene, Entry 5) failed to afford cyclic ketone 80, although both solutions were homogeneous throughout.

The fact that BINAP had failed to provide the cyclic ketone was surprising and we speculated that this may be due to a slow complexation with the palladium source. We therefore decided to synthesise and isolate a palladium-BINAP complex 109 according to a known procedure (Scheme 58).

\[
Pd_2(dba)_3 + (\pm)-\text{BINAP} \xrightarrow{\text{benzene, rt, 2 h}} \text{Pd}[(\pm)-\text{BINAP}](dba) 78\%
\]

\begin{center}
Scheme 58
\end{center}

Pleasingly, the complex 109 was isolated in an excellent yield of 78% and showed identical spectroscopic data to that previously reported. With a palladium(0)/phosphine catalyst in hand, its effect on the rearrangement was assessed. Unfortunately, no rearrangement was observed in either acetonitrile or acetonitrile/toluene mixtures (Scheme 59).

\begin{center}
Scheme 59
\end{center}
We next decided to study a more electron rich chiral ligand and turned our attention to commercially available \((R,R)\)-DIOP 110. Once again, under identical conditions to the BINAP mediated reactions, the rearrangement was found to be unsuccessful (Table 11, Entry 1).

<table>
<thead>
<tr>
<th>Entry</th>
<th>x mol%</th>
<th>Solvent</th>
<th>Yield / % (ee / %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30</td>
<td>MeCN</td>
<td>&lt;5 (-)(^a)</td>
</tr>
<tr>
<td>2</td>
<td>60</td>
<td>MeCN</td>
<td>&lt;5 (-)(^a)</td>
</tr>
<tr>
<td>3</td>
<td>100</td>
<td>MeCN</td>
<td>49 (-)(^b)</td>
</tr>
<tr>
<td>4</td>
<td>60</td>
<td>PhMe/(\text{Et}_2)\text{AlCl} (0.5 eq)</td>
<td>&lt;5 (-)(^a)</td>
</tr>
<tr>
<td>5</td>
<td>60</td>
<td>THF</td>
<td>&lt;5 (-)(^a)</td>
</tr>
<tr>
<td>6</td>
<td>60</td>
<td>DMF</td>
<td>&lt;5 (-)(^a)</td>
</tr>
<tr>
<td>7</td>
<td>60</td>
<td>DMSO(^c)</td>
<td>36 (&lt;5)(^d)</td>
</tr>
</tbody>
</table>

\(^a\) Starting material recovered (>80%)
\(^b\) ee not determined
\(^c\) Heated for 36 hours
\(^d\) ee determined \textit{via} chiral GC with purified material

Increasing the loading of the ligand initially proved fruitless (Entry 2), however when one equivalent was used, a modest 49% yield of the cyclic ketone 80 was isolated (Entry 3). It should be noted that in acetonitrile, the precipitation of elemental palladium black was observed in all cases. To minimise this formation, a solvent screen was undertaken. Using a variety of solvents initially did not solve the problem. Toluene (Entry 4) failed to mediate the rearrangement. Using more polar solvents, tetrahydrofuran and \(N,N\)-dimethylformamide (Entries 5 and 6) also failed, each were accompanied by formation of palladium black. Pleasingly, when dimethyl sulfoxide was utilised, no precipitation was observed. Disappointingly however, cyclic ketone
was isolated in a poor 36% yield and was determined to be essentially racemic by chiral stationary phase gas chromatography.

Other ligands screened included (R,S)-JosiPhos 111 (Table 12, Entries 1 and 2), (R,R)-DiPhos 112 (Entry 3) and (S,S)-Me-DuPhos 113 (Entries 4 and 5). Use of these ligands gave 80 in moderate yields (40-48%) and in all cases, 80 was determined to be racemic. Pleasingly, when (R)-iPrPhox 114 (Entry 6) was used, cyclohexanone 80 was obtained in a 25% ee, albeit in a moderate yield of 45%.

![Chemical Structure](image.png)

<table>
<thead>
<tr>
<th>Entry</th>
<th>L (mol%)</th>
<th>Conditions</th>
<th>Yield / % (ee / %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(R,S)-111 (40)</td>
<td>MeCN, 40 °C, 48 h</td>
<td>0 (-)(^b)</td>
</tr>
<tr>
<td>2</td>
<td>(R,S)-111 (40)</td>
<td>PhMe/Et(_2)AlCl (0.5 eq), 40 °C, 48 h</td>
<td>40 (&lt;5)(^c)</td>
</tr>
<tr>
<td>3</td>
<td>(R,R)-112 (40)</td>
<td>MeCN, 40 °C, 48 h</td>
<td>48 (&lt;5)(^c)</td>
</tr>
<tr>
<td>4</td>
<td>(S,S)-113 (20)</td>
<td>MeCN, 40 °C, 48 h</td>
<td>0 (-)(^b)</td>
</tr>
<tr>
<td>5</td>
<td>(S,S)-113 (20)</td>
<td>PhMe/Et(_2)AlCl (0.5 eq), 40 °C, 48 h</td>
<td>40 (&lt;5)(^c)</td>
</tr>
<tr>
<td>6</td>
<td>(R)-114 (60)</td>
<td>MeCN, 40 °C, 48 h</td>
<td>45 (25)(^c)</td>
</tr>
</tbody>
</table>

\(^a\)See Figure 6 for ligand structure

\(^b\)Starting material recovered (>80%)

\(^c\)ee determined via chiral-GC with purified material

Of all the ligands used in this transformation, none of them were able to provide excellent yields of cyclohexanone 80 (the highest being 112 with 48%). Additionally, only (R)-114 gave any reasonable levels of enantioselectivity.
To explore potential reasons for the consistently low levels of enantioselectivity observed in the palladium-catalysed rearrangement, we considered the potential intermediates in this process (Scheme 60). For the chiral catalyst system to give high enantioselectivity, two scenarios can be envisaged: (1) a single stereoisomer of the π-allyl complex intermediate 83 is generated that is reactive. (2) a rapidly equilibrating mixture of diastereomeric complexes are formed that have different reactivities.
One mechanism of isomerisation is via $\pi$-facial migration of the palladium-complex,\textsuperscript{61} this should be controllable by modulating reaction concentration. An alternative sequence would be via $\pi$-$\sigma$-$\pi$ interconversion, however, this process would lead to a syn-anti complex that would be unfavourable due to A\textsuperscript{1,3} strain. Therefore, in the case of substrate 79, it may be that inhibition of the $\pi$-facial isomerisation results in essentially enantiospecific rearrangement of each enantiomer of the racemic substrate, thereby providing the product in low ee.

However, if $\pi$-$\sigma$-$\pi$ interconversion is in operation, it appears that the cyclisation occurs through only two of the three possible equilibrium pairs, as no Z-olefin is observed in these reactions (indeed, as outlined earlier Z-substrates are cleanly isomerised to E-products). In order to further clarify this important issue, we opted to prepare enantioenriched substrates in an effort to explore the potential for these reactions to proceed enantiospecifically. This will be described in a later section.

This analysis highlighted that the $\pi$-$\sigma$-$\pi$ interconversion could well be promoted by the use of a terminal olefin containing substrate, as it would eliminate the unfavourable A\textsuperscript{1,3} interactions, which occur in the $\pi$-$\sigma$-$\pi$ isomerisation process at the terminal $\pi$-allyl moiety. Such rapid isomerisation may help establish chiral ligand control in the key C-C bond forming step. A proposed route for the synthesis of terminal alkene enol ether 115 is described in Scheme 61.
Using chemistry developed by Maier, pyranyl ether 117 can be obtained by cyclising alcohol 118. This alcohol can be obtained by Grignard addition to monoprotected dialdehyde 119, accessed via the ozonolysis of cyclopentene in the presence of methanol.

Indeed, ozonolysis of cyclopentene in the presence of methanol, allowed access to monoprotected aldehyde 119 in a moderate 47% yield (Scheme 62). Although not ideal, ozonolysis can be carried out on a large scale and the obtained aldehyde was found to be stable towards degradation over time.

![Scheme 62]

The addition of the vinyl Grignard reagent to the aldehyde 119 occurred smoothly (Scheme 63), yielding alcohol 118 which was of sufficient purity to be used directly in subsequent reactions.

![Scheme 63]

Immediate cyclisation of alcohol 118 in the presence in sub-stoichiometric amounts of camphorsulfonic acid yielded pyranyl acetal 117 in an excellent 75% yield over the two steps. Importantly, it was found that 117 is a volatile intermediate and care had to be taken during work up and purification stages. Although excellent yields were recorded on a gram scale, yields did diminish when milligram amounts of material were used.
From here on, the synthesis of enol ether 115 followed the procedure developed for the other enol ether substrate synthesis. Therefore, heating pyranyl ether 117 in the presence of triphenylphosphine tetrafluoroborate gave phosphonium salt 116 in excellent yield (Scheme 64).

![Scheme 64]

Phosphonium salt 116 was then subjected to the optimised Wittig conditions (Scheme 65) to give the desired enol ether 115 in good yield.

![Scheme 65]

With enol ether 115 in hand, we carried out a screen of the same chiral ligands employed with the n-butyl substrate 79. Standard rearrangement conditions were used in order to obtain a racemic sample of 121 (Table 13, Entry 1). The first chiral ligand used was (R,R)-DIOP 110 (Entry 2). Pleasingly, a good yield of 62% was obtained, the first time any rearrangement using a chiral ligand had proceeded further than 50%. Additionally, the cyclic ketone 121 was formed in 13% ee. Compared to the n-butyl substrate, the terminal alkene appeared not only to be more reactive, but also provided product with higher ee values.

Building upon the success of the DIOP ligand, other chiral ligands that were used included (R,S)-JosiPhos 111 (Entry 3), (R,R)-DiPhos 112 (Entry 4) and (S,S)-Me-DuPhos 113 (Entries 5-6). Except for DuPhos, the rearrangement progressed in very good yields, but unfortunately in all cases, 121 was found to be racemic.
At this point, we decided to use chiral ligands that had been successful for asymmetric addition to palladium-$\pi$-allyl complexes in particular those reactions which closely related to our rearrangement reaction.\textsuperscript{64} Firstly, the ligand developed by Trost, (\textit{R,\textit{R})-DACH 122 (Figure 7), was used. Unfortunately, using acetonitrile, 1,4-dioxane and toluene as solvent only starting enol ether was returned (Entries 7-9).
Finally, we returned to the (S)-PrPhox ligand 114, the only ligand to give a promising ee in the \(^n\)butyl system. Pleasingly, after only 18 hours, cyclohexanone 121 was isolated in a 93% yield, and had an ee of 33% (Entry 10). Using a bulkier analogue, the (S)-\(^t\)BuPhox 42 also gave a high yield of the rearrangement product but in 49% ee (Entry 11).

In an effort to improve the ee, several solvents were screened. These included solvents which have been previous reported for similar palladium/ligand systems. The results are summarized in Table 14.

\[
\begin{array}{|c|c|c|}
\hline
\text{Entry} & \text{Solvent} & \text{Yield / %} & \text{ee / %}^a \\
\hline
1 & \text{MeCN} & 84 & 49 \\
2 & \text{DMF} & 78 & 37 \\
3 & \text{DMSO} & 0^b & 0 \\
4 & \text{CH}_2\text{Cl}_2 & 0^b & 0 \\
5 & 1,4-dioxane & 75 & 43 \\
\hline
\end{array}
\]

Table 14

\(^a\) ee determined via chiral GC with purified material

\(^b\) Starting material recovered (>80%)

Unfortunately, none of the additional solvents screened were able to improve the yield or ee of the reaction. Of the seven chiral ligands examined, only the Phox-class of ligands afforded cyclic ketones with moderate degree of enantiopurity. In addition, the chiral catalyst system was more effective for the terminal alkene 115 than the \(^n\)butyl analogue 79.
3.3 CHEMISTRY TOWARDS THE SYNTHESIS OF ENANTIOPURE ENOL ETHERS

3.3.1 n-BUTYL ENOL ETHER

As highlighted earlier, in an effort to explore some critical stereochemical aspects of the rearrangement reaction, we identified the synthesis of enantioenriched substrates as being of potential value. However, the synthesis of enantiopure enol ethers was a task that did not look easy. Several possible routes were considered, but many were lengthy and the insertion of the required stereocentre did not appear optimal. The route that initially appeared to be the most promising is highlighted in Scheme 66.

To access the required enol ether, phosphonium salt 103 should be generated via pyranyl ether 102, as in the racemic route. We further envisaged that 102 could be accessed via cyclisation of alcohol 123. This itself could be assembled from the addition of Grignard 124 to chiral epoxide 125, making use of Jacobsen hydrolytic kinetic resolution (HKR) of racemic epoxide 125. Aldehyde 127 could be used to synthesis epoxide 125 via chloro-alcohol 126.

The synthesis began by preparing chloro-alcohol 126 using methodology developed by Lautens. Accordingly, aldehyde 127 was treated with chloromethylolithium, itself generated in situ by lithium-halogen exchange of chloroiodomethane with n-butylithium (Scheme 67).
This transformation proceeded smoothly, however, problems were encountered because of the volatility of chloro-alcohol 126. Nonetheless, by simply avoiding prolonged exposure to low vacuum, 126 was obtained in quantitative yield with no purification required.

Chloro-alcohol 126 was transformed to the epoxide 125 by a substitution reaction, promoted via in situ Finkelstein substitution of the chloride with sodium iodide (Scheme 68).

Not surprisingly, epoxide 125 was also found to be very volatile, so care was required to minimise losses. In spite of this, epoxide 125 was obtained in quantitative yield. Notably, attempts to further purify this material by column chromatography on silica gel resulted in significant decomposition. With epoxide 125 in hand, HKR was then attempted in order to obtain enantiopure epoxide 125, as shown in Scheme 69.
The catalyst was prepared in situ from its precursor (S,S)-128 (Figure 8), by treatment with acetic acid, the epoxide 125 and water. Monitoring the reaction proved troublesome as TLC analysis was impractical. In the event, the reaction was conveniently monitored by $^1$H NMR spectroscopy, where the olefin signals for the epoxide and the diol side product 129 were used to judge conversion. The time that was required for a ~50% conversion varied, depending on the room temperature and the quantities of residual solvent still present with the epoxide 125. Determination of the ee of the epoxide at this stage proved difficult. The epoxide was too volatile for chiral-GC analysis and HPLC failed to provide any separation. Therefore, the ee of the substrate was to be determined at a later stage.

![Figure 8](image)

Ring opening of the epoxide was attempted next. We expected that this reaction would occur regioselectively at the methylene of the epoxide, rather than at the allylic methine, or via conjugate addition. The Grignard 124 (Büchi Grignard) was generated in situ from the bromide acetal 130. This was added to epoxide 125 in the presence of a copper catalyst (Scheme 70).

Due to difficulties encountered in purification of this product, the crude alcohol 123 was carried on to the cyclisation stage. This occurred smoothly, where cyclisation proceeded in the presence of methanol and dry hydrochloric acid.
Unfortunately, the desired pyranyl ether 102 was not observed by $^1$H NMR spectroscopy. What was found however was the product that resulted from Grignard 124 opening at the allylic methine to give alcohol 131. This in turn cyclised to give presumably acetal 132 (Scheme 71).

The structure of 132 is proposed by comparing the $^1$H NMR spectra with those of similar substrates ($\delta$ 3.20 (dd, $J = 11.5, 9.5$ Hz, alkene-CH$_2$O)). As this route was not successful, an alternative sequence was required. As the synthesis of epoxide 125 was an attractive method for installing the allylic C-O bond enantioselectively, we devised a route that made use of this material (Scheme 72).
Phosphonium salt 103 can be accessed from hemi-acetal 133 by an analogous method to other phosphonium salt syntheses. The hemi-acetal can be obtained from reduction of lactone 134, which itself is the result of a reduction of the $\alpha,\beta$-unsaturated lactone 135. This can be acquired from the cyclisation of $\alpha,\beta$-unsaturated carboxylic acid 136, via reduction of the alkyne 137.$^{68}$ Finally, this alkyne is the result of ring opening of epoxide 125 with propiolic acid.

Using chemistry that had been developed by Carlson, terminal epoxides can be ring opened at the methylene position with the dianion of propiolic acid.$^{69}$ This is generated in situ from the acid upon addition of four equivalents of lithium diisopropylamide, as shown in Scheme 73.
This reaction was found to be very sluggish, with only a 54% yield of the desired product 137 after 3 days. The material obtained was also very difficult to handle, being a thick oil which was fairly insoluble in most common solvents, hence any attempts to purify this material returned poor yields.

Therefore, the crude material was processed to the hydrogenation stage. This was carried out using Lindlar’s catalyst at room temperature. Pleasingly, 137 was fully soluble in tetrahydrofuran and extended stirring in the presence quinoline under a balloon of hydrogen at atmospheric pressure yielded the desired alkene 136 (Scheme 74).

\[
\text{H}_2, \quad \text{Lindlar catalyst, quinoline,} \quad \begin{array}{c}
\text{OH} \\
\text{Bu}^n
\end{array} \rightarrow \begin{array}{c}
\text{OH} \\
\text{Bu}^n
\end{array} \quad \text{PhMe} \\
\text{THF, rt, 36 h} \quad \text{reflux, 16 h} \quad \text{69% (2 steps)}
\]

Scheme 74

We found alkene 136 to be equally difficult to handle so this material was taken on to the cyclisation step without purification. This was a simple process of refluxing 136 in toluene to give the desired \(\alpha,\beta\)-unsaturated lactone 135 in 69% yield over the two steps.\(^{70}\) Finally, 135 was subject to reduction to lactone 134 via 1,4-conjugate addition with Stryker’s reagent.\(^{71}\) The reaction appeared to occur smoothly, however only a trace amount of the desired lactone 134 was isolated. Extraction of the acidified aqueous phase after work-up (saturated with sodium chloride), gave a reasonable amount of reduced, ring opened material 138 (Scheme 75).

\[
\begin{array}{c}
\text{O} \\
\text{Bu}^n
\end{array} \rightarrow \begin{array}{c}
\text{O} \\
\text{Bu}^n
\end{array} \quad \begin{array}{c}
\text{CuH(PPh)}_3 \end{array}_6 (0.5 \text{ eq}) \quad \text{PhH, rt, 48 h} \\
\text{OH} \quad \text{CO}_2\text{H} \quad \text{PhMe} \quad \text{reflux, 16 h} \quad \text{18% (2 steps)}
\]

Scheme 75
Applying the crude alcohol 138 to cyclisation conditions as with the \(\alpha,\beta\)-unsaturated lactone 135 gave, after column chromatography, lactone 134 is a modest 18% yield. The major loss of material is presumed to occur in the work-up from the Stryker reduction. Several attempts were made at this point to improve the isolation yields of lactone 134 or alcohol 138. This included extracting the aqueous phase with more polar solvents, not employing a basic workup and simply removing the copper salts by filtration and cyclising the crude material. All of these attempts proved fruitless and 18% was the optimal yield recorded for the two steps.

From here on in, the chemistry performed towards enantiopure enol ether 79 had already been developed within the group.\(^5\) Accordingly, the lactone 134 was reduced with diisobutylaluminium hydride in the presence of chlorotrimethylsilane (Scheme 76).

Scheme 76

The hemi-acetal 133 was isolated cleanly, by filtering the reaction mixture through Celite\(^5\), so no further purification as attempted. As discussed in Scheme 52, pyranyl ether 133 was heated at reflux with triphenylphosphonium tetrafluoroborate to obtain the phosphonium salt 103 (Scheme 77).

Scheme 77
As previously described, the Wittig salt 103 was isolated cleanly after several triturations. Application of the previously described Wittig conditions (Scheme 55), gave non-racemic enol ether 79 after column chromatography on Florisil® (Scheme 78).

![Scheme 78]

Although a good yield of 79 was obtained, the ee (determined via chiral-GC) was found to be very low. There are a number of possible reasons for this. Either the HKR did not go to completion or that at some point in synthesis, a degree of epimerisation had occurred. Nonetheless, the rearrangement chemistry was attempted on this material. The O→C rearrangement conditions used were identical to those previously described. Pleasingly, cyclic ketone 80 was isolated in a good yield of 71% (Scheme 79).

![Scheme 79]

Disappointingly however, the product ee was found to be <5%. Considering that the starting enol ether had an ee of 35%, this shows that the rearrangement process is not stereospecific, under these conditions. The inefficiency of the enantioselective substrate synthesis meant that we were unable to carry out the rearrangement under a selection of conditions that would demonstrate whether some level of stereochemical retention was possible. We therefore sought a more efficient route to non-racemic rearrangement substrates, in particular, one that would provide higher levels of enantiomeric purity.
3.3.2 TERMINAL ALKENE ENOL ETHER

The route towards enantiopure terminal alkene phosphonium salt 116 follows a similar route in which lactone 140 is a key intermediate (Scheme 80). This lactone can be obtained via a Wittig olefination of the corresponding aldehyde 141, resulting from the oxidation of the alcohol 142. The route to alcohol 142 follows a known procedure, involving an asymmetric aldol, followed by Baeyer-Villiger oxidation.

Scheme 80

The asymmetric aldol reaction between cyclopentanone and formaldehyde was achieved using organocatalysis. The best catalyst for this transformation was found to be L-threonine (Figure 9). The reaction occurs smoothly over 48 hours and alcohol 143 was isolated in a reasonable yield of 62% after chromatography (Scheme 81).

Scheme 81

\[ \text{HCHO} \quad \text{cyclopentanone (2.5 eq)} \quad \text{CH}_2\text{Cl}_2, \text{rt}, 48 \text{ h} \quad \begin{array}{c}
\text{OH} \\
143
\end{array} \quad [\alpha]_D^{22} -92.3 (c 4.5 \text{ CHCl}_3) \\
\text{lit: } [\alpha]_D^{23} -54.7 (c 4.5 \text{ CHCl}_3, 75\% \text{ ee})^{73} \]
The organocatalysed aldol reaction can be performed on a large scale, and around 6 grams of 143 could be synthesised in a single operation. This compound can be stored in the freezer over an extended period of time with no significant decomposition. The Baeyer-Villiger oxidation also occurred smoothly, additionally on a reasonable scale, to give alcohol 142 in quantitative yield (Scheme 82).

Although excellent yields of the alcohol were obtained in this process, some optimisation was required. The reaction itself appeared to proceed to 100% conversion, however, after work-up, only 20% of the desired alcohol was isolated. It was found that a significant amount of the alcohol was soluble in aqueous media (saturated sodium thiosulfate and sodium bicarbonate are typically used upon work-up). Accordingly, aqueous work-up was avoided and the crude reaction was filtered through Celite® and purified directly by chromatography.

Unlike its precursor, alcohol 142 was found to decompose over time in the freezer, so it had to be used almost immediately. Oxidation to aldehyde 141 followed a known procedure, with pyridinium dichromate (Scheme 83). This aldehyde is reported to degrade very rapidly, therefore no attempts were made to purify and isolate it (only filtration to remove insoluble chromium salts). Instead, all the solvent was removed and the crude material was used directly in the next stage. This involved forming the terminal alkene lactone via Wittig olefination with methyl triphenylphosphonium bromide.
Lactone 140 was isolated in a reasonable 26% yield over the 2 steps after purification. This yield obtained is on a par with those reported for oxidations and Wittig reactions on similar systems. The low yield may possibly be due to the volatility of the lactone and aldehyde, as well as the ability of aldehyde 141 to degrade and the fact that the crude oxidation product was used in the Wittig olefination.

With lactone 140 in hand, the route towards the enol ether employed chemistry previous described. Accordingly, reduction of the lactone to hemi-acetal 139 occurred smoothly in excellent yield (Scheme 84).

Formation of the phosphonium salt 116 occurred in a disappointing yield of 20% (Scheme 85). The reason behind this is unknown, although the extreme volatility of hemi-acetal 139 may be factor.
Pleasingly when 116 was subjected to the Wittig reaction, enol ether 115 was obtained in a good yield of 66% (Scheme 86). Furthermore, 115 was found to have an ee of 46%, as determined by chiral-gas chromatography.

![Scheme 86](image)

When enol ether 115 was subjected to the rearrangement conditions, this substrate efficiently afforded cyclohexanone 121 in an excellent 80% yield (Scheme 87). Unfortunately however, the cyclohexanone was found to be racemic.

![Scheme 87](image)
3.4 MECHANISTIC STUDIES

Despite the setback from the results of the rearrangement of enantioenriched enol ether substrates, we set out to establish a plausible mechanism of the rearrangement. In particular, some stereochemical factors that we wanted to better understand included: (1) is the isolation of a single diastereomer of the cyclic ketone the result of kinetic diastereoselectivity, or product epimerisation at the $\alpha$-centre? (2) why does the ee of the cyclic ketones not proceed past 50%?

With respect to addressing the first question, previous studies within the laboratory showed that conducting the rearrangement with a catalyst system consisting of an electron poor phosphine/palladium source led to formation of cyclic ketone diastereoisomers 80 and 88 (Scheme 88).³³

The mixture of diastereomers was subsequently subjected to the optimal rearrangement conditions (electron rich phosphine cf Scheme 57). In the event, an increase in the $\text{trans}$-diastereomer 80 was observed (Scheme 89).
However, using the (S)-\textsuperscript{t}Bu-Phox ligand 42 in place of \textit{n}-tributylphosphine resulted in the total epimerisation of 144 albeit over a slightly extended reaction time (Scheme 90).

Scheme 90

The use of an electron rich phosphine/palladium catalyst appears to lead to epimerisation of the \textit{cis}-cyclic ketone to the \textit{trans}-isomer. However, the process as to how this happens remains unclear. It is postulated that the phosphine is basic enough to promote deprotonation of the $\alpha$-proton followed by reprotonation to obtain the \textit{trans}-cyclic ketone. Another possible process is that the ring closure reaction is reversible (Scheme 91).

Scheme 91
Studies to further determine the origin of the epimerisation were carried out by J.-O. Zirimwabagabo,\textsuperscript{76} the outcomes of which are highlighted below. Exposure of 88 to (S)-\textsuperscript{1}Bu-Phox, in the absence of a palladium source, resulted in no detectable epimerization. This result excludes the protonation/reprotonation proposal (Scheme 92).

![Scheme 92](image)

With regard to gathering evidence for the ring opening of the cyclic ketone, the alkene of 88 was reduced under H-Cube\textsuperscript{®} flow conditions to give the cyclic ketone 145. Subjection of this to a palladium/phosphine catalyst resulted in total epimerisation to 146 suggesting that epimerization via $\pi$-allyl complex formation is not in operation (Scheme 93).

![Scheme 93](image)

From these experiments, it has been postulated that a palladium-enolate intermediate is formed during the process of the rearrangement, potentially via C-H insertion (Scheme 94).
Even though this reaction mode is plausible, further experiments are required to further support this mechanism.

The focus of attention was next switched to the use of chiral ligands in the rearrangement process. The maximum ee obtain thus far was 49% utilizing the (S)-\textsuperscript{3}Bu-Phox \textsuperscript{42} ligand with enol ether \textsuperscript{115} (Table \textbf{14}, page 50). To try to understand the processes taking place, the ee of the cyclic ketone was monitored via gas chromatography by carefully taking aliquots of the reaction mixtures. The collated results of two independent reactions are highlighted in Table \textbf{15}. Additionally, the ee of the enol ether \textsuperscript{115} could also be determined under identical gas chromatography condition and thus a conversion could be calculated.
\[
\begin{align*}
\text{115} & \quad \text{Pd(OAc)}_2 (10 \text{ mol%}) \\
& \quad (S)-\text{Bu-Phox} (60 \text{ mol%}) \\
& \quad \text{MeCN, 55 }^\circ\text{C} \\
\Rightarrow & \quad \text{121}
\end{align*}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Time / h</th>
<th>Conversion / %\textsuperscript{a}</th>
<th>Cyclic ketone ee / %\textsuperscript{b}</th>
<th>Enol ether ee / %\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
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<td>6</td>
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<tr>
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<td>54</td>
<td>24</td>
<td>6</td>
</tr>
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</tr>
<tr>
<td>4\textsuperscript{c}</td>
<td>2</td>
<td>63</td>
<td>34</td>
<td>13</td>
</tr>
<tr>
<td>5\textsuperscript{c}</td>
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<td>79</td>
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<td>20</td>
</tr>
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<td>6\textsuperscript{d}</td>
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<td>7\textsuperscript{d}</td>
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<td>14\textsuperscript{c}</td>
<td>18</td>
<td>100</td>
<td>40</td>
<td>-</td>
</tr>
</tbody>
</table>

\textbf{Table 15}

\textsuperscript{a} Conversion determined via chiral GC with crude reaction material

\textsuperscript{b} ee determined via chiral GC with crude reaction material

\textsuperscript{c} Run 1

\textsuperscript{d} Run 2

These results are presented in graphical form in Figure 10.
These studies showed that the chiral catalyst itself appears to be very active. After just 30 seconds, the reaction had already reached 27% conversion (Table 15, Entry 1) and was almost complete after 7 hours (Entry 13). As the reactions progressed, the ee of the cyclic ketone slowly increased (Entries 2 to 6), albeit after proceeding without any ee initially (Entry 1). This could explain why the ee of the cyclic ketone is low after complete conversion. However, at high conversion, the ee stalls (Entries 7-13), and essentially remains the same until complete conversion. However, the most surprising aspect of the reaction is in regard of the enol ether enantioselectivity. Although the ee remains low during the initial stages of the reaction, the ee starts to climb once the ee of the cyclic ketone has reached its maximum value.

Although these results gave little insight into how the enol ether and the active catalyst are interacting, it does show that one particular enantiomer is significantly more “matched” to the system. This opens the prospect of developing a kinetic resolution protocol to obtain enantioenriched enol ethers.
3.5 DEVELOPMENT OF A KINETIC RESOLUTION PROTOCOL

To simplify the establishment of a kinetic resolution protocol, we conducted our development studies using single enol ether isomers. To do this, a procedure was required to obtain both enol ether diastereoisomers in significant amounts. This was done simply by changing the base used in the Wittig olefination. The use of potassium bis(trimethylsilyl)amide could only provide a 9 : 1 ratio of the enol ether in favour of the E-isomer. Exchanging with lithium bis(trimethylsilyl)amide improved the ratio significantly to 1 : 1 (Scheme 95).

![Scheme 95]

Although the individual isomers could be isolated via careful column chromatography on silica gel, significant amounts of decomposition occurred. However, separation with no appreciable decomposition could be achieved via preparative HPLC using a C18 column.

Optimisation of the kinetic resolution protocol was performed by J.-O. Zirimwabagabo utilizing (S)-{\textsuperscript{1}}Bu-Phox 42,\textsuperscript{76} the results of which are highlighted in Table 16. Carefully adjusting the reaction temperature and time, racemic Z-79 enol ether could be isolated in enantiopure form (up to 99% ee), and in recovered yields ranging from 33-38%. Unfortunately, the cyclic ketone 80, could not be isolated enantiopure, instead generally between -25 and -10% ee.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature / °C</th>
<th>Time / h</th>
<th>Unreacted enol ether / %</th>
<th>Cyclic ketone conv / %</th>
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<tr>
<td>1</td>
<td>60</td>
<td>1</td>
<td>38 (+66)</td>
<td>62 (-48)</td>
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<tr>
<td>2</td>
<td>60</td>
<td>4</td>
<td>33 (+96)</td>
<td>67 (-29)</td>
</tr>
<tr>
<td>3</td>
<td>60</td>
<td>16</td>
<td>15 (+99)</td>
<td>85 (-10)</td>
</tr>
<tr>
<td>4</td>
<td>60</td>
<td>40</td>
<td>10 (+99)</td>
<td>90 (-5)</td>
</tr>
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<td>-c (+47)</td>
<td>-c (-48)</td>
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</tr>
<tr>
<td>8</td>
<td>40</td>
<td>6.5</td>
<td>36 (+99)</td>
<td>63 (-5)</td>
</tr>
</tbody>
</table>

Table 16

*a* conversion and ee measure via HPLC with crude reaction material

*b* “+” ee refers to the first enantiomer observed on HPLC is the major. The reverse applies to “-” ee.

*c* conversion not calculated

Indeed, entry 8 highlights an excellent kinetic resolution protocol, providing ideal yield and ee in a consistent manner. The chemistry was found to be reproducible in my hand, utilizing both enantiomers of the tBu-Phox ligand, providing both enantiomers of enol ether Z-79 in essentially enantiopure form (Scheme 96).

Although the chemistry is reproducible, several measures needed to be taken in order to achieve this. The enol ether substrate was required to be as dry as possible as the presence of other solvents inhibited the yield significantly. The reaction vessel needed to be free of all molecular oxygen. This was achieved by placing the reaction vessel under high vacuum for a continuous two minute period before back filling with argon. This method also served to degas the dimethyl sulfoxide.
Finally, to achieve reproducible results, the reaction vessels needed to remain at the same temperature throughout. Any fluctuations resulted in poor conversion and $ee$. If all the measures were adhered to, the kinetic resolution worked reliably up to scales of 500 milligrams.

Unfortunately, applying the same reaction conditions to enol ether $E$-$79$ resulted in poor conversion and $ee$. The reason behind this observation was unclear, however with a subtle change in reaction conditions, the kinetic resolution proceeded with acceptable results (Scheme 97).
Again, all the measures outlined for the kinetic resolution of the Z-enol ether substrate apply in this case. Compared to the Z-enol ether, the E-enol ether required more forcing conditions, an increase in temperature and time. The slower reaction time implies that the E-enol ether is not as well matched to the catalyst system as the Z-enol ether.

These results can be compared quantitatively by calculating the selectivity factor ($s$-factor) for both kinetic resolutions. The $s$-factors are calculated using the following formulae:

$$s = \frac{\ln[(1 - c). (1 - ee)]}{\ln[(1 - c). (1 + ee)]}$$

where $s$ is the selectivity factor, $c$ is the conversion decimalised and $ee$ is the enantioexcess of the recovered enol ether decimalised. Generally, accepted $s$-factors for kinetic resolutions are 15.0 and above. Applying the formula to the results of the kinetic resolution, we see that the Z-enol ether has $s$-factors of 16.1 (Scheme 96, equation (1)) and 14.2 (Scheme 96, equation (2)). However, the E-enol ether has $s$-factors of 7.4 (Scheme 96, equation (1)) and 5.7 (Scheme 96, equation (2)).

With highly enantioenriched enol ethers in hand, we decided to re-examine the stereospecificity of the rearrangement. This is an extension of the chemistry discussed in chapter 3.3.1. However, rather than exclusively utilising none enantiopure phosphine ligands (such as P$n$Bu$_3$), both enantiomers of the $t$Bu-Phox, as well as the racemic form and an achiral analogue were used. All ligands used were prepared in house on a multigram scale.

The $t$Bu-Phox analogues were prepared using the protocol developed by Stoltz, as illustrated in Scheme 98. 78
An achiral analogue, 2-[2-(diphenylphosphino)phenyl]-4,5-dihydro-oxazole (H-Phox), was prepared according to the procedure by Pfaltz (Scheme 99).\textsuperscript{79}

All syntheses used cheap, commercially available reagents and could be handled without the need for oxygen-free conditions.
The rearrangements were carried out using a procedure optimised elsewhere, the results of which are highlighted in Table 17.

![Chemical structure](image)

**Table 17**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand&lt;sup&gt;a&lt;/sup&gt;</th>
<th>enol ether</th>
<th>Yield / %&lt;sup&gt;b&lt;/sup&gt;</th>
<th>ee / %&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(S)-&lt;sup&gt;−&lt;/sup&gt;1Bu-Phox</td>
<td>Z; +99% ee</td>
<td>84</td>
<td>+98</td>
</tr>
<tr>
<td>2</td>
<td>(R)-&lt;sup&gt;−&lt;/sup&gt;1Bu-Phox</td>
<td>Z; +99% ee</td>
<td>86</td>
<td>+99</td>
</tr>
<tr>
<td>3</td>
<td>(±)-&lt;sup&gt;−&lt;/sup&gt;1Bu-Phox</td>
<td>Z; +94% ee</td>
<td>83</td>
<td>+92</td>
</tr>
<tr>
<td>4</td>
<td>H-Phox</td>
<td>Z; +96% ee</td>
<td>80</td>
<td>+90</td>
</tr>
<tr>
<td>5</td>
<td>(R)-&lt;sup&gt;−&lt;/sup&gt;1Bu-Phox</td>
<td>E; +77% ee</td>
<td>74</td>
<td>+73</td>
</tr>
<tr>
<td>6</td>
<td>(±)-&lt;sup&gt;−&lt;/sup&gt;1Bu-Phox</td>
<td>E; +71% ee</td>
<td>85</td>
<td>+68</td>
</tr>
</tbody>
</table>

<sup>a</sup> See Figure 11 for ligand structures

<sup>b</sup> Yields adjusted to account for dba contamination

<sup>c</sup> ee’s measured via HPLC with isolated materials

Pleasingly, when enantiopure enol ether Z-79 was subject to rearrangement with (S)-<sup>−</sup>1Bu-Phox, very little erosion of the ee was observed. Indeed, additionally utilising (R)-<sup>−</sup>1Bu-Phox and (±)-<sup>−</sup>1Bu-Phox gave identical results. Even using a achiral variant of the Phox ligand (H-Phox), resulted in no significant ee loss. Likewise, enantioenriched E-enol ether rearrangement proceeded with good levels of stereoretention.
3.6 DETERMINATION OF A STEREOCHEMICAL MODEL

In order to establish a stereochemical model for the kinetic resolution, and to determine if the rearrangement of enantiopure enol ether occurred with retention of configuration, the absolute stereochemical assignments of enantiopure enol ethers and cyclic ketones had to be determined. To accomplish this, derivatisation of the enol ether and cyclic ketone to molecules with known absolute stereochemistry was required. Our proposed routes to accomplish this are outlined in Scheme 100.

With regard to the enol ether, selective oxidative cleavage of the enol ether-alkene would yield lactone 134. Hydrogenation of the alkene would then provide known lactone 147 (equation (1)). The cyclic ketone would undergo carbonyl reduction to cyclohexane 148, followed by oxidative cleavage/reduction to furnish alcohol 149 (equation (2)).

Our initial efforts to oxidatively cleave the enol ether employed ozonolysis. However, in this case, no enol ether or lactone based material was isolated. This is possibly due to the acidic nature of the ozone/dichloromethane combination (although the addition of small amounts of sodium hydrogen carbonate also failed to provide the desired material) and/or ozonolysis of the allylic ether olefin leading to unstable or volatile intermediates.
Instead, a milder oxidation system was utilised. The use of ruthenium(III) chloride and oxone\textsuperscript{®} in the presence water/acetonitrile proved to be the most consistent method of oxidation to the lactone intermediate (\textbf{Scheme 101})\textsuperscript{82}. Other \textit{in situ} oxidations, such as sodium metaperiodate and alternative solvent mixtures gave poor yields. This reaction was carried out on enantioenriched material derived from kinetic resolution with (S)-Phox (+99\% ee).

\begin{center}
\textbf{Scheme 101}
\end{center}

With lactone \textbf{134} in hand, attention turned to the hydrogenation. Unfortunately, standard palladium/carbon catalysed hydrogenation under a balloon of hydrogen gas failed to reduce the alkene to any extent. Gratifyingly, stirring the lactone in the presence of Adam’s catalyst for an extended period under a hydrogen atmosphere led to complete consumption (\textbf{Scheme 102}). Although only a 52\% yield of lactone \textbf{147} was isolated, it was free from contaminants.

\begin{center}
\textbf{Scheme 102}
\end{center}
A rotation value was recorded for the purified lactone and compared with the literature value. From this we concluded that the lactone 147 isolated has (S)-stereochemistry. This lactone must then have been derived from the (R)-enol ether (Note: the assignment switch is due to the different priority values in applying the Cahn-Ingold-Prelog rules and is not meant to imply a switch in configuration).

On this basis, we have established that the Z-enol ether isolated from the kinetic resolution with (S)-^1-Bu-Phox is enantiopure (R)-Z-enol ether. Therefore, (S)-Z-enol ether is the enantiomer that is matched to the (S)-^1-Bu-Phox/palladium system.

With data from the stereochemical proof in hand, we decided to formulate a proposal for the enantiocontrol observed in the kinetic resolution. The chemistry of \( \pi \)-allyl palladium complexes bearing Phox-ligands has been studied in detail with respect to the nucleophilic addition step. Specifically, nucleophiles tend to add to the carbon atom trans to the phosphine group, as this is a better \( \pi \)-acceptor than the imine-moiety. This has the effect of rendering the carbon atom trans to the phosphine ligand more electrophilic than the carbon trans to the nitrogen atom, which is not a \( \pi \)-acceptor. Additional evidence for this effect has been provided by Helmchen, where the two carbon-palladium bond lengths have been determined to be distinct via X-ray crystallography, as illustrated in Figure 12.

As such, the carbon-palladium bond trans to the phosphorus is weaker than the carbon-palladium bond trans to the nitrogen, making it more susceptible to nucleophilic attack.
In addition and with regard to stereochemical control, the exo-diastereomer of the π-allyl palladium complex is subject to less steric strain and predominates over the corresponding endo-isomer (Scheme 103).\textsuperscript{83}

![Scheme 103](image)

Taken together, these arguments have been used by several research groups to explain the stereochemical outcome of such reactions.\textsuperscript{83,86}

In the context of our kinetic resolution and based on the assumption that the oxidative insertion event follows a similar pathway to the nucleophilic addition described above (i.e. it is the reverse process), a model for the kinetic resolution of enol ethers by palladium-Phox catalysts can be put forward (Scheme 104). We propose that two modes of insertion are possible, each with the allylic ether in an equatorial orientation, and the phosphorus atom trans to the breaking C-O bond.

Coordination of the palladium-Phox in an endo like mode should be subject to steric interactions with the phosphine-phenyl group resulting in a slow ionisation step. In contrast, the other enantiomer can ionise to form the more favoured exo mode, and should therefore undergo rearrangement more easily. Assuming the rearrangement proceeds with double inversion, the product should contain epimeric stereogenicity at C-3 relative to the recovered starting material.
To ascertain further evidence for this proposal, we set about determining the absolute stereochemistry of the cyclic ketone. If the rearrangement of (R)-enol ether does indeed proceed with retention of configuration, the cyclic ketone should have (2S,3R) stereochemistry, as outlined in Scheme 105.

In the event, we carried out a rearrangement of (R)-Z-enol ether under standard conditions but using racemic Phox catalyst (Table 17). Using enol ether of +77% ee gave cyclic ketone 80 in 82% yield with +75% ee utilising (±)-t-Bu-Phox.
With enantioenriched cyclic ketone in hand, derivatisation to known compound 149 was undertaken as highlighted earlier in Scheme 100. Attempts to reduce the carbonyl group under Clemmensen conditions failed to furnish the desired cyclohexane. However, using a modification of the Wolff-Kishner reduction developed by Charette\(^{87}\) gave trans-cyclohexane 148 in an overall yield of 46\% (Scheme 106). Yields of up to 80\% were achieved on the racemic substrate. This drop in yield may be due to the presence of dibenzylideneacetone impurity in the cyclic ketone sample, which co-elutes with the cyclic ketone.

![Scheme 106]

With cyclohexane 148 in hand, oxidative cleavage was accomplished by ozonolysis followed by a reductive quench with excess sodium borohydride to yield trans-cyclohexane 149 in an overall yield of 40\% (Scheme 107).

![Scheme 107]
With derivatisation complete, the cyclohexane 149 isolated had the (1S,2S) stereochemistry. By inference therefore, the parent cyclic ketone 80 has the required (2S,3R) stereochemistry. This stereochemical proof therefore provided strong evidence that the rearrangement of the enol ethers occurs with retention of stereochemistry. A summary of the kinetic resolution/rearrangement chemistry is highlighted in Scheme 108.

Racemic enol ether Z-79 can undergo a kinetic resolution in the presence of (S)-1Bu-Phox. The recovered materials are enantiopure (R)-enol ether and enantioenriched (2R,3S) cyclic ketone. Subjection of enantiopure (R)-enol ether to a palladium/Phox ligand system leads to a rearrangement with retention of the stereocentre to yield enantiopure cyclic ketone (2S,3R)-80. This cyclic ketone is the opposite enantiomer to that isolated from the kinetic resolution, where (S)-enol ether undergoes rearrangement.
\[ (\pm)-Z-79 \]

\[
\begin{align*}
& \text{Kinetic Resolution} \\
& (S)-\text{Bu-Phox}
\end{align*}
\]

\[ (R)-Z-79 \]

\[ + \]

\[ (2R,3S)-80 \rightarrow (\pm)-80 \rightarrow (2S,3R)-80 \]

\[ +94\% \text{ ee} \]

\[ -18\% \text{ ee} \]

\[ +92\% \text{ ee} \]

Scheme 108
3.7 CONCLUSIONS AND FUTURE WORK

The scope of the palladium catalysed O→C rearrangement chemistry has been expanded to show that heteroaromatics can participate in this process. We can now conclude that the rearrangement chemistry is viable for a range of alkyl and various aryl enol ethers.

The development of a chiral palladium/ligand system showed promise. Although cyclic ketones have been formed with a modest degree of enantiopurity (~50% ee) we hoped that screening alternative ligands (especially those based on Phox) will result in an effective enantioselective process. Attempts to study the rearrangement of enantiopure enol ethers had been thwarted by challenging substrate synthesis using classical approaches.

Whilst trying to understand mechanistic details of the reaction, it became apparent that a kinetic resolution was occurring between the enol ethers and the palladium/Phox system. After extensive experimentation, an excellent kinetic resolution protocol has been developed. This led to the prospect of obtaining enol ethers with high levels of enantiopurity and recovery. Additionally, enantiopure cyclic ketones can be accessed via rearrangement of enantiopure enol ethers.

This kinetic resolution protocol is to be developed further, which will give access to enantiopure alkyl, aromatic and terminal alkene enol ether and cyclic ketones. It is hoped that these substrates can be utilised in the asymmetric total synthesis of natural products. For example, various analogues of the cannabinoid family can be obtained from enantiopure cyclic ketones (Scheme 109)

![Scheme 109]

Tetrahydrocannabinol (THC) core

Scheme 109
4 DEVELOPMENT OF AN IRON MEDIATED REARRANGEMENT SYSTEM

With the successful development of a palladium-catalysed method for the formation of functionalised cyclic ketones to complement the cobalt/Lewis acid-mediated rearrangement chemistry, attention turned further generalising this strategy. Although high degrees of success were noted with the cobalt and palladium promoted methods, there are drawbacks associated with each of the methods developed.

The propargyl enol ether rearrangement required the use of stoichiometric amounts of cobalt hexacarbonyl; cobalt compounds are listed as potential carcinogens and can impair fertility. In addition, the palladium mediated O→C rearrangement, although used in substoichiometric amounts, required the use of an expensive transition metal. Despite their high success, these drawbacks have an adverse impact on their appeal.

The new paradigm would make use of the cation stabilising potential of cyclobutadieneiron tricarbonyl complex (see chapter 4.1.2 for discussion on this effect), as illustrated in Scheme 110.

Cyclobutadieneiron tricarbonyl was chosen based on the ease of preparation on multigram scale, the diversity of chemistry that the complex can undergo (chapter 4.1.2), and the use of relatively cheap and benign starting materials.
4.1 BACKGROUND

4.1.1 CYCLOBUTADIENEIRON TRICARBONYL

The preparation of cyclobutadieneiron tricarbonyl 151 was first described by Pettit in 1965. This was achieved by exposing cis-3,4-dichlorocyclobutene 150 to diiron nonacarbonyl (Scheme 111).

\[
\text{Cl} \quad \text{Cl} \quad \text{Fe}_2(\text{CO})_9 \quad \text{Cl} \quad \text{Cl} \quad \text{Fe}(\text{CO})_3
\]

Scheme 111

Several other methods have been developed to access cyclobutadieneiron tricarbonyl 151. Rosenblum utilised photolysis of \(\alpha\)-pyrone 152 to give photoproduct 153 which, following the addition of iron pentacarbonyl gave complex 151, albeit in a poor 15% yield (Scheme 112).

\[
\text{O} \quad \text{O} \quad \text{h} \nu \quad \text{Et}_2\text{O} \quad \text{O} \quad \text{O} \quad \text{h} \nu \quad \text{Fe}(\text{CO})_5 \quad \text{Fe}(\text{CO})_3
\]

Scheme 112

Another common method was developed by Grubbs, where cis-3,4-carbonyldioxycyclobutene 154 was treated with either disodium iron tetracarbonyl or diiron nonacarbonyl to give complex 151 in a yield of 37% (Scheme 113).

\[
\text{O} \quad \text{O} \quad \text{Na}_2\text{Fe}(\text{CO})_4 \quad \text{Fe}(\text{CO})_3 \quad \text{Fe}_2(\text{CO})_9
\]

Scheme 113
Aside from the parent complex, the above methods have been utilised in the preparation of simple substituted cyclobutadieneiron tricarbonyls. Indeed, Adams prepared a variety of cyclobutenes $^{156}$, in 7 steps from diisopropyl squarate $^{155}$, which underwent complexation with diiron nonacarbonyl to yield cyclobutadieneiron tricarbonyls $^{157}$ in moderate to excellent yields (Scheme 114).$^{92}$

![Scheme 114](image)

Snapper has utilised the photolysis method to prepare a methyl ester iron complex $^{159}$ in a good yield from pyrone $^{158}$. This proved to be a useful handle to further derivatise cyclobutadienes (Scheme 115).$^{93}$

![Scheme 115](image)

King and Davis prepared highly functionalised iron complex $^{161}$ via thermal dimerisation of silyl ynamides $^{160}$. Despite the poor yields, numerous amines could be prepared which can lead to further functionalization (Scheme 116).$^{94}$

![Scheme 116](image)
4.1.2 DERIVATISATION CYCLOBUTADIENEIRON TRICARBONYL

Subsequent to his seminal work on the formation of cyclobutadieneiron tricarbonyl, Pettit showed how the complex behaves like an aromatic system. This is despite the fact that the organic ligand is a cyclic, 4 \( \pi \) electron compound that would otherwise be classified as anti-aromatic. However, X-ray crystallography of cyclobutadieneiron tricarbonyl shows that the cyclobutadiene is not a perfect square. There are two different C-C bond lengths (1.420 Å and 1.430 Å respectively). As such, the cyclobutadiene could be potentially be viewed as two individual double bonds.

Nonetheless, Scheme 117 highlights the various electrophilic aromatic substitution reactions iron complex 151 can undergo.

![Scheme 117](image-url)
Although no yields or experimental procedures were reported, iron complex **151** was documented to readily undergo Friedel-Crafts, chloromethylation, Vilsmeier-Haack formylation, mercuration, aminomethylation and deuterium exchange. The driving force behind these reactions was proposed to be the formation of a stable π-allyl-iron tricarbonyl cation **162** (*Figure 13*). Indeed, prior to reporting the formation of cyclobutadieneiron tricarbonyl, Pettit prepared examples of iron tricarbonyl allyl-salts. 

![Figure 13](image)

Schmalz has extended the π-allyl-iron tricarbonyl cation to include side chain cation stability. Based on experimental observations, alcohol **163** readily afforded ether **164** in the presence of ethanol and catalytic acid (*Scheme 118*). This substitution proceeded with retention of stereochemistry.

![Scheme 118](image)

Alcohol **163** was prepared from Corey-Bakshi-Shibata reduction of ketone **165**, a result of Friedel-Crafts acylation of cyclobutadieneiron tricarbonyl **151** (*Scheme 119*).
The retention of stereochemistry lead to Schmalz to propose the reaction intermediates as highlighted in Scheme 120. Loss of the leaving group $X$ would leave cation intermediate 166, which is in resonance with 167. This leaves a $\pi$-allyl-iron tricarbonyl cation and an alkene, in coordination with the iron tricarbonyl. Therefore, subsequent nucleophilic attack would result in retention of stereochemistry.

![Scheme 120](image.png)

In addition to undergoing electrophilic aromatic substitution, cyclobutadiene-iron tricarbonyl can be readily deprotonated with sec-butyl lithium, forming organolithium complex 168. Bunz has shown that the lithium species 168 can be quenched with a variety of electrophiles in good yields (Scheme 121).  

![Scheme 121](image.png)

<table>
<thead>
<tr>
<th>Electrophile</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{SiMe}_3\text{Cl}$</td>
<td>59%</td>
</tr>
<tr>
<td>$\text{ICH}_2\text{CH}_2\text{I}$</td>
<td>67%</td>
</tr>
<tr>
<td>$\text{SMe}_2$</td>
<td>61%</td>
</tr>
<tr>
<td>$\text{SnMe}_3\text{Cl}$</td>
<td>60%</td>
</tr>
<tr>
<td>$\text{PPh}_2\text{Cl}$</td>
<td>58%</td>
</tr>
<tr>
<td>$\text{Cl}_3\text{CCL}_3$</td>
<td>26%</td>
</tr>
<tr>
<td>$\text{MeI}$</td>
<td>58%</td>
</tr>
</tbody>
</table>
Snapper has expanded this protocol to include the preparation of organomagnesium complex 169, which was used for the addition to aldehyde 170 (Scheme 122).100

\[
\begin{align*}
\text{Snapper has expanded this protocol to include the preparation of organomagnesium complex 169, which was used for the addition to aldehyde 170 (Scheme 122).100}
\end{align*}
\]

Bunz has also demonstrated that iodo-cyclobutadieneiron tricarbonyl 171 can readily undergo a palladium catalysed cross coupling reaction with stannane 172 to afford acetylene complex 173 in good yield (Scheme 123).101

\[
\begin{align*}
\text{Bunz has also demonstrated that iodo-cyclobutadieneiron tricarbonyl 171 can readily undergo a palladium catalysed cross coupling reaction with stannane 172 to afford acetylene complex 173 in good yield (Scheme 123).101}
\end{align*}
\]

Additionally, stannanes can undergo reaction with iodo complex 171 promoted by a radical initiator.102 Indeed, in the presence of azobisisobutyronitrile, coupling occurred presumably via radical complex 174 (Scheme 124).

\[
\begin{align*}
\text{Additionally, stannanes can undergo reaction with iodo complex 171 promoted by a radical initiator.102 Indeed, in the presence of azobisisobutyronitrile, coupling occurred presumably via radical complex 174 (Scheme 124).}
\end{align*}
\]
4.1.3 CLEAVAGE OF IRON TRICARBONYL

The most common process for the removal of the iron tricarbonyl motif involves oxidative methods. Indeed, in the seminal publication relating to the preparation of cyclobutadieneiron tricarbonyl, Pettit showed that the iron tricarbonyl can be removed in the presence of ceric ammonium nitrate (Scheme 125).

\[ \text{Fe(CO)}_3 \rightarrow \text{Ce(IV)} \rightarrow \text{LiCl/acetone} \]

Scheme 125

A saturated lithium chloride solution was required to trap cyclobutadiene and to prevent polymerisation. Ceric ammonium nitrate has been used widely for the removal of iron tricarbonyl. Once removed, the resulting reactive cyclobutadiene has been trapped with a variety of alkenes in a [4+2] cycloaddition reaction. Indeed, Snapper has demonstrated that internal alkenes can readily undergo cycloadditions in the preparation of numerous natural products (Scheme 126).

\[ (\text{OC})_3\text{Fe} \rightarrow \text{CAN} \rightarrow \text{60-92\%} \]

Scheme 126

Additionally, trimethylamine N-oxide can be used in the removal of the iron tricarbonyl group. Snapper has shown that this proceeds in a similar system to those depicted in Scheme 126 with 63% yield. Notably, Paquette showed that trimethylamine N-oxide can promote [4+2] cycloadditions with external alkenes.
Expanding on the cycloadditions chemistry, Snapper has demonstrated that dienes can also undergo cycloadditions in a [4+2] fashion where the cyclobutadiene acts as the dienophile. In this way, fused cyclohexenes are generated in the presence of either ceric ammonium nitrate or trimethylamine N-oxide. These reactions generally proceed in low yield due to competing cycloadditions whereby cyclobutadiene acts as the diene component (Scheme 127).

\[
\text{(OC)}_3\text{Fe} \quad \text{CAN or} \quad \text{TMAO} \quad \text{32-66\%}
\]

Scheme 127

Aromatic motifs can also be prepared. This is accomplished by [4+2] cycloadditions between cyclobutadiene and tethered alkynes followed by thermolysis. Grubbs prepared two examples in yields of around 50% (Scheme 128).\(^{106}\)

\[
\text{(OC)}_3\text{Fe} \quad \text{CAN} \quad \text{50\%}
\]

Scheme 128

However, if the oxidation/thermolysis is performed in the presence of carbon monoxide, a formal [2+2+1] reaction takes place to provide cyclopentenones. Snapper has prepared several examples highlighted in Scheme 129.\(^{107}\)

\[
\text{(OC)}_3\text{Fe} \quad \text{CAN} \quad \text{CO} \quad \text{29-91\%}
\]

\[X = \text{O, CMe}_2, \text{NTs} \]
\[R^2 = \text{H, OR}^3\]

Scheme 129
4.2 PREPARATION OF ENOL ETHER IRON COMPLEX

We hoped to exploit the rich chemistry of the cyclobutadiene iron complexes to expand the scope of our metal promoted rearrangement chemistry. We envisaged that the desired enol ether substrates 175 could be prepared via an appropriate phosphonium salt in an identical fashion to the palladium chemistry. **Scheme 130** highlights the route sought to achieve this.

![Diagram](attachment:image.png)

**Scheme 130**

The phosphonium salt 176 would be installed using chemistry already described (**Scheme 77**, page 57) from lactol 177. This can be accessed from the intermediate 178, from addition to aldehyde 180 with a protected aldehyde organometallic 179. Aldehyde 180 can be prepared using known chemistry from parent iron complex 151.

Cyclobutadieneiron tricarbonyl 151 can be prepared on a large scale in accordance to the procedure developed by Pettit. In the event, complexation of iron to cyclobutadiene occurred smoothly in a useful 61% yield (**Scheme 131**).
Complex 151 was stable enough to be purified via Kugelrohr distillation under vacuum and not exceeding 100 °C. This had to be performed carefully to avoid contamination with triiron dodecacarbonyl. However, iron carbonyl impurities could be readily removed if necessary via silica gel chromatography with no significant decomposition. Complex 151 could be stored in the freezer under nitrogen without degradation for a significant period of time.

With iron complex 151 in hand, addition turned to the formation of aldehyde 180. This was to be accomplished via a Vilsmeier-Haack formylation. Attempts to achieve this using N,N-dimethylformamide proved fruitless, with starting material returned in all cases. Pleasingly, utilizing N-methylformanilide in excess phosphorus oxychloride gave the desired aldehyde in a 79% yield (Scheme 132). ¹⁰⁹

\[
\begin{array}{c}
\text{PhN(Me)CHO (2.3 eq)} \\
\text{POCl₃, 50 °C, 16 h}
\end{array}
\]

\[
\begin{array}{c}
\text{O} \\
\text{79%}
\end{array}
\]

\[
\begin{array}{c}
\text{H} \\
\text{Fe(CO)₃}
\end{array}
\]

\[
\begin{array}{c}
\text{180}
\end{array}
\]

\[
\begin{array}{c}
\text{151}
\end{array}
\]

Scheme 132

Like the parent complex, aldehyde 180 was stable to silica gel chromatography and prolonged freezer storage.

Installation of the methylene backbone of the pyran can be achieved utilizing acetal 183. This was prepared on a 16 gram scale starting with ethyl 4-bromobutanoate using a known procedure (Scheme 133). ¹¹⁰

Ester 181 was reduced with diisobutylaluminium hydride at low temperature to give aldehyde 182. The crude aldehyde was subsequently protected with ethylene glycol performed under Dean-Stark conditions to give acetal 183 in an excellent 87% yield over 2 steps.
Several organometallic reagents derived from acetal 183 were prepared, namely organozinc, magnesium and lithium, and reacted with aldehyde 180. Using zinc, with the aid of a Lewis acid resulted in a complex mixture of unidentifiable products. Generating the Grignard reagent prior to addition of aldehyde 180 gave the desired alcohol 184 in a moderate yield of 62%. However, this product was difficult to purify and was contaminated with a diacetal complex, a result of homo-Wurtz coupling with compound 183.

Pleasingly, utilising the organolithium reagent, derived from tert-butyllithium, smoothly gave alcohol 184. Due to the instability of this alcohol, the crude reaction mixture was taken on to the subsequent cyclisation step. Refluxing in an acetone/water mixture in the presence of acid gave lactol 177 in 66% yield over 2 steps (Scheme 134).\textsuperscript{103(b)}
Subjecting lactol 177 to the standard phosphonium salt forming conditions (Scheme 77, page 57) appeared to progress well, providing a solid with an overall yield of 70%. Unfortunately, the desired phosphonium salt 176 was not isolated. What was isolated however was aldehyde 185 (Scheme 135).
A plausible mechanism for the formation of aldehyde 185 is outlined in Scheme 136. The formed oxocarbenium 186 can break open to give an aldehyde and a cation 187 stabilised by the cyclobutadieneiron motif. This cation was quenched with triphenylphosphine to give phosphonium salt 185.

Despite this set back, the potential presence of an iron stabilised cation gave promise that the proposed O→C chemistry is viable. In one further attempt to form phosphonium salt 176, it was sought to form acetal 188. This acetal is known to form phosphonium salts (Scheme 52, page 35). Unfortunately, acetal 188 was not formed (Scheme 137).

Formation of acetal 189 presumably proceeds via a similar route to that in Scheme 136. Again, this gave further proof of the formation of a stabilised cation and further impetus that O→C chemistry would work.
Despite the setback, another route to the desired enol ether substrates was next examined. Installation of the double bond could be achieved via a Julia olefination. To achieve this, lactone 190 would be required, possibly accessible via oxidation of lactol 177 (Scheme 138).

In the event however, although several methods were attempted to perform this oxidation, in all cases, no lactone 190 was observed (Table 18). Starting material was returned in all cases. It should be noted that only mild conditions were used for the oxidations as it has been shown that manganese(IV) oxide and pyridinium chlorochromate can remove the iron tricarbonyl group in diene systems. It was feared that using harsh oxidising conditions could lead to oxidative cleavage of the iron tricarbonyl.
In light of these results, an alternative route to lactone 190 was sought. We envisaged that this compound could be accessed in a similar manner to before, but employing a carboxylic acid (Scheme 139).
As discussed in chapter 4.1.2, the parent cyclobutadieneiron tricarbonyl complex can undergo Friedel-Crafts acylation with acid anhydrides.\textsuperscript{98} We therefore hoped that by using glutaric anhydride (193) followed by reduction we could access alcohol 191.

In the event, the Friedel-Crafts reaction between cyclobutadieneiron tricarbonyl and glutaric anhydride occurred smoothly in the presence of aluminium trichloride (Scheme 140).

\begin{center}
\begin{tikzpicture}
\node (1) at (0,0) \text{Fe(CO)}_3; 
\node (2) at (1,0) \text{O} \text{O}; 
\node (3) at (2,0) \text{HO}; 
\node (4) at (3,0) \text{Fe(CO)}_3; 
\node (5) at (1.25,0) \text{O} \text{O}; 
\node (6) at (2.25,0) \text{O} \text{O}; 
\node (7) at (1,0) \$151$; 
\node (8) at (2,0) \$193$; 
\node (9) at (3,0) \$192$; 
\node (10) at (5,0) \text{CH}_2\text{Cl}_2, -20 \degree\text{C}, 4 \text{ h} \rightarrow \text{AlCl}_3 (2.1 \text{ eq}) \rightarrow \text{Scheme 140} \rightarrow 54\% \text{ yield} \rightarrow \text{TMSCHN}_2 (1.5 \text{ eq}) \rightarrow \text{MeOH:PhMe (1:3)} \rightarrow \text{rt, 1 hr} \rightarrow \text{Scheme 141} \rightarrow 80\% \rightarrow \text{Scheme 141} ;
\end{tikzpicture}
\end{center}

Although acid 192 was prepared in a reasonable yield, there were issues with isolation. Firstly, removal of the aluminium salts upon quenching with water proved extremely troublesome. This was ultimately achieved by extracting the reaction mixture with sodium hydrogen carbonate solution. Acidification followed by further extraction gave the crude acid 192. This acid was extremely difficult to handle and streaked during purification by silica gel chromatography, even after buffering with acetic acid.

In view of this, the crude acid 192 was transformed to the ester 194 using (trimethylsilyl)diazomethane (Scheme 141). This readily improved handling and purification.
Reduction of the carbonyl with excess sodium borohydride also occurred smoothly. However, this material was unstable to chromatography and so was subjected to cyclisation conditions as the crude mixture. Unfortunately, lactone 190 formation proved difficult (Scheme 142).

![Scheme 142](image)

Refluxing alcohol 195 in the presence of catalytic acid failed to furnish lactone 190. Instead, what was presumed to be alkene 196 was observed by crude NMR spectroscopy. This could potentially have formed via the loss of water leaving a stabilised cation. Pleasingly, refluxing in the absence of acid cleanly gave lactone 190 in a 69% yield over 2 steps.

With lactone 190 in hand, attention turned to forming the necessary sulfones to explore the Julia olefination. To trial this chemistry, only one sulfone was prepared. This was one that could be readily prepared on large scale. Using a known procedure, commercially available 2-mercaptopbenzothiazole 197 was alkylated with benzyl bromide to give sulfide 198 in quantitative yield (Scheme 143).
Numerous methods are reported for the oxidation of sulfides to sulfones. In the event, \( m \)-chloroperbenzoic acid readily performed the oxidation in excellent yield and sulfone 199 was isolated without the need for chromatography (Scheme 144).\(^{115}\)

Unfortunately however, attempts to perform Julia olefinations with lactone 190 and sulfone 199 to give enol ether 200 proved fruitless. Results of this study are highlighted in Table 19.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Comment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LiHMDS</td>
<td>One Pot</td>
<td>Return of Starting Materials</td>
</tr>
<tr>
<td>2</td>
<td>LiHMDS</td>
<td>Sulfone/base premix</td>
<td>Return of Starting Materials</td>
</tr>
<tr>
<td>3</td>
<td>( n )BuLi</td>
<td>One Pot</td>
<td>Observation of 201</td>
</tr>
</tbody>
</table>

Table 19
The use of lithium bis(trimethylsilyl)amide failed to promote a reaction. Starting lactone was isolated in both cases, even pre-treatment of sulfone 199 with lithium bis(trimethylsilyl)amide (which resulted in a colour change of colourless to orange) failed. Switching to a more powerful base, n-butyllithium looked promising as no lactone or sulfone was recovered. Unfortunately, hemi-acetal 201 was isolated rather than enol ether 200.

Attempts to dehydrate hemi-acetal 201 to enol ether 200 using several conditions are highlighted in **Scheme 145**.

Utilising acid, base or molecular sieves to promote dehydration did not give enol ether 200. Under room temperature conditions, starting material was returned; whereas with heating, decomposition occurred. It is possible that the enol ether was formed in all cases, but is extremely sensitive to the reaction conditions.

As access to substituted enol ethers via Wittig and Julia olefinations had proved fruitless thus far, attention turned to accessing the enol ether core by mild methods of olefination of lactone 190. Three methods were envisaged to achieve this, using known procedures for olefination of lactones. These included using a carbon tetrachloride/triphenylphosphine protocol previously employed within the group, as well as utilising Petasis and Tebbe’s reagents (**Scheme 146**).
Unfortunately in all cases, none of the desired enol ether was produced when each of these transformations was attempted. In the case of the carbon tetrachloride/triphenylphosphine conditions, only what appeared to be alkene 196 was observed. Using freshly prepared Petasis reagent, from titanocene dichloride and methylmagnesium bromide,\textsuperscript{118} failed to promote a reaction; lactone 190 was isolated with >90% recovery. Employing commercially available Tebbe’s reagent led to complete decomposition of starting material and/or products.

In a final attempt, a non-cyclic enol ether complex was targeted as it was felt that this substrate would be easier to access and would allow confirmation of the proposed O→C rearrangement. To achieve this, crude alcohol 195 was acylated with acetic anhydride to give acetate 202 (Scheme 147).
Unfortunately, attempts to form the corresponding enol ether using Petasis and Tebbe’s reagents led to total decomposition. This further highlights the potential instability of enol ether substrate bearing an iron tricarbonyl motif.

With the goal of designing substrates that could more easily incorporate the iron-diene complex, a new strategy was sought in which an O→C rearrangement would take place with a further stabilisation from an adjacent heteroatom. Inspiration for this comes from work by Scharf where methylene dioxolanes were found to undergo rearrangement in the presence of acid catalysis (Scheme 148).\textsuperscript{119}

\[\text{Scheme 148}\]

Preparation of the desired methylene dioxolane would be derived from the necessary dioxolanone. These dioxolanones were prepared via a known condensation reaction between an aldehyde and a $\alpha$-hydroxy acid.\textsuperscript{120} To test the suitability of this chemistry, trial runs were performed on known substrates before using aldehyde 180 (Scheme 149).

Attempts to prepare dioxolanones direct from the lactic acid failed. However, using the bis-trimethylsilyl protected lactic acid 203 gave promising results.\textsuperscript{121} Purification of 203 proved troublesome, however, when used crude in the condensation reaction with simple aldehydes, reactions were found to be successful. In the event, pivalaldehyde and benzaldehyde formed dioxolanones 204 and 205 with 60 and 55% yield respectively. Unfortunately, using aldehyde 180 with the same batch of 203 failed to provide dioxolanone 206 after several attempts; starting aldehyde was returned in all cases.
Finally, an alternative route to provide functionalised cyclohexanones taking advantage of the stabilised cation chemistry was sought. To this end, the route presented in Scheme 150 was explored.

The key to formation of functionalised cyclohexanones 207 is the creation of cation complex 208. Schmalz (see chapter 4.1.2, page 88) has shown that alcohols adjacent to the iron tricarbonyl complex, such as in 209, can give access to the required cation 208. These intermediate can be trapped with a variety of nucleophiles, in our case, we hoped to exploit an enol ether.
A significant component of this route was gaining access to aldehyde 210. In this respect, it has been shown that dioxinone 211 can undergo conjugate addition and alkylation via the extended enolate.\textsuperscript{122,123} The route of choice involved alkylation with allyl bromide followed by hydroboration/oxidation and a further oxidation stage.

In the event, alkylation of dioxinone 211 proved to be extremely poor yielding. After several attempts, 31\% was the highest yield recorded using excess allyl bromide (Scheme 151).
Unfortunately, hydroboration of alkene 212 proved to be rather troublesome. After utilising several borane species, as highlighted in Scheme 152, none of the desired alcohol 213 was observed. Despite the observation of complete consumption of alkene 212 by TLC analysis, it was isolated after workup in greater than 80% recovery in all cases.

We next decided to access aldehyde 210 without proceeding via alcohol 213. The initial approach to achieve this used propargyl bromide in place of allyl bromide, followed by hydroboration/oxidation. Using identical conditions to those in Scheme 151, alkylation of dioxinone 211 proceeded in a similar yield of 40% (Scheme 153).

Unfortunately, hydroboration/oxidation again failed. Using the same reagents as shown in Scheme 152 only led to the recovery of alkyne 214. This is despite conducting control reactions that confirmed that the borane reagents would undergo successful hydroboration/oxidation on simple linear alkenes and alkynes.
In a final attempt to access aldehyde 210, an oxidative cleavage protocol was used. To achieve this, 4-bromo-1-butene was used in the alkylation, under identical conditions to those previously presented (Scheme 154).

![Scheme 154](image)

Although isolated in a poor yield, alkene 215 was successful oxidised to aldehyde 210 in moderate yield using the ruthenium(III) chloride/sodium periodate protocol (Scheme 155).

![Scheme 155](image)

With aldehyde 210 in hand, attention turned to the alkylation of the cyclobutadieneiron tricarbonyl complex 151. It has been shown by Bunz, that the iron complex 151 can undergo deprotonation with sec-butyllithium. The resulting organolithium can then react with a variety of electrophiles (chapter 4.1.2). Literature chemistry was repeated beforehand to ensure reproducibility.
In the event, iron complex 151 was successfully deprotonated with sec-butyllithium and trapped with methyl iodide and chlorotrimethylsilane with yields of 45% and 50% respectively (Scheme 156). Additionally, hexanal was effectively reacted to give 216 in a good yield of 65%; this was performed in an attempt to mimic the chemistry of aldehyde 210. Unfortunately, aldehyde 210 did not undergo addition with the iron complex 151. After two attempts, none of the desired product 217 was observed and only the iron complex 151 was isolated. Aldehyde 210 was not recovered in both cases, presumably this decomposed under the reaction conditions.

Scheme 156
4.3 CONCLUSIONS AND FUTURE WORK

The development of a Lewis acid mediated rearrangement utilising the cation stabilising effects of iron tricarbonyl has thus far proved fruitless. Although late stage intermediates were prepared, the synthesis of key intermediates was unsuccessful. This is presumably due to the instability of these intermediates. Specifically the preparation of enol ether substrates failed in part due to the requirement to prepare them in media to which they were susceptible to decomposition.

All steps in the preparation of the intermediates required substantial effort to improve yield and aid isolation due to the sensitive nature of handling the iron complex, especially in case where the stabilised cation could be formed (e.g. in preparation of the phosphonium salts). Despite these draw backs, the potential presence for the desired stabilised cation gave impetus to pursue chemistry to take advantage of this.

In spite of these failures, development of a rearrangement protocol still remains a possibility. This would require a different route to prepare the desired substrates. As complexes involving the iron tricarbonyl motif are unstable, the installation of the cyclobutadieneiron tricarbonyl should occur as late as possible in the synthesis. This should improve handling of intermediates and reduce potential side reactions occurring due to the presence of the iron moiety.
5 EXPERIMENTAL

5.1 GENERAL CONSIDERATIONS

All reactions were conducted in oven or flame-dried glassware under an inert atmosphere of dry nitrogen. Flash chromatography was performed on silica gel (Davisil). Thin layer chromatography was performed on aluminium backed plates pre-coated with silica (0.2 mm, Merck DC-alufolien Kieselgel 60 F254) which were developed using standard visualizing agents: Ultra Violet light or potassium permanganate.

$^1$H NMR spectra were recorded on a Bruker AC-250 (250 MHz) or AMX-400 (400 MHz) or AV1-250 instruments or AMX-400 or AV1-400 instruments supported by an Aspect 3000 data system, unless otherwise stated. Chemical shifts are reported in ppm with the solvent resonance as the internal standard (CHCl$_3$: $\delta$ 7.27 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants ($J$) in Hz, and assignment.

$^{13}$C NMR spectra were recorded on a Bruker AC-250 (63 MHz) or AMX-400 (100 MHz) with complete proton decoupling. Chemical shifts are reported in ppm with the solvent resonance as the internal standard (CDCl$_3$: $\delta$ 77.0 ppm).

Infrared (FTIR) spectra were recorded on a Perkin Elmer Paragon 100 FTIR spectrophotometer, $\nu_{\text{max}}$ in cm$^{-1}$. Bands are characterized as broad (br), strong (s), medium (m) and weak (w). Samples were recorded as thin films from a CH$_2$Cl$_2$ solution using sodium chloride plates.

Low resolution mass spectra were recorded on Micromass Autospec, operating in E.I., C.I. or FAB mode; or a Perkin-Elmer Turbomass Benchtop GC-MS operating in either E.I. or C.I mode. High-resolution mass spectra (HRMS) recorded for accurate mass analysis, were performed on either a MicroMass LCT operating in Electrospray mode (TOF ES$^+$) or a MicroMass Prospec operating in either FAB (FAB$^+$), EI (EI$^+$) or CI (CI$^+$) mode.
Melting points, performed on recrystallised solids, were recorded on a Gallenkamp melting point apparatus and are uncorrected.

All solvents and reagents were purified using standard laboratory techniques according to methods published in “Purification of Laboratory Chemicals” by Perrin, Armarego, and Perrin (Pergamon Press, 1996), where necessary.

Determination of enantiomeric excess by GC analysis was performed using PerkinElmerArnel Autosystem XL Gas Chromatography with a β-cyclodextrin / permethyl (ASTEC, 30 m) GC column.

Determination of enantiomeric excess by HPLC analysis was performed using Gilson HPLC with a Phenomenex “Lux 3u Cellulose-1” or “Lux 3u Cellulose-2” column (250 mm x 4.6 mm).

GRUBBS’ SOLVENT SYSTEM

The departmental dry solvent system is a Grubbs type one manufactured by Innovative Technology. In an individual solvent line the untreated solvent is contained within a lined metal reservoir and, using nitrogen gas pressure, forced through a pair of metal columns each containing either activated alumina or molecular sieve. If oxygen removal is also required one of the cylinders contains a catalyst instead. The water and oxygen removal occurs as the solvent passes over the drying agents. The dried solvent is then dispensed to a suitable collection vessel under vacuum via a Schlenk line system.
5.2 PREPARATION OF SUBSTRATES

PREPARATION OF 2-(BENZENESULPHONYL)TETRAHYDRO-6-METHOXY-2H-PYRAN 99

A suspension of sodium benzenesulphinate (40 g, 242.0 mmol) in hydrochloric acid (1 M in water, 300 mL) was stirred for 45 minutes at room temperature. The reaction mixture was extracted with dichloromethane (2 x 250 mL). The combined extracts were washed with brine, dried with magnesium sulfate and concentrated to afford benzene sulphinic acid (31.1 g, 21.9 mmol). The formed benzenesulphinic acid was dissolved in dichloromethane (500 mL). 3,4-Dihydro-2-methoxy-2H-pyran 100 (24.8 g, 217.6 mmol) was added and resulting solution stirred for 2 hours at room temperature. The reaction was quenched with water and extracted with diethyl ether. The organic layer was washed with water, dried over magnesium sulfate, filtered through Celite® and concentrated. The crude residue was purified by flash chromatography on silica gel (70 : 30 petroleum ether/ethyl acetate) to give 99 as a white crystalline solid (39.0 g, 152.3 mmol, 70%) containing a 9 : 1 mixture of diastereoisomers; M.p. = 75-77 °C (Lit. 77-78 °C); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.98-7.90 (2H, m, Ar-H), 7.72-7.50 (3H, m, Ar-H), 4.75 (0.9H, t, J = 2.5 Hz, OCHSO\(_2\)Ph), 4.65 (0.9H, dd, J = 10.5, 2.5 Hz, OCHOMe), 4.40 (0.1H, dd, J = 10.5, 2.5 Hz, OCHSO\(_2\)Ph), 4.24 (0.1H, dd, J = 9.0, 2.0 Hz, OCHOMe), 3.23 (0.3H, s, CH\(_3\)), 2.93 (2.7H, s, OCH\(_3\)), 2.24-2.07 (1H, m, CH\(_{\text{CH}}\)), 1.92-1.55 (5H, m, 5 x CH\(_3\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) major isomer: \(\delta\) 136.4, 133.9, 129.4, 128.8, 99.8, 84.8, 54.7, 28.7, 22.7, 17.1.
To a solution of 1-hexyne (5.7 mL, 50.6 mmol) in toluene (50 mL) at 0 °C was added diisobutylaluminium hydride (1 M in toluene, 52.5 mL, 52.5 mmol) dropwise. The resulting solution was stirred at 40 °C for 2 hours, cooled to -78 °C and a solution of cyclic sulphone 99 (10 g, 39.0 mmol) in dichloromethane (15 mL) was added via cannula. The resulting solution was stirred at -78 °C for 2 hours, then at room temperature for a further 16 hours. The reaction was quenched with water (50 mL), filtered through Celite® and washed with ethyl acetate and the filtrate was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over magnesium sulfate and concentrated in vacuo. The crude residue was purified by flash chromatography on silica gel (92 : 2 petroleum ether/ethyl acetate) to give 102 as a yellow oil (6.3 g, 31.8 mmol, 81%) as a 4 : 1 mixture of diastereoisomers; 1H NMR (400 MHz, CDCl3): δ 5.71 (1H, dtd, J = 15.0, 6.5, 1.0 Hz, CH₂-alkene-H), 5.54-5.40 (0.8H, ddt, J = 15.0, 7.0, 1.5 Hz, CH-alkene-H and 0.2H, m, CH-alkene-H), 4.73 (0.8H, m, OCHO₉me), 4.34 (0.2H, d, J = 9.0, 2.0 Hz, OCHOMe), 4.17-4.08 (0.8H, m, pyran-CH₂), 3.88-3.82 (0.2H, m, pyran-OCH), 3.49 (0.6H, s, OCH₃), 3.37 (2.4H, s, OCH₃), 2.08-1.97 (2H, m, CH₂), 1.91-1.24 (10H, m, 5 x CH₃), 0.88 (3H, t, J = 7.0 Hz, CH₂CH₃); 13C NMR (100 MHz, CDCl₃) major isomer: δ 132.5, 130.9, 98.6, 69.4, 54.5, 32.0, 31.4, 31.2, 29.4, 22.3, 18.0, 14.0; FTIR (CH₂Cl₂, υmax cm⁻¹): 2933 (s), 2873 (s), 1458 (m), 1439 (m), 1195 (m), 1125 (s), 1062 (s), 1022 (s), 968 (m), 948 (s); HRMS (El) m/z [M]+ calcd for C₁₂H₂₂O₂: 198.1620, found 198.1624.
SYNTHESIS OF HYDROGENTRIPHENYLPHOSPHONIUM TETRAFLUORBORATE

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PPh_3 + HBF_4 \rightarrow HPPh_3BF_4
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To a solution of triphenylphosphine (38.5 g, 0.145 mol) in toluene (110 mL) was added tetrafluoroboric acid solution (48% in water, 19.8 mL, 0.145 mol). The resulting suspension was stirred at room temperature for 2 hours. The water was azeotropically removed using a Dean-Stark trap. The white suspension was concentrated in vacuo.

The resulting white solid was dissolved in chloroform (500 mL), dried over magnesium sulfate, concentrated in vacuo, washed with hexane/diethyl ether (1 : 1, 300 mL) to give HPPh_3BF_4 as a white solid (48 g, 94%); M.p. = 157-159 °C (Lit. 160-164 °C); \(^1\)H NMR (250 MHz, CDCl_3): \(\delta\) 7.80-7.54 (15H, m, Ar-H); \(^31\)P NMR (63 MHz, CDCl_3): \(\delta\) 2.6.

PREPARATION OF A KHMDS SOLUTION IN THF

To a suspension of potassium hydride (washed with tetrahydrofuran, 300 mg, 7.48 mmol) in tetrahydrofuran (6.0 mL) was added dropwise freshly distilled hexamethyldisilazane (1.00 mL, 4.79 mmol) at room temperature. The suspension was stirred for 1 hour at room temperature. After this time, the solution was stored at -20 °C under inert atmosphere and was left to settle for 12 hours before use. The molarity was assumed at 0.68 M, based on the quantity of hexamethyldisilazane used.
To a suspension of 4 Å molecular sieves (20 g) and a solution of HPPh₃BF₄ (22.2 g, 63.4 mmol) in acetonitrile (80 mL) was added a solution of pyranyl ether 102 (6.3 g, 31.8 mmol) in acetonitrile (80 mL). The resulting suspension was heated at reflux for 20 hours. Upon cooling to room temperature, the suspension was diluted with dichloromethane, filtered through Celite® and the filtrate concentrated in vacuo to give a thick pale yellow oil. To this was added dichloromethane (2 mL) then diethyl ether/petroleum ether (1 : 1, 100 mL) followed by vigorous stirring for 15 minutes. The clear solution was decanted and the process repeated five times to the remaining pale yellow gum. Upon final decantation, the yellow gum was concentrated in vacuo to give 103 as a white solid (15.97 g, 97%) as a 5 : 1 mixture of diastereoisomers; ¹H NMR (250 MHz, CDCl₃): δ 7.88-7.56 (15H, m, Ar-H), 5.99-5.45 (2H, m, CH₂-alkene-H), 5.39-5.20 (1H, m, CH-alkene-H), 4.57-4.46 (0.2H, m, pyran-OC₃H), 4.38-4.15 (0.8H, m, pyran-OC₃H), 2.24-1.49 (7H, m, 7 x CH), 1.44-1.09 (5H, m, 5 x CH), 0.87 (3H, t, J = 7.0 Hz, CH₃); ¹³C NMR (63 MHz, CDCl₃): δ 135.2, 134.4 (JCP = 8.5 Hz), 133.4, 130.4 (JCP = 12.5 Hz), 129.4, 116.4 (JCP = 84.5 Hz), 81.0 (JCP = 11.5 Hz), 73.0 (JCP = 70.0 Hz), 31.8, 31.1, 25.4, 22.6, 22.4, 22.0, 13.9; ³¹P NMR (250 MHz, CDCl₃): δ 19.9.
PREPARATION OF (E/Z)-3-((6-((E)-HEX-1-ENYL)TETRAHYDRO-2H-PYRAN-2-YLIDENE)MERTHYL PYRIDINE 106

To a solution of phosphonium salt 103 (250 mg, 0.483 mmol) in tetrahydrofuran (5 mL) at -78 °C was added potassium hexamethyldisilazide (0.68 M in tetrahydrofuran, 0.80 mL, 0.544 mmol) dropwise at -78 °C. The resulting red solution was stirred at -78 °C for 5 minutes then 3-pyridinecarboxaldehyde (63 mg, 0.581 mmol) was added at -78 °C. The resulting yellow solution was stirred at -78 °C for 45 minutes, then at room temperature for a further 60 minutes. The resulting yellow solution was quenched with water and extracted with diethyl ether. The organic layer was washed three times with a mixture of 3 : 3 : 1 brine/ water/methanol, dried over sodium sulfate and concentrated in vacuo. The crude residue was purified by flash chromatography on Florisil® (3 : 1 petroleum ether/ethyl acetate) to give 106 as a colourless oil (95 mg, 76%) as a 9 : 1 mixture of diastereoisomers; \(^1\)H NMR (250 MHz, CD\(_3\)OD): \(\delta\) 8.40-8.11 (2H, m, Ar-H), 7.64-7.53 (1H, m, Ar-H), 7.34-7.25 (1H, m, Ar-H), 5.92 (0.9H, m, O-alkene-H), 5.78-5.63 (1H, m, CH\(_2\)-alkene-H), 5.57-5.42 (1H, m, CH-alkene-H), 5.34 (0.1H, m, O-alkene-H), 4.33-4.23 (0.1H, m, pyran-OCH), 4.18-4.06 (0.9H, m, pyran-OCH), 2.67-2.53 (1H, m, CH), 2.31-1.91 (3H, m, 3 x CH), 1.87-1.46 (4H, m, 2 x CH\(_2\)), 1.39-1.24 (4H, m, 2 x CH\(_2\)), 0.94-0.80 (3H, m, CH\(_3\)); \(^{13}\)C NMR (63 MHz, CD\(_3\)OD) major diastereoisomer: \(\delta\) 178.8, 159.2, 149.9, 146.7, 137.8, 133.8, 131.5, 124.9, 106.1, 81.2, 33.1, 32.5, 32.0, 25.9, 23.3, 22.6, 14.4; FTIR (CH\(_2\)Cl\(_2\), \(\nu_{\text{max}}\) cm\(^{-1}\)): 3086 (w), 3063 (w), 3029 (m), 2828 (s), 2857 (s), 1714 (s), 1674 (m), 1496 (m), 1454 (m), 969 (m); HRMS (El) \(m/z\) [M]\(^+\) calcd for C\(_{17}\)H\(_{24}\)NO: 258.1858, found 258.1848.
PREPARATION OF 3-((E)-HEX-1-ENYL)-2-(PYRIDIN-3-YL)CYCLOHEXANONE 107

To a solution of palladium(II) acetate (3.4 mg, 10 mol%) in acetonitrile (1 mL) was added tri-n-butylphosphine (38 μL, 0.15 mmol). The solution was heated at reflux for 20 minutes. The resulting yellow solution was cooled to 55 °C and enol ether 106 (39 mg, 0.15 mmol) in acetonitrile (1.0 mL) was added. The resulting yellow solution was heated at 55 °C for 36 hours. Upon cooling to room temperature, the yellow solution was diluted with diethyl ether, filtered through Celite® and concentrated in vacuo. The crude residue was purified by flash chromatography on silica gel (1 : 1 / petroleum ether/diethyl acetate) to give 107 as a colourless oil (29 mg, 73%); ¹H NMR (250 MHz, CDCl₃): δ 8.46 (1H, m, Ar-H), 8.25 (1H, m, Ar-H), 7.39 (1H, m, Ar-H), 7.29-7.17 (1H, m, Ar-H), 5.20-4.99 (2H, m, alkene-H), 3.41 (1H, d, $J = 12.0$ Hz, (CO)CH), 2.67-2.42 (3H, m, alkene-CH, CH₂), 2.26-1.60 (6H, m, 3 x CH₂), 1.13-0.82 (4H, m, 2 x CH₂), 0.74 (3H, t, $J = 6.5$ Hz, CH₃); ¹³C NMR (100 MHz, CDCl₃): δ 208.4, 150.6, 147.7, 137.4, 133.1, 132.5, 131.3, 123.1, 60.7, 49.6, 41.8, 32.8, 31.8, 31.2, 25.9, 21.6, 13.8; FTIR (CH₂Cl₂, $ν_{max}$ cm⁻¹): 3026 (w), 2946 (s), 2922 (s), 2858 (m), 1711 (s), 1575 (w), 1458 (w), 1422 (m), 1166 (m), 1021 (w), 965 (m), 797 (w); HRMS (EI) m/z [MH]⁺ calcd for C₁₇H₂₄NO: 258.1858, found 258.1848.
PREPARATION OF $(E/Z)$-2-BENZYLIDENE-6-((E)-PENT-1-ENYL)TETRAHYDRO-2H-PYRAN \textsuperscript{79}\textsuperscript{53}

To a solution of Wittig salt 103 (380 mg, 0.736 mmol) in tetrahydrofuran (8 mL) at -78 °C was added potassium hexamethyldisilazide (0.68 M in tetrahydrofuran, 1.14 mL, 0.773 mmol) dropwise at -78 °C. The resulting red solution was stirred at -78 °C for 5 minutes then benzaldehyde (93 μL, 0.883 mmol) was added at -78 °C. The resulting yellow solution was stirred at -78 °C for 45 minutes, then at room temperature for a further 60 minutes. The resulting yellow solution was quenched with water and extracted with diethyl ether. The organic layer was washed three times with a mixture of 3 : 3 : 1 brine/water/methanol, dried over sodium sulfate and concentrated \textit{in vacuo}. The crude residue was purified chromatography on Florisil® (99 : 1 petroleum ether/ethyl acetate) to give \textit{79} as a colourless oil (132 mg, 70%) as a 9 : 1 mixture of diastereoisomers; $^1$H NMR (250 MHz, CD$_3$OD): $\delta$ 7.32-7.01 (5H, m, Ar-H), 6.02 (0.9H, m, O-alkene-H), 5.85-5.68 (1H, m, CH$_2$-alkene-H), 5.65-5.46 (1H, m, CH-alkene-H), 5.38 (0.1H, m, O-alkene-H), 4.31-4.21 (0.1H, m, pyran-OC$_H$), 4.19-4.08 (0.9H, m, pyran-OC$_H$), 2.80-2.64 (1H, m, CH), 2.37-1.99 (3H, m, 3 x CH), 1.92-1.49 (4H, m, 2 x CH$_2$), 1.47-1.25 (4H, m, 2 x CH$_2$), 1.01-0.82 (3H, m, CH$_3$); $^{13}$C NMR (100 MHz, CD$_3$OD) major diastereoisomer: $\delta$ 156.7, 137.9, 133.6, 131.7, 129.8, 129.1, 126.7, 110.8, 81.3, 33.0, 32.5, 32.4, 26.0, 23.2, 23.1, 14.3.
PREPARATION OF 3-((E)-HEX-1-ENYL)-2-PHENYLCYCLOHEXANONE 80$^{53}$

To a solution of palladium(II) acetate (10 mg, 10 mol%) in acetonitrile (4 mL) was added tri-n-butylphosphine (75 $\mu$L, 0.28 mmol). The solution was heated at reflux for 20 minutes. The resulting yellow solution was cooled to 55 °C and enol ether 79 (119 mg, 0.46 mmol) in acetonitrile (4.5 mL) was added. The resulting yellow solution was heated at 55 °C for 24 hours. Upon cooling to room temperature, the yellow solution was diluted with diethyl ether, filtered through Celite® and concentrated in vacuo. The crude residue was purified by flash chromatography on silica gel (95 : 5 petroleum ether/ethyl acetate) to give 80 as a white solid (98 mg, 82%); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.32-7.20 (3H, m, Ar-H), 7.05-6.98 (2H, m, Ar-H), 5.18 (1H, dt, $J = 15.5, 6.0$ Hz, CH$_2$-alkene-H), 5.11 (1H, dd, $J = 15.5, 7.0$ Hz, CH-alkene-H), 3.36 (1H, d, $J = 11.5$ Hz, (CO)CH), 2.70-2.60 (1H, m, alkene-CH), 2.58-2.40 (2H, m, CH$_2$), 2.20-2.11 (1H, m, CH), 2.07-1.98 (1H, m, CH), 1.91-1.67 (4H, m, 2 x CH$_2$), 1.14-0.92 (4H, m, 2 x CH$_2$), 0.77 (3H, t, $J = 7.0$ Hz, CH$_3$); $^{13}$C NMR (63 MHz, CDCl$_3$): $\delta$ 209.7, 137.3, 132.1, 131.5, 129.6, 128.1, 126.7, 63.4, 49.1, 42.0, 32.7, 32.0, 31.4, 25.9, 21.7, 13.9.
GENERAL PROCEDURE FOR THE CHIRAL LIGAND PROMOTED REARRANGEMENT FOR THE SYNTHESIS OF CYCLOHEXANONE 80

To a solution of palladium(II) acetate (10 mol%) in acetonitrile and/or toluene (0.05 M) was added ligand (30-100 mol%). The solution was heated at reflux for 20 minutes. The resulting solution was cooled to 55 °C and enol ether 79 (1 eq) in acetonitrile and/or toluene (0.05 M) was added. The resulting solution was heated at 55 °C. Upon cooling to room temperature, the solution was diluted with diethyl ether, filtered through Celite® and concentrated in vacuo. The crude residue was purified by flash chromatography on silica gel (95 : 5 petroleum ether/ethyl acetate) to give 80 as a white solid. Resolution between the enantiomers was determined using chiral stationary phase gas chromatography with a Chiracel-bonded column (30 m × 0.25 m, β-cyclodextrin / permethyl); T = 150 °C isothermal, H₂ carrier gas at 14 psi.

DIOP 110 (Table 11, Entry 7): First component: 26.427 min; Second component: 27.040 min; <5% ee;

JosiPhos 111 (Table 12, Entry 2): First component: 26.349 min; Second component: 27.158 min; <5% ee;

DiPhos 112 (Table 12, Entry 3): First component: 26.507 min; Second component: 27.103 min; <5% ee;

Me-DuPhos 113 (Table 12, Entry 5): First component: 26.910 min; Second component: 27.525 min; <5% ee;

Pr-Phox 114 (Table 12, Entry 6): First component: 26.312 min; Second component: 26.928 min; 25% ee.
Ozone was bubbled through a stirring -78 °C solution of cyclopentene (4.0 mL, 45 mmol) in dichloromethane (250 mL) and methanol (50 mL) until a blue colour remained. Nitrogen was bubbled through the reaction mixture until the blue colour disappeared. The cold bath was removed, p-toluenesulfonic acid monohydrate (1.1 g) was added and the reaction was stirred at room temperature for 90 minutes. After this time, sodium hydrogen carbonate (2.0 g) was added and the reaction mixture was stirred for 30 minutes after which time a solution of triphenylphosphine (17.5 g) in dichloromethane (50 mL) was added dropwise. After stirring for 12 hours, the reaction mixture was concentrated to approximately 50 mL by rotary evaporation. Dichloromethane (100 mL) was added and the mixture was washed with water. The aqueous layer was extracted with dichloromethane and the combined organic extracts were washed with brine, dried over sodium sulfate and concentrated in vacuo. The crude residue was purified by flash chromatography on silica gel (60 : 40 petroleum ether/ethyl acetate) to give 119 as a colourless oil (3.1 g, 47%); \(^1\)H NMR (250 MHz, CDCl\(_3\)): \(\delta\) 9.77 (1H, t, \(J = 1.5\) Hz, CHO), 4.36 (1H, t, \(J = 5.5\) Hz, CH(OMe)\(_2\)), 3.31 (6H, s, CH(OCH\(_3\))\(_2\)), 2.52-2.44 (2H, m, CH\(_2\)), 1.78-1.56 (4H, m, 2 x CH\(_2\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 202.4, 104.3, 53.0, 43.6, 31.9, 17.4.
To a stirred solution of aldehyde 119 (1.5 g, 10.26 mmol) in tetrahydrofuran (140 mL) at 0 °C was added dropwise vinylmagnesium bromide (1 M in tetrahydrofuran, 11.3 mL, 11.30 mmol). The orange reaction solution was stirred for 90 minutes. The reaction was quenched with water, extracted with diethyl ether and the combined organic extracts were washed with brine, dried over sodium sulfate and concentrated in vacuo. The crude residue (1.8 g) was dissolved in dichloromethane (170 mL), and camphorsulfonic acid (240 mg, 1.03 mmol) was added. The reaction was stirred at room temperature for 1 hour. Sodium hydrogen carbonate (4.3 g, 51.3 mmol) was added and the reaction was stirred for another 30 minutes. The mixture was filtered and the filtrate was carefully concentrated in vacuo (care: the compound is volatile). The crude residue was purified by flash chromatography on silica gel (90 : 10 pentane/diethyl ether) to give 117 as an colourless oil (1.1 g, 75% over two steps) as a 1 : 2 mixture of diastereoisomers; 1H NMR (400 MHz, CDCl3): δ 5.94-5.79 (1H, m, alkene-\(\text{H}^1\)), 5.29-5.21 (1H, m, alkene-\(\text{H}^2\)), 5.12-5.07 (1H, m, alkene-\(\text{H}^2\)), 4.75 (0.33H, m, OCHOME), 4.36 (0.66H, dd, \(J = 9.0, 2.0\ Hz\), OCHOME), 4.22-4.15 (0.33H, m, pyran-OCH), 3.94-3.86 (0.66H, m, pyran-OCH), 3.50 (2H, s, OCH3), 3.36 (1H, s, OCH3), 1.92-1.23 (6H, m, 3 x \(\text{CH}_2\)); 13C NMR (100 MHz, CDCl3) major diastereoisomer: δ 138.7, 114.7, 103.2, 76.6, 56.1, 31.0, 22.1, 18.0.
To a suspension of 4 Å molecular sieves (4.5 g) and a solution of \( \text{HPPh}_3\text{BF}_4 \) (4.9 g, 14.0 mmol) in acetonitrile (35 mL) was added a solution of pyranyl ether 117 (1.0 g, 7.0 mmol) in acetonitrile (35 mL). The resulting suspension was heated at reflux for 20 hours. Upon cooling to room temperature, the suspension was diluted with dichloromethane, filtered through Celite® and the filtrate concentrated \textit{in vacuo} to give a thick pale yellow oil. To this was added dichloromethane (2 mL) then diethyl ether/petroleum ether (1 : 1, 100 mL) followed by vigorous stirring for 15 minutes. The clear solution was decanted and the process repeated five times to the remaining pale yellow gum. Upon final decantation, the yellow gum was concentrated \textit{in vacuo} to give 116 as a white solid (3.0 g, 93%); \(^1\text{H NMR (250 MHz, CDCl}_3\text{): } \delta 7.87-7.59 \text{ (15H, m, Ar-H)}, 5.91-5.57 \text{ (2H, m, CHP, alkene-H)}, 5.16-4.93 \text{ (2H, m, alkene-H)}_2\), 4.39 \text{ (1H, m, pyran-OC)}, 2.19-1.52 \text{ (5H, m, 5 x CH)}, 1.45-1.21 \text{ (1H, m CH)}; \(^{13}\text{C NMR (100 MHz, CDCl}_3\text{): } \delta 137.6, 135.3, 134.5 (J_{CP} = 9.0 \text{ Hz}), 130.5 (J_{CP} = 12.0 \text{ Hz}), 116.5 (J_{CP} = 84.0 \text{ Hz}), 80.6 (J_{CP} = 10.5), 72.8 (J_{CP} = 44.5 \text{ Hz}), 30.9, 25.6, 22.4, 22.3; \(^{31}\text{P NMR (250 MHz, CDCl}_3\text{): } \delta 20.5. \)
PREPARATION OF 2-BENZYLIDENE-6-VINYLTETRAHYDRO-2H-PYRAN 115\textsuperscript{53}

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\begin{align*}
\text{O} & \quad \text{PPh}_3\text{BF}_4 \\
\rightarrow & \\
\text{O} & \quad \text{Ph} \\
\rightarrow & \\
\end{align*}
\]

To a solution of phosphonium salt \textbf{116} (250 mg, 0.543 mmol) in tetrahydrofuran (5 mL) at -78 °C was added potassium hexamethyldisilazide dropwise at -78 °C (0.68 M, 0.84 mL, 0.570 mmol). The resulting red solution was stirred at -78 °C for 5 minutes then benzaldehyde (70 μL, 0.650 mmol) was added at -78 °C. The resulting yellow solution was stirred at -78 °C for 45 minutes, then at room temperature for a further 60 minutes. The resulting yellow solution was quenched with water and extracted with diethyl ether. The organic layer was washed three times with a mixture of 3 : 3 : 1 brine/water/methanol, dried over sodium sulfate and concentrated \textit{in vacuo}. The crude residue was purified chromatography on Florisil\textsuperscript{®} (99 : 1 petroleum ether/ethyl acetate) to give \textbf{115} as a colourless oil (76 mg, 70%) as a 9 : 1 mixture of diastereoisomers; \textsuperscript{1}H NMR (400 MHz, CD\textsubscript{3}OD): \(\delta\) 7.31-7.11 (5H, m, Ar-H), 6.05 (0.9H, m, O-alkene-H), 6.04-5.90 (0.1H, m, alkene-H), 5.95 (0.9H, ddd, \(J = 17.0, 10.5, 5.5\) Hz, alkene-H) 5.42 (0.1H, m, O-alkene-H), 5.39-5.35 (0.1H, m, alkene-H\textsubscript{2}), 5.33 (0.9H, dt, \(J = 17.0, 1.5\) Hz, alkene-H\textsubscript{2}), 5.21-5.13 (0.9H, dt, \(J = 10.5, 1.5\) Hz, alkene-H\textsubscript{2} and 0.1H, m, alkene-H\textsubscript{2}), 4.33-4.27 (0.1H, m, pyran-OCH), 4.21-4.14 (0.9H, m, pyran-OCH), 2.78-2.70 (1H, m, CH), 2.41-2.16 (1H, m, CH), 1.96-1.54 (4H, m, 2 x CH\textsubscript{2}); \textsuperscript{13}C NMR (100 MHz, CD\textsubscript{3}OD) major diastereoisomer: \(\delta\) 156.5, 140.0, 137.9, 129.8, 129.2, 126.7, 115.5, 110.9, 81.2, 32.0, 26.0, 23.1.
PREPARATION OF 2-PHENYL-3-VINYLCYCLOHEXANONE 121

![Chemical Structure]

To a solution of palladium(II) acetate (5.6 mg, 10 mol%) in acetonitrile (2 mL) was added $n$-tributylphosphine (40 $\mu$L, 0.15 mmol). The solution was heated at reflux for 20 minutes. The resulting yellow solution was cooled to 55 °C and enol ether 115 (50 mg, 0.25 mmol) in acetonitrile (3 mL) was added. The resulting yellow solution was heated at 55 °C for 24 hours. Upon cooling to room temperature, the yellow solution was diluted with diethyl ether, filtered through Celite® and concentrated in vacuo. The crude residue was purified by flash chromatography on silica gel (95 : 5 petroleum ether/ethyl acetate) to give 121 as a white solid (42 mg, 84%); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.38-7.24 (3H, m, Ar-H), 7.11-7.06 (2H, m, Ar-H), 5.56 (1H, ddd, $J$ = 17.5, 10.0, 7.5 Hz, alkene-H), 4.90-4.82 (2H, m, alkene-H$_2$), 3.43 (1H, d, $J$ = 11.5 Hz, (CO)CH), 2.82-2.71 (1H, m, alkene-CH), 2.63-2.44 (2H, m, CH$_2$), 2.27-2.17 (1H, m, CH), 2.14-2.05 (1H, m, CH), 1.97-1.75 (2H, m, CH$_2$); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 209.3, 140.4, 137.1, 129.6, 128.3, 127.0, 115.1, 62.9, 49.5, 41.9, 31.9, 25.8.
To a solution of palladium(II) acetate (10 mol%) in acetonitrile and/or toluene (0.05 M) was added ligand (30-60 mol%). The solution was heated at reflux for 20 minutes. The resulting solution was cooled to 55 °C and enol ether 115 (1 eq) in acetonitrile and/or toluene (0.05 M) was added. The resulting solution was heated at 55 °C. Upon cooling to room temperature, the solution was diluted with diethyl ether, filtered through Celite® and concentrated in vacuo. The crude residue was purified by flash chromatography on silica gel (95 : 5 petroleum ether/ethyl acetate) to give 121 as a white solid. Resolution between the enantiomers was determined using chiral stationary phase gas chromatography with a Chiracel-bonded column (30 m × 0.25 m, β-cyclodextrin / permethyl); T = 120 °C isothermal, H₂ carrier gas at 14 psi.

DIOP 110 (Table 13, Entry 2): First component: 26.715 min; Second component: 27.658 min; 13% ee;
JosiPhos 111 (Table 13, Entry 3): First component: 26.853 min; Second component: 27.859 min; <5% ee;
DiPhos 112 (Table 13, Entry 4): First component: 26.368 min; Second component: 27.221 min; <5% ee;
Pr-Phox 114 (Table 13, Entry 10): First component: 26.605 min; Second component: 27.523 min; 25% ee;
Bu-Phox 42 (Table 13, Entry 11): First component: 26.536 min; Second component: 27.448 min; 49% ee.
PREPARATION OF (3E)-1-CHLOROOCT-3-EN-2-OL 126

To a stirred solution of aldehyde 127 (1.31 mL, 9.89 mmol) in tetrahydrofuran (20 mL) at -78 °C was added chloroiodomethane (1.10 mL, 14.83 mmol) followed by the slow addition of n-butyllithium (1.1 M in hexanes, 13.4 mL, 14.83 mmol). The resulting cloudy solution was stirred at -78 °C for 2 hours. The reaction was quenched by the addition of ammonium chloride solution and extracted with diethyl ether. The aqueous layer was further extracted with diethyl ether and the combined organic layers were dried over sodium sulfate and carefully concentrated in vacuo to give 126 as a pale yellow oil (1.85 g, 100%); ¹H NMR (400 MHz, CDCl₃): δ 5.82 (1H, dtd, J = 15.5, 7.0, 1.0 Hz, CH₂-alkene-H), 5.48 (1H, ddt, J = 15.5, 6.5, 1.5 Hz, CH-alkene-H), 4.34-4.28 (1H, m, CH), 3.62 (1H, dd, J = 11.0, 4.0 Hz, CH₆H₂), 3.51 (1H, dd, J = 11.0, 7.5 Hz, CH₆H₆), 2.36 (1H, ddd, J = 15.0, 7.0, 1.5 Hz, OH), 2.07 (2H, q, J = 6.5 Hz, CH₂), 1.44-1.25 (4H, m, 2 x CH₂), 0.93-0.89 (3H, m, CH₃); ¹³C NMR (100 MHz, CDCl₃): δ 134.8, 128.2, 72.3, 49.7, 31.9, 31.1, 22.6, 14.0.
PREPARATION OF 2-[[1E]-HEX-1-ENYL]OXIRANE 125

A suspension of sodium hydride (60% suspension in mineral oil, 1.075 g, 16.12 mmol) and sodium iodide (220 mg, 1.46 mmol) in tetrahydrofuran (35 mL) at 0 °C was stirred for 10 minutes. Alcohol 126 (1.85 g, 14.65 mmol) in tetrahydrofuran (10 mL) was added via cannula at 0 °C over 30 minutes and the resulting suspension was stirred at 0 °C for 2 hours. The reaction was quenched by the addition of ammonium chloride solution and extracted with diethyl ether. The aqueous layer was further extracted with diethyl ether and the combined organic layers were dried over sodium sulfate and carefully concentrated in vacuo to give 125 as a pale yellow oil (1.44 g, 100%); 1H NMR (400 MHz, CDCl3): δ 5.98 (1H, dt, J = 15.5, 7.0 Hz, CH2-alkene-H), 5.14 (1H ddt, J = 15.5, 8.5, 1.5 Hz, CH-alkene-H), 3.36-3.31 (1H, m, CH), 2.96 (1H, dd, J = 5.0, 4.0 Hz, CHαHβ), 2.67 (1H, dd, J = 5.0, 3.0 Hz, CHαHβ), 2.13-2.06 (2H, m, CH2), 1.44-1.20 (4H, m, 2 x CH2), 0.91 (3H, t, J = 7.0 Hz, CH3); 13C NMR (63 MHz, CDCl3): δ 137.2, 127.4, 52.4, 48.7, 32.0, 31.0, 25.6, 14.0.
HYDROLYTIC KINETIC RESOLUTION OF 2-[(1E)-HEX-1-ENYL]OXIRANE 125\textsuperscript{66}

To a solution (S,S)-128 (34 mg, 0.057 mmol), epoxide 125 (1.44 g, 11.41 mmol) and acetic acid (12 µL, 0.02 mmol) at 0 °C was added water (113 µL, 6.27 mmol) and the resulting dark red solution stirred at room temperature until crude NMR analysis showed 1 : 1 epoxide 125 to diol 129. The resulting red solution was purified chromatography on Florisil\textsuperscript{®} (100 : 0 to 0 : 100 petroleum ether/diethyl ether) to give enantioenriched 125 as a colourless oil (720 mg, ~50%). The compound showed identical NMR spectroscopic data to racemic 125.
PREPARATION OF \((E)-5\)-HYDROXYUNDEC-6-EN-3-YNOIC ACID 137

To a stirred solution of diisopropylamine (3.76 mL, 26.68 mmol) in tetrahydrofuran (15 mL) at -78 °C was added \(n\)-butyllithium (2.0 M in hexanes, 13.4 mL, 26.68 mmol). After 15 minutes, hexamethylphosphoramide (2.25 mL) was added followed by propiolic acid (750 \(\mu\)L, 12.15 mmol) in tetrahydrofuran (5 mL). The resulting grey solution was stirred at 0 °C for 3 hours before the addition of enantioenriched epoxide 125 (750 mg, 5.95 mmol). The resulting thick red/brown solution was stirred at room temperature for 3 days. The reaction mixture was concentrated \textit{in vacuo} to give a deep red residue which was dissolved in water and extracted with dichloromethane. The aqueous solution was treated with concentrated hydrochloric acid to pH 1, saturated with sodium chloride and extracted with ethyl acetate. The organic extracts were dried over sodium sulfate and concentrated \textit{in vacuo} to give 137 as a dark red oil (620 mg, 54%); \(^1\)H NMR (250 MHz, CDCl\(_3\)): \(\delta\) 5.78 (1H, dt, \(J = 15.5, 7.0\) Hz, CH\(_2\)-alkene-\(H\)), 5.53 (1H ddt, \(J = 15.5, 7.0, 1.5\) Hz, CH-alkene-H), 4.37 (1H, q, \(J = 6.5\) Hz, CH), 2.13-2.02 (2H, m, alkyne-CH\(_2\)), 1.42-1.27 (6H, m, 3 x CH\(_2\)), 0.91 (3H, t, \(J = 7.0\) Hz, CH\(_3\)); \(^{13}\)C NMR (63 MHz, CDCl\(_3\)): \(\delta\) 180.2, 132.4, 128.6, 92.2, 73.3, 69.2, 33.3, 32.5, 24.8, 23.2, 14.1.
PREPARATION OF (E)-6(HEX-1-ENYL)-5,6-DIHYDRO-2H-PYRAN-2-ONE 135

A suspension of alcohol 137 (620 mg, 3.21 mmol), Lindlar’s catalyst (110 mg) and quinoline (1.0 mL) in tetrahydrofuran (10 mL) was stirred under an atmosphere of hydrogen (via balloon at atmospheric pressure) at room temperature for 36 hours. The resulting black suspension was concentrated in vacuo and partitioned between ethyl acetate and 1M hydrochloric acid. The organic layer was extracted a further 3 times with hydrochloric acid, passed through Celite®, dried over sodium sulfate and concentrated to give a dark oil. The crude material was dissolved in toluene and heated at reflux for 16 hours. The water was azeotropically removed using a Dean-Stark trap. The resulting solution was concentrated in vacuo to give 135 as a dark solid (400 mg, 69%); 1H NMR (250 MHz, CDCl3): δ 6.89 (1H, dt, J = 9.5, 4.0 Hz, C(O)-alkene-H), 6.06 (1H dt, J = 9.5, 2.0 Hz, CH2-alkene-H), 5.84 (1H, dtd, J = 15.5, 7.0, 0.5 Hz, CH2-alkene-H), 5.59 (1H, ddt, J = 15.5, 7.0, 1.0 Hz, CH-alkene-H), 4.89 (1H, q, J = 7.0 Hz, pyran-OCCH), 2.48-2.40 (2H, m, CH2), 2.14-2.03 (2H, m, CH2), 1.47-1.25 (4H, m, 2 x CH2), 0.98-0.85 (3H, m, CH3); 13C NMR (63 MHz, CDCl3): δ 170.4, 150.8, 134.8, 124.4, 121.9, 81.5, 34.9, 32.7, 32.0, 22.9, 14.1.
PREPARATION OF (E)-6-(HEX-1-ENYL)TETRAHYDRO-2H-PYRAN-2-ONE 134

To a solution of lactone 135 (400 mg, 2.22 mmol) in degassed benzene (5 mL) was added (triphenylphosphine)copper hydride (Stryker’s reagent, 2.00 g, 1.02 mmol). The resulting red solution was stirred at room temperature for 48 hours then exposed to air for 1 hour. Saturated sodium hydrogen carbonate was added and the reaction mixture extracted with diethyl ether. The aqueous layer was treated with concentrated hydrochloric acid to pH 1, saturated with sodium chloride and extracted with ethyl acetate. The organic extracts were dried over sodium sulfate and concentrated in vacuo to give a thick, dark oil. The crude material was dissolved in toluene and heated at reflux for 16 hours. The water was azeotropically removed using a Dean-Stark trap. The resulting solution was concentrated in vacuo to give a dark solid which was purified by flash chromatography on silica gel (75 : 25 to 0 : 100 petroleum ether/ethyl acetate) to give 134 as a colourless oil (35 mg, 18%); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 5.75 (1H, dtd, $J = 15.5$, 7.0, 1.0 Hz, alkene-$H$), 5.48 (1H, ddt, $J = 15.5$, 6.5, 1.5 Hz, alkene-$H$), 5.78-5.71 (1H, m, OCH), 2.61-2.52 (1H, m, C(O)CH$_m$H$_b$), 2.50-2.40 (1H, m, C(O)CH$_m$H$_b$), 2.08-2.00 (2H, m, CH$_2$), 1.98-1.82 (2H, m, CH$_2$), 1.67-1.59 (1H, m, CH), 1.40-1.26 (5H, m, 5 x CH), 0.88 (3H, t, $J = 7.0$ Hz, CH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 171.4, 134.6, 127.9, 80.7, 31.8, 31.0, 29.5, 28.4, 22.1, 18.2, 13.9.
To a stirred solution of lactone 134 (35 mg, 0.19 mmol) in dichloromethane (1 mL) at -78 °C was added diisobutylaluminium hydride (1 M in hexanes, 190 μL, 0.28 mmol) followed by chlorotrimethylsilane (60 μL, 0.47 mmol). The resulting reaction mixture was stirred at -78 °C for 2.5 hours. After this period, methanol (0.5 mL) and potassium carbonate (500 mg in 0.5 mL of water) was added to the reaction mixture which was stirred at room temperature for a further 16 hours at room temperature. Afterwards, sodium sulfate was added, and the reaction mixture stirred for 15 minutes, filtered through Celite®, washed with dichloromethane and concentrated in vacuo to give 133 as a colourless oil (20 mg, 57%) as a 1 : 1 mixture of diastereoisomers; 1H NMR (400 MHz, CDCl₃): δ 5.76-5.66 (1H, m, CH₂-alkene-H), 5.55-5.42 (1H, m, CH-alkene-H), 5.37-5.33 (0.5H, m, CHO), 4.81-4.74 (0.5H, m, CHO), 4.47-4.40 (0.5H, m, pyran-OCH), 3.96-3.90 (0.5H, m, pyran-OCH), 3.30-3.23 (0.5H, m, OH), 2.85-2.79 (0.5H, m, OH), 2.10-1.99 (2H, m, CH₂), 1.93-1.84 (2H, m, CH₂), 1.76-1.50 (4H, m, 2 x CH₂), 1.42-1.24 (4H, m, 2 x CH₂), 0.90 (3H, t, J = 7.5 Hz, CH₃); 13C NMR (63 MHz, CDCl₃): δ 131.7, 130.6, 124.8, 123.5, 95.3, 94.7, 71.5, 71.0, 35.7, 35.6, 33.3, 33.2, 32.7, 32.6, 32.5, 32.4, 32.2, 23.2, 16.6, 16.5, 14.2, 14.1.
PREPARATION OF \((E)-(6-\text{HEX-1-ENYL})\text{TETRAHYDRO-2H-PYRAN-2-YL)TRIPHENYLPHOSPHONIUM TETRAFLUOROBORATE 103}\)

\[
\begin{align*}
\text{nBu} & \quad \text{OH} \\
\Longrightarrow & \quad \text{OH} \quad \text{PPh}_3\text{BF}_4
\end{align*}
\]

To a suspension of 4 Å molecular sieves (1.0 g) and a solution of HPPh$_3$BF$_4$ (200 mg, 0.57 mmol) in acetonitrile (2.5 mL) was added a solution of hemi-acetal 133 (20 mg, 0.11 mmol) in acetonitrile (2.5 mL). The resulting suspension was heated at reflux for 20 hours. Upon cooling to room temperature, the suspension was diluted with dichloromethane, filtered through Celite® and the filtrate concentrated \textit{in vacuo} to give a thick pale yellow oil. To this was added dichloromethane (1 mL) then diethyl ether/petroleum ether (1 : 1, 40 mL) followed by vigorous stirring for 15 minutes. The clear solution was decanted and the process repeated five times to the remaining pale yellow gum. Upon final decantation, the yellow gum was concentrated \textit{in vacuo} to give 103 as a white solid (20 mg, 35%). The compound showed identical NMR spectroscopic data to racemic 103.
PREPARATION OF \((E/Z)-2\text{-BENZYLIDENE-6-((E)-PENT-1-ENYL)}\text{TETRAHYDRO-2H-PYRAN}\)

79

To a solution of phosphonium salt 103 (20 mg, 0.038 mmol) in tetrahydrofuran (500 µL) at -78 °C was added potassium hexamethyldisilazide (0.68 M in tetrahydrofuran, 80 µL, 0.054 mmol) dropwise at -78 °C. The resulting red solution was stirred at -78 °C for 5 minutes then benzaldehyde (6.7 µL, 0.066 mmol) was added at -78 °C. The resulting yellow solution was stirred at -78 °C for 45 minutes, then at room temperature for a further 60 minutes. The resulting yellow solution was quenched with water and extracted with diethyl ether. The organic layer was washed three times with a mixture of 3 : 3 : 1 brine/water/methanol, dried over sodium sulfate and concentrated \textit{in vacuo}. The crude residue was purified by flash chromatography on Florisil® (99 : 1 petroleum ether/ethyl acetate) to give 79 as a colourless oil (7 mg, 72%) as a 5 : 1 mixture of diastereoisomers. The compound showed identical NMR spectroscopic data to racemic 79. Resolution between the enantiomers was determined using chiral stationary phase gas chromatography with a Chiracel-bonded column (30 m × 0.25 m, \(\beta\)-cyclodextrin / permethyl); T = 150 °C isothermal, H\(_2\) carrier gas at 14 psi. First component: 23.954 min; Second component: 24.558 min; 35% ee.
To a solution of palladium(II) acetate (1 mg, 10 mol%) in acetonitrile (0.5 mL) was added \( n \)-tributylphosphine (7 \( \mu \)L, 0.028 mmol). The solution was heated at reflux for 20 minutes. The resulting yellow solution was cooled to 55 °C and enol ether \( 79 \) (7 mg, 0.046 mmol) in acetonitrile (0.5 mL) was added. The resulting yellow solution was heated at 40 °C for 24 hours. Upon cooling to room temperature, the yellow solution was diluted with diethyl ether, filtered through Celite® and concentrated \textit{in vacuo}. The crude residue was purified by flash chromatography on silica gel (95 : 5 petroleum ether/ethyl acetate) to give \( 80 \) as a white solid (5 mg, 71%). The compound showed identical NMR spectroscopic data to racemic \( 80 \). Resolution between the enantiomers was determined using chiral stationary phase gas chromatography with a Chiracel-bonded column (30 m × 0.25 m, \( \beta \)-cyclodextrin / permethyl); \( T = 150 \) °C isothermal, \( \text{H}_2 \) carrier gas at 14 psi. First component: 27.123 min; Second component: 27.637 min; <5% \( ee \).
A suspension of cyclopentanone (35.0 g, 416 mmol) and L-threonine (6.0 g, 50.4 mmol) in dichloromethane (200 mL) was stirred at room temperature for 1 hour. Formaldehyde solution (37% in water, 5.0 mL, 166.5 mmol) was added and the mixture was stirred vigorously for 48 hours. The organic phase was separated and concentrated in vacuo. The crude residue was purified by flash chromatography on silica gel (50 : 50 to 0 : 100 petroleum ether/ethyl acetate) to give 143 as a colourless oil (6.0 g, 62%); $^1$H NMR (250 MHz, CDCl$_3$): $\delta$ 3.89-3.68 (2H, m, CH$_2$OH), 2.58 (1H dd, $J$ = 8.0, 4.0 Hz, CH), 2.45-2.30 (2H, m, C(O)CH$_2$), 2.25-2.03 (3H, m CH$_2$ and OH), 1.89-1.67 (2H, m, CH$_2$); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 222.3, 62.1, 50.6, 38.5, 26.1, 20.9; $[\alpha]_D^{22}$ -92.3 (c 4.5 CHCl$_3$), $[\alpha]_D^{23}$ -54.7 (c 4.5 CHCl$_3$) reported for (S)-2-(hydromethyl)cyclopentanone with 75% ee.$^{72}$
PREPARATION OF 6-(HYDROXYMETHYL)TETRAHYDRO-2H-PYRAN-2-ONE 142

A suspension of alcohol 143 (1.00 g, 8.77 mmol), sodium hydrogen carbonate (4.5 g, 55.56 mmol) and 3-chloroperbenzoic acid (>77% w/w, 8.0 g, 35.70 mmol) in dichloromethane (100 mL) was stirred at room temperature for 1 hour. The reaction was quenched by the addition of sodium thiosulphate and sodium hydrogen carbonate, dried over sodium sulfate, filtered through Celite® and concentrated in vacuo. The crude residue was purified by flash chromatography on silica gel (100 : 0 to 90 : 10 dichloromethane/methanol) to give 142 as a colourless oil (1.2 g, 100%); $^1$H NMR (250 MHz, CDCl$_3$): $\delta$ 4.38-4.27 (1H, m, C(O)OC$_\text{H}_2$), 3.68 (1H dd, $J = 12.0$, 3.5 Hz, CH$_\text{A}$CH$_\text{B}$), 3.58 (1H dd, $J = 12.0$, 5.5 Hz, CH$_\text{A}$H$_\text{B}$), 2.57-2.27 (2H, m, C(O)CH$_2$), 1.89-1.56 (4H, m, 2 x CH$_2$); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 171.7, 80.6, 64.9, 31.4, 24.4, 18.3.
The reaction was conducted in duplicate and the reaction mixtures combined upon workup. A suspension of alcohol 142 (100 mg, 0.76 mmol), pyridinium dichromate (2.25 g, 5.98 mmol) and activated 4 Å molecular sieves (1.0 g) in dichloromethane (7.5 mL) was stirred vigorously at room temperature for 1 hour. The reaction mixtures were combined, diluted with pentane, filtered through Celite®, washed with pentane and carefully concentrated *in vacuo* to give a dark oil. A suspension of methyltriphenylphosphonium bromide (825 mg, 2.31 mmol) and potassium t-butoxide (225 mg, 2.01 mmol) in tetrahydrofuran (15 mL) was stirred at 0 °C for 15 minutes. The crude dark oil was dissolved in tetrahydrofuran (10 mL) and added to the resulting bright yellow solution at 0 °C via cannula. The resulting dark solution was stirred at room temperature for 16 hours. After this, the reaction mixture was diluted in pentane, carefully concentrated *in vacuo*, washed with pentane and the filtrate carefully concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica gel (90 : 10 to 0 : 100 pentane/diethyl ether) to give 140 as a colourless oil (50 mg, 26% over 2 steps); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 5.90 (1H, ddd, $J = 17.5, 10.5, 5.5$ Hz, alkene-$H$), 5.37 (1H, dt, $J = 17.5, 1.5$ Hz, alkene-$H_2$), 5.26 (1H, dt, $J = 10.5, 1.5$ Hz, alkene-$H_2$), 4.88-4.82 (1H, m, pyran-OC$H$) 2.67-2.46 (2H, m, CH$_2$), 2.07-1.84 (3H, m, 3 x CH), 1.75-1.64 (1H, m, CH); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 170.5, 138.9, 115.6, 80.4, 29.5, 27.8, 18.0.
PREPARATION OF 6-VINYLTETRAHYDRO-2H-PYRAN-2-OL 139

To a stirred solution of lactone 140 (50 mg, 0.40 mmol) in dichloromethane (2 mL) at -78 °C was added diisobutylaluminium hydride (1 M in hexanes, 555 µL, 0.55 mmol) followed by chlorotrimethylsilane (126 µL, 0.99 mmol). The resulting reaction mixture was stirred at -78 °C for 2.5 hours. After this period, methanol (0.2 mL) and potassium carbonate (500 mg in 0.4 mL of water) was added to the reaction mixture which was stirred at room temperature for a further 16 hours. Afterwards, sodium sulfate was added, the reaction mixture stirred for 15 minutes, filtered through Celite®, washed with dichloromethane and concentrated in vacuo to give 139 as a colourless oil (50 mg, 98%) as a 1 : 1 mixture of diastereoisomers; ¹H NMR (400 MHz, CDCl₃): δ 5.96-5.81 (1H, m, alkene-H), 5.39-5.34 (0.5H, m, CHOH), 5.31-5.21 (1H, m, alkene-H₂), 5.14-5.08 (1H, m, alkene-H₂), 4.79-4.82 (0.5H, m, CHOH), 4.53-4.46 (0.5H, m, pyran-OCH), 4.02-3.95 (0.5H, m, pyran-OCH), 3.71-3.64 (0.5H, m, OH), 3.05-2.98 (0.5H, m, OH), 1.94-1.22 (6H, m, 3 x CH₂); ¹³C NMR (100 MHz, CDCl₃): δ 139.2, 138.2, 115.2, 115.0, 96.5, 91.9, 69.7, 68.9, 32.4, 31.2, 30.4, 29.5, 21.9, 17.2.
PREPARATION OF TRIPHENYL(6-VINYL)-TETRAHYDRO-2H-PYRAN-2-YL)-PHOSPHONIUM TETRAFLUOROBORATE 116

To a suspension of 4 Å molecular sieves (400 mg) and a solution of HPPh$_3$BF$_4$ (373 mg, 0.78 mmol) in acetonitrile (5 mL) was added a solution of hemi-acetal 139 (50 mg, 0.39 mmol) in acetonitrile (5 mL). The resulting suspension was heated at reflux for 20 hours. Upon cooling to room temperature, the suspension was diluted with dichloromethane, filtered through Celite® and the filtrate concentrated in vacuo to give a thick pale yellow oil. To this was added dichloromethane (1 ml) then diethyl ether / petroleum ether (1 : 1, 40 mL) followed by vigorous stirring for 15 minutes. The clear solution was decanted and the process repeated five times to the remaining pale yellow gum. Upon final decantation, the yellow gum was concentrated in vacuo to give 116 as a white solid (35 mg, 20%). The compound showed identical NMR spectroscopic data to racemic 116.
To a solution of phosphonium salt 116 (35 mg, 0.076 mmol) in tetrahydrofuran (1 mL) at -78 °C was added potassium hexamethyldisilazide (0.68 M in tetrahydrofuran, 0.60 mL, 0.41 mmol) dropwise at -78 °C. The resulting red solution was stirred at -78 °C for 5 minutes then benzaldehyde (40 μL, 0.36 mmol) was added at -78 °C. The resulting yellow solution was stirred at -78 °C for 45 minutes, then at room temperature for a further 60 minutes. The resulting yellow solution was quenched with water and extracted with diethyl ether. The organic layer was washed three times with a mixture of 3 : 3 : 1 brine/water/methanol, dried over sodium sulfate and concentrated in vacuo. The crude residue was purified by flash chromatography on Florisil® (99 : 1 petroleum ether/ethyl acetate) to give 115 as a colourless oil (10 mg, 66%). The compound showed identical NMR spectroscopic data to racemic 115. Resolution between the enantiomers was determined using chiral stationary phase gas chromatography with a Chiracel-bonded column (30 m × 0.25 m, β-cyclodextrin / permethyl); T = 120 °C isothermal, H₂ carrier gas at 14 psi. First component: 23.029 min; Second component: 24.565 min; 46% ee.
To a solution of palladium(II) acetate (1.1 mg, 10 mol%) in acetonitrile (1 mL) was added n-tributylphosphine (7.5 μL, 0.03 mmol). The solution was heated at reflux for 20 minutes. The resulting yellow solution was cooled to 55 °C and enol ether 115 (10 mg, 0.05 mmol) in acetonitrile (1 mL) was added. The resulting yellow solution was heated at 55 °C for 48 hours. Upon cooling to room temperature, the yellow solution was diluted with diethyl ether, filtered through Celite® and concentrated in vacuo. The crude residue was purified by flash chromatography on silica gel (95 : 5 petroleum ether/ethyl acetate) to give 121 as a white solid (8 mg, 80%). The compound showed identical NMR spectroscopic data to racemic 121. Resolution between the enantiomers was determined using chiral stationary phase gas chromatography with a Chiracel-bonded column (30 m × 0.25 m, β-cyclodextrin / permethyl); T = 120 °C isothermal, H₂ carrier gas at 14 psi. First component: 27.120 min; Second component: 28.160 min; <5% ee.
PREPARATION OF (E)-2-BENZYLIDENE-6-((E)-PENT-1-ENYL)TETRAHYDRO-2H-PYRAN E-79 and (Z)-2-BENZYLIDENE-6-((E)-PENT-1-ENYL)TETRAHYDRO-2H-PYRAN Z-79

To a stirred solution of phosphonium salt 103 (1.00 g, 1.938 mmol) in tetrahydrofuran (20 mL) at -78 °C was added dropwise lithium hexamethyldisilazide (1.0 M in tetrahydrofuran, 2.3 mL, 2.33 mmol, 1.2 eq). The resulting red solution was stirred at -78 °C for 10 minutes, then the dry-ice bath was removed and stirred for 10 minutes further. Benzaldehyde (250 mg, 2.33 mmol, 1.2 eq) was added via syringe and the resulting yellow solution was stirred at room temperature for 16 hours. Water (5 mL) then hydrogen peroxide (1 mL) was added and stirred at room temperature for 1 hour. The reaction mixture was quenched with water and extracted with diethyl ether. The ether layer was washed with a 3 : 3 : 1 brine/water/methanol mixture (3 x 25 mL), dried over sodium sulfate, filtered and concentrated in vacuo. The crude mixture was purified via column chromatography on Florisil® (99 : 1 petroleum ether/ethyl acetate) to give enol ethers E-79 and Z-79 as colourless oil (357 mg, 1.395 mmol, 72% yield) containing a 1 : 1 E/Z mixture of diastereoisomers. Separation of the diastereoisomers was accomplished via preparative HPLC using an Alltech “Alltima HP C18 5u” column (150 mm x 22 mm) to give (E)-enol ether (150 mg, 0.586 mmol, 30%) and (Z)-enol ether (130 mg, 0.508 mmol, 26%); conditions: 15 : 85 / water : methanol/ammonium hydroxide (1%), 20.0 mL/min, 254 nm.
(E-79): \(^1\)H NMR (250 MHz, CD\(_3\)OD): \(\delta\) 7.33-7.22 (2H, m, Ar-H) 7.20-7.09 (3H, m, Ar-H), 6.02 (1H, s, O-alkene-H), 5.85-5.69 (1H, m, CH\(_2\)-alkene-H), 5.54 (1H, dd, \(J = 15.5, 6.5\) Hz, CH-alkene-H), 4.20-4.05 (1H, m, CH), 2.81-2.64 (1H, m, CH), 2.28-2.04 (3H, m, 3 x CH), 0.92 (3H, t, \(J = 7.0\) Hz, CH\(_3\)); \(^{13}\)C NMR (63 MHz, CD\(_3\)OD): \(\delta\) 156.6, 137.9, 133.6, 131.7, 129.8, 129.1, 126.7, 110.8, 81.3, 33.0, 32.4, 32.3, 26.0, 23.2, 23.1, 14.3; FTIR (CH\(_2\)Cl\(_2\), \(\nu_{\text{max}}\) cm\(^{-1}\)): 2965 (s), 2929 (s), 2860 (m), 1652 (s), 1234 (s), 1138 (s) 1035 (s), 969 (m) 922 (m); HRMS (El) m/z [MH]\(^+\) calcd for C\(_{18}\)H\(_{25}\)O: 257.1905, found 257.1895.

(Z-79): \(^1\)H NMR (250 MHz, CD\(_3\)OD): \(\delta\) 7.67-7.45 (2H, m, Ar-H), 7.22-7.13 (2H, m, Ar-H), 7.10-6.98 (1H, m, Ar-H), 5.90-5.69 (1H, m, CH\(_2\)-alkene-H), 5.60 (1H, ddt, \(J = 15.5, 6.0, 1.5\) Hz, CH-alkene-H), 5.38 (1H, m, O-alkene-H), 4.35-4.09 (1H, m, pyran-OCH), 2.37-2.21 (2H, m, CH\(_2\)), 2.15-2.03 (2H, m, CH\(_2\)), 1.91-1.56 (4H, m, 2 x CH\(_2\)), 1.44-1.38 (4H, m, 2 x CH\(_2\)), 0.94 (3H, t, \(J = 7.0\) Hz, CH\(_3\)); \(^{13}\)C NMR (63 MHz, CD\(_3\)OD): \(\delta\) 155.8, 137.9, 133.7, 131.5, 129.2, 128.9, 126.2, 108.1, 80.4, 33.0, 32.5, 32.1, 31.1, 23.5, 23.1, 14.3; FTIR (CH\(_2\)Cl\(_2\), \(\nu_{\text{max}}\) cm\(^{-1}\)): 2928 (s), 2859 (m), 1655 (m), 1166 (m), 1030 (s), 968 (m), 928 (m), 1496 (m), 1454 (m), 969 (m); HRMS (El) m/z [MH]\(^+\) calcd for C\(_{18}\)H\(_{25}\)O: 257.1905, found 257.1899.
REPRESENTATIVE PROCEDURE FOR THE KINETIC RESOLUTION OF (Z)-2-BENZYLIDENE-6-((E)-PENT-1-ENYL)TETRAHYDRO-2H-PYRAN Z-79

To a reaction vial was added racemic enol ether Z-79 (1 eq), bis(dibenzylideneacetone)palladium(0) (5 mol%) and 1Bu-Phox (6 mol%). The vial was sealed with a rubber septum, evacuated under reduced pressure and back filled with argon. Dimethyl sulfoxide (0.4 M) was added under argon, and the vial evacuated for ca. 2 minutes. The vial was back filled with argon and stirred in a preheated heating block at 40 °C for 6.5 hours. The reaction vial was cooled to room temperature, and directly purified via column chromatography on Florisil® (99 : 1 to 90 : 10 petroleum ether/ethyl acetate) to give enantioenriched enol ethers Z-79 as colourless oils. The compounds showed identical NMR spectroscopic data to racemic enol ether Z-79. The ee’s were determined by HPLC analysis using a Phenomenex “Lux 3u Cellulose-2” column (250 mm x 4.6 mm); conditions: n-hexane (100%), 1.0 mL/min, 254 nm.

(S)-1Bu-Phox (Scheme 96, equation (1)): First component: 8.180 min; Second component: 9.110 min; +94% ee; [α]D23 -20.0 (c 1.0 MeOH).

(R)-1Bu-Phox (Scheme 96, equation (2)): First component: 10.210 min; Second component: 10.983 min; -97% ee; [α]D20 +20.0 (c 1.0 MeOH).
REPRESENTATIVE PROCEDURE FOR THE KINETIC RESOLUTION OF (E)-2-BENZYLIDENE-6-((E)-PENT-1-ENYL)TETRAHYDRO-2H-PYRAN E-79

To a reaction vial was added racemic enol ether E-79 (1 eq), bis(dibenzylideneacetone)palladium(0) (5 mol%) and Bu-Phox (6 mol%). The vial was sealed with a rubber septum, evacuated under reduced pressure and back filled with argon. Dimethyl sulfoxide (0.4 M) was added under argon, and the vial evacuated for ca. 2 minutes. The vial was back filled with argon and stirred in a preheated heating block at 55 °C for 9.5 hours. The reaction vial was cooled to room temperature, and directly purified via column chromatography on Florisil® (99:1 to 90:10 petroleum ether/ethyl acetate) to give enantioenriched enol ethers E-79 as colourless oils. The compounds showed identical NMR spectroscopic data to racemic enol ether E-79. The ee of the enol ethers were determined by HPLC analysis using a Phenomenex “Lux 3u Cellulose-2” column (250 mm x 4.6 mm); conditions: n-hexane (100%), 1.0 mL/min, 254 nm.

(S)-Bu-Phox (Scheme 97, equation (1)): First component: 9.170 min; Second component: 12.610 min; +77% ee; [α]D22 -50.0 (c 1.0 MeOH).

(R)-Bu-Phox (Scheme 97, equation (2)): First component: 13.720 min; Second component: 19.967 min; -75% ee.
GENERAL PROCEDURE FOR THE O→C REARRANGEMENT OF ENANTIOPURE 2-BENZYLIDENE-6-((E)-PENT-1-ENYL)TETRAHYDRO-2H-PYRANS

![Chemical structure]

To a reaction vial was added enantioenriched enol ether 79 (1 eq), bis(dibenzylideneacetone)palladium(0) (5 mol%) and ¹Bu-Phox (6 mol%). The vial was sealed with a rubber septum, evacuated under reduced pressure and back filled with argon. Dimethyl sulfoxide (0.4 M) was added under argon, and the vial evacuated for ca. 2 minutes. The vial was back filled with argon and stirred in a preheated heating block at 80 °C for 12 hours. The reaction vial was cooled to room temperature, and directly purified via column chromatography on silica gel (90 : 10 petroleum ether/ethyl acetate) to give enantioenriched cyclic ketones 80 as solids contaminated with dibenzylideneacetone. The compounds showed identical NMR spectroscopic data to racemic cyclic ketone 80. The ee’s of the cyclic ketones were determined by HPLC analysis using a Phenomenex “Lux 3u Cellulose-1” column (250 mm x 4.6 mm); conditions: 95 : 5 n-Hexane/iso-propanol, 1.0 mL/min, 220 nm.

Example (Table 17, Entry 1): First component: 7.390 min; Second component: 9.107 min; +98% ee; [α]_{D}^{22} -30.0 (c 1.0 CH_{3}Cl).
To a stirred solution of enantiopure enol ether Z-79 (37 mg, 0.145 mmol, +98% ee) and ruthenium(III) chloride (1.1 mg, 0.005 mmol, 3.5 mol%) in acetonitrile/water (1 : 1, 0.5 mL) at room temperature was added portionwise a mixture of oxone® (133 mg, 0.217 mmol) and sodium hydrogen carbonate (56 mg, 0.664 mmol) over 10 minutes. The reaction mixture was stirred for 2 hours and the dark suspension quenched with saturated sodium thiosulfate solution and extracted with dichloromethane. The organic layer was washed twice with water, brine, dried over sodium sulfate and concentrated in vacuo. The crude mixture was purified via column chromatography on silica gel (90 : 10 petroleum ether/ethyl acetate) to give lactone 134 as a colourless oil (13.3 mg, 0.073 mmol, 50% yield); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 5.75 (1H, dtd, $J$ = 15.5, 7.0, 1.0 Hz, alkene-$H$), 5.48 (1H, ddt, $J$ = 15.5, 6.5, 1.5 Hz, alkene-$H$), 5.78-5.71 (1H, m, OCH), 2.61-2.52 (1H, m, C(O)CH$_A$H$_B$), 2.50-2.40 (1H, m, C(O)CH$_A$H$_B$), 2.08-2.00 (2H, m, CH$_2$), 1.98-1.82 (2H, m, CH$_2$), 1.67-1.59 (1H, m, CH), 1.40-1.26 (5H, m, 5 x CH), 0.88 (3H, t, $J$ = 7.0 Hz, CH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 171.4, 134.6, 127.9, 80.7, 31.8, 31.0, 29.5, 28.4, 22.1, 18.2, 13.9; FTIR (CH$_2$Cl$_2$, $\nu_{\text{max}}$ cm$^{-1}$): 2956 (m), 2928 (m), 2876 (w), 1735 (s), 1237 (m), 1037 (m), 970 (w); HRMS (El) $m/z$ [MH]$^+$ calcd for C$_{11}$H$_{19}$O$_2$: 183.1385, found 183.1392.
A solution of lactone 134 (13.3 mg, 0.073 mmol) and platinum(IV) oxide (Adam’s catalyst, 1.3 mg, 10% w/w) in ethyl acetate (5 mL) was stirred at room temperature under an atmosphere of hydrogen (balloon) for 4 hours. Upon completion, the atmosphere was replaced with nitrogen, and the dark solution filtered through Celite®, washed with ethyl acetate and concentrated in vacuo. The crude mixture was purified via column chromatography on silica gel (80 : 20 petroleum ether/ethyl acetate) to give lactone 147 as a colourless oil (7.0 mg, 0.038 mmol, 52% yield); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 4.32-4.22 (1H, m, OCH), 2.63-2.52 (1H, m, C(O)CH$_3$H$_2$), 2.50-2.38 (1H, m, C(O)CH$_3$H$_2$), 1.96-1.84 (3H, m, 3 x CH), 1.74-1.65 (1H, m, CH), 1.60-1.45 (3H, m, 3 x CH), 1.32-1.25 (7H, m, 7 x CH), 0.91-0.85 (3H, m, CH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 172.0, 80.6, 35.9, 31.7, 29.5, 29.1, 27.8, 24.9, 22.6, 18.5, 14.0; FTIR (CH$_2$Cl$_2$, $\nu_{\max}$ cm$^{-1}$): 1735 (s), 1465 (w), 1342 (w), 1242 (s); HRMS (EI) m/z [MH]$^+$ calcld for C$_{11}$H$_{21}$O$_2$: 185.1542, found 185.1541; $[\alpha]_D^{20}$ -33.3 (c 0.9 CHCl$_3$), $[\alpha]_D^{20}$ +46.1 (c 0.61 CHCl$_3$) reported for (R)-6-hexyltetrahydro-2H-pyran-2-one with 98% ee. 80
A solution of enantioenriched cyclic ketone 80 (73 mg, 0.285 mmol, +75% ee) and p-toluenesulfonyl hydrazine (80 mg, 0.428 mmol) in methanol (1.5 mL) was stirred at room temperature for 16 hours. To this was added a solution of zinc chloride (27 mg, 0.199 mmol) and sodium cyanoborohydride (27 mg, 0.428 mmol) in methanol (0.75 mL) via cannula. The reaction mixture was heated at 65 °C for 4 hours. Upon completion, the reaction mixture was cooled to room temperature and diluted with ethyl acetate, washed with 1M hydrochloric acid, sodium hydrogen carbonate, brine, dried over sodium sulfate and concentrated \textit{in vacuo}. The crude mixture was purified \textit{via} column chromatography on silica gel (100% petroleum ether) to give trans-cyclohexane 148 as a colourless oil (32 mg, 0.132 mmol, 46% yield); $^1$H NMR (250 MHz, CDCl$_3$): $\delta$ 7.30-7.19 (2H, m, Ar-H), 7.18-7.07 (3H, m, Ar-H), 5.18-4.93 (2H, m, 2 x alkene-H), 2.33-2.06 (2H, m, CH$_2$), 1.92-1.64 (6H, m, 3 x CH$_2$), 1.49-1.22 (4H, m, 2 x CH$_2$), 1.13-0.94 (4H, m, 2 x CH$_2$), 0.74 (3H, t, $J$ = 7.0 Hz, CH$_3$); $^{13}$C NMR (63 MHz, CDCl$_3$): $\delta$ 146.5, 134.3, 129.7, 128.0, 127.8, 125.6, 50.7, 46.4, 35.4, 33.7, 32.1, 31.6, 26.8, 26.2, 21.7, 13.8; FTIR (CH$_2$Cl$_2$, $\nu_{\text{max}}$ cm$^{-1}$): 2956 (s), 2924 (s), 2852 (s), 1446 (w), 965 (w), 754 (w), 698 (w); HRMS (EI) m/z [M] calcd for C$_{18}$H$_{26}$: 242.2034, found 242.2024.
A stirred solution of cyclohexane \textbf{148} (30 mg, 0.124 mmol) in methanol/dichloromethane (1 : 1, 5.0 mL) containing a small amount of sodium hydrogen carbonate at -78 °C was bubbled with ozone until a blue colour persisted. At this point, nitrogen was bubbled through the solution until disappearance of the blue colour. Sodium borohydride (28 mg, 0.744 mmol) was added and the reaction mixture stirred at room temperature for 1 hour. The reaction mixture quenched with ethyl acetate and washed with water, brine, dried over sodium sulfate and concentrated \textit{in vacuo}. The crude mixture was purified via column chromatography on silica gel (90 : 10 petroleum ether/ethyl acetate) to give \textit{trans}-cyclohexane \textbf{149} as a colourless oil (9.5 mg, 0.050 mmol, 40% yield); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.34-7.26 (2H, m, Ar-H), 7.24-7.16 (3H, m, Ar-H), 3.37 (1H, dd, $J = 11.0, 4.0$ Hz, CH$_4$H$_6$OH), 3.23 (1H, dd, $J = 11.0, 4.0$ Hz, CH$_4$H$_6$OH), 2.33 (1H, td, $J = 11.5, 3.5$ Hz, CH$^\alpha$), 2.00-1.93 (1H, m, CH$^\alpha$), 1.90-1.77 (3H, m, 3 x CH), 1.54-1.44 (2H, m, CH$_2$), 1.41-1.35 (2H, m, CH$_2$), 1.23-1.20 (1H, m, CH$^\alpha$); $^{13}$C NMR (63 MHz, CDCl$_3$): $\delta$ 145.8, 128.6, 127.4, 126.3, 66.6, 47.4, 45.3, 35.5, 29.9, 26.7, 26.1; FTIR (CH$_2$Cl$_2$, $\nu_{\max }$ cm$^{-1}$): 3368 (br), 2923 (s), 2851 (m), 1452 (m), 1029 (m), 757 (m), 700 (s); HRMS (EI) $m/z$ [M] calcd for C$_{13}$H$_{18}$O: 190.1358, found 190.1352; $[\alpha]_D^{22} +26.3$ (c 1.9 CHCl$_3$), $[\alpha]_D^{25} +33.7$ (c 1.5 CHCl$_3$) reported for (1S,2S)-2-phenyl-cyclohexanemethanol with 96% ee.$^{81}$
To a stirred solution of cis-3,4-dichlorocyclobutene (2.00 g, 16.26 mmol) in anhydrous benzene (12.5 mL) at room temperature was added diironnonacarbonyl (2.00 g). The resulting dark solution was heated to 55 °C where the evolution of carbon monoxide commenced. Once stopped, further portions of diironnonacarbonyl were added over 3 hours, governed by carbon monoxide evolution (total amount of diironnonacarbonyl used was 14.0 g, 38.48 mmol). Upon addition of the last portion, the dark reaction solution was stirred at 50 °C for 1 hour. The reaction mixture was cooled to room temperature, diluted with pentane, filtered through Celite® and the filtrate concentrated in vacuo to give a dark green oil. Kugelrohr distillation at 75-100 °C under 40 mmHg gave cyclobutadieneiron tricarbonyl 151 as a pale yellow oil (1.9 g, 9.89 mmol, 61%); ^1^H NMR (400 MHz, CDCl₃): δ 3.97 (4H, s, 4 x CH); ^1^C NMR (100 MHz, CDCl₃): δ 214.5, 63.8; FTIR (CDCl₃, ν max cm⁻¹): 2923 (m), 2852 (m), 2049 (s), 1965 (s); HRMS (El) m/z [M] calcd for C₇H₄FeO₃: 191.9510, found 191.9517.
To N-methylformanilide (520 mg, 3.84 mmol) at 0 °C was added phosphorus oxychloride (4.0 mL) and the resulting solution stirred at 0 °C for 30 minutes. Cyclobutadieneiron tricarbonyl 151 (330 mg, 1.72 mmol) was added and the resulting yellow solution stirred at 50 °C for 16 hours. The red reaction mixture was poured onto ice/water and extracted twice with dichloromethane. The combined dichloromethane washings were washed with water (3 x 10 mL), hydrochloric acid (1 M in water, 3 x 10 mL), saturated sodium hydrogen carbonate solution (2 x 10 mL), brine (10 mL), dried with sodium sulphate and concentrated in vacuo. The crude residue was purified by flash chromatography on silica gel (3 : 1 petroleum ether/diethyl ether) to give 180 as a dark red oil (300 mg, 1.36 mmol, 79%); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 9.21 (1H, s, CHO), 4.67 (2H, s, 2 x CH), 4.53 (1H, s, CH); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 211.2, 187.6, 71.6, 69.6, 65.0; FTIR (CDCl$_3$, $\nu_{max}$ cm$^{-1}$): 2924 (s), 2852 (s), 2061 (s), 1989 (s), 1671 (m), 1561 (w), 1432 (w); HRMS (EI) m/z [M] calcd for C$_8$H$_4$FeO$_4$: 219.9459, found 219.9452.
To a stirred solution of ethyl 4-bromobutanoate 181 (19.5 g, 0.10 mol) in dichloromethane (180 mL) at -78 °C was added diisobutylaluminium hydride (1.0 M in hexanes, 100 mL, 0.1 mol) dropwise. The reaction mixture was stirred at -78 °C for 90 minutes. The reaction mixture was quenched by pouring into ice-cold hydrochloric acid (4 M in water) and stirred at 0 °C for 1 hour. The organic phase was separated, and the aqueous extracted with dichloromethane. The combined organic extracted were washed subsequently with water, and brine then dried over sodium sulphate and concentrated in vacuo, to give crude aldehyde 182 as yellow oil (17.0 g); ¹H NMR (400 MHz, CDCl₃): δ 9.81 (1H, s, CHO), 3.45 (2H, t, J = 6.5 Hz, CH₂Br), 2.67 (2H, dt, J = 7.0, 0.5 Hz, CH₂), 2.17 (2H, quin, J = 6.5 Hz, CH₂). The residue was dissolved in toluene (350 mL), then ethylene glycol (46.0 g, 0.75 mol) and p-toluenesulfonic acid (0.68 g, 4.0 mmol) was added followed by refluxing of the reaction mixture with a Dean-Stark trap. Once all the water was removed, the reaction mixture was allowed to cool to room temperature, and sodium hydrogen carbonate (3 g) was added. After stirring for 10 minutes, the reaction mixture was washed with saturated sodium hydrogen carbonate solution, dried with potassium carbonate and concentrated in vacuo. The crude residue was purified by Kugelrohr distillation at 94-96 °C under 10 mmHg to give acetal bromide 183 as a pale yellow oil (16.8 g, 0.09 mol, 87%); ¹H NMR (400 MHz, CDCl₃): δ 4.86 (1H, t, J = 4.5 Hz, CH), 3.95-3.90 (2H, m, -OCH₂CH₂O-), 3.83-3.78 (2H, m, -OCH₂CH₂O-), 3.42 (2H, t, J = 7.0 Hz, -CH₂Br), 1.99-1.92 (2H, m, CH₂), 1.81-1.74 (2H, m, CH₂); ¹³C NMR (100 MHz, CDCl₃): δ 103.7, 64.9, 33.5, 32.3, 27.2; FTIR (CDCl₃, νmax cm⁻¹): 2958 (s), 2884 (s), 2765 (w), 1735 (s), 1440 (s), 1410 (s), 1252 (s), 1131 (s), 943 (s).
To a stirred solution of acetal-bromide 183 (800 mg, 4.145 mmol) in diethyl ether (9.0 mL) at -78 °C was added tert-butyllithium (1.5 M in pentane, 5.4 mL, 8.290 mmol) dropwise over 5 minutes. The cloudy reaction mixture was stirred at -78 °C for 1 hour, then at 0 °C for 1 hour before cooling back to -78 °C. To the reaction mixture was added a solution of aldehyde 180 (200 mg, 1.04 mmol) in diethyl ether (2.5 mL) slowly via cannula. The red reaction mixture was stirred at -78 °C for 45 minutes, then at 0 °C for 45 minutes. The reaction mixture was quenched by the addition of saturated ammonium chloride solution and extracted with diethyl ether (x3). The combined organic extracts were dried over sodium sulphate and concentrated in vacuo, to give crude alcohol 184 as yellow oil. To a stirred solution of the crude residue in acetone/water (2 : 1, 20 mL) was added pyridinium toluene-4-sulfonate (200 mg, 0.800 mmol) and the reaction mixture heated at reflux for 16 hours. The reaction mixture was diluted with diethyl ether, the aqueous separated and extracted with further diethyl ether. The combined organic extracts were dried over sodium sulphate and concentrated in vacuo. The crude residue was purified by flash chromatography on silica gel (3 : 1 petroleum ether/diethyl ether) to give lactol 177 as a yellow oil (200 mg, 0.685 mmol, 66%) as a 1 : 1 mixture of diastereoisomers; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 5.30 (0.5H, s, CHO$_2$), 4.72 (0.5H, br t, $J = 6.5$ Hz, CHO$_2$), 4.37 (0.5H, d, $J = 11$ Hz, pyran-OC$_2$H), 4.18-4.00 (3H, m, 3 x CH$_3$), 3.86 (0.5H, d, $J = 11$ Hz, pyran-OC$_2$H), 3.37 (0.5H, d, $J = 5.5$ Hz, OH), 2.85 (0.5H, s, OH), 1.78-1.15 (6H, m, 3 x CH$_2$); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 215.5, 214.4, 96.6, 92.0, 86.9, 84.7, 71.9, 64.4, 62.9, 62.5, 62.3, 61.9, 32.2, 30.6, 29.6, 29.4, 21.8, 17.0; FTIR (CDCl$_3$, $\nu_{\text{max}}$ cm$^{-1}$): 3446 (br), 2956 (s), 2924 (s), 2853 (s), 2046 (s), 1969 (s); HRMS (EI) $m/z$ [M] calcd for C$_{12}$H$_{13}$FeO$_5$: 292.0034, found 292.0036.
To a suspension of 4 Å molecular sieves (400 mg) and a solution of HPPh$_3$BF$_4$ (400 mg, 1.00 mmol) in acetonitrile (2.5 mL) was added a solution of lactol 177 (160 mg, 0.57 mmol) in acetonitrile (2.5 mL). The resulting suspension was heated at reflux for 20 hours. Upon cooling to room temperature, the suspension was diluted with dichloromethane, filtered through Celite® and the filtrate concentrated in vacuo to give a thick pale yellow oil. To this was added 2 mL of dichloromethane, then diethyl ether/petroleum ether (1 : 1, 100 mL) followed by vigorous stirring for 15 minutes. The clear solution was decanted and the process repeated four times to the remaining pale yellow gum. Upon final decantation, the yellow gum was concentrated in vacuo to give 185 as a yellow solid (250 mg, 0.40 mmol, 70%); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 9.62 (1H, s, CHO), 7.87-7.72 (15H, m, ArH), 4.23-4.13 (1H, m, CHP), 4.11 (1H, s, CH), 3.92 (1H, d, $J = 9.0$ Hz, CH), 3.43 (1H, d, $J = 9.0$ Hz, CH), 2.56-2.43 (2H, m, CH$_2$), 2.14-2.00 (1H, m, CH), 1.96-1.82 (2H, m, CH$_2$), 1.31-1.21 (1H, m, CH); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 212.5, 201.4, 135.2, 133.9 ($J_{CP} = 10.0$ Hz), 130.5 ($J_{CP} = 12.0$ Hz), 116.9 ($J_{CP} = 82.0$ Hz), 75.2, 65.3, 64.3, 62.8, 42.4, 34.6 ($J_{CP} = 43.0$ Hz), 27.6, 20.6 ($J_{CP} = 10.0$ Hz); $^{31}$P NMR (100 MHz, CDCl$_3$): $\delta$ 27.0; FTIR (CDCl$_3$, $\nu_{\text{max}}$ cm$^{-1}$): 2925 (w), 2050 (s), 1981 (s), 1721 (w), 1440 (m), 1110 (m), 1059 (s), 725 (m); HRMS (El) m/z [M-BF$_4$]$^+$ calcd for C$_{30}$H$_{26}$FeO$_5$P: 537.0918, found 537.0921.
PREPARATION OF 1-(1,5,5-TRIMETHOXYPENTYL)CYCLOBUTA-1,3-DIENEIRON TRICARBONYL 189

To a stirred solution of acetal-bromide 183 (1.20 g, 6.218 mmol) in diethyl ether (15.0 mL) at -78 °C was added tert-butyllithium (1.7 M in pentane, 7.2 mL, 12.240 mmol) dropwise over 5 minutes. The cloudy reaction mixture was stirred at -78 °C for 1 hour, then at 0 °C for 1 hour before cooling back to -78 °C. To the reaction mixture was added a solution of aldehyde 180 (400 mg, 2.08 mmol) in diethyl ether (5.0 mL) slowly via cannula. The red reaction mixture was stirred at -78 °C for 45 minutes, then at 0 °C for 45 minutes. The reaction mixture was quenched by the addition of saturated ammonium chloride solution and extracted with diethyl ether. The organic extracts dried over sodium sulphate and concentrated in vacuo, to give crude alcohol 184 as yellow oil. To a stirred solution of the crude residue in methanol (20 mL) was added pyridinium toluene-4-sulfonate (200 mg, 0.800 mmol) and the reaction mixture heated at reflux for 16 hours. The reaction mixture was diluted with diethyl ether, the aqueous separated and extracted with further diethyl ether. The combined organic extracts were dried over sodium sulphate and concentrated in vacuo. The crude residue was purified by flash chromatography on silica gel (4 : 1 petroleum ether/diethyl ether) to give acetal 189 as a yellow oil (500 mg, 1.420 mmol, 68%); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 4.35 (1H, t, $J = 5.0$ Hz, CH(OMe)$_2$CH$_2$), 4.13 (1H, s, CH), 4.06 (2H, s, 2 x CH), 3.53-3.45 (1H, m, CCH(OMe)CH$_3$), 3.37 (3H, s, OCH$_3$), 3.31 (6H, s, 2 x OCH$_3$), 1.67-1.40 (6H, m, 3 x CH$_2$); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 214.5, 104.4, 85.6, 76.5, 63.2, 62.9, 62.6, 57.1, 52.7, 34.1, 32.2, 20.7; FTIR (CDCl$_3$, $\nu_{\text{max}}$ cm$^{-1}$): 2919 (s), 2045 (s), 1970 (s), 1737, (w), 1467 (w), 1126 (m); HRMS (El) m/z [M] calcd for C$_{15}$H$_{20}$FeO$_6$: 352.0609, found 352.0614.
PREPARATION OF 5-(CYCLOBUTA-1,3-DIEN-1-YL)-5-OXOPENTANOIC ACIDIRON TRICARBONYL 192

\[ \text{Fe(CO)}_3 \overset{\text{O}}{\longrightarrow} \text{Fe(CO)}_3 \]

To a stirred solution of cyclobutadieneiron tricarbonyl 151 (200 mg, 1.04 mmol) and glutaric anhydride (125 mg, 1.10 mmol) in dichloromethane (1.0 mL) at -20 °C was added aluminium(III) chloride (300 mg, 2.19 mmol) portionwise over 15 minutes. After 4 hours at -20 °C, the reaction mixture was poured onto saturated sodium hydrogen carbonate solution and extracted with dichloromethane. The aqueous layer was adjusted to pH 1 with concentrated HCl and extracted with ethyl acetate, dried over sodium sulfate and concentrated in vacuo. The crude residue was purified by flash chromatography on silica gel (3 : 1 petroleum ether/ethyl acetate with 1% acetic acid) to give acid 192 as a brown oil (167 mg, 0.54 mmol, 54%); \(^1\)H NMR (250 MHz, CDCl\(_3\)): \(\delta\) 10.61 (1H, br, CO\(_2\)H), 4.56 (2H, s, 2 x CH), 4.43 (1H, s, CH), 2.40 (2H, t, \(J = 7.0\) Hz, CH\(_2\)), 2.32 (2H, t, \(J = 7.0\) Hz, CH\(_2\)), 1.92 (2H, quin, \(J = 7.0\) Hz, CH\(_2\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 211.8, 199.2, 179.1, 69.7, 69.6, 64.6, 36.5, 32.9, 19.1; FTIR (CDCl\(_3\), \(\nu_{\text{max}}\) cm\(^{-1}\)): 3360 (br), 2924 (s), 2853 (m), 2059 (m), 1988 (m), 1710 (m), 1591 (s), 1439 (s); HRMS (EI) \(m/\zeta [\text{MH}]^+\) calcd for C\(_{12}\)H\(_{11}\)FeO\(_6\): 306.9905, found 306.9902.
PREPARATION OF METHYL 5-(CYCLOBUTA-1,3-DIEN-1-YL)-5-OXOPENTANOATE IRON TRICARBONYL \(194\)

\[
\begin{align*}
\text{O} & \quad \text{OH} \\
\text{Fe(CO)}_3 & \quad \text{O} \\
\end{align*}
\]

To a stirred solution of acid \(192\) (240 mg, 0.781 mmol) in methanol/toluene (1 : 3, 6 mL) at room temperature was added (trimethylsilyl)diazomethane solution (2.0 M in hexanes, 0.6 mL, 1.171 mmol) dropwise. The reaction mixture was stirred at room temperature for 1 hour and concentrated \textit{in vacuo}. The crude residue was purified by flash chromatography on silica gel (3 : 1 petroleum ether/ethyl acetate) to give ester \(194\) as a yellow oil (200 mg, 0.625 mmol, 80%); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 4.56 (2H, s, 2 x CH), 4.42 (1H, s, CH), 3.67 (3H, s, CH\(_3\)), 2.37-2.25 (4H, m, 2 x CH\(_2\)), 1.97-1.85 (2H, m, CH\(_2\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 211.8, 199.1, 173.4, 69.5, 64.7, 51.6, 36.7, 32.8, 29.7, 19.3; FTIR (CDCl\(_3\), \(\nu_{\text{max}}\) cm\(^{-1}\)): 2056 (s), 1980 (s), 1736 (m), 1668 (w), 1436 (w), 1201 (w); HRMS (EI) \(m/z\) [MH]\(^+\) calcd for C\(_{13}\)H\(_{13}\)FeO\(_6\): 321.0062, found 321.0059.
PREPARATION OF METHYL 5-(CYCLOBUTA-1,3-DIEN-1-YL)-5-OXOPENTANOATE IRON TRICARBONYL 190

To a stirred solution of ester 194 (160 mg, 0.500 mmol) in ethanol/1,4-dioxane (4 : 1 , 10 mL) at 0 °C was added sodium borohydride (57 mg, 1.500 mmol). After stirring at 0 °C for 3 hours, the reaction was quenched with water and extracted with ethyl acetate, dried over sodium sulfate and concentrated in vacuo. The crude residue was dissolved in benzene (10 mL). Activated 4 Å molecular sieves (200 mg) were added and the resulting suspension heated at reflux for 24 hours and cooled to room temperature. The reaction mixture was filtered through Celite®, washed with ethyl acetate and concentrated in vacuo. The crude residue was purified by flash chromatography on silica gel (2 : 1 petroleum ether/ethyl acetate) to give lactone 190 as a yellow oil (100 mg, 0.345 mmol, 69%); 1H NMR (400 MHz, CDCl3): δ 4.73 (1H, dd, J = 11.0, 3.5 Hz, >CHO(C(O)), 4.24-4.13 (3H, m, 3 x CH), 2.64-2.54 (1H, m, C(O)CH₃H₅), 2.50-2.39 (1H, m, C(O)CH₃H₅), 2.02-1.94 (3H, m, 3 x CH), 1.57-1.46 (1H, m, CH); 13C NMR (100 MHz, CDCl3): δ 210.4, 170.9, 92.9, 63.6, 62.9, 60.4, 31.5, 29.4, 18.9; FTIR (CDCl₃, νmax cm⁻¹): 2928 (w), 2855 (w), 2046 (s), 1966 (s), 1737 (m), 1234 (w), 613 (m), 590 (m); HRMS (EI) m/z [M]⁺ calcd for C₁₂H₁₀⁵⁶FeO₅: 289.9878, found 289.9882.
A stirred suspension of benzyl bromide (1.00 g, 5.84 mmol), 2-mercaptobenzothiazole 197 (980 mg, 5.84 mmol) and potassium carbonate (1.62 g, 11.69 mmol) in acetone (10 mL) was heated at reflux for 3 hours. The reaction mixture was cooled to room temperature, filtered and concentrated in vacuo, to give sulfide 198 as a yellow solid (1.53 g, 5.95 mmol, >99%); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.91 (1H, d, \(J = 8.0\) Hz, Ar-H), 7.76 (1H, d, \(J = 8.0\) Hz, Ar-H), 7.50-7.41 (3H, m, Ar-H), 7.38-7.28 (4H, m, Ar-H), 4.62 (2H, s, CH\(_2\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 166.4, 153.1, 136.1, 135.3, 129.1, 128.7, 127.7, 126.0, 124.3, 121.5, 121.0, 37.7; HRMS (El) \(m/z\) [M]\(^+\) calcd for C\(_{14}\)H\(_{12}\)NS\(_2\): 258.0411, found 258.0407.
PREPARATION OF 2-(BENZYL SULFONYL)BENZO[D]THIAZOLE 199\textsuperscript{115}

![Chemical structure](image)

To a stirred solution of sulfide 198 (1.53 g, 5.95 mmol) in chloroform (15 mL) at 0 °C was added a solution of \textit{m}-chloroperbenzoic acid (70\%, 3.375 g, 13.69 mmol) in chloroform (35 mL) dropwise over 45 minutes. Upon addition, the reaction mixture was stirred at 0 °C for 30 minutes then at room temperature overnight. The reaction mixture was poured into saturated sodium hydrogen carbonate solution and stirred for 15 minutes. The layers were separated and the aqueous extracted further with chloroform. The combined organic extracted were washed subsequently with saturated sodium hydrogen carbonate solution, saturated sodium thiosulfate solution and water then dried and concentrated \textit{in vacuo}, to give sulfone 199 as a white solid (1.50 g, 5.53 mmol, 93\%); \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \(\delta\) 8.27 (1H, d, \(J = 8.0\) Hz, Ar-\(H\)), 7.95 (1H, d, \(J = 8.0\) Hz, Ar-\(H\)), 7.66 (1H, td, \(J = 7.5, 1.0\) Hz, Ar-\(H\)), 7.59 (1H, td, \(J = 7.5, 1.0\) Hz, Ar-\(H\)), 7.36-7.27 (5H, m, Ar-\(H\)), 4.77 (2H, s, CH\textsubscript{2}); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): \(\delta\) 165.2, 152.6, 137.1, 131.1, 129.2, 128.9, 128.0, 127.6, 126.3, 125.5, 122.3, 61.0; FTIR (CDCl\textsubscript{3}, \(\nu_{\max}\) cm\textsuperscript{-1}): 2924 (m), 2853 (w), 1471 (m), 1457 (m), 1333 (s), 1154 (s), 1126 (m), 763 (s) 730 (w); HRMS (El) \(m/z\) [MH]\textsuperscript{+} calcd for C\textsubscript{14}H\textsubscript{12}NO\textsubscript{2}S\textsubscript{2}: 290.0309, found 290.0304.
PREPARATION OF METHYL 5-(ACETYLOXY)-5-(CYCLOBUTA-1,3-DIEN-1-YL)PENTANOATEIRON TRICARBONYL 202

To a stirred solution of ester 194 (100 mg, 0.31 mmol) in ethanol (10 mL) at 0 °C was added sodium borohydride (35 mg, 0.93 mmol). After stirring at 0 °C for 3 hours, the reaction was quenched with water and extracted with ethyl acetate, dried over sodium sulfate and concentrated in vacuo. To crude residue dissolved in dichloromethane (10 mL) was added 4-dimethylaminopyridine (2 mg, 0.016 mmol), acetic anhydride (150 μL, 1.55 mmol), triethylamine (216 μL, 1.55 mmol) and the reaction mixture stirred at room temperature for 16 hours. To the reaction mixture was poured onto saturated potassium carbonate solution and extracted with ethyl acetate. The aqueous layer was washed with water, brine, dried over sodium sulfate and concentrated in vacuo. The crude residue was purified by flash chromatography on silica gel (3 : 1 petroleum ether/ethyl acetate) to give diester 202 as a brown oil (50 mg, 0.13 mmol, 42%); 1H NMR (400 MHz, CDCl3): δ 5.27-5.10 (1H, m, CH3C(O)OC<), 4.16 (1H, s, CH), 4.04 (2H, s, 2 x CH), 3.66 (3H, s, C(O)OC3), 2.38-2.26 (2H, m, CH2), 2.05 (3H, s, C(O)CH3), 1.71-1.52 (4H, m, 2 x CH2); 13C NMR (100 MHz, CDCl3): δ 214.1, 173.5, 170.3, 68.2, 63.6, 63.2, 62.9, 60.4, 51.6, 33.3, 32.9, 20.8; FTIR (CDCl3, μmax cm⁻¹): 2982 (w), 2961 (w), 2046 (s), 1965 (s), 1736 (m), 1234 (m), 592 (m).
To a stirred solution of diisopropylamine (485 μL, 3.47 mmol) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (3 mL) in tetrahydrofuran (20 mL) at -78 °C was added n-butyllithium (2.4 M in hexanes, 1.25 mL, 3.00 mmol) dropwise. After stirring at -78 °C for 20 minutes, the reaction mixture was stirred at room temperature for 5 minutes, and then cooled back to -78 °C. Dioxinone 211 (278 μL, 2.10 mmol) was added dropwise at -78 °C and stirred for 30 minutes. After this time, allyl bromide (1100 μL, 12.82 mmol) was added dropwise and the reaction mixture allowed to warm to room temperature over 17 hours. The reaction mixture was quenched by the addition of saturated ammonium chloride solution and extracted with diethyl ether. The combined organic extracts were washed with brine, dried over sodium sulfate and concentrated in vacuo. The crude residue was purified by flash chromatography on silica gel (3 : 1 petroleum ether/diethyl ether) to give alkene 212 as a yellow oil (116 mg, 0.67 mmol, 31%); ¹H NMR (400 MHz, CDCl₃): δ 5.76-5.63 (1H, m, CHCH₂), 5.16 (1H, s, CH), 5.04-4.90 (2H, m, CHCH₂), 2.29-2.19 (4H, m, 2 x CH₂), 1.60 (6H, s, 2 x CH₃); ¹³C NMR (100 MHz, CDCl₃): δ 171.0, 161.2, 135.9, 116.1, 106.3, 93.4, 32.8, 29.6, 25.0; FTIR (CDCl₃, νmax cm⁻¹): 2998 (w), 2923 (w), 1732 (s), 1635 (m), 1391 (m), 1273 (m), 1205 (m), 1015 (m); HRMS (EI) m/z [MH]+ calcd for C₁₀H₁₅O₃: 183.1021, found 183.1014.
To a stirred solution of diisopropylamine (1000 μL, 6.94 mmol) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (6 mL) in tetrahydrofuran (40 mL) at -78 °C was added n-butyllithium (2.4 M in hexanes, 2.50 mL, 6.00 mmol) dropwise. After stirring at -78 °C for 20 minutes, the reaction mixture was stirred at room temperature for 5 minutes, and then cooled back to -78 °C. Dioxinone 211 (500 μL, 4.20 mmol) was added dropwise at -78 °C and stirred for 30 minutes. After this time, propargyl bromide (2000 μL, 25.64 mmol) was added dropwise and the reaction mixture allowed to warm to room temperature over 17 hours. The reaction mixture was quenched by the addition of saturated ammonium chloride solution and extracted with diethyl ether. The combined organic extracts were washed with brine, dried over sodium sulfate and concentrated in vacuo. The crude residue was purified by flash chromatography on silica gel (3 : 1 petroleum ether/ethyl acetate) to give alkyne 214 as a yellow oil (300 mg, 1.67 mmol, 40%); ¹H NMR (400 MHz, CDCl₃): δ 5.13 (1H, s, CH), 2.28-2.24 (4H, m, 2 x CH₂), 1.80 (1H, s, CCH), 1.50 (6H, s, 2 x CH₃); ¹³C NMR (100 MHz, CDCl₃): δ 169.2, 160.7, 106.5, 94.2, 93.6, 70.1, 32.3, 24.8, 15.0; FTIR (CDCl₃, νmax cm⁻¹): 3290 (w), 3000 (w), 1728 (s), 1638 (m), 1393 (m), 1274 (m), 1254 (m), 1204 (m); HRMS (EI) m/z [MH]+ calcd for C₁₀H₁₃O₃: 181.0865, found 181.0857.
To a stirred solution of diisopropylamine (812 μL, 5.81 mmol) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (6 mL) in tetrahydrofuran (30 mL) at -78 °C was added n-butyllithium (2.0 M in hexanes, 2.50 mL, 5.00 mmol) dropwise. After stirring at -78 °C for 20 minutes, the reaction mixture was stirred at room temperature for 5 minutes, and then cooled back to -78 °C. Dioxinone 211 (467 μL, 3.52 mmol) was added dropwise at -78 °C and stirred for 30 minutes. After this time, 4-bromo-1-butene (1000 μL, 9.85 mmol) was added dropwise and the reaction mixture allowed to warm to room temperature over 17 hours. The reaction mixture was quenched by the addition of saturated ammonium chloride solution and extracted with diethyl ether. The combined organic extracts were washed with brine, dried over sodium sulfate and concentrated in vacuo. The crude residue was purified by flash chromatography on silica gel (3 : 1 petroleum ether/diethyl ether) to give alkene 215 as a yellow oil (84 mg, 0.43 mmol, 12%); 1H NMR (400 MHz, CDCl3): δ 5.81-5.68 (1H, m, CHCH2), 5.21 (1H, s, CH), 5.06-4.96 (2H, m, CHCH2), 2.24-2.17 (2H, m, CH2), 2.11-2.04 (2H, m, CH2), 1.66 (6H, s, 2 x CH3), 1.65-1.60 (2H, m, CH2); 13C NMR (100 MHz, CDCl3): δ 171.7, 161.3, 137.3, 115.7, 106.3, 93.3, 32.8 (x2), 25.0, 24.8; FTIR (CDCl3, υmax cm⁻¹): 2999 (w), 2940 (w), 1731 (s), 1636 (m), 1377 (m), 1273 (m), 1205 (m), 1013 (w), 903 (w), 807 (w); HRMS (EI) m/z [MH]+ calcd for C11H17O3: 197.1178, found 197.1170.
PREPARATION OF 4-(2,2-DIMETHYL-4-OXO-4H-1,3-DIOXIN-6-YL)BUTANAL 210

To a stirred solution of alkene 215 (66 mg, 0.33 mmol) and ruthenium(III) chloride (4 mg, 0.02 mmol, 5.0 mol%) in acetonitrile/water (6 : 1, 3.5 mL) at room temperature was added sodium periodate (252 mg, 1.18 mmol) and the mixture stirred for 2.5 hours. The dark suspension was quenched with saturated sodium thiosulfate solution and extracted with diethyl ether. The organic layer was washed with brine, dried over sodium sulfate and concentrated in vacuo. The crude mixture was purified via column chromatography on silica gel (2 : 1 petroleum ether/ethyl acetate) to give aldehyde 210 as a yellow oil (31 mg, 0.16 mmol, 47% yield); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 9.78 (1H, t, $J$ = 1.0 Hz, CHO), 5.24 (1H, s, CH), 2.53 (2H, td, $J$ = 7.0, 1.0 Hz, CH$_2$CHO), 2.26 (2H, t, $J$ = 7.5, CH$_2$CH$_2$CH$_2$CHO), 1.87 (2H, tt, $J$ = 7.5, 7.0 Hz, CH$_2$CH$_2$CH$_3$), 1.67 (6H, s, 2 x CH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 200.9, 170.6, 161.1, 106.5, 93.7, 42.6, 32.7, 25.0, 18.2; FTIR (CDCl$_3$, $\nu_{\text{max}}$ cm$^{-1}$): 2933 (w), 2855(w), 1724 (s), 1633 (m), 1392 (m), 1274 (m), 1204 (m), 1014 (m); HRMS (EI) m/z [MH]$^+$ calcd for C$_{10}$H$_{15}$O$_4$: 199.0970, found 199.0961.
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