Aspects of some alkylation reactions

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Aspects of Some Alkylation Reactions.

by

Moharem Taha El Gihani

A Doctoral Thesis
Submitted in partial fulfilment of the requirements for the award of Doctor of Philosophy of the
Loughborough University of Technology

December 1995

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Statement

The experimental work in this thesis was carried out in the Department of Chemistry of Loughborough University of Technology by Moharem T. El Gihani between October 1992 and September 1995. The work has not previously been presented and is not being presented for any other degree.

To my family
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Abstract

Friedel-Crafts reactions of the (-)-8-phenylmenthyl and (+)-trans-2-(α-cumyl)cyclohexyl arylhydroxyacetates catalysed by trimethylsilyl triflate (TMSOTf) and equivalents in the presence of electron rich heterocycles gave the expected diarylacettes in high de 88%, via a planar cation.

The interaction of trifluoromethanesulfonic (triflic) acid (TfOH) with either bis-trimethylsilyl -acetamide (BSA) or -urea (BSU) can be used to generate stoichiometric amounts of trimethylsilyl triflate (TMSOTf) "in situ", the system can be used efficiently to remove triflic acid from TMSOTf and to generate catalytic amounts of TMSOTf from TfOH for use in a range of trimethylsilyl triflate (TMSOTf) catalysed reactions.

Similarly the interaction of fluorosulfonic acid (FSA) with either bis-trimethylsilyl -acetamide (BSA) or -urea (BSU) can be used to generate catalytic amounts of trimethylsilylfluorosulfonate (TMSOFs) "in situ" for use in a wide range of reactions as an alternative to trimethylsilyltriflate (TMSOTf)

Scandium(III) trifluoromethanesulfonate and copper(II) trifluoromethanesulfonate can be used to catalyse aromatic alkylation with arylhydroxyacetates. Scandium(III) trifluoromethanesulfonate also proved to be a recyclable catalyst for these reactions.

A number of Pictet-Spengler cyclisation reactions were also catalysed by Scandium(III) trifluoromethanesulfonate and copper(II) trifluoromethanesulfonate.

Mannich reactions of a number of calix[4]resorcinarene derivatives with (R)-(+)α-methylbenzylamine under alkaline conditions lead to the formation of single diastereomeric tetrakis(1,3-dihydrobenzoxazine) derivatives in high yields; the reactions using the (S)-(−)-α-methylbenzylamine afford the enantiomers. The products react with protic acids to afford equilibrium mixtures of diastereomers.
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<tr>
<td>bp</td>
<td>Boiling point</td>
</tr>
<tr>
<td>Bn</td>
<td>Benzyl</td>
</tr>
<tr>
<td>BSA</td>
<td>$N,O$-Bis(Trimethylsilyl)acetamide</td>
</tr>
<tr>
<td>BSU</td>
<td>1,3-Bis(Trimethylsilyl)urea</td>
</tr>
<tr>
<td>DCM</td>
<td>Dichloromethane</td>
</tr>
<tr>
<td>de</td>
<td>Diastereomeric excess</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethylsulfoxide</td>
</tr>
<tr>
<td>ee</td>
<td>Enantiomeric excess</td>
</tr>
<tr>
<td>Et</td>
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</tr>
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<td>FSA</td>
<td>Fluorosulfonic acid</td>
</tr>
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</tr>
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</tr>
<tr>
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<td>Methyl</td>
</tr>
<tr>
<td>mmol</td>
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</tr>
<tr>
<td>mp</td>
<td>Melting point</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear Magnetic Resonance</td>
</tr>
<tr>
<td>Ph</td>
<td>Phenyl</td>
</tr>
<tr>
<td>Tf</td>
<td>Triflate or trifluoromethanesulfonate</td>
</tr>
<tr>
<td>TMS</td>
<td>Trimethylsilyl</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin layer chromatography</td>
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Chapter 1

1 Introduction

Friedel-Crafts alkylation is truly one of the most significant C-C bond forming processes in organic synthesis with both great synthetic and industrial importance.

Historically, it appears that the original "Friedel-Crafts" reaction was carried out by Zincke some eight years before Charles Friedel and James Mason Crafts first made known their now famous work on aromatic electrophilic substitution. The reaction which Zincke inadvertently discovered was the alkylation of benzene with benzyl chloride using copper metal as a catalyst to give diphenylmethane (1) as shown in Equation 1.

\[
\begin{align*}
\text{C}_6\text{H}_5 & \quad + \quad \text{C}_6\text{H}_5\text{CH}_2\text{Cl} & \quad \text{Cu} & \quad \rightarrow & \quad \text{C}_6\text{H}_5\text{CH}_2\text{C}_6\text{H}_5 & \quad + \quad \text{HCl} \\
\end{align*}
\]

Equation 1

1.1 Friedel-Crafts Alkylation

In broad terms the whole area of Friedel-Crafts reactions has been defined as, "any organic reaction effected by the catalytic action of AlCl₃, or related catalysis". Friedel-Crafts alkylation is in itself a broad area of organic synthesis and has accordingly been reviewed extensively notably by Olah, amongst others.

A wide variety of alkylation agents have been employed to effect Friedel-Crafts alkylation. The list includes alkyl halides, alkenes, alcohols, alkynes, ethers, esters (organic or inorganic) and ketones generally employed under Lewis acid or protic acid catalysis.

1.1.1 Friedel-Crafts Catalysts

The diversity of alkylation agents is mirrored in the number of catalysts that have been used.

One of the most important groups of catalyst are the acidic halides or Lewis acids of which AlCl₃ and BF₃ are the most typical examples. These two catalysts have

2
achieved pre-eminence in the field of Friedel-Crafts chemistry for different reasons. Aluminium chloride has been particularly attractive because of its high reactivity in the catalysis of a wide variety of reactions and because it is readily available at low cost, factors which are industrially significant. Boron trifluoride derives its importance from being a low-boiling gas (bp-101°C) making it easy to handle and remove from the reaction mixture. A selection of other frequently used Lewis acids which find use in all manner of Friedel-Crafts reactions includes; ZnCl₂, TiCl₄, SnCl₄ and FeCl₃ to name but a few. Although their use is long established, recent advances include a study by Yoneda⁵ in the use of polar solvents as a method of enhancing the catalytic activity of ZnCl₂ in the benzylation of benzene. The characteristic feature of Lewis acids is the electron deficiency of the central atom which can, as a consequence, accept electrons from basic substances.

Recent developments with this kind of catalyst include the introduction of gallium dichloride-mediated reductive Friedel-Crafts reactions of carbonyl compounds, or their dimethyl acetals, with various aromatics.⁶ Here gallium dichloride is acting as a double salt comprising of univalent gallium acting in a reductive manner to form an intermediate alkoxide before the Lewis acid character of trivalent gallium generates a cation to affect alkylation in the usual manner. An example of the alkylation of anisole in this way is given in Equation 2.

\[
\begin{align*}
\text{OMe} + \text{CHO} & \xrightarrow{\text{Ga₂Cl₄, CS₂, reflux, 24h}} \text{OMe} \\
\text{para} & \text{Yield 66\% 100\% para}
\end{align*}
\]

**Equation 2**

A similar type of Lewis acid are the trifluoromethanesulfonates (triflates) of boron, aluminium and gallium which have been shown by Olah et al.⁷ to be effective catalysts for the alkylation of simple aromatics.

With environmental and economic factors in mind the significance of the lanthanide trihalides as reusable catalysts is evident. The fact that these catalysts can be reused with no apparent loss of catalytic activity puts them at an advantage over most other Lewis acids which usually cannot be reused. The dysprosium (III) chloride catalysed
alkylation of benzene with benzyl chloride to give diphenylmethane in 74% yield exemplifies this approach.\textsuperscript{8}

Again with an eye on economic and environmental considerations the acidic oxides or zeolites appear to be an important area of current interest and industrial potential. Various types of aluminosilicates both synthetic and natural (clays) have found use as catalyst supports. Transition metal oxides such as TiO\textsubscript{2} incorporated on synthetic aluminosilicates (Tisial), have been found to show excellent acidic properties thereby serving as effective recyclable catalysts in a variety of alkylations.\textsuperscript{9} Natural kaolinitic clays containing the transition metals Fe and Ti in their lattice and treated with 2M HCl have been shown to be excellent solid acid catalysts in the alkylation of benzene with benzyl chloride. Significantly, these catalysts show enhanced activity and 100% product selectivity to diphenylmethane when compared with synthetic alkylation catalysts such as TiO\textsubscript{2}-SiO\textsubscript{2}-AlO\textsubscript{3} and clays used at lower temperatures such as K\textsubscript{10} montmorillonites exchanged with Lewis acids.\textsuperscript{10}

Much attention has been devoted to the clay montmorillonite K\textsubscript{10} which has a Lewis acidity at least as effective as AlCl\textsubscript{3} and, importantly, is commercially available at low cost. This clay is known to catalyse the alkylation of benzene with benzyl chloride at room temperature over a period of 24 hours to afford the product diphenylmethane in a creditable 57% yield.\textsuperscript{11} Such mild reaction conditions are clearly very attractive and can be further enhanced if these high surface area materials are modified by treatment with standard Lewis acids. When clayzic, (ZnCl\textsubscript{2} supported on montmorillonite K\textsubscript{10}) is used to catalyse the same reaction the reaction time is dramatically reduced to 15 minutes and the isolated yield of diphenylmethane is improved to 80%.\textsuperscript{11} The high activity of clayzic as a catalyst is thought to be due to a high local concentration of Zn\textsuperscript{+} ions in the structural mesopores rather than a surface area effect.\textsuperscript{12} This zinc supported reagent, paradoxically has higher activity in comparison with AlCl\textsubscript{3} supported reagents which is counter-intuitive as AlCl\textsubscript{3} is clearly much more acidic than ZnCl\textsubscript{2} in an unsupported form.

The alkylating agents employed with these modified montmorillonite K\textsubscript{10} catalysts need not be limited to alkyl halides as Laszlo has shown in some early work in this field. Alcohols and olefins were also used as alkylating agents in the presence of montmorillonite K\textsubscript{10} modified with various transition metal cations, principally Ti (IV) and Zr(IV), as catalyst.\textsuperscript{13}

On balance then, the advantages that these modified clays have over standard Lewis acids in the catalysis of Friedel-Crafts alkylations is not only confined to an improved
yield. The other advantages include reduced reaction times, milder conditions, a decrease in the amount of catalyst required, the facility to regenerate the catalyst and an improvement in regioselectivity.

The ability of these zeolites to perform selective transformations is due to their well defined crystal structure. They contain pores of discrete diameters (<1 nm) and shapes making them capable of quite sophisticated molecular-sieving. These characteristics lead to selectivity with regard to the reactants, as only a specific part of the reacting molecule can fit into the catalyst pores. Similarly only product molecules with the correct pore size are able to diffuse out. Restrictions even apply to the transition state, as reactions will only occur where the transition state 'fits' the internal cavity.

Acidic cation-exchange resins, which are sulfonated styrene-divinylbenzene cross-linked polymers, are also used as catalysts for alkylation. Dowex 50 and Amberlite IR-112, for example, are effective in catalysing the alkylation of phenols, alkenes, alkyl halides and alcohols.\textsuperscript{14}

Friedel-Crafts alkylation of aromatics have also been catalysed by solid superacids. Most notably DuPont's Nafion-H\textsuperscript{®}, a solid perfluorinated resinsulfonic acid has been found to be an effective catalyst in the benzylation of benzene and substituted benzenes with benzyl alcohols under mild conditions. Similarly intramolecular cyclisation reactions have also been reported together with trimerisation and tetramerisation reactions of methoxybenzyl alcohols, as exemplified in \textbf{Equation 3}. The products were obtained cleanly in good yield with the Nafion-H\textsuperscript{®} catalyst being easily recovered for re-use without any loss in catalytic activity.\textsuperscript{15}

\textbf{Equation 3}
1.2 Mechanism of Friedel-Crafts Alkylation of Aromatics

The process of Friedel-Crafts alkylation with respect to aromatic substrates can be described simplistically by Equations 4a-b.

\[
\begin{align*}
\text{a)} \quad & \text{Ar·H} + \text{R·X} \rightarrow \text{Ar·R} + \text{H·X} \\
\text{b)} \quad & \text{Ar·H} + \text{Alkene} \xrightarrow{HY\ or\ LA} \text{Ar·R} + \text{H·Y}
\end{align*}
\]

\(X=\text{OH, OR, F, Cl, Br, etc.}\)
\(Y=\text{halogen}\)

Equation 4a-b

Mechanistically, the alkylation of arenes initially involves an interaction between the Lewis acid or protic acid catalyst and the alkylating agent in question. This may then result in cation formation in an \(SN_1\) type process. Alternatively, weaker interaction between the catalyst and the alkylating agent may result in a polarised complex which is then susceptible to nucleophilic attack in an \(SN_2\) type process. This then leads to the alkylated product via a Wheland intermediate.

\[
\begin{align*}
\text{L.A.} \\
\text{SN}_1\ mechanism
\end{align*}
\]

\[
\begin{align*}
\text{L.A.} \\
\text{SN}_2\ mechanism
\end{align*}
\]

Scheme 1

Whether the alkylating agent reacts with the arene in a \(SN_1\) manner or requires the formation of a complex with a Lewis acid to increase its electrophilicity is dependent on the extent of polarisation of the alkylating agent i.e. the electronegativity of the \((C\text{-X})\) bond. The Lewis acid employed also has an influence on the mechanistic pathway of the reaction.
Friedel-Crafts reactions are complex reactions with no single mechanism being applicable to all examples. The $S_N1$ and $S_N2$ mechanisms are two extremes; however the existence of Wheland intermediates is established as such intermediates have been isolated. Such an example, compound (3) in *Equation 5*, has been isolated as an orange crystalline solid that melts at $-15^\circ\text{C}$ to yield the alkylated product (4).16

![Equation 5](image)

**Equation 5**

### 1.2.1 Reactions with Alkyl Halides

The precise mechanism for alkylation with alkyl halides is uncertain and depends largely on the type of alkyl halide, i.e. (primary, secondary or tertiary).

Despite these uncertainties it is possible to generalise and recognise certain trends. It can be said that reactions involving primary alkyl halides proceed via an $S_N2$ type mechanism while those involving tertiary alkyl halides go via an $S_N1$ type mechanism, with secondary alkyl halides having characteristics that are intermediate between these two extremes. Evidence for the lack of ionisation of these complexes is supplied by Byrne17 who showed that methyl chloride forms a non ionised 1:1 complex with tin tetrachloride or antimony pentachloride at low temperature. Further evidence is supplied by Brown18 who showed that a complex of methyl bromide and aluminium bromide was free of any alkyl cation.

### 1.2.2 Reactions with Alcohols and Alkenes

Electrophiles for reaction in Friedel-Crafts alkylation can be generated from alcohols both by interaction with Lewis acids, typically BF$_3$ and ZnCl$_2$, and through interaction with protic acids. Transient cationic intermediates are generated when tertiary and secondary alcohols are treated with the latter.
Highly acidic systems have been used to prepare cations at low temperatures as in Equation 6.19

\[
\begin{align*}
\text{Bu'OH} + \text{SbF}_5 + 2 \text{FSO}_3\text{H} & \rightarrow \text{C(CH}_3)_3 + \text{SbF}_5 + 2 \text{FSO}_3 + \text{H}_2\text{O} \\
\end{align*}
\]

Equation 6

The same is not true for primary and secondary alcohols which, although protonated by fluorosulfonic acid / antimony pentafluoride at low temperatures (-60°C), do not form cations and on warming tend to dehydrate and polymerise.20

Cations can be formed under less drastically acidic conditions if the alcohol is α to a stabilising group such as an electron rich aromatic. Diphenyl methanol can be treated with relatively milder acid catalysts such as sulphuric acid, ZnCl₂ or BF₃ to induce the formation of the stable diphenyl methyl cation.21, 22

In order to affect alkylation with alkenes, strong acids such as triflic acid are required to protonate the alkene and thus form the reactive cation, Equation 7. Lewis acids are therefore inadequate as catalysts unless they have traces of water or acid present.23

\[
\begin{align*}
\text{R}^-\text{C}=\text{CH}_2 + \text{H}^+ & \rightarrow \text{R}^\text{CHCH}_3 \\
\end{align*}
\]

Equation 7

Alkylation with alkenes can suffer from polymerisation associated problems since the acid generated cation, for example from isobutene, can react with the starting alkene.

Related alkylating agents, such as ethers, again require trace amounts of water along with a Lewis acid catalyst which can readily complex to the ether followed by probable cation formation. Alkylation then takes place with the most highly substituted alkyl group.23 Other alkylating agents such as thiols and sulphides also give the corresponding carbenium ion under "stable ion conditions".24

Under the conditions of Friedel-Crafts reactions it is important to note that these intermediate cations only exist transiently and are only detectable in appreciable amounts in the absence of a nucleophile.
Polarised complexes, if considered as ion pairs, behave similarly to cationic intermediates in these sort of reactions. Overall, it is perhaps better to think of these Friedel-Crafts reactions as nucleophilic displacements by the arene and not electrophilic attack by the alkylation agent. 

1.3 Substituent Effects and Regiochemistry

Friedel-Crafts alkylation reactions when compared with acylations suffer from a number of problems. In cases where the incoming alkyl group is electron releasing the initial product becomes activated to further alkylation so di- and poly-alkylated species can be observed.

The alkylation of substituted arenes containing functionality such as -NO₂, -OH, -OR, -NH₂ and the like, can be drastically inhibited as these groups readily coordinate with the Lewis acid catalyst, thereby reducing the desired co-ordination between the alkylation agent and catalyst. For this reason substrates such as nitrobenzene cannot be alkylated under normal Lewis acid catalysed conditions. This is despite the fact that nitrobenzene can be substituted readily by other relatively weak electrophiles such as NO₂⁺. It is only relatively recently that Shen has overcome these problems by using sulfuric acid to catalyse the ethylation of nitrobenzene with ethanol. In a similar fashion other substituted benzenes with meta-directing groups such as benzaldehyde, acetophenone and ethyl benzoate were ring alkylated with alcohols such as isopropyl and n-butyl alcohol under protic acid catalysis.

One of the biggest problems is the poor regiochemical control exhibited by Friedel-Crafts alkylation reactions. The regiochemistry is dependent on a number of factors, namely the Lewis acid, alkylation agent, solvent, and temperature. One of the most important factors is the electrophilicity of the alkylation agent and this has been investigated by Olah who conducted a study of TiCl₄ catalysed alkylations of toluene with a series of 4-substituted benzyl chlorides, Equation 8, and Table 1.

![Equation 8](image-url)
<table>
<thead>
<tr>
<th>X</th>
<th>$K_{\text{toluene}}$</th>
<th>ortho</th>
<th>meta</th>
<th>para</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{NO}_2$</td>
<td>2.5</td>
<td>59.6</td>
<td>6.2</td>
<td>34.2</td>
</tr>
<tr>
<td>Cl</td>
<td>6.2</td>
<td>40.1</td>
<td>5.6</td>
<td>54.9</td>
</tr>
<tr>
<td>H</td>
<td>6.3</td>
<td>40.5</td>
<td>4.3</td>
<td>55.2</td>
</tr>
<tr>
<td>$\text{CH}_3$</td>
<td>29.0</td>
<td>31.4</td>
<td>2.1</td>
<td>66.5</td>
</tr>
<tr>
<td>$\text{OCH}_3$</td>
<td>97.0</td>
<td>28.6</td>
<td>1.5</td>
<td>69.9</td>
</tr>
</tbody>
</table>

Table 1

Clearly then there is a trend in the substitution pattern. Where X is an electron withdrawing group poor regiochemical control is observed while when X is electron donating group better regiochemical control was observed with the \textit{para}-isomer predominating. This observation is best rationalised by Fleming\textsuperscript{28b} if one considers a benzene ring with a single electron releasing substituent then although more charge resides at the \textit{ortho}- position rather than at the \textit{para}- position the frontier electron population is greatest at the \textit{para}- position. One would then expect that softer electrophiles would give more \textit{para}-substitution.

1.4 Alkylation of Arenes

Having briefly outlined the catalysis and mechanistic aspects of Friedel-Crafts alkylation reactions it is convenient to discuss the reaction according to various alkylation agents. Due to the extensive nature of the literature on the subject, only recent developments in the field are surveyed here. More extensive reviews and accounts of the subject have been produced, most notably by Olah\textsuperscript{3,4,20}

1.4.1 Alkyl Halides

The use of chiral alkylation agents to produce chiral products was initially thought not to be feasible as complete racemisation was thought to take place\textsuperscript{29} This is because the cationic intermediate associated with Friedel-Crafts alkylation would destroy the chirality of the starting material. However, under carefully controlled conditions of low temperature and short reaction times Suga\textsuperscript{30} has demonstrated that a degree of stereoselectivity is possible.

\[
\text{H} \quad \text{Cl} \quad \text{AlCl}_3 / \text{Benzene} \quad \text{-30°C / 50 seconds} \quad \text{Ph} \quad \text{H} \\
\]

Equation 9
As can be seen from Equation 9 the AlCl₃ catalysed alkylation of benzene with (+)-2-chlorobutane proceeded with inversion of configuration to give (-)-2-phenylbutane. The modest level of stereoselectivity, 24 % ee, was attributed to racemisation of the starting material and the product by the Lewis acid.

Higher levels of stereocontrol have been achieved by Masuda and co-workers who were able to alkylate benzene with (-)-2-chloro-1-phenylpropane (5) and (+)-1-chloro-2-phenylpropane (6) to yield the same product (-)-1,2-diphenylpropane (7).³¹

\[
\begin{align*}
\text{(5)} & \quad \text{(i)} \quad \text{(6)} \\
\text{(7)} & \quad \text{(ii)} \\
\text{(8)}
\end{align*}
\]

Reagents: (i) AlCl₃ (ii) Benzene

Scheme 2

Significantly, no racemisation of the chiral alkylating agents occurred and the reaction proceeded mainly with retention of configuration. A phenyl π-assisted cation, as in Scheme 2 exerting a neighbouring group effect has been proposed to account for the asymmetric induction.³²

Neighbouring group effects have also been invoked to account for the inversion of configuration in the alkylation of benzene with optically pure 3-chlorobutanol or 3-chlorobutanoic acid and their esters, Equation 10.

\[
\begin{align*}
\text{Ph} + \text{YCH₂Cl} & \quad \xrightarrow{\text{AlCl₃}} \quad \text{PhCH₂Y} \\
\text{Y} = & \quad \text{CH₂OH, COOH, COOEt, CH₂OCOPh, CH₂COCH₃}
\end{align*}
\]

Equation 10
Under these reaction conditions the products were not racemised. However, the starting materials were partially racemised thereby reducing the overall stereoselectivity of the reaction. Taking this into account the calculated enantiomeric excess for the reaction is approximately 90%. The stereochemical aspects of the reaction were explained in terms of a cyclic alkylating intermediate. The Lewis acid complexes to the alkylating agent, fixing its stereochemistry in place, before an SN2 displacement of the chlorine by the benzene occurs leading to inversion of stereochemistry in the product, Scheme 3.

\[
\begin{align*}
\text{Scheme 3} \\
\text{It is thought that the cyclic nature of the complexed alkylating agent helps prevent racemisation occurring by reducing the likelihood of cation formation.}
\end{align*}
\]

Chiral aryl \( \alpha \)-amino acids have also been prepared using Friedel-Crafts alkylation chemistry. Electron rich aromatics such as 1-methoxynaphthalene or 1,4-dieithoxybenzene have been alkylated with the chiral cation generated from the bis-lactam ether of cyclo-(L-Val-Gly) (9).

\[
\begin{align*}
\text{Scheme 4}
\end{align*}
\]
On treatment of the substrate (9) with SnCl₄, it is proposed that an ion pair (10), is formed. The aryl group is then introduced 

\textit{trans} to the isopropyl group of the original valine. Subsequent hydrolysis leads to the formation of the appropriate arylglycine derivative, in this case product (11) is formed in 65% chemical yield and 90% ee.²⁴²⁵

### 1.4.2 Alkylation with Alcohols

Alcohols are an extremely important class of Friedel-Crafts alkylating agent. Problems with selectivity and rearrangements, particularly with primary alcohols, can be minimised through careful choice of catalyst and reaction conditions. Generally larger amounts of catalyst and more forcing conditions are required compared with alkylations with alkyl halides.

Recent notable developments with this class of alkylating agent have featured intramolecular cyclisation reactions with some measure of stereocontrol. The first reported stereoselective alkylation with a simple alcohol, however, was achieved by Rosenberg³⁵ who was able to alkylate benzene with (+)-2-butanol using aluminium bromide as the catalyst. The reaction proceeded with inversion of configuration to yield the expected 2-phenylbutane in an SN₂ type mechanism. The relatively modest level of stereocontrol achieved (27% ee) was due to extensive racemisation that is a consequence of cation formation as Suga³² experienced with his 2-chlorobutane alkylations.

Intramolecular Friedel-Crafts alkylations featuring a dicobalt hexacarbonyl(alkyne) moiety as a stereochemical influence in the reaction have been carried out by Grove and co-workers.³⁶ᵃ⁻ᵇ These cobalt-mediated cycloalkylation reactions give 4a-substituted-octahydrophenanthrenes with exclusive \textit{cis}-stereochemistry. Equation 11.

\begin{equation}
\text{Equation 11}
\end{equation}
The reaction precedes in good chemical yield, (78%) and when performed at low temperature the cis-stereoisomer (13), being the kinetic product, is formed stereoselectivity. A tentative explanation of this selectivity has been suggested by the authors, and is essentially a product based analysis which does not address matters regarding conformational preferences of the cobalt-stabilised cations. It is argued that evidence from molecular models suggests that steric interactions exist between the axial organocobalt moiety and the three axial hydrogens in (14). These steric interactions are less severe in the more stable conformation (13) thereby favouring its formation. It is assumed that the steric interactions observable in the two products are in some way reflected in their respective transition states.

Phenanthrene derivatives have been synthesised using other similar strategies. The cyclisation of aryl-alkyl carbinols to give cis fused ring systems, Equation 12 proceeds via a cationic intermediate which is subject to rearrangements prior to cyclisation. 37

![Equation 12](image)

A novel synthesis of dibenzobicyclo[3.2.2]nonane systems via a double Friedel-Crafts alkylation of phenol is outlined in Equation 13. 38

![Equation 13](image)

The reaction of the diol (15) with phenol in the presence of anhydrous aluminium chloride affords the dibenzobicyclo[3.2.2]nonane derivative (16) in 70% yield. Mechanistically the reaction is thought to involve the initial formation of an aryltetralin derivative of (15) which then undergoes an intramolecular Friedel-Crafts reaction via a dienone derivative ultimately giving the product (16).
1.4.3 Alkylation with Aldehydes

Aldehydes can be used to alkylate arenes initially forming aryl alcohols. However, the products frequently undergo a second Friedel-Crafts alkylation to form a diarylalkane, Equation 14. This problem is difficult to overcome especially if the aryl moiety in question is electron rich. The difficulty in stopping the reaction at the first stage is due to the fact that the intermediate alcohol is more reactive than the aldehyde as the aryl group can stabilise cation formation. This process is exemplified in the reaction of thiophene with alkyl carboxaldehydes under acid catalysis. The di-2-thienyl alkane is formed as the 2-thienyl alcohol intermediate cannot be isolated.\(^{39}\)

\[
\begin{array}{c}
\text{R= Alkyl, } \text{Ar = electron rich aromatic} \\
\end{array}
\]

Equation 14

With less electron rich aromatic systems the reaction often stops at the alcohol stage and does not lead to the formation of bis-aryl derivatives. Bigi\(^{40}\) and co-workers have synthesised a number of chiral 2-hydroxymandelic esters (18) by the Friedel-Crafts ortho-hydroxyalkylation of phenols with terpenyl glyoxylates (17). The best selectivities were obtained using 8-phenylmenthol as the chiral auxiliary in conjunction with titanium tetrachloride as the Lewis acid catalyst to give an excellent 97% de, Equation 15.

\[
\begin{array}{c}
\text{R}^1= 3\text{-Bu}, \text{4-OMe, H} \\
\text{R}^2= 8\text{-phenylmenthyl} \\
\end{array}
\]

Equation 15

This methodology has been further developed by Bigi to include the stereoselective \textit{para}-functionalization of phenols, which are biologically important targets.\(^{41}\)
In order to avoid ortho-alkylation the phenol was protected as the tert-butyldimethylsilyl ether (19) thereby favouring electrophilic attack at the para position. Tin tetrachloride proved to be the best Friedel-Crafts catalyst with regard to giving good para-regioselectivity, good chemical yield and diastereocontrol. As the results in Scheme 5 indicate excellent levels of diastereocontrol were achieved. With the (-)-8-phenylmenthyl glyoxalate (20) as the chiral alkylating agent, the diastereomer (21) predominates as the product. Slightly lower levels of stereocontrol were achieved with the (-)-trans-2-phenylcyclohexyl glyoxylate (20), but it is noteworthy that the other diastereomer (22) predominated, thereby making both 4-hydroxymandelic esters readily accessible. The hydrolysis of these two diastereomers furnishes the appropriate enantiomerically pure 4-hydroxymandelic acid.

Bigi has also synthesised some ephedrine-like compounds (24) by alkylating para-substituted phenols with aldehydes derived from amino acids (23). The reaction is thought to proceed via a phenol-metal-aldehyde complex, Scheme 6.
The ortho product is formed exclusively with a diastereoselectivity of 76%. It should be noted that the reaction stops at the alcohol stage and does not proceed to a bis­
phenol derivative because the metal is thought to co-ordinate to the two alcohols thereby stabilising the initial product.\footnote{43}

1.4.4 Alkylation with Ethers

Examples of the use of acyclic ethers as Friedel-Crafts alkylating agents in the literature are scant. The use of cyclic ethers however has been more successful, with epoxides, oxetanes and tetrahydrofurans all finding application.

Suga has studied the stereoselective alkylation of benzene with optically active epoxides. (R)-(+)­propylene oxide has proved to be effective in the stereoselective alkylation of benzene to give (R)-(+)­2­phenylpropanol (25) in 95% ee, Scheme 7.\footnote{44}
The Lewis acid also reacts with the epoxide to form chloropropanols which explains the relatively modest yield. Mechanistically the reaction is thought to proceed in an $\text{SN}_2$ fashion with benzene attacking an epoxide Lewis acid complex to give inversion of stereochemistry in the product.\(^{45}\)

Similarly Suga has also used chiral epoxides with an adjacent methylene group as the stereocontrol element in the alkylation of benzene with (R)-(++)-1-epoxybutane.\(^{46}\) The reaction gives the expected (R)-(++)-2-phenylbutan-1-ol (26) in a reported 100\% ee as well as the unexpected 3-phenylbutan-1-ol (27) in 24\% ee. Chlorobutanols are also formed, it is thought this occurs by the epoxide ring opening and rearranging by means of a hydrogen shift. A chloride ion is then captured in a stereospecific manner to form 3-chlorobutan-1-ol.

\[
\begin{align*}
\text{Cyclic epoxide} & \xrightarrow{\text{AlCl}_3 / \text{Benzene}} \text{Ph} \quad (26) \\
& \quad 100\% \text{ ee} \\
\text{Cyclic epoxide} & \xrightarrow{\text{AlCl}_3 / \text{Benzene}} \text{Ph} \quad (27) \\
& \quad 24\% \text{ ee}
\end{align*}
\]

**Equation 16**

The use of chiral epoxides in cyclisation reactions has been studied by Taylor who investigated the tin tetrachloride catalysed cyclisation of cis- and trans-1-phenyl-3-epoxypentane.\(^{47}\) The six membered ring was formed preferentially with the cis-epoxide (28) giving the cis-methyltetrol (29) and the trans-epoxide (30) giving the trans-methyltetrol (31) in 63-66\% yield, **Equations 17a and 17b**.

\[
\begin{align*}
(28) & \xrightarrow{\text{SnCl}_4 / \text{DCM}} (29) \\
(30) & \xrightarrow{\text{SnCl}_4 / \text{DCM}} (31)
\end{align*}
\]

**Equation 17a and 17b**

Mechanistically the reaction is thought to proceed in a concerted manner with inversion of stereochemistry.
Taylor has also found that the chiral epoxide 5-epoxycyclodecene reacts to alkylate solvents like toluene in a highly stereoselective manner that results in the formation of an additional two chiral centres. It is thought that the reaction occurs in a concerted or near concerted manner to afford 1-hydroxy-4-aryl-cis-decalin (32), **Equation 18**.48

![Equation 18](image)

Generally, Friedel-Crafts alkylations involving higher cyclic ethers are problematic. The reactions are often accompanied by side reactions although there are exceptions. The ease with which cyclic ethers can alkylate arenes also decreases with increasing ring size.

Despite these factors, chiral oxetanes have found use as successful alkylating agents in much the same way as epoxides. Besides their reduced reactivity, relative to epoxides, oxetanes have also been found to be less stereoselective in the alkylation of benzene. Optically pure 2-methyloxetane, on complexing to the Lewis acid catalyst, undergoes nucleophilic attack by benzene in an SN2 type ring opening yielding 3-phenylbutan-1-ol (33) with inversion of stereochemistry.49

![Equation 19](image)

As can be seen in the table accompanying **Equation 19**, quite respectable selectivity is possible with tin tetrachloride as the Lewis acid although the chemical yield is poor. The converse is true when a stronger Lewis acid like AlCl₃ is used, with a poor selectivity of 20% ee being attained all be it in good chemical yield. The poor
selectivity obtained with AlCl₃ is probably due to racemisation of the starting material and product.

Similarly chiral tetrahydrofurans have been used by Brauman et al.⁵⁰ in the alkylation of benzene with (S)-(+)−2-methyltetrahydrofuran to give (R)-(−)-4-phenyl-1-pentanol (34), Equation 20.

\[
\text{H}_{\text{Me}}\text{O} \xrightarrow{\text{AlCl₃ / Benzene}} \text{Ph}\text{H}_{\text{Me}}\text{O} \quad \text{(34)}
\]

35% ee, 50% Yield

**Equation 20**

The reaction proceeds with inversion of configuration and, as with oxetanes, the reactivity is reduced compared to epoxides, hence a more powerful Lewis acid is employed. However, as a result, the stereoselectivity of the reaction is compromised.

1.4.5 Alkylation with Esters (Organic and Inorganic)

Brauman has also examined the use of optically pure lactones, namely (S)-(−)-γ-valerolactone in the alkylation of benzene to give (R)-(−)-4-phenylvaleric acid (35). The reaction is quantitative and a 40% ee was obtained with inversion of configuration. Mechanistically the reaction is thought to proceed through an ion pair (36). It should be noted that the analogous reaction with acyclic (R)- or (S)-2-butylacetate shows complete racemisation which lends credence to the cyclic intermediate (36) postulated for the (S)-(−)-γ-valerolactone reaction, Equation 21.⁵⁰

\[
\text{H}_{\text{Me}}\text{O} \xrightarrow{\text{AlCl₃ / Benzene}} \text{Ph}\text{H}_{\text{Me}}\text{O} \quad \text{(35)}
\]

Proposed Intermediate:

**Equation 21**
Sulphonates which can be regarded as inorganic esters have been used by Piccolo\textsuperscript{51} in the first example of a highly stereoselective acyclic Friedel-Crafts alkylation reaction. Specifically, optically pure α-sulfonyl propionates (37) have been used to alkylate benzene along with other arenes such as toluene, chlorobenzene and naphthalene. The reaction proceeds in an $S_N2$ fashion giving optically pure aryl propionates which find application as non-steroidal anti-inflammatory agents, \textbf{Equation 22}.

![Equation 22](image)

**Equation 22**

The high selectivity observed in this reaction is attributed to an intermediate complex formed between the alkylating agents (37) and the Lewis acid which leaves the nucleophile to attack the chiral carbon of (37) selectively from the back side. By coordinating to the leaving group in this way the Lewis acid is also preventing the formation of a cation which would cause racemisation. Although the reaction is general for a number of arenes, problems with regiochemistry means that the usefulness of this reaction is limited to benzene as the substrate.

Alkylating agents containing sulfonate leaving groups have also been exploited by Kronenthal\textsuperscript{52} who was able to alkylate benzene stereospecifically with cis- and trans-N-benzoyl-4-mesyloxy-L-proline (38) producing the cis- and trans-4-phenylproline (39) derivatives, \textbf{Equation 23}.

![Equation 23](image)

**Equation 23**

Mechanistically the reaction is thought to undergo an $S_N2$ type process with inversion of configuration. Again some degree of co-ordination between the Lewis
acid and the amide bond of (38) is thought to play a role in this highly stereoselective process. The presence of an electron-withdrawing nitrogen residue near the leaving group in (38) plays an important role too as it inductively destabilizes any cationic character that might lead to racemisation.

A somewhat unusual example involves the enzyme-catalysed electrophilic aromatic substitution of L-tryptophan with dimethylallyl diphosphate, **Equation 24.** The reaction is catalysed by dimethylallyltryptophan (DMAT) synthase which is a member of the prenyltransferase family of enzymes which are known to catalyse the alkylation of electron rich substrates.

![Equation 24](image)

Alkylation occurs regioselectively at the C-4 position of the indole ring which although an activated site is not the expected position of electrophilic attack. Electrophilic aromatic substitution is however still a plausible mechanism if one accepts that the regiochemistry of the reaction is dictated by binding interactions between the enzyme and the substrate.

### 1.4.6 Miscellaneous Alkylating Agents

Although systematic, the rigid categorisation of alkylating agents in the manner above does not serve to highlight some of the more unusual examples. For this reason some recent contributions by Ryu are presented here.

In what is thought to be the first use of 1,3-dicyclohexylcarbodiimide (DCC) as an electrophile in electrophilic aromatic substitution, Ryu and co-workers managed to alkylate a number of arenes in the presence of aluminium chloride or concentrated
sulphuric acid. Equation 25 shows the alkylation of benzene which, in the case of sulphuric acid, gives the product (42) in 98% yield.

\[
\text{N} = \text{C} = \text{N} - \text{R}^{2} \quad \xrightarrow{\text{Benzene}} \quad \begin{array}{c} \text{H} \\ \text{H} \\ \text{H} \\ \text{R}^{1} \end{array} \quad \xrightarrow{\text{H}_{2}\text{SO}_{4} / \text{reflux} / 3.5\text{h}} \quad \begin{array}{c} \text{H} \\ \text{H} \\ \text{H} \\ \text{R}^{1} \end{array} \quad \xrightarrow{\text{AlCl}_{3} / \text{rt} / 3.5\text{h}} \quad \begin{array}{c} \text{H} \\ \text{H} \\ \text{H} \\ \text{R}^{1} \end{array}
\]

**Equation 25**

The mono-cyclohexylated product was obtained as the major product by performing the reaction in the aromatic substrate as the solvent, thus any small amounts of polycyclohexylated product could be easily separated out by distillation. The reaction was also applicable for other arenes such as toluene, p-xylene, mesitylene and naphthalene although the reaction with chlorobenzene was low yielding.

Ryu and co-workers have also examined the use of various amide derivatives as electrophilic sources in Friedel-Crafts alkylation reactions. Taking benzene as a representative arene substrate, ureas, amides, and sulphonamides were all examined as suitable alkylating agents in the presence of aluminium chloride or sulphuric acid as catalyst, Scheme 8.

\[
R^{2} \quad \xrightarrow{\text{Benzene}} \quad \begin{array}{c} \text{H} \\ \text{H} \\ \text{H} \\ \text{R}^{1} \end{array} \quad \xrightarrow{\text{H}_{2}\text{SO}_{4} / \text{reflux} / 3.5\text{h}} \quad \begin{array}{c} \text{H} \\ \text{H} \\ \text{H} \\ \text{R}^{1} \end{array} \quad \xrightarrow{\text{AlCl}_{3} / \text{rt} / 3.5\text{h}} \quad \begin{array}{c} \text{H} \\ \text{H} \\ \text{H} \\ \text{R}^{1} \end{array}
\]

**Scheme 8**

The product, cyclohexylbenzene (46) was produced in good to excellent yields, Table 3 with these amide bond containing alkylating agents. Other products can be synthesised depending on \( R^{2} \) which departs as a carbocationic species from the Lewis basic carbonyl or sulfonyl group.
### Table 3

<table>
<thead>
<tr>
<th>Reagent</th>
<th>$R^1$</th>
<th>$R^2$</th>
<th>Cat.</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>(43)</td>
<td>Cyclohexyl</td>
<td>Cyclohexyl</td>
<td>$\text{H}_2\text{SO}_4$</td>
<td>68%</td>
</tr>
<tr>
<td>(44)</td>
<td>Phenyl</td>
<td>Cyclohexyl</td>
<td>$\text{AlCl}_3$</td>
<td>79%</td>
</tr>
<tr>
<td>(45)</td>
<td>p-tolyl</td>
<td>Cyclohexyl</td>
<td>$\text{H}_2\text{SO}_4$</td>
<td>96%</td>
</tr>
</tbody>
</table>

#### 1.4.7 Friedel-Crafts Reactions with $\pi$-Stabilised Cations

The inductive stabilising effect of electron rich aryl groups makes for the facile formation of cations at the carbon $\alpha$- to aryl residues. Electrophilic attack can then occur easily in the presence of another arene which facilitates the formation of diaryl compounds with a new chiral centre. This process although undesirable in certain circumstances, Equation 14, has been exploited in the asymmetric syntheses of a number of diaryl containing natural products.

Bergman, in his total synthesis of Yuehchukene, uses this principle in the final step of the synthesis where the alcohol (46) serves in the asymmetric Friedel-Crafts alkylation of indole, Equation 26.

![Equation 26](image)

#### Equation 26

An intramolecular example of this methodology has been performed by Pelter in his synthesis of the lignan (-)-4-deoxyisopodophyllotoxin (48) from synthetic (-)-6-epi-podorhizol (47). The cyclisation gave rise to a single diastereomer in quantitative yield, Equation 27.
1.5 Summary

The recent development of new reagent systems and catalysts for Friedel-Crafts alkylation is a particularly important trend which has been highlighted. The environmental and industrial significance of reagents like the lanthanide trihalides, Nafion-H™ and clays such as clayzic stems from their ability to be recycled.

The development and exploitation of stereoselective Friedel-Crafts alkylation chemistry in the synthesis of challenging molecular targets remains an important theme in the literature.
Chapter 2

Results and Discussion

Chiral Auxiliaries in Friedel-Crafts
Alkylation Reactions

2.1 Introduction

2.1.1 The Use of 8-Phenylmenthol as a Chiral Auxiliary

Corey's cyclohexyl-based 8-phenylmenthol, Figure 1, is a highly effective chiral auxiliary that has been known to provide levels of control that exceed 1000:1 and routinely affords > 90% d.e.\(^5\)

![Figure 1](image)

Asymmetric induction can be introduced either near or further along from the oxygen-carbon linkage that joins the substrate to 8-phenylmenthol.

For a particular chiral auxiliary to be a viable proposition it must not only be reusable, it must also be easily synthesised from readily available materials in reasonable quantities as it is required in stoichiometric amounts. 8-Phenylmenthol fits the first criteria well, being fairly stable and hence readily recoverable; however, although it is commercially available, its great expense is an indication that its synthesis is non-trivial. This disadvantage has however not precluded its widespread use, a testament to its importance and high efficacy as a chiral auxiliary.

The application of 8-phenylmenthol as a chiral auxiliary is wide ranging. It has, for example, been incorporated into the diene portion in a Diels-Alder reaction, Equation 28.\(^5\) Chirality is controlled at the point of linkage to the diene as well as at the other two stereocenters created in the reaction.
The commonest form of asymmetric induction with 8-phenylmenthol occurs at the position \( \beta \) to the heteroatomic linkage. This is to be expected as this is the closest position to the auxiliary that is not actually directly effected on removal of the substrate in contrast to the \( \alpha \) position.

Nucleophilic addition reactions of glyoxylate and substituted glyoxylate esters have furnished the highest levels of control that have so far been observed using cyclohexyl-based chiral auxiliaries like 8-phenylmenthol. A prime example of this, with an alkene as the nucleophile, exhibiting an exceptionally high level of stereocontrol is illustrated in Equation 29.\(^{58}\)

These ene reactions of glyoxylates have found important application in natural product synthesis. For example, the key step in the synthesis of Xylomollin, Equation 30, has been achieved using 8-phenylmenthol. Here 8-phenylmenthol not only acts to induce the correct stereochemistry in the product but also influences the process by first selecting between the two enantiomers of the diene, in a fashion that is more reminiscent of an enzymatic process.
Several other nucleophiles, for example alkyl and aryl organomagnesium reagents, have been added to 8-phenylmenthol substrates with similarly impressive levels of stereocontrol.\(^{58}\)

### 2.2 The Use of 8-Phenylmenthol in the Diastereoselective Synthesis of Diarylacetates

The objectives of my work initially centred on the synthesis of diarylacetates and their derivatives with a high level of stereocontrol. Specifically, this involved the joining of two aryl moieties using Friedel-Crafts methodology to yield the desired diarylacetates in high yield and with high diastereoselectivity. The source of this stereochemical control was derived from a chiral auxiliary, with 8-phenylmenthol initially being chosen. A chiral auxiliary can theoretically be incorporated into the process in a number of ways. We chose to incorporate 8-phenylmenthol as the chiral acetate in an aryl glyoxylate. The literature precedence for the use of 8-phenylmenthol glyoxylates is well known, and is outlined in Equation 29.

Our approach involved these chiral glyoxylates being reduced to their respective alcohols. A cationic intermediate was then generated by the action of either TMSOTf or pyrophosphoryl chloride (PPC) on these α-hydroxyesters. A suitable aryl nucleophile was then used to attack the cation and generate the required diarylacetate. The nucleophile was generally achiral, however, the use of a chiral nucleophile introduced further stereochemical implications. That is to say, chiral auxiliaries were incorporated into both the electrophile and the nucleophile. The interaction of these two chiral auxiliaries can theoretically lead to either synergism or mismatch. The general procedure for the synthesis of these diarylacetates is outlined in Scheme 9.
In this way, the objective of synthesising chiral diarylacetates with good to excellent diastereoselectivities was realised. **Scheme 10.**

(i) Benzylpyrrole  
(ii) 1,2-Dimethylindole  
(iii) (R)-α-Methylbenzylpyrrole
The above diastereoselectivities are more a reflection on the fact that pyrophosphoryl chloride (PPC) is not as reactive as TMSOTf at low temperature and hence the reactions with PPC were conducted at higher temperatures which compromised the levels of stereocontrol.

Recrystallization of the major diastereomer and a single crystal X-ray structure determination, shown below, **Scheme 11**, as a MolDraw representation taken from the X-ray co-ordinates, confirmed the absolute stereochemistry at the new chiral centre in compound (51) as (S).59

**Scheme 11**

The best diastereoselectivity however was obtained with compound (50), which was prepared with a d.e. of 88% as the reaction was conducted at -78°C using TMSOTf. The same product (50) was also prepared in a reverse sense in that the pyrrolyl hydroxyester (53) was prepared and reacted with N-methylindole instead of the indolyl hydroxyester (49) being coupled to N-benzylpyrrole. The diastereoselectivity of this second procedure was all but identical to the first at 87%, **Equation 31**.
This shows that compound (50) can be prepared from two different substrates having differing π systems associated with their heterocyclic moieties with virtually identical selectivities. One can conclude from the results that difference in π-electron density associated with the heterocyclic moieties of the 8-phenylmenthol hydroxyesters (49) and (53) may not have a major effect on the diastereoselectivity of the product.

The use of a chiral nucleophile (R)-N-(1-phenylethyl)pyrrole in the preparation of compound (52) does not seem to be a significant factor in determining the diastereoselectivity of the reaction as much the same diastereoselectivity is attained in the analogous reaction using the achiral nucleophile 1,2-dimethylindole.

Using the methodology outlined in Scheme 9 the racemic methyl ester analogue of compound (50) was prepared.

The purpose of preparing compound (54) was to serve as a model study in the derivatisation of the ester (50) to its crystalline 3,5-dinitrobenzoate ester. Compound (54) derivatised to its 3,5-dinitrobenzoate ester would also serve as a racemic standard for use in chiral HPLC studies of the 3,5-dinitrobenzoate ester derivative of (50). The general methodology for the reductive removal of 8-phenylmenthol and the consequent derivatisation to the 3,5-dinitrobenzoate ester is outlined below.
Scheme 12

<table>
<thead>
<tr>
<th>Ester</th>
<th>Alcohol</th>
<th>Yield</th>
<th>3, 5-Dinitrobenzoate ester</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>(50)</td>
<td>(55)</td>
<td>97%</td>
<td>(57)</td>
<td>93%</td>
</tr>
<tr>
<td>(54)</td>
<td>(56)</td>
<td>96%</td>
<td>(58)</td>
<td>85%</td>
</tr>
</tbody>
</table>

Table 4

Chiral HPLC analysis of the two enantiomeric 3, 5-dinitrobenzoate esters (57) and the racemic (58) using a Chiralpak AD column indicated that there was a 1:3.9 ratio in the peaks for compound (57) which translates to an ee of 59%, (Appendix 1). This figure is less than the NMR derived de of 88% for the parent 8-phenylmenthol ester (50). This disparity in the apparent de may be due to racemisation of the alcohol (55) and or of the parent ester (50). The removal of the electron withdrawing ester group and the possible involvement of the corresponding diarylethene by loss of water from the alcohol (55) is conceivably how this racemisation process occurs. Thus, this method of direct determination of selectivity is found not to be useful.

2.3 Trans-2-(α-Cumyl) Cyclohexanol an Alternative Chiral Auxiliary to 8-Phenylmenthol

Chiral auxiliary mediated asymmetric synthesis has enabled the realisation of a range of chemical transformations which have been carried out with high levels of stereocontrol. Although highly effective the major disadvantage is that they are required in stoichiometric amounts. This necessitates that for a chiral auxiliary to be effective it must be readily accessible in reasonable amounts in its enantiomerically pure form. As was previously mentioned, enantiopure (−)-8-phenylmenthol (59)
although highly effective as a chiral auxiliary, is only available commercially at high price. Alternatively it can be prepared in five steps from (+)-pulegone.\textsuperscript{60}

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figures/figure3.png}
\caption{(-)-8-phenylmenthol \quad (+)-trans-2-(\alpha-cumyl)cyclohexanol}
\end{figure}

It is for this reason that alternatives to (-)-8-phenylmenthol (59) have been sought. Whitesell\textsuperscript{61} initially developed trans-2-(\alpha-cumyl)cyclohexanol, ((+)-TCC) (60) from 1-trimethylsilyloxy cyclohexane and cumyl chloride in a five step synthesis which does not represent a simple enough route. A much simpler route has been developed by Comins\textsuperscript{62a, b} that utilises an enzymatic resolution procedure. The initial step to form racemic TCC involves the opening of cyclohexene oxide with \alpha-cumyl potassium. Although this reaction is reported to proceed in high chemical yield (94\%), in our hands only a relatively modest 59\% was achieved. Nonetheless this still represents an excellent route to (+)-TCC (60) as only the high yielding resolution step is left in this two stage process.

\begin{scheme}[h]
\centering
\includegraphics[width=0.5\textwidth]{figures/scheme13.png}
\caption{Scheme 13}
\end{scheme}

The racemic (+)-TCC (60) is then subjected to an enzymatic resolution procedure with the lipase Candida Rugosa. An equivalent of lauric acid together with this lipase in a cyclohexane solution at 40\textdegree C resulted in a mixture of (+)-TCC (60), in 81\% ee and the laurate ester of (-)-TCC which were readily separable by distillation. Re-exposure of this enriched (+)-TCC (60), to this enzymatic resolution procedure
furnished even more enantiomerically enriched alcohol (+)-TCC, (98% ee in an overall yield of 72%).

**First Enzymic Resolution**

\[
\text{HO} \quad \text{Ph} \\
\text{C}_{11} \text{H}_{23} \text{OH} \quad \text{C Candida Rugosa} \\
\text{Cyclohexane, 40°C} \quad \text{41 h}
\]

First Enzymic Resolution

\[
\text{HO} \quad \text{Ph} \\
\text{C}_{11} \text{H}_{23} \text{O} \quad \text{C Candida Rugosa} \\
\text{Cyclohexane, 40°C} \quad \text{41 h}
\]

Second Enzymic Resolution

\[
\text{HO} \quad \text{Ph} \\
\text{C}_{11} \text{H}_{23} \text{OH} \quad \text{C Candida Rugosa} \\
\text{Cyclohexane, 40°C} \quad \text{48 hours} \quad 2) \text{K}_2 \text{CO}_3 \text{1 h}
\]

Scheme 14

In this way relatively large quantities of enantiomerically pure (+)-TCC are readily accessible with the only limitation being the amount of the recyclable *Candida Rugosa* enzyme that is available. The (-)-TCC enantiomer is also readily accessible by saponification of the laurate ester of (-)-TCC followed by the two stage enzymatic resolution procedure yielding enantiomerically pure (-)-TCC, the (1R, 2S) enantiomer.

With the enantiopure (+)-TCC in hand analogues of the (-)-8-phenylmenthol diaryl acetic acid derivatives outlined in Section 2.2 could be prepared with (+)-TCC as the chiral auxiliary. This would provide a direct comparison between the effectiveness of these two chiral auxiliaries in this particular reaction that involves nucleophilic attack with an electron rich heterocycle β to the chiral auxiliary. To this end, in an analogous fashion to the procedures employed for the (-)-8-phenylmenthol derivatives in Section 2.2, the (+)-TCC analogues were synthesised. Treatment of *N*-methylindole with oxalyl chloride furnished the corresponding acid chloride which was then
reacted with (+)-TCC in the presence of triethylamine to yield (+)-trans-2-(α-cumyl)cyclohexyl(N-methyl-3-indolyl)glyoxylate (61) in 52% yield, Equation 32.

\[
\text{Scheme 15}
\]

Subsequent reduction of (+)-trans-2-(α-cumyl)cyclohexyl(N-methyl-3-indolyl)glyoxylate (61) with sodium borohydride in methanol yielded the hydroxy ester (+)-trans-2-(α-cumyl)cyclohexyl(N-methyl-3-indolyl)hydroxyacetate (62) in 79% yield and with a small degree of selectivity, namely 38% de. Treatment of this hydroxy ester (62) with an \textit{in situ} generated catalytic amount of TMSOFs led to the formation of a planar cationic intermediate. This obviously renders the diastereoselectivity of the reduction step inconsequential. In order that the nucleophilic attack of 1,2-dimethylindole on this planar cationic centre should proceed in a selective manner the phenyl group associated with the trans-2-(α-cumyl)cyclohexyl moiety must be preferentially shielding one face. This indeed
appears to be the case as (+)-trans-2-(α-cumyl)cyclohexyl (N-methyl-3-indolyl)-(1,2-dimethyl-3-indolyl)acetate (63) is obtained with a selectivity, determined by NMR, of 65% de and a chemical yield of 92%.

There is no doubt about the efficacy of 8-phenylmenthol and to a lesser extent trans-2-(α-cumyl)cyclohexanol as powerful and versatile chiral auxiliaries. The origin of stereocontrol is, however, uncertain and has been subject to a great deal of speculation. To date the process is still not fully understood but one of the most popular rationalisations that is championed by Corey, Oppolzer and Whitesell, has been the notion that some sort of π-π stacking interaction is taking place between the phenyl moiety of 8-phenylmenthol and other π systems within the substrate. On the other hand, general studies on the nature of π-π interactions by Sanders and Hunter hold that π-π interactions are not due to an attractive interaction between the two π-systems but occur when the attractive interactions between the π-system and the σ-framework outweigh any repulsion from other π-electrons.

It seems that current opinion favours the π stacking theory as a means to explain the origin of these observed selectivities. Although π stacking has been clearly defined as the positioning of a multiple bond (either C=O or C=C) parallel to and approximately 3.5 Å over an aromatic ring. The precise nature of this interaction is still the subject of conjecture. That is to say, it is not known whether this attractive force is due to charge-transfer or van der Waals forces.

Our work has demonstrated the effectiveness of both (-)-8-phenylmenthol and (+)-TCC as chiral auxiliaries in Friedel-Crafts reactions involving the interaction of planar cations and nucleophilic aromatic substrates. This methodology can be used to control the absolute configuration at a new chiral centre in esters of diarylacetic acid derivatives. It was found that (-)-8-phenylmenthol is a more effective chiral auxiliary than (+)-TCC in this particular reaction with diastereoselectivities of 88% and 65% being attained for the respective ester analogues (50) and (63). The absence of a 5-methyl group on the cyclohexyl ring in TCC is the only structural variation from 8-phenylmenthol. It is thought that the flexibility of the cyclohexyl ring in TCC is greater than that of 8-phenylmenthol because of the absence of this 5-methyl group. That is to say the 5-methyl group on 8-phenylmenthol imparts greater rigidity on the cyclohexyl ring. As a consequence of this added rigidity in the ring system, the π stacking phenyl moiety is also held in place more rigidly. This leads to a more stereochemically constrained system in 8-phenylmenthol compared with TCC, which is reflected in the observed differences in selectivities.
2.4 Attempted Intramolecular Cyclisations

As has been shown in the previous section cations can be generated from \(\alpha\)-hydroxy esters after treatment with a Lewis acid. These cations can then be attacked by a nucleophile to yield the desired diaryl acetic acid derivative. In an effort to extend this methodology it was reasoned that cations generated in this way might be nucleophilically attacked in an intramolecular manner by an electron rich moiety associated with the \(\alpha\)-hydroxy ester. If one considers the \(\alpha\)-hydroxy esters of benzyl pyrrole derivatives with electron rich phenyl groups then potentially a synthesis for dihydroindolizine derivatives could be envisaged.

As with the previously discussed intermolecular reactions, a chiral auxiliary such as \((-\)-8-phenylmenthol or \((+\)-TCC could be employed. In this way, one face would be shielded from nucleophilic attack. This could then lead to the formation of a stereocenter \(\alpha\)- to the pyrrole moiety, of the dihydroindolizine derivative, in a stereoselective manner.

To this end a model study was undertaken with the synthetic target being the methyl ester (64) as the potential precursor to cyclisation.
This involved the synthesis of the corresponding N-3,4-dimethoxybenzylpyrrole (65) which was accomplished using the well known Clauson-Kaas pyrrole synthesis. This was accomplished in an chemical yield of 81\%, Equation 33.

\[
\text{NH}_2 + \text{Acetic acid} \xrightarrow{\text{Toluene, } 19\text{h, } 80^\circ\text{C}} \text{(65)} \quad \text{Yield 81\%}
\]

**Equation 33**

Oxalylolation of this pyrrole (65) with oxalyl chloride followed by treatment of the intermediate acid chloride with triethylamine and methanol led to the formation of the corresponding glyoxylic ester (66) in 80\% yield. Reduction of (66) with NaBH\(_4\) led to formation of the required \(\alpha\)-hydroxyester (64) in 79\% yield.

\[
\text{(65)} \xrightarrow{1) (COCl)_2, 1h 25^\circ\text{C}} \xrightarrow{2) \text{Et}_3\text{N, MeOH 3h}} \text{(66)} \quad \text{Yield 80\%}
\]

\[
\text{(65)} \xrightarrow{\text{NaBH}_4, 20^\circ\text{C, 15 mins}} \text{(64)} \quad \text{Yield 79\%}
\]

**Scheme 17**
Attempts to cyclise α-hydroxyester (64) using TMSOTf in catalytic and stoichiometric amounts at -78°C only led to formation of complex polymeric mixtures and the isolation of some starting material.

![Equation 34](image)

**Equation 34**

It was argued that the analogous 3,5-dimethoxybenzyl substrate (67) could potentially be a better precursor to cyclisation than hydroxyester (64). Theoretically, greater electron density resides at the desired point of cyclisation in (67), when compared to (64).

![Figure 5](image)

**Figure 5**

The synthesis of the corresponding precursors was undertaken. Since the Clauson-Kaas\textsuperscript{65} method worked well for \(N\)-3,4-dimethoxybenzylpyrrole (65) it was thought that the synthesis of the required \(N\)-3,5-dimethoxybenzylpyrrole (68) would be straightforward using the same methodology. This involved refluxing 3,5-dimethoxybenzylamine under acidic conditions in the presence of an excess of 2,5-dimethoxymethyltetrahydrofuran. However all attempts to synthesise \(N\)-3,5-dimethoxybenzylpyrrole (68) in this manner failed with only a complex mixture of products being obtained. An alternative amine based pyrrole synthesis developed by Chan\textsuperscript{66} was thought appropriate as it would also allow the use of the available 3,5-dimethoxybenzylamine. This procedure involved two steps, firstly treatment of 2,5-dimethoxytetrahydrofuran with trimethylchlorosilane yields
1,4-dichloro-1,4-dimethoxybutane which can be subsequently reacted with the appropriate amine in the presence of Amberlyst A-21 ion exchange resin to furnish the required pyrrole.

![Equation 35](Image)

Equation 35

It was found that at best the required 1,4-dichloro-1,4-dimethoxybutane was obtained in 77% yield at ambient temperature in dichloromethane. This was after an excessively long reaction time of ten days. In comparison an 86% yield was obtained by Chan\textsuperscript{66} over a period of two days although chloroform was used as solvent. With the 1,4-dichloro-1,4-dimethoxybutane in hand Chan's procedure was followed in order to synthesise the desired pyrrole (68).

![Equation 36](Image)

Equation 36

This involved the use of the weakly basic ion-exchange resin Amberlyst A-21 as a neutralising agent in the reaction of 1,4-dichloro-1,4-dimethoxybutane with 3,5-dimethoxybenzylamine. Under the mild conditions prescribed, the desired \textit{N}-3,5-dimethoxybenzylpyrrole (68) was isolated in only 17% yield. Although this particular pyrrole has not been synthesised in this way before, the yield was nonetheless disappointing given that other pyrroles such as benzylpyrrole have been prepared by Chan\textsuperscript{66} in near quantitative yield. Clearly then this approach to the synthesis of \textit{N}-3,5-dimethoxybenzylpyrrole (68) was not satisfactory from the point of view of poor yield as well as the introduction of the additional step to synthesise 1,4-dichloro-1,4-dimethoxybutane, a more reactive equivalent of succindialdehyde than 2,5-dimethoxytetrahydrofuran.
An alternative synthetic strategy, **Scheme 18**, was devised with the retrosynthetic approach centring on *N*-alkylation of pyrrole with the desired moiety instead of a pyrrole synthesis based on the appropriate amine.

![Scheme 18](image)

This approach utilises the high yielding procedure for the *N*-alkylation of heterocycles with an alkyl halide under polar aprotic conditions devised by Heaney and Ley. The required 3,5-dimethoxybenzyl bromide (70) was synthesised in two high yielding steps. Reduction of 3,5-dimethoxybenzaldehyde with lithium aluminium hydride furnished 3,5-dimethoxybenzyl alcohol (69) in 75% yield, **Equation 37**.

![Equation 37](image)

Conversion of this alcohol (69) to the required alkyl halide (70) was achieved using phosphorus tribromide in diethyl ether yielding 3,5-dimethoxybenzyl bromide in 91% yield, **Equation 38**.

![Equation 38](image)

With this alkyl halide in hand the synthesis of 3,5-dimethoxybenzylpyrrole (68) was accomplished in 99% yield as outlined in **Equation 39**.

![Equation 39](image)
Having found a high yielding route to 3,5-dimethoxybenzylpyrrole (68) the required α-hydroxy ester (67) was prepared in order to set up an intramolecular cyclisation to the target dihydroindolizine derivative.

Acylation of \(N\)-3,5-dimethoxybenzylpyrrole (68) with oxalyl chloride followed by treatment of the resultant acid chloride intermediate with triethylamine and methanol furnished the desired glyoxylate (71) in 96% yield. Reduction of this glyoxylate with \(\text{NaBH}_4\) produced the corresponding \(\alpha\)-hydroxyester (67) in 65% yield. The cyclisation of hydroxyester (67) to the target dihydroindolizine was then attempted, \(\text{Equation } 40\).
Initially, as with the previously discussed intermolecular version of this reaction, TMSOTf was chosen as the cyclising agent. The exposure of the \( \alpha \)-hydroxyster (67) to both stoichiometric and catalytic amounts of TMSOTf at \(-78^\circ C\) and at ambient temperature in dichloromethane did not result in the formation of any cycloadduct. Only unreacted starting material was recovered. The cyclisation was also attempted using scandium(III) trifluoromethanesulfonate, a Lewis acid that was found to catalyse similar intermolecular reactions, (Section 4.2.1), but this also proved to be ineffective with unreacted starting material being recovered after four hours, while prolonged exposure to Sc(OTf)\(_3\) led to decomposition of the \( \alpha \)-hydroxyester (67).

This failure to form the desired cycloadducts from \( \alpha \)-hydroxyesters (67) and (64) was not thought to be due to a lack of electron density in the phenyl moiety. The lack of reactivity was instead rationalised in terms of the cyclisation being too sterically demanding. That is to say, the direction of approach of the activated benzene moieties of \( \alpha \)-hydroxyesters (67) and (64) to the planar cation presumably must be linear.

Clearly, the formation of this planar cationic intermediate is energetically unfavourable as it involves an early transition state, Figure 6 (b). The cyclisation does not seem to be proceeding via a lower energy later transition state, Figure 6 (a).
Assuming that there is a linear approach of the activated phenyl moieties of α-hydroxyesters (67) and (64) to the planar cation, it was argued that greater flexibility of these electron rich phenyl moieties would be required to achieve cyclisation. By extending the length of the tether on the pyrrole cyclisation precursor from an N-benzyl moiety to an N-phenylethyl moiety, an early transition state might be realised. Such a possibility was investigated using the hydroxyester (74) as the precursor to the annelation reaction.

Using the established methodology N-(3,4-dimethoxyphenylethyl)-pyrrole (72), was synthesised using the Clauson-Kaas procedure. The corresponding glyoxylate (73) and hydroxyester (74) were synthesised in 96% and 66% yield respectively, Scheme 20, using the same procedures as with the previous analogues.
Unfortunately, attempts to cyclise hydroxyester (74) using TMSOTf and Sc(OTf)3 in catalytic and stoichiometric amounts at -78°C and at ambient temperature in dichloromethane failed, Equation 41. Only complex polymeric mixtures and some starting material were isolated.

Although it has been demonstrated in Sections 2.3 and 2.4 that the intermolecular version of these Friedel-Crafts alkylations occur readily, the intramolecular version of this reaction does not. The reason behind the failure of these cyclisation reactions is
obscure. Naturally, since these model cyclisations did not occur this precluded any work on the asymmetric versions.
Chapter 3

The *In Situ* Generation of Trimethylsilyl Trifluoromethanesulfonate and Trimethylsilyl Fluorosulfonate

3 Introduction

3.1 Trimethylsilyl Trifluoromethanesulfonate in Organic Synthesis

Trimethylsilyl trifluoromethanesulfonate, (TMSOTf), is a versatile reagent that acts both as a powerful silylating agent and as a Lewis acid catalyst. Its versatility is matched by its high reactivity, factors which have combined to ensure its widespread application and extensive use since its inception over 20 years ago.\(^6\)\(^9\)

TMSOTf was introduced as a reagent in organic synthesis by Vorbruggen who used it catalytically in the synthesis of nucleosides,\(^7\)\(^0\) although Noyori is often erroneously accredited with its first use.

The importance of TMSOTf is derived not only from its versatility, but also because it exhibits certain unique properties which are not common to more conventional Lewis acids. These properties are as a consequence of the nature of the Si–O bond in TMSOTf which, although covalent rather than ionic in character, is nevertheless highly polarised. The extreme electron withdrawing properties of the trifluoromethanesulfonyl moiety are responsible for this high degree of polarisation and ultimately this means that the Si atom is endowed with considerable electron deficiency. This in turn leads to the consequent interaction of the electrophilic trimethylsilyl moiety with heteroatoms, most notably oxygen, in various organic substrates resulting in the formation of onium ions with only a background of feebly nucleophilic triflate counter ions. The existence of these unique singly co-ordinated intermediates is due to the fact that silicon is inherently 4-co-ordinate in the ground state. Therefore with the trimethylsilyl moiety, only co-ordination to a single heteroatom is possible. This is in contrast to more conventional Lewis acids such as SnCl\(_4\) and TiCl\(_4\) which contain transition metal atoms that can exist in a variety of oxidation states. This allows co-ordination of the metal atoms to more than one functional group. Invariably, this precludes the formation of singly co-ordinated intermediates, of the kind formed by the trimethylsilyl species.\(^6\)\(^9\)
Thus organic substrates activated by TMSOTf through such one-centred electrophilic co-ordination of trimethylsilyl moiety can act as a supercationic species that along with displaying unique chemical behaviour also have the advantage of avoiding the problems associated with ordinary Lewis acids, like aggregation or ligand exchange. The unique advantages that TMSOTf displays over the other more conventional Lewis acids is perhaps best illustrated in nucleoside chemistry. The following example serves well to underline these particular advantages in a reaction between a silylated pyrimidine (75) and an O-protected 1-O-acyl sugar (76).71

\[
\text{Equation 42}
\]

Here the nucleoside is synthesised in high yield, which is an improvement on the analogous reaction catalysed by SnCl4. This is because of the ideally acidic properties of TMSOTf which are sufficient to form the reactive sugar cation, Figure 7, but mild enough to significantly reduce σ-complex formation with the silylated bases, relative to SnCl4. Practically TMSOTf also offers advantages over SnCl4 in that no emulsions or colloids are formed during workup.

\[
\text{Figure 7}
\]

TMSOTf can also function as a highly efficient silylating agent, with its silylating potential reckoned to be $10^9$ that of chlorotrimethylsilane.69a The silylation of cyclic saturated ketones to silylenol ethers is illustrated in Equation 43. Various other carbonyl containing substrates can also be silylated in a similar fashion.
Another reaction of interest involves the conversion of oxiranes to allylic alcohols. This example involves a steroidal substrate and demonstrates both the regiochemical and stereochemical scope of TMSOTf mediated reactions, Equation 44. Here ring opening takes place at the more substituted carbon, standard deprotection then affords the allylic alcohol.

Equation 44

More recently the use of TMSOTf has been demonstrated to good effect by Padwa in the synthesis of heterocyclic ring systems. Specifically catalytic amounts of TMSOTf were used to promote intramolecular [4+2] annulation of N-acetoacetylated alkenyl amides, Equation 45.

Equation 45
Although this annelation reaction can be catalysed by other Lewis acids such as BF₃·OEt₂, TMSOTf was found to be unique in its ability to effect the reaction successfully in truly catalytic amounts. The complete stereospecificity of the process is also worth noting, as it was found that the cycloadduct (78) was the only product from the treatment the lactam (77) with diketene and TMSOTf.

Clearly then, TMSOTf is an important tool in organic synthesis as this brief and by no means exhaustive review of the literature outlines. The major drawback however is that it is extremely sensitive to moisture and is therefore difficult both to handle and to store without contamination. Its relative expense has meant that these problems have had to be addressed. Various solutions to the problem have been tried ranging from the simple but practically unattractive proposition by Noyori that it should be purified by twice distilling from ca. 1% by volume of triethylamine prior to use. Alternatively, attempts have been made to circumvent these problems by generating the reagent in situ. Olah for example, recommended the in situ generation of TMSOTf from triflic acid and allyltrimethylsilane. It has also been suggested that TMSOTf can be generated by the interaction of triflic acid with the commercially available silylating agent 3-trimethylsilyl-2-oxazolidinone.

Perhaps the most elegant approach to date has been to immobilise TMSOTf on a polymer bead. It can then be simply used as required, and stored easily over long periods of time with no foreseeable degradation of the reagent. This approach was developed by Noyori and involves the silylation of Nafton-H® with chlorotrimethylsilane to yield the trimethylsilyl ester of Nafton-H®. This can then be used in both catalytic and stoichiometric reactions in an equivalent fashion to standard TMSOTf but without the associated problems. This approach offers great operational simplicity and increases the utility of TMSOTf, but in common with the previously outlined methods for the in situ generation of TMSOTf, has not found wide application as a synthetic procedure.

3.2 The Use of Bis-trimethylsilyl-acetamide (BSA) and -urea (BSU) in Trimethylsilyl Trifluorosulfonate and -Fluorosulfonate Catalysed Reactions

The problems in keeping high quality samples of TMSOTf because of its contamination with triflic acid (TfOH), due to its high moisture sensitivity are well known. Our experience of these problems was initially observed with the following reaction.
Previous experience had indicated that TMSOTf was an excellent catalyst for the above procedure so it soon became apparent that the problem lay in using contaminated samples of TMSOTf. We reasoned that as the problem was with the presence of TfOH, the acid scavenger bis-trimethylsilyl-acetamide (BSA) could be used to remove this unwanted acid, thereby decontaminating the TMSOTf and allowing the reaction to proceed as expected. To this end we repeated the reaction using a reverse addition procedure, the same sample of contaminated TMSOTf and an excess of BSA. This methodology proved to be successful for this and other analogous reactions.

In acting as an acid scavenger BSA theoretically interacts with the TfOH acid to generate TMSOTf according to Scheme 21.
In this way not only is TfOH being removed but TMSOTf is also being generated in the process. Potentially then TfOH and BSA, both cheap and readily available reagents, could be used to generate TMSOTf \textit{in situ} thereby overcoming the problems associated with handling and storing a reagent like TMSOTf. A number of silylation reactions were investigated but instead of using TMSOTf directly, TfOH and BSA were combined in an attempt to generate enough TMSOTf to silylate the particular substrate. These reactions were however unsuccessful indicating that this methodology does not generate TMSOTf in stoichiometric amounts.

Despite the finding that TMSOTf is not generated in stoichiometric amounts it was argued that this methodology could be used to generate TMSOTf for use in catalytic reactions. We have demonstrated the effectiveness of this methodology in a variety of literature reactions. Yields compare favourably with the yields quoted in the literature making this method of \textit{in situ} TMSOTf generation an inexpensive, ideal and effective way of carrying out TMSOTf catalysed reactions. Besides using BSA in conjunction with TfOH to generate TMSOTf, it was found that bis-trimethylsilyl-urea (BSU), Figure 8, acted as an acid scavenger in a similar and equivalent fashion to BSA.$^{77}$

![Bis-Trimethylsilyl-urea (BSU)](image)

\textbf{Figure 8}

This use of BSU in place of BSA was found to have no effect on reaction yields, but being a less expensive reagent it further increased the utility of the method.

The literature methods for the \textit{in situ} generation of TMSOTf generally utilise triflic acid as the source of the triflate anion but crucially differ from our own method in the choice of silylating agent. Olah's procedure involves the use of allyltrimethylsilane or tetramethylsilane as the TMS source and a few drops of triflic acid.$^{74}$ Although the method is effective in the silylation of carboxylic acids and alcohols, quantitative amounts of triflic acid were required for the conversion of ketones to silyl enol ethers. The method is also generally disadvantaged by the emission of flammable gaseous by-products like propene and by the use of relatively expensive starting materials. Palomo$^{75}$ on the other hand, chose to use the commercially available silylating agent
3-trimethylsilyl-2-oxazolidinone. This procedure also has the disadvantage of using a relatively expensive silylating agent. It is also an extremely exothermic process, with temperatures of 90°C reported, which is impracticable for many TMSOTf catalysed reactions. The practical requirement of removing the by-product oxazolidinone is also a disadvantage of this method. Our methodology in contrast, merely generates acetamide or urea as by-products, which are easily removed or precipitate out in the latter's case.

We noted the recent development by Lipshutz whereby trimethylsilylfluorosulfonate (TMSOFs) was generated in situ by the interaction of fluorosulfonic acid (FSA) with allyl trimethylsilane. TMSOFs prepared in this manner, acts essentially as a TMSOTf equivalent.\(^{78}\)

\[
\begin{align*}
\text{Me}_3\text{Si-O-S-F} & \\
\text{TMSOFs}
\end{align*}
\]

\textbf{Figure 9}

The use of TMSOFs has not been as widespread as TMSOTf but, with the exception of its ineffectiveness in nucleoside synthesis, (presumably because it is a stronger Lewis acid than TMSOTf), it can be treated as a practical alternative.\(^{71}\)

Lipshutz chose to generate TMSOFs in an analogous fashion to Olah's procedure for the in situ generation of TMSOTf, namely by the interaction of FSA in place of triflic acid with allylsilane. The attractive feature of this procedure is the use of FSA, a much cheaper reagent than triflic acid and one that is available industrially on a large scale. We sought to increase the utility of our initial procedure by substituting triflic acid with FSA and replacing allyltrimethylsilane with BSA or BSU as before, thereby further reducing the cost of the procedure. Essentially the same set of TMSOTf catalysed reactions was then carried out using this procedure for generating TMSOFs and proved to be just as effective in terms of yield and reactivity.\(^{79}\)

The practical simplicity and inexpensive nature of our procedures are clear, and as such should be the method of choice in reactions catalysed by TMSOTf and its equivalents. The suitability of our methodology is not only confined to reactions on a small scale it was found to be equally effective in larger scale reactions where only a 1% equivalent of FSA and BSA were required to catalyse an acetalization reaction on a 100 mmol scale, (Equation 51, Table 7).
Our procedure in its various combinations, Figure 10, has been demonstrated for a number of standard reactions that are normally catalysed by TMSOTf.

![Figure 10](image)

**Figure 10**

### 3.3 TMSOTf Catalysed Aldol-type Reactions of Silyl Enol Ethers and Acetals

Using this methodology for the *in situ* generation of TMSOTf and TMSOFs, the following literature reaction, normally catalysed by the direct use of TMSOTf, was found to proceed equally well in terms of both yield and stereoselectivity using our methodology.80

\[
\begin{align*}
\text{Ph} & \quad \text{OMe} \\
\text{OMe} & \quad \text{Ph}
\end{align*}
\]

Equation 47

![Table 5](image)

**Table 5**

- Recently this reaction amongst other similar ones has been catalysed by scandium trifluoromethanesulfonate (Sc(OTf)_3).81 This new catalytic procedure proceeds smoothly in high yield and has the added advantage of the catalyst being easily
extracted and reused with no decrease in yield. This reusable catalyst is an excellent way of performing these aldol reactions. However, the initial cost of Sc(OTf)3 means that our methodology still represents the best approach to these reactions in terms of cost.

Other aldol reactions of this type have also been performed using this *in situ* method for generating TMSOTf equivalents, Equation 48.

\[
\text{Equation 48}
\]

\[
\begin{align*}
\text{OMe} + \text{MeO} & \xrightarrow{\text{FSA/BSA, -78°C}} \text{OMe} \\
\text{yield 81%}
\end{align*}
\]

Again this compares favourably with the literature yield of 87%.\(^8^0\) Another example that in contrast is not so high yielding, Equation 49, involves furaldehyde diethoxyacetal and 1-trimethylsilyloxy cyclohexene. The reaction, which is not a literature reaction, is accomplished in only 19% yield. The reaction was repeated several times with similar results suggesting that it was the sensitivity of the furan substrate and not our methodology that was to blame.

\[
\text{Equation 49}
\]

\[
\begin{align*}
\text{OTMS} + \text{FSA/BSU} & \xrightarrow{-78°C} \text{(81)} \\
\text{yield 19%}
\end{align*}
\]

3.4 The Silyl Modified Sakurai, (SMS), Reaction

The silyl modified Sakurai (SMS) reaction, a recent development by Markó,\(^8^2\) is another reaction catalysed by TMSOTf. The following series of results serves to further demonstrate the effectiveness of our methodology for generating TMSOTf and TMSOFs, Equation 50, Table 6.
The observed yields in Table 6, compare favourably with the literature benchmark of 92%. It is worth noting that Lipshutz who examined this reaction in reference to his work in generating TMSOFs from TfOH and allyltrimethylsilane obtained similarly high yields. It is also apparent that in this reaction allyltrimethylsilane is already present as one of reactants. Clearly then, by implication, one has to justify the presence of our silylating agents BSA and BSU as the reaction can proceed in their absence. Their presence can be justified on two grounds; firstly their inclusion obviates the need to use an excess of the relatively expensive allyltrimethylsilane and secondly because of the fact that BSA and BSU are excellent acid scavengers their presence serves to ensure that on addition of the substrates the reaction will be free from any acid or moisture which can impede the reaction. It is worth noting in relation to this, that we observed a substantially reduced yield of only 50% when only FSA was added as a catalyst, Scheme 24. This and other reactions that are catalysed by the acid alone are discussed in Section 3.8. In this case it is clearly necessary to ensure that the substrates in the SMS reaction are not exposed to large quantities of the acid, hence the presence of BSA or BSU is important in order to ensure the success of the reaction in high yield.

Table 6

<table>
<thead>
<tr>
<th>Acid (a)</th>
<th>Silyl Source (b)</th>
<th>% Yield (82)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIOH</td>
<td>BSA</td>
<td>90</td>
</tr>
<tr>
<td>TIOH</td>
<td>BSU</td>
<td>92</td>
</tr>
<tr>
<td>FsOH</td>
<td>BSA</td>
<td>95</td>
</tr>
<tr>
<td>FsOH</td>
<td>BSU</td>
<td>91</td>
</tr>
</tbody>
</table>

The observed yields in Table 6, compare favourably with the literature benchmark of 92%. It is worth noting that Lipshutz who examined this reaction in reference to his work in generating TMSOFs from TfOH and allyltrimethylsilane obtained similarly high yields. It is also apparent that in this reaction allyltrimethylsilane is already present as one of reactants. Clearly then, by implication, one has to justify the presence of our silylating agents BSA and BSU as the reaction can proceed in their absence. Their presence can be justified on two grounds; firstly their inclusion obviates the need to use an excess of the relatively expensive allyltrimethylsilane and secondly because of the fact that BSA and BSU are excellent acid scavengers their presence serves to ensure that on addition of the substrates the reaction will be free from any acid or moisture which can impede the reaction. It is worth noting in relation to this, that we observed a substantially reduced yield of only 50% when only FSA was added as a catalyst, Scheme 24. This and other reactions that are catalysed by the acid alone are discussed in Section 3.8. In this case it is clearly necessary to ensure that the substrates in the SMS reaction are not exposed to large quantities of the acid, hence the presence of BSA or BSU is important in order to ensure the success of the reaction in high yield.
3.5 Acetalization of Carbonyl Compounds with Alkoxy silanes

Noyori has used TMSOTf to catalyse the formation of acetals from carbonyl compounds and alkoxy silanes. The reaction is thought to proceed via a trimethylsilyloxy carbocation. In order to increase the utility of our method, we sought to demonstrate that our procedure for the in situ generation of either TMSOTf or TMSOFs would effect the catalysis of reactions on larger scales.

\[
\text{(C)} + \begin{array}{c}
\text{OTMS} \\
\text{OTMS}
\end{array} \xrightarrow{a,b; -78^\circ C} \text{(83)}
\]

Equation 51

<table>
<thead>
<tr>
<th>(a) FSA mmol.</th>
<th>(b) Silyl Source mmol.</th>
<th>(c) Ketone mmol.</th>
<th>(d) Alkoxy silane mmol.</th>
<th>% Yield (83)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2 BSU</td>
<td>3</td>
<td>4</td>
<td>97</td>
</tr>
<tr>
<td>1</td>
<td>2 BSA</td>
<td>100</td>
<td>133</td>
<td>84</td>
</tr>
</tbody>
</table>

Table 7

An analogous reaction, Equation 52, with cyclohexanone in place of 4-methylcyclohexanone was also performed, the results are outlined in Table 8.

\[
\text{(C)} + \begin{array}{c}
\text{OTMS} \\
\text{OTMS}
\end{array} \xrightarrow{a,b; -78^\circ C} \text{(84)}
\]

Equation 52
3.6 The Conversion of Acetals to Homoallylic Ethers

Besides the SMS reaction an alternative route to homoallylic ethers from the acetal as opposed to the aldehyde exists.\textsuperscript{84} Again the reaction is catalytic in TMSOTf and our procedure is again demonstrated to be at least as effective as the direct use of TMSOTf which yields 88\% for this particular allylation of benzaldehyde dimethoxy acetal.

\begin{equation}
\begin{array}{c}
\text{OMe} \\
\text{Ph} \\
\text{TMS}
\end{array}
\text{+}
\begin{array}{c}
\text{OMe} \\
\text{OMe}
\end{array}
\xrightarrow[n, b]{-78^\circ C}
\begin{array}{c}
\text{OMe} \\
\text{Ph}
\end{array}
\end{equation}

\textbf{Equation 53}

<table>
<thead>
<tr>
<th>Acid (a)</th>
<th>Silyl Source (b)</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>TfOH</td>
<td>BSA</td>
<td>76</td>
</tr>
<tr>
<td>TfOH</td>
<td>BSU</td>
<td>82</td>
</tr>
</tbody>
</table>

\textbf{Table 8}

The excellent yields attained for this allylation reaction are detailed in Table 9. The same arguments that are pertinent to the Sakurai reaction regarding the necessity of BSA and BSU, also apply here and are also covered in Section 3.8 where the use of just acid and no trialkylsilyl source is investigated for this reaction amongst others.

3.7 Reduction of Acetals to Ethers

This mild method for the reduction of acetals to ethers utilises triethylsilane as the reducing agent and, classically, TMSOTf as the catalyst. Various acetals have been reduced in excellent yield to their corresponding ethers using our methodology of
generating TMSOTf or TMSOFs in situ; the only problem encountered was the isolation and purification of the low molecular weight ethers.

![Scheme 22](image)

The results of the above Scheme 22 are given in Table 10.

<table>
<thead>
<tr>
<th>Acetal</th>
<th>Acid (a)</th>
<th>Silyl Source (b)</th>
<th>Product</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>(i)</td>
<td>FsOH</td>
<td>BSU</td>
<td>(86)</td>
<td>83</td>
</tr>
<tr>
<td>(ii)</td>
<td>TIOH</td>
<td>BSA</td>
<td>(87)</td>
<td>88</td>
</tr>
<tr>
<td></td>
<td>TIOH</td>
<td>BSU</td>
<td></td>
<td>85</td>
</tr>
<tr>
<td></td>
<td>FsOH</td>
<td>BSA</td>
<td></td>
<td>76</td>
</tr>
<tr>
<td></td>
<td>FsOH</td>
<td>BSU</td>
<td></td>
<td>97</td>
</tr>
<tr>
<td>(iii)</td>
<td>FsOH</td>
<td>BSU</td>
<td>(88)</td>
<td>82</td>
</tr>
</tbody>
</table>

Table 10

These reductions when performed with the direct use of TMSOTf are thought to proceed with the trialkysilyl moiety, originally from the catalytic amount of TMSOTf, playing the chain carrying role. The hydride ion, from triethylsilane, then acts as the nucleophile leading to the resultant reduction of the acetal to the ether. Naturally, our methodology is also applicable to these reactions.
The use of triflic acid as a catalyst in its own right in trialkylsilane reductions has precedent in the literature with reference to the ionic hydrogenation of alkenes. This kind of reduction generally proceeds rapidly in excellent yield.\textsuperscript{86} We reasoned that the aforementioned acetal reductions could theoretically be conducted in a like manner. This indeed proved to be the case as exemplified in Equation 54, which is, as far as we are aware, a new procedure for the reduction of acetals.

\[ \text{EtO} \text{OEt} + \text{Et}_3\text{SiH} \rightarrow \text{FsOH} \rightarrow \text{OEt} \text{ (86)} \]

Equation 54

The reduction of simple monofunctional compounds of this kind can be efficiently conducted with the use of fluorosulfonic acid as the catalyst in place of TMSOTf or TMSOFs; however where selective reduction is required with more sensitive multifunctional substrates the original system of generating TMSOTf or TMSOFs in situ is probably the best option. Mechanistically FsOH catalysed reductions have been rationalised to proceed in the following manner.

\[ \text{R} - \text{OMe} + 2 \text{FsOH} \rightarrow \text{R} - \text{OMe} + \text{MeOH}_2 \]

2 $\text{FSO}_3^-$

Scheme 23

3.8 The use of TfOH and FsOH as the Sole Catalytic Entities in Reactions Normally Catalysed by the Silyl Analogues

The success of the acetal reduction with only FsOH as the catalyst can conceivably be facilitated by the previously outlined mechanism, Scheme 23. Triethylsilylfluorosulfonate is formed in this process and gradually takes over itself as the catalyst in the reaction.
The previous set of reactions all share a common feature with the triethylsilane reduction, namely the presence of a trialkylsilyl moiety as a constituent part of one of the substrates. This raises the question as to whether these reactions can be catalysed solely by the acid, either TfOH or FsOH, thereby obviating the need for BSA or BSU. Representative reactions, Scheme 24, were chosen and instead of generating TMSOTf or TMSOFs in situ in the usual way only FsOH was added as the potential catalyst.

Scheme 24

Clearly then these results show that the interaction of BSA or BSU with TfOH or FsOH is essential if the above reactions are to be carried out in satisfactory yield. The SMS reaction proved to be the most successful of these FsOH catalysed reactions with a yield of 50% presumably because of the presence of two trimethylsilyl moieties amongst the substrates which could interact usefully with the acid. Nevertheless the yield for this reaction does not compare favourably with the excellent yields obtained with reactions catalysed by TMSOTf and TMSOFs generated in situ. The acetalisation reaction and the aldol-type reaction are even less satisfactory.
In conclusion then, TMSOTf catalysed reactions can best be carried out by generating TMSOTf or TMSOFs in situ from the interaction of TfOH or FsOH with either BSA or BSU. The reduction of acetals to ethers can best be accomplished by just using the acid as the catalyst.\textsuperscript{77,79}
Chapter 4

Scandium(III) and Copper(II) Trifluoromethanesulfonate (Triflate) Catalysed Reactions

4.1 Introduction

4.1.1 Scandium(III) Trifluoromethanesulfonate

Scandium(III) trifluoromethanesulfonate, Sc(OTf)$_3$, is a Lewis acid catalyst that has recently attracted much interest in its application to a variety of carbon-carbon bond forming reactions.

The chemical properties of elemental scandium are known to be intermediate between those of aluminium and those of the lanthanides. Sc(OTf)$_3$ is simply prepared by the treatment of scandium oxide (Sc$_2$O$_3$) with trifluoromethanesulfonic acid (TfOH), Equation 55.$^{87}$

\[
\text{Sc}_2\text{O}_3 + 6 \text{TfOH} \rightarrow 2 \text{Sc(OTf)}_3 + 3 \text{H}_2\text{O}
\]

Equation 55

Scandium triflate has been found to be an effective Lewis acid catalyst in various aldol reactions of aldehydes or acetals with silyl enolates. This chemistry has been reviewed by Shû Kobayashi who has also carried out much of the recent work.$^{88}$ The reactions proceed smoothly at $-78^\circ$C, or room temperature, and require only 5 mol\% of Sc(OTf)$_3$. The reactivity of Sc(OTf)$_3$ in these transformations was found to be greater than the lanthanide triflates. Furthermore, because Sc(OTf)$_3$ is stable in water it can perform these transformations in both aqueous and organic media. These unique characteristics are also enhanced by the fact that Sc(OTf)$_3$ was found to be almost quantitatively recoverable from the aqueous layer on completion of the reaction. The recovered catalyst was found to be effective in repeat reactions; comparable yields were produced on reuse of the Sc(OTf)$_3$. These features are illustrated by a representative example, Equation 56.
Kobayashi also investigated the use of Sc(OTf)₃ as a catalyst in Michael reactions of α,β-unsaturated ketones with silyl enolates. Again, only catalytic amounts of Sc(OTf)₃ are required to afford 1,5-dicarbonyl compounds (89), in high yield via a 1,4-addition process.⁸⁵ᵇ

**Equation 56**

Other chemical transformation catalysed by Sc(OTf)₃ include Diels-Alder reactions of carbonyl-containing dienophiles with cyclopentadiene,⁸⁹ as well as the allylation of carbonyl compounds with tetraallyltin to give homoallylic alcohols.⁸⁷

Recent developments include the use of Sc(OTf)₃ to activate imines for reaction with silyl enolates and dienes to afford the corresponding β-amino ester derivatives and Diels-Alder adducts.⁹⁰

Friedel-Crafts acylations, reactions which usually require quantitative amounts of conventional Lewis acid catalysts such as AlCl₃ or BF₃, have been performed using catalytic amounts of Sc(OTf)₃.⁹¹ These acylations of substituted benzenes with acid chlorides or anhydrides proceed smoothly in good yield, **Equation 58**.

**Equation 58**

The acylations are truly catalytic with only 0.01 equivalents of Sc(OTf)₃ required. In comparative studies Sc(OTf)₃ proved to be much more active than lanthanide triflate analogues in catalysing these acylation reactions. Furthermore, simple aqueous
extraction enables recovery of up to 95% of the Sc(OTf)₃ catalyst which upon re-use produced comparable yields to the first run.

The advantages of carrying out aqueous reactions of organic compounds in aqueous solutions go further than merely avoiding the use of potentially harmful organic solvents, although this in itself is advantageous. The solubility properties of certain substrates such as unprotected sugars or peptides mean that reactions in aqueous media are more suitable. Compounds containing water of crystallization are also more suited to reactions in aqueous media in order that tedious procedures for the removal of the water can be avoided. Although it is desirable to perform aqueous reactions in circumstances such as these, the fact that water is detrimental to many organic reactions can be problematic. Reagents such as conventional Lewis acids are particularly susceptible to moisture, with even moderate amounts of water being detrimental to the progress of the reaction. The requirement for water stable reagents in order to realise aqueous reactions, for whatever reason, is clearly self-evident. The unique properties of Sc(OTf)₃ make it a reagent of great potential and form the stimulus for our studies of Sc(OTf)₃ as a catalyst in Friedel-Crafts alkylation and cyclisation reactions.

4.1.2 Copper(II) Trifluoromethanesulfonate

The use of copper(II) trifluoromethanesulfonate, Cu(OTf)₂, is limited in comparison to Sc(OTf)₃. Cu(OTf)₂ has been used as catalyst in the dehydration of alcohols. The reaction performed under mild conditions requires only a catalytic amount of Cu(OTf)₂ to give high yields of the desired alkene product. Mechanistically it appears that Cu(OTf)₂ is behaving as a Lewis acid as the predominance of Saytzev oriented products indicates a carbocationic mechanism. The Lewis acid type interaction of the electron deficient copper with alcohols in this way leads to dehydration but potentially the formation of the carbocation can be exploited in other ways, namely attack by a nucleophile.
4.2 Sc(OTf)₃ and Cu(OTf)₂ as Friedel-Crafts Alkylation Catalysts

4.2.1 Alkylations with α-Hydroxyesters

The aforementioned unique properties of Sc(OTf)₃ in particular prompted a study of the suitability of both Sc(OTf)₃ and Cu(OTf)₂ as potential catalysts in the alkylation of arenes with α-hydroxyesters, reactions which have been previously catalysed by TMSOTf and equivalents, Section 2.2. The use of metal triflates like Zn(OTf)₂ with activated alcohols in the N-alkylation of tetrazoles has been reported by Fortin. The reaction can be carried out in dichloromethane but proceeds faster in the more polar acetonitrile. Substrates with an electron rich aryl moiety α– to the alcohol leaving group produce the best yields, with non activated non-aromatic alcohols such as dodecanol not reacting. These results suggest that an SN₁ type mechanism is operating in the latter reactions. The potential for metal triflates to act as Lewis acid catalysts in alkylation reactions with activated alcohols is therefore evident.

Our initial studies in this regard centred on the alkylation of 1,2-dimethylindole (90) with methyl (N-methylindolyl)hydroxyacetate (91). The formation of the cation (92) from this hydroxy ester is energetically favourable as conjugation effects from the lone pair on the indole nitrogen coupled with the general electron rich nature of indole stabilise this intermediate.

![Stabilised cation](image)

Scheme 25

Catalytic amounts of Zn(OTf)₂, Cu(OTf)₂ and Sc(OTf)₃ were all screened as potential catalysts for this alkylation. The reaction was carried out in dichloromethane at ambient temperature using 20 mol% of metal triflate catalyst. It was found that both Cu(OTf)₂ and Sc(OTf)₃ were highly effective in catalysing this alkylation with the formation of the product diarylacetate (93) in under thirty minutes. The stronger Zn(OTf)₂ resulted in a complex mixture of products and decomposition of the starting materials.
A summary of the yields obtained for this reaction are presented in Table 11. It can be seen that Cu(OTf)$_2$ being the stronger Lewis acid produces the marginally higher yield of 92% although yields of 88% and 89% with Sc(OTf)$_3$ indicates the suitability of this catalyst especially bearing in mind that it can be recycled. The reaction was complete in a matter of minutes at room temperature which compares favourably with the reactivity of TMSOTf and equivalent catalysts.

<table>
<thead>
<tr>
<th>Compound</th>
<th>M(OTf)$_n$</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>(93)</td>
<td>Sc(OTf)$_3$</td>
<td>88%</td>
</tr>
<tr>
<td>(93)</td>
<td>Cu(OTf)$_2$</td>
<td>92%</td>
</tr>
<tr>
<td>(93)</td>
<td>Recycled Sc(OTf)$_3$</td>
<td>89%</td>
</tr>
</tbody>
</table>

Table 11

In the present work the actual recovery of the Sc(OTf)$_3$ has been shown to be a simple process which typically involves treatment of the reaction mixture with water. The products from the reaction can then be extracted into an organic solvent, for example dichloromethane, with the Sc(OTf)$_3$ remaining in the aqueous phase. Recovery then of active catalyst simply requires removal of water. In our hands up to 87% of Sc(OTf)$_3$ was recoverable from reactions using this methodology while almost quantitative recovery of catalyst has been reported.$^{88}$

An analogous reaction using methylmandelate in the alkylation of N-methylindole was attempted. Although the phenyl moiety α- to the hydroxyl offers a degree of stabilisation for the formation of a cation, it did not have such a strong stabilising effect as the indole in the previous example. This was born out in the more forcing conditions that were necessary to effect the reaction and the lower yields that were obtained.
In a mechanistic investigation of this reaction methyl (S)-(−)-mandelate (96) was used in place of racemic methyl mandelate to alkylate N-methylindole under the same conditions. Optical rotation analysis of the product methyl (N-methyl-3-indolyl)-(phenyl)acetate (95) indicated that it was racemic. That is to say the reaction had proceeded via a planar cation that resulted in the consequent formation of a racemic product. This observed racemisation indicates that the reaction is proceeding via an SN1 mechanism which unfortunately precludes the use of the recently reported Lewis acid chiral catalyst system of Sc(OTf)3 co-ordinated to (R)-(−)-binaphthol and a tertiary amine that has been used with success in asymmetric Diels-Alder reactions.

For this type of chiral Lewis acid catalyst to be viable for our alkylation reactions, an SN2 type mechanism would probably have to be in operation.

A similar alkylation reaction involving the alkylation of 1,2-dimethylindole with an α-hydroxy amide (98) was also found to be catalysed by Sc(OTf)3 and Cu(OTf)2. The α-hydroxy amide (98) alkylation agent was synthesised in two steps as outlined in Scheme 26.
Preparation of α-hydroxy amide Alkylation Agent

Thus, treatment of N-methylindole with oxalyl chloride formed the intermediate acid chloride which was then reacted with (−)-α-methylbenzylamine in the presence of triethylamine, to furnish the required amide. Reduction of this (−)-α-methylbenzyl(N-methyl-3-indolyl)-glyoxamide (97) with sodium borohydride gave the hydroxyamide (98) in 86% yield.

Treatment of α-hydroxyamide (98) with Sc(OTf)₃ and Cu(OTf)₂ yielded the desired amide (99) in 59% and 71% respectively. It was found that the (−)-α-methylbenzylamine moiety did not exert any stereochemical influence on the newly formed chiral centre in these products.
4.2.2 Alkylations With Indole-3-methanol

Indole-3-methanol (100) was obtained by the reduction of the corresponding indole-3-carboxaldehyde with sodium borohydride in methanol.\cite{95}

\[
\text{Indole-3-carboxaldehyde} \xrightarrow{\text{NaBH}_4, \text{MeOH, 2h}} \text{Indole-3-methanol (100)} \quad \text{Yield 64%}
\]

Equation 62

Although easily prepared indole-3-methanol (100) is problematic in that it is prone to 'dimerisation' to 3,3'-di-indolylmethane (101) through exposure to acid or heat. This can be overcome by careful storage under refrigerated conditions in the presence of a small amount of triethylamine. Protonation and subsequent ionisation occurs so readily because of conjugation involving the indole nitrogen.\cite{96}

![Scheme 27](image-url)
In view of the oxophilic nature of both Sc(OTf)₃ and Cu(OTf)₂ and our success in using these reagents as catalysts in the alkylation of heterocycles with α-hydroxyesters and α-hydroxyamides we reasoned that the utility of these reagents could be extended further to include the alkylation of arenes with an alkylating agent like indole-3-methanol (100).

To this end Sc(OTf)₃ was added to a solution of indole-3-methanol (100) and 1,2-dimethylindole in dichloromethane at room temperature. Analysis of the reaction mixture by thin layer chromatography prior to the addition of the Sc(OTf)₃ catalyst did not indicate the formation of any product. This contrasted with the observed rapid formation of the 3,3'-(indole)-1,2-dimethylindolemethane (103) upon addition of the Sc(OTf)₃, indicating unequivocally that it had catalysed the reaction. Similarly Cu(OTf)₂ was also found to effectively catalyse this reaction in a slightly higher yield.

<table>
<thead>
<tr>
<th>Compound</th>
<th>M(OTf)ₙ</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>(103)</td>
<td>Sc(OTf)₃</td>
<td>49%</td>
</tr>
<tr>
<td>(103)</td>
<td>Cu(OTf)₂</td>
<td>53%</td>
</tr>
<tr>
<td>(103)</td>
<td>Recycled Sc(OTf)₃</td>
<td>52%</td>
</tr>
</tbody>
</table>

Table 12
The moderate yields obtained in this reaction with both \( \text{Sc(OTf)}_3 \) and \( \text{Cu(OTf)}_2 \) are not surprising. It is likely that some of the indole-3-methanol (100) was diverted by the process outlined in Scheme 27. Thin layer chromatography indicated the presence of di-3-indolylmethane although that product was not isolated from the complex reaction mixture. The reaction was also performed with recycled \( \text{Sc(OTf)}_3 \) yielding 3,3'-((indole)-1,2-dimethylindolemethane (103) in a similar yield.

An analogous reaction was carried out in which \( N \)-methylindole was alkylated to give 3,3'-((indole)-\( N \)-methylindolemethane (104), Equation 64. Similar yields were obtained for this reaction with \( \text{Cu(OTf)}_2 \) producing a marginally better yield.

![Chemical structure](image)

**Equation 64**

<table>
<thead>
<tr>
<th>Compound</th>
<th>( M(\text{OTf})_n )</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>(104)</td>
<td>( \text{Sc(OTf)}_3 )</td>
<td>56%</td>
</tr>
<tr>
<td>(104)</td>
<td>( \text{Cu(OTf)}_2 )</td>
<td>58%</td>
</tr>
</tbody>
</table>

**Table 13**

One can conclude that both \( \text{Sc(OTf)}_3 \) and \( \text{Cu(OTf)}_2 \) are effective catalysts for the alkylation of heterocycles with alcohols with \( \text{Cu(OTf)}_2 \) being the marginally more active catalyst. However, the recyclable nature of \( \text{Sc(OTf)}_3 \) is both industrially and economically important significant.

### 4.2.3 Alkylation with Benzyl Alcohol

The potential for these reagents to form other stabilised cations was examined. The simple benzylation of arenes with benzyl alcohol was investigated, Equation 65. Anisole was chosen as a substrate, because of its activation to electrophilic attack, while benzyl alcohol was chosen as the alkylating agent as it is known to form
stabilised cations. Nitromethane was used as solvent as polar aprotic solvents aid in the stabilisation of cations. A catalytic amount of Cu(OTf)2 (20 mol%), was added to a solution of benzyl alcohol in nitromethane. After addition of the anisole, the solution was heated at 100°C for 18 hours. Although some benzyl alcohol remained, the desired benzylated product (105) was formed in 90% yield.

\[
\text{OMe} + \text{PhCH} \xrightarrow{\text{Cu(OTf)}_2, 20 \text{ mol\%}, \text{MeNO}_2, 100^\circ\text{C}} \text{Bn}
\]

**Equation 65**

Although a mixture of alkylation products was obtained due to the formation of regioisomers, only a small amount of the di-alkylation product, with m/z=288 (M+), was detected by GC-mass spectrometry. The vast majority of product corresponded to the monoalkylated product (105) with m/z=198 (M+). Evidence from $^1$H and $^{13}$C nmr also confirmed the formation of the monoalkylated product (105). The reaction was repeated under identical conditions but with Sc(OTf)3 (20 mol%) in place of the Cu(OTf)2, however only unreacted starting materials were obtained. This agrees with our general finding that Cu(OTf)2 is a more powerful Lewis acid catalyst than Sc(OTf)3. Nevertheless this reaction demonstrates the suitability of Cu(OTf)2 as a Lewis acid catalyst for the Friedel-Crafts alkylation of anisole. Only catalytic amounts of Cu(OTf)2 are required and a predominance for the formation of the monoalkylated isomers is observed. This is of particular note as alkylations of this type activate the parent arenes to further alkylation and thus result in complex mixtures of di- and polyalkylated products.

Having established that catalytic amounts of Cu(OTf)2 result in formation of the benzyl cation from benzyl alcohol in nitromethane attempts to extend the scope of this alkylation to include other substrates did not meet with success. Surprisingly, electron rich heterocycles such as N-methylindole and 2-methylfuran could not be alkylated at all under similar conditions.
4.3 Modified Pictet-Spengler Cyclisations

Generally the Pictet-Spengler synthesis is an acid catalysed cyclisation that has been used extensively in the synthesis of isoquinolines. The cyclisation itself is essentially an electrophilic substitution reaction. The initial generation of an iminium ion which facilitates aminoalkylation has been achieved using a number of reagents. Besides the common use of hydrochloric acid, other cyclising reagents including sulphuric acid, acetic acid, phosphoryl chloride and phosphorus pentoxide have been used. A general outline of a classical Pictet-Spengler synthesis is given in Scheme 29, and involves the initial formation of an intermediate imine or Schiff base which on treatment with a cyclising agent forms an iminium ion which then reacts with the aromatic ring in the actual cyclisation step.

![Scheme 29]

The classical Pictet-Spengler synthesis has been subject to a number of procedural modifications. One such development, utilising the important developments in Mannich chemistry in general, is the use of an N-acyliminium ion (106) in place of the iminium ion (107).

![Figure 11]

N-acyliminium ions, by virtue of their carbonyl moiety making the associated imino carbon more electron deficient, are more electrophilic than iminium ions and hence
they are more reactive. This coupled with the fact that \(N\)-acyliminium ions are easily generated by various methods\(^97\) make their use in place of the conventional iminium ion in the Pictet-Spengler synthesis common place.\(^98\) The use of \(O,N\)-acetals based on alkoxy lactams as a precursor, is one such variation which has been employed, Scheme 30.\(^98\)

![Scheme 30](image)

This approach is exemplified by some recent work by Padwa in the boron trifluoride etherate catalysed synthesis of the tetrahydroisoquinoline (108) in 91% yield, Equation 66.\(^99\)

![Equation 66](image)

Another example involving cyclisation on to non-activated arenes in good yield serves to demonstrate the effectiveness of \(N\)-acyliminium ions as precursors in these Pictet-Spengler type reactions. Here, Frehel uses this methodology in the key step in the synthesis of praziquantel (109), Equation 67.\(^100\) In contrast, 'classical' Pictet-Spengler cyclisations involving iminium ions give poor yields with unactivated arenes.
The use of \( O,N \)-acetals in general and examples based on alkoxy lactams as precursors to these Pictet-Spengler cyclisations has been accomplished using a variety of reagents. Lewis acid catalysts such as TMSOTf and TiCl\(_4\)\(^{101}\) have been used as well as phosphorus-based reagents like pyrophosphoryl chloride (P\(_2\)O\(_3\)Cl\(_4\)) and phosphoryl chloride (POCl\(_3\))\(^{101}\).

With a view to developing new catalytic systems for this process and extending the synthetic utility of Sc(OTf)\(_3\) and Cu(OTf)\(_2\) we aimed to exploit the unique properties of these two reagents, especially the reusable nature of Sc(OTf)\(_3\).

The synthesis of the precursor \( O,N \)-acetals based on alkoxy lactams was readily accomplished by the treatment of the corresponding imines with a catalytic amount of sodium metal in methanol for a period of 48 hours at ambient temperature.\(^{102}\)
These readily accessible O,N-acetals based on alkoxy lactams were all prepared in excellent yield making them ideal substrates for the subsequent Pictet-Spengler cyclisations which were carried out using 20 mol% of the metal triflate catalyst in refluxing dichloromethane, Scheme 32.
Excellent yields, (90-96%), are attainable for the above Pictet-Spengler cyclisations with a 20% excess of pyrophosphoryl chloride over the precursor. However, the expense of using stoichiometric amounts of pyrophosphoryl chloride and the environmental problems associated with the disposal of the phosphorus residues make the development of other cyclising agents desirable. It was found that the cyclisation of the above precursors using a 20 mol% of either Sc(OTf)3 or Cu(OTf)2 resulted in the successful formation of the cyclised products, Table 14. Overall the yields, although good, did not match the excellent yields which have been reported with pyrophosphoryl chloride. The possible complexation of the metal triflate Lewis acids to the methoxy groups on the primary ring of the substrates could be responsible for these lower yields. This is because the complexation of Sc(OTf)3 or Cu(OTf)2 to the oxygen lone pairs on the 3,4-dimethoxyphenyl-precursors could have the effect of disfavouring cyclisation as total reversal of the electron-donating ability of the
methoxy groups is known to occur. The formation of the trihydro-β-carboline derivative (114) in such a high yield, (94%) with Cu(OTf)₂ supports this hypothesis as the precursor (110) does not possess any methoxy groups which could form a complex with the catalyst. In general, the yields obtained with Cu(OTf)₂ are greater than those obtained with Sc(OTf)₃ for the same substrate. This is in common with the previous results which also suggest that Cu(OTf)₂ is a more powerful Lewis acid catalyst than Sc(OTf)₃.

<table>
<thead>
<tr>
<th>Compound</th>
<th>M(OTf)ₙ</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>(114)</td>
<td>Cu(OTf)₂</td>
<td>94%</td>
</tr>
<tr>
<td></td>
<td>Sc(OTf)₃</td>
<td>56%</td>
</tr>
<tr>
<td>(115)</td>
<td>Cu(OTf)₂</td>
<td>56%</td>
</tr>
<tr>
<td></td>
<td>Sc(OTf)₃</td>
<td>54%</td>
</tr>
<tr>
<td>(116)</td>
<td>Cu(OTf)₂</td>
<td>73%</td>
</tr>
<tr>
<td></td>
<td>Sc(OTf)₃</td>
<td>76%</td>
</tr>
<tr>
<td>(117)</td>
<td>Cu(OTf)₂</td>
<td>64%</td>
</tr>
<tr>
<td></td>
<td>Sc(OTf)₃</td>
<td>61%</td>
</tr>
</tbody>
</table>

Table 14

In summary, it has been found that catalytic amounts of both Sc(OTf)₃ and Cu(OTf)₂ are effective in catalysing Friedel-Crafts type alkylations of various aromatic substrates with alcohols, hydroxy esters and hydroxy amides. They have also been found to be effective catalysts in the generation of acyliminium ions in Pictet-Spengler type cyclisations.

The tolerance of Sc(OTf)₃ to aqueous conditions does not merely mean simplified reaction conditions. It also means that the catalyst can be recovered with simple aqueous extractions. This enables its reuse in subsequent experiments to produce comparable yields. The reuse of Sc(OTf)₃ in this way has significant environmental, industrial, and economic implications. Potentially Sc(OTf)₃ could find application in similar synthetic transformations, with the advantages of using a truly catalytic, non-harmful, reusable reagent in place of more common Lewis acids such as AlCl₃ being obvious.
Chapter 5

Calix[4]resorcinarene Derivatives

5.1 Introduction

Calix[4]resorcinarenes are cyclic tetrameric structures which are part of the family of macromolecules known collectively as calixarenes. They are so named because of their resemblance in shape to a Greek vase or calix. It is this shape, sometimes referred to as basket-like, which has attracted interest as these easily assembled macromolecules have great potential as molecular hosts.\textsuperscript{104}

4.1.1 Preparation and Structure of Calix[4]resorcinarenes

Calix[4]resorcinarenes are, as the name suggests, derived from resorcinol as the arene component in the acid-catalysed reaction with an aldehyde. Much work in terms of the preparation and characterisation of these compounds has been undertaken by Högberg\textsuperscript{105a,b} with adaptation by Cram.\textsuperscript{105c} Significantly, this resorcinol-aldehyde reaction furnishes these calix[4]resorcinarenes as a single compound in high yield. This is remarkable considering that conformational and configurational factors mean that a large number of isomers are possible. This fourfold condensation of various aldehydes with resorcinol is represented simplistically in Equation 68.

\[
\text{HO-CH-CH-OH} + \text{RCHO} \xrightarrow{\text{H}^+ \text{Ehanol} / \text{H}_2\text{O}} \text{HO-CH-CH-OH} \quad \text{(118) R}
\]

Equation 68

Mechanistically, the reaction can be interpreted as a simple electrophilic aromatic substitution reaction. It is however not known whether cyclisation occurs from a simple hydroxymethyl linear tetramer or if cyclodimerisation of a pair of hydroxymethylated dimers occurs. The driving force behind the cyclisation is also unresolved. It is known that the eight extraannular hydroxyls cannot engage in circular hydrogen bonding although pairwise hydrogen bonding is possible and may play an important role in organizing the cyclisation.\textsuperscript{106}
A clearer representation of these octols (118) and one showing the $C_{4v}$ symmetry associated with the predominating stereoisomer is depicted in Figure 12.

![Figure 12](image)

This conformation with all the aryl groups uniformly pointing upwards represents the classical calix structure and is known as the 'cone' conformation. Its well-defined uniform geometry provides the basis for functionalisation to a variety of important compounds. The other possible conformations are thought to be; the 'flattened partial cone' which differs from the cone in having one of the aryl moieties pointing downwards, the '1, 3-alternate' with two opposite aryls pointing upwards and lastly the 'flattened partial cone'.

Studies by Högberg$^{105b}$ have shown that there is an equilibrium between the diastereomers. The predominating diastereomer, the all-cis isomer, being the thermodynamic product can be isolated virtually exclusively after about ten hours from the reaction mixture.

It should be noted that it is a structural feature of these calix[4]resorcinarenes that the eight hydroxyl groups occupy exo-positions relative to the calix ring. This is as a consequence of the inherent structural features of the calix as the resorcinol units joined via alkylidene bridges at the 4,6-positions simply direct the hydroxyl groups outwards. This has important implications as it means that cyclic intramolecular hydrogen bonding does not occur which is in contrast to calixarenes derived from $p$-substituted phenols which have all the hydroxyl groups in endo-positions thereby enabling them to form cyclic intramolecular hydrogen bonds. The eight hydroxyl groups which form the hydrophilic rim of calix[4]resorcinarenes are however capable of hydrogen bonding in that four independent sites are available for the bonding of guests.$^{107}$
5.1.2 Complex Formation with Calix[4]resorcinarenes

Aoyama's C-undecylcalix[4]resorcinarene (119), Figure 13, the homologue derived from dodecanal as the aldehyde component in the condensation reaction with resorcinol, is an important member of the series.

\[
R = (\text{CH}_2)_\text{10} \cdot \text{Me}
\]

C-undecylcalix[4]resorcinarene

Figure 13

Initially simple complexation studies of this lipophilic host with a variety of non-ionic polar hosts were examined. The more important challenge of molecular recognition was then undertaken with C-undecylcalix[4]resorcinarene (119) being utilised by Aoyama to form selective hydrogen bonded complexes to sugars such as ribose in apolar organic solvents. Ribose was bound to (119) highly selectively in the \(\alpha\)-pyranose form with discrimination between pyranose and furanose and crucially between \(\alpha\)- and \(\beta\)-anomers. C-undecylcalix[4]resorcinarene (119), in its capacity as a multidentate host has also been used to form a two-point hydrogen bonded fixation with dicarboxylic acids in a remarkably selective manner.

5.2 Functionalisation of Calix[4]resorcinarene

Calix[4]resorcinarenes having inherently uniform, well-defined geometry inevitably lend themselves to functional elaboration as they provide an excellent platform on which to synthesise important compounds.

To date the functionalisation of calix[4]resorcinarenes has been limited to a few examples despite the obvious potential. Leigh treated C-phenylcalix[4]resorcinarene with dipropylamine and paraformaldehyde leading to the formation of the cavitand (120).
The Mannich base (120) is chiral by virtue of having a helical nature. This arises because the hydrogen bonding between the resorcinol hydroxyl groups and the aminoalkyl group (OH···N) has to be unidirectional in each molecule otherwise a hydrogen bond is lost which would mean a structure of significantly higher energy. The helical nature of this cavitand is obviously something that has potential in terms of discrimination between chiral guest molecules.

In a similar vein, work by Matsushita,¹¹² again utilising a Mannich reaction to aminomethylete the calix[4]resorcinarene with a variety of primary and secondary amines led to the formation of similar helical structures, Figure 15.

The helical nature is more clearly evident from this plan view. The origin of this helicity is presumably attributable to similar hydrogen bonding interactions to those
outlined for (120). In other words the initial aminomethylation step is identical and serves to set up the energetically favourable helix. The formation of the benzoxazine ring can then only proceed in one way thereby preserving the unidirectional nature of the structure. The benzoxazine ring in structure (121) serves to fix the direction of the helix whereas the helix in the tetraamine (120) is merely held in place by hydrogen bonding.

As an extra dimension to this work, and in keeping with our general theme of using chiral auxiliaries, we decided to synthesise helical calix[4]resorcinarenes similar to benzoxazines (121) but with chiral primary amines.

Using standard literature conditions,\textsuperscript{105} outlined in Equation 68, the following calix[4]resorcinarenes were prepared ready for functionalization.

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>R</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>C\textsubscript{5}H\textsubscript{11}</td>
<td>78%</td>
</tr>
<tr>
<td>Me</td>
<td>74%</td>
</tr>
<tr>
<td>C\textsubscript{11}H\textsubscript{23}</td>
<td>54%</td>
</tr>
<tr>
<td>Ph(CH\textsubscript{2})\textsubscript{2}</td>
<td>65%</td>
</tr>
</tbody>
</table>

**Table 15**

With these readily accessible calix[4]resorcinarenes in hand, functional elaboration was achieved by carrying out aminomethylation under Mannich conditions using paraformaldehyde and either (R)-(\textsuperscript{+})-\(\alpha\)-methylbenzylamine or (S)-(\textsuperscript{-})-\(\alpha\)-methylbenzylamine as the chiral primary amine.
Details of the chemical yield and the rotation of the various analogues that were synthesised are given in Table 16.

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>α-Methylbenzylamine</th>
<th>% Yield</th>
<th>$[\alpha]_D^{25}$ c=0.05, CHCl₃</th>
</tr>
</thead>
<tbody>
<tr>
<td>(124)</td>
<td>Me</td>
<td>(R)</td>
<td>57</td>
<td>+132</td>
</tr>
<tr>
<td>(125)</td>
<td>Me</td>
<td>(S)</td>
<td>64</td>
<td>-130</td>
</tr>
<tr>
<td>(126)</td>
<td>C₅H₁₁</td>
<td>(R)</td>
<td>79</td>
<td>+118</td>
</tr>
<tr>
<td>(127)</td>
<td>C₅H₁₁</td>
<td>(S)</td>
<td>74</td>
<td>-116</td>
</tr>
<tr>
<td>(128)</td>
<td>Ph(CH₂)</td>
<td>(R)</td>
<td>81</td>
<td>+122</td>
</tr>
<tr>
<td>(129)</td>
<td>Ph(CH₂)</td>
<td>(S)</td>
<td>73</td>
<td>-124</td>
</tr>
<tr>
<td>(130)</td>
<td>C₁₁H₂₃</td>
<td>(R)</td>
<td>79</td>
<td>+112</td>
</tr>
<tr>
<td>(131)</td>
<td>C₁₁H₂₃</td>
<td>(S)</td>
<td>68</td>
<td>-110</td>
</tr>
</tbody>
</table>

Table 16

These tetrakis(dihydro-1,3-benzoxazines) were all formed in excellent yields and significantly the $^1$H and $^{13}$C NMR spectra indicated that the product was formed with very high diastereoselectivity as only one diastereomer was detected.
The use of (R)-(+)\(\alpha\)-methylbenzylamine and (S)-(\(-\))\(\alpha\)-methylbenzylamine furnished analogues (122) and (123) that are related as enantiomers (they have identical \(^1\)H and \(^{13}\)C NMR spectra and rotated the plane of plane polarised light in opposite directions but with equal magnitude). As these pairs of analogues are related as enantiomers and knowing the fixed stereochemistry of the chiral \(\alpha\)-methylbenzylamine it follows that the helicity of the two analogues must be of an opposite sense otherwise a diastereomeric relationship would be observable.

\[ R, R \quad \text{Enantiomers} \]

\[ S, R \]

\[ R, S \]

\[ S, S \]

Scheme 33

As the reaction only forms these tetrakis(dihydro-1,3-benzoxazines) with all four benzoxazine rings in the same sense it follows that there are four possible isomers. For simplicity, the stereochemistry of the calix is defined as R when the direction of groups around the upper rim is clockwise, and S when the direction is anti-clockwise. Taking the C-methylcalix[4]resorcinarene as an example, Scheme 33, it can be seen that the experimental observation of pairs of enantiomers (124) and (125) must either
be the S,S and R,R pairing (i.e. the stereochemistry of the helix and the α-methylbenzylamine are the same) or the R,S and S,R pairing where the stereochemistry of the helix and the α-methylbenzylamine are opposite. The corollary of this being that pairs of products with diastereomeric relationships are not observed.

Further structural investigation of these calix[4]resorcinarene tetrakis(dihydro-1,3-benzoazines) was undertaken with an X-ray structure being obtained for the analogue derived from C-hexanalcalix[4]resorcinarene and (R)-(+-)-α-methylbenzylamine (126). Crystallisation was achieved from a (1:1) mixture of diethyl ether and dichloromethane thereby allowing the helicity of the structure to be established, Figure 16.

The X-ray crystallographic studies, carried out by Alex Slawin, shows this enantiomer to be the S,R as the sense of the helix is clearly anticlockwise and the fixed stereochemistry of the (R)-(+-)-α-methylbenzylamine is also observable. A plan view of the same crystal structure, Figure 17, serves to highlight the anticlockwise sense of the helix.
Having established the anticlockwise helicity and knowing that this tetrakis(dihydro-1,3-benzoxazine analogue (126) is derived from C-hexanalcalix[4]resorcinarene and (R)-(−)-α-methylbenzylamine then it clearly is the S,R enantiomer. The other enantiomer obtained with (S)-(−)-α-methylbenzylamine is therefore the R,S enantiomer, that is to say, it posses a clockwise helix.

In conclusion, the formation of these tetrakis(dihydro-1,3-benzoxazine) derivatives proceeds via a highly diastereoselective process possibly involving a similar hydrogen bonding process to that outlined by Leigh in the formation of his Mannich base cavitands (120), Figure 14. It is thought that a combination of this hydrogen bonding effect and a steric gearing effect by the chiral auxiliary act in tandem to produce this chiral cone structure. Specifically the initial aminoalkylation with hydrogen bonding between one of the phenolic residues and the aminoalkyl group acts in synergy with the steric gearing effect to set up the helicity. The chiral secondary amine must be ultimately responsible for the sense of the helix as the two products are enantiomers. The effect of this steric gearing has a cascade effect round the calix so that ultimately the closure of the dihydro-1,3-benzoxazine ring can only occur in one sense leading to this 'locked' helical structure.

5.3 Acid Catalysed Epimerisation Reactions

Having synthesised these helical chiral tetrakis(dihydro-1,3-benzoxazine) calix[4]resorcinarene derivatives their application as potential discriminating hosts was investigated. The chiral nature of these potential hosts together with their four phenolic groups as potential hydrogen bonding sites being particularly attractive features. In view of the previously mentioned work by Aoyama Figure 13, that
involved C-undecylicalix[4]resorcinarene (119) acting as a multidentate host via hydrogen bonding to dicarboxylic acids in a remarkably selective manner, a similar investigation involving our tetrakis(dihydro-1,3-benzoxazine) calix[4]resorcinarene derivatives was undertaken. Initially we chose to use glutaric acid (0.04 mmol) and the compound (126, R= C5H11) (0.04 mmol) as the potential host in an NMR experiment in CDCl3. The 13C NMR spectrum, taken after a period of twelve hours, showed duplication for almost every carbon in the original spectrum. The 1H NMR spectrum also showed additional resonances. The key feature of the 1H NMR spectrum is the A-B quartet $\delta_H = 4.96$ and $5.15$ ppm ($J = 10.2$ Hz) for the diastereotopic protons between the oxygen and nitrogen atoms in the dihydrobenzoxazine rings. It was this quartet that proved to be diagnostically important, as the acid treated sample clearly showed an additional A-B quartet centred at 4.77 and 5.06 ppm ($J = 10.0$ Hz) [1H NMR spectrum ii] which corresponds to the diastereomer of compound (126, R= C5H11).

\[
\begin{array}{ccc}
\text{i) } & \text{ii) } \\
\end{array}
\]

Part of the $^1$H nuclear magnetic resonance spectra for the compound (2) taken (i) on the crude reaction product and (ii) after leaving with normal CDCl3 for eight days.

Figure 18

The ratio of the two diastereomers after 12h was ca. 4:1; with further epimerisation taking place the ratio decreased to ca. 2:1 after 48h. This ratio remained constant within the experimental error of the nmr experiment with no further changes in the NMR ratio being observed after a further week.
Similarly the exposure of these tetrakis(dihydro-1,3-benzoxazine) calix[4]resorcinarene derivatives to CDCl₃ for prolonged periods also led to epimerisation. This problem can be overcome by recording the nmr spectra for these compounds in acid free CDCl₃. This can be achieved by passing the solvent through a pad of sodium hydrogen carbonate prior to dissolving the sample. Confirmation of the epimerisation process is reflected in the values recorded for the specific rotation of compound (126, R= C₅H₁₁) in CDCl₃, Table 17.

<table>
<thead>
<tr>
<th>Time / days</th>
<th>[α]ᵢ₂⁵ (c= 0.5, CDCl₃)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>+130</td>
</tr>
<tr>
<td>2</td>
<td>+120</td>
</tr>
<tr>
<td>3</td>
<td>+112</td>
</tr>
<tr>
<td>7</td>
<td>+80</td>
</tr>
</tbody>
</table>

Table 17

The specific rotation value reached a low of +80 after seven days and remained constant with time thereafter. A plausible mechanism for this epimerisation process is shown below, Scheme 34.

Although the epimerisation process is presumably random the simplicity of the ¹H and ¹³C NMR spectrum, Figure 18 ii, indicates the presence of only two diastereomers, compound (126, R= C₅H₁₁) and its diastereomer with the direction of the calix reversed. The presence of only two isomers can be rationalised in terms of the energetics. The two products due to the gearing process have a uniform...
arrangement of the dihydro-1,3-benzoxazine rings thereby preserving the helicity. The two products can be presumed to be in energy wells with the unequal ratio being attributed to differences in their thermodynamic stability. This in turn, is thought to be due to differences in the efficiencies of the gearing process in the two diastereomers. In contrast, the other four possible random arrangements that can be obtained on acid catalysed ring opening and closing of the four dihydro-1,3-benzoxazine rings are at too higher an energy to be formed due to unfavourable steric interaction of the gearing process and are therefore not observed.

In another attempt at utilising these tetrakis(dihydro-1,3-benzoxazine) calix[4]resorcinarene derivatives as potential discriminating hosts racemic mandelic acid (0.04 mmol) and compound 126, (R= C5H11) (0.04 mmol), as the potential host, were stirred together in CDCl3 in an NMR experiment. The 1H NMR spectrum of this mixture indicated shifts in the methine proton of mandelic acid from 5.25 ppm in the normal unbound form to 5.18 ppm on exposure to compound 126, (R= C5H11). Further evidence for some sort of co-ordination was evident by the disappearance of the phenolic proton of compound 126, (R= C5H11) from 7.68 ppm indicating that a hydrogen bonding interaction had occurred. This co-ordination was however academic as the acidic conditions resulted in the epimerisation of compound 126, (R= C5H11) as in the previous case. Obviously this acid catalysed epimerisation complicates any useful host guest interactions and precludes the use of these particular chiral tetrakis(dihydro-1,3-benzoxazine) calix[4]resorcinarene derivatives as potential reagents for the resolution of racemic compounds under acidic conditions.

5.4 Attempted Functionalisations

5.4.1 O-Methylation

These tetrakis(dihydro-1,3-benzoxazine) calix[4]resorcinarene derivatives are generally stable compounds, remaining homogeneous after prolonged periods of storage provided they are not exposed to acidic conditions. Initial attempts to functionalise these compounds centred around overcoming this sensitivity to acidic conditions. The strategy involved the methylation of the four phenolic groups on the calix which although not preventing acid protonation of the four dihydro-1,3-benzoxazine rings would prevent any epimerisation as the helix would effectively be 'locked'.

91
Various approaches to effect this methylation were investigated for several of the tetrakis(dihydro-1,3-benzoxazine) calix[4]resorcinarenes which are summarised in Table 18.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>(a) conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>122, (R = C_{11}H_{23})</td>
<td>KOH, Mel, DMSO</td>
</tr>
<tr>
<td>122, (R = Me)</td>
<td>CH$_2$N$_2$</td>
</tr>
<tr>
<td>123, (R = C$<em>5$H$</em>{11}$)</td>
<td>K$_2$CO$_3$, Mel, Acetone</td>
</tr>
</tbody>
</table>

Table 18

The use of MeI as the alkylating agent with potassium hydroxide under polar aprotic conditions using dimethylsulfoxide did not result in any $O$-methylation despite refluxing the mixture for twelve hours. Only unreacted starting material was recovered. It is possible that the steric crowding around the four phenolic groups of the calix[4]resorcinarene could have contributed to this lack of reactivity. Literature precedence for the $O$-methylation of the phenolic groups of calixarenes in general features the use of a weaker base, potassium carbonate, with MeI as the alkylating agent in acetone.$^{113}$ Duplication of these conditions in an effort to form the tetramethyl ether of 122 (R = C$_5$H$_{11}$) again resulted in no $O$-methylation and recovery of the starting material. This seems to suggest, that the lack of reactivity is, as previously mentioned, due to steric crowding of the four phenolic groups by the dihydro-1,3-benzoxazine rings with associated $\alpha$-methylbenzylamine moieties. The use of diazomethane as a reagent for the $O$-methylation of phenols is well known to be high yielding under mild conditions. The sterically unencumbered and highly reactive carbene species was therefore thought suitable for our purposes. A measure of success was achieved in that although a complex mixture of products was obtained
evidence for the formation of a methyl ether was detected by $^1$H NMR and I.R. spectroscopy. The presence of unreacted starting material as well indicated that partial $O$-methylation could be occurring thereby producing a complex mixture of products. In an effort to address this problem a large excess of an ether solution of diazomethane ca. (33 mmol) to 122, (R= Me) (0.1 mmol) was stirred at 25°C for up to 3 days but this did not result in complete reaction of the substrate. Attempts at purification of the reaction mixture did not enable isolation of any of the desired tetramethylether (132).

5.4. 2 Esterifications

Following the same strategy of functionalising the four phenolic groups on the calix as a means of preventing acid catalysed epimerisation, standard conditions were employed in a bid to effect esterification of the phenolic groups. Compound 122, (R= C$_5$H$_{11}$) (0.1 mmol) and acetyl chloride (5 mmol) were stirred together in a co-solvent system of toluene and triethylamine along with a catalytic amount of dimethylaminopyridine. Analysis of the reaction by thin layer chromatography and $^1$H NMR spectroscopy indicated quite rapid decomposition of the substrate.

$$\text{Equation 71}$$

In similar studies where acetic anhydride was employed in place of acetyl chloride rapid decomposition of the substrate also occurred. The failure of these esterifications can be attributed to the instability of dihydro-1,3-benzoxazines in general towards electrophiles. 114

5.5 Conclusion

Our studies 115 on Mannich reactions of a number of calix[4]resorcinarene derivatives with (R)-(+)-$\alpha$-methylbenzylamine lead to the formation of single diastereomeric tetrakis(dihydro-1,3-benzoxazine) derivatives in high yields, studies which have also recently been confirmed independently by Böhmer. 116 The absolute configuration of
the helix in the tetrakis(dihydro-1,3-benzoxazine) (126), derived from C-hexanalcalix[4]resorcinarene and (R)-(+)−α-methylbenzylamine, was determined by X-ray crystallographic analysis. Reactions involving (S)-(−)-α-methylbenzylamine yielded the other enantiomer.

These products were found to react with protic acids to afford an equilibrium mixture of diastereomers. Attempts to functionalise these compounds centred around overcoming this sensitivity to acidic conditions. The strategy involved the attempted functionalisation of the four phenolic groups on the calix. Unfortunately attempts at such functionalisations did not meet with any success.
Chapter 6

Experimental

6.1 General Information About Procedures

Solvents and Reagents

The solvents were dried, distilled and stored over 4Å molecular sieves unless stated otherwise.

dichloromethane: distilled from phosphorus pentoxide,
diethyl ether: distilled from calcium chloride and stored over sodium wire,
DMSO: dried over calcium hydride for 12 h, decanted and distilled under reduced pressure,
ethanol: distilled from magnesium turnings and iodine,
ethyl acetate: distilled from calcium chloride,
methanol: distilled from magnesium turnings and iodine,
petroleum ether: distilled from calcium chloride,
toluene: distilled from phosphorus pentoxide,
triethylamine: distilled from and stored over potassium hydroxide.

Chromatographic Procedures

Analytical thin layer chromatography (TLC) was carried out using aluminium backed plates coated with Merck Kieselgel 60 GF254. Flash chromatography was carried out using Kieselgel 60 H silica or Matrex Silica 60.

Spectroscopic Techniques

Infrared spectra were recorded in the range 4000-600 cm\(^{-1}\) using a Nicolet FT-250 spectrometer. Spectra were recorded as either liquid films between sodium chloride plates or as a nujol mull. \(^1\)H and \(^13\)C NMR spectra were recorded using Bruker AC-250 and Bruker WH-400 instruments. The samples were dissolved in deuterated chloroform with all values quoted in ppm relative to the internal standard, tetramethylsilane. Signals are described as singlets (s), doublets (d), triplets (t), quartets (q) etc. Coupling constants \(J\) are reported when possible in (Hz). Diastereomer ratios were obtained by integration of suitable peaks in the proton NMR
spectrum of the unseparated product. Mass spectra were recorded on a Kratos MS-80 spectrometer by electron impact.

**Other Data and Instrumentation**

Melting points were recorded on Reichert-Kofler hot stage apparatus or with an Electrothermal digital melting point apparatus and are uncorrected. Optical rotations were measured using an Optical Activity Ltd. polarimeter, with a 10 cm cell and chloroform as the solvent at 25°C. Elemental analyses were carried out on a Perkin Elmer 2400 Elemental Analyser.

The following experiments were carried out under an atmosphere of nitrogen unless obviously unnecessary.

### 6.2 Experimental for Chapter 2

(-)-S-Phenylmenthyl (N-methyl-3-indoly)hydroxyacetate

![Chemical Structure](image)

(-)-S-Phenylmenthyl (N-methyl-3-indoly)hydroxyacetate (49) as a viscous colourless oil (0.356g, 96%); Found M⁺, 419.2448 C27H33N03 requires 419.2460; \( \nu_{\text{max}}/\text{cm}^{-1} \) 1723 (ester C=O), 3507 (OH); (major diastereomer) \( \delta_H \) (250 MHz; CDCl₃) 0.71-2.03 (8H, m), 0.85 (3H, d, \( J=6.13 \) Hz), 0.89 (3H, s), 0.96 (3H, s), 2.40 (1H, broad), 3.69 (3H, s), 4.82 (1H, dt, \( J=4.33 \) and 10.68 Hz), 5.13 (1H, s), 7.06-7.24 (9H, m), 7.61 (1H, m); \( \delta_C \) (62.9; CDCl₃) 21.71 (CH₃), 26.08 (CH₃), 26.25 (CH₃), 26.85 (CH₂), 31.32 (CH), 32.69 (N-CH₃), 34.42 (CH₂), 39.68 (C), 41.52 (CH), 50.32 (CH), 68.05 (CH), 76.82 (CH), 109.17 (CH), 112.65 (C), 119.57 (CH),
Trimethylsilyl triflate (111mg, 0.50 mmol) was added to a solution of (-)-8-phenylmenthyl (N-menthyl-3-indolyl)hydroxyacetate (49) (105mg, 0.25 mmol) and N-benzylpyrrole (78mg, 0.50 mmol) in dichloromethane (30 cm³) at -78 °C. After 0.5 hours at this temperature the reaction mixture was treated with a saturated aqueous solution of sodium hydrogencarbonate (30 cm³), extracted with dichloromethane (3x30 cm³), dried over (MgSO₄) and the solvent evaporated. Flash chromatography on silica gel eluting with diethyl ether-light petroleum (1:5) gave (-)-8-phenylmenthyl (N-benzyl-2-pyrrolyl)-(N-menthyl-3-indolyl)acetate (50) as a viscous yellow oil (130mg, 93%); Found M⁺ 558.3251 C₃₈H₄₂N₂O₂ requires 558.3246; νmax/cm⁻¹ 1733 (ester C=O); δH (400 MHz; CDCl₃) 0.76-1.03 (3H, m), 0.83 (3H, d, J=6.5Hz), 1.12 (3H, s), 1.14 (3H, s), 1.40-1.56 (3H, m), 1.86-1.94 (2H, m), 3.69 (3H, s), 4.60 (1H, s), 4.77 (1H, d x t, J=4.4 and 10.7Hz) 4.92 (2H, br), 6.05-6.06 (1H, m), 6.08-6.10 (1H, m), 6.56-6.57 (1H, m), 6.87-7.27 (15H, m) ppm; The minor diastereomer showed diagnostic resonances at δH (CDCl₃) 0.76 (3H, d, J=6.5Hz), 1.06 (3H, s), 1.12 (3H, s), 3.61 (3H, s), 4.80 (1H, s), 4.86 4.90 (2H, AB q, J=13.8Hz) ppm.; δC (62.9 MHz; CDCl₃) 21.73 (Me), 25.93 (Me), 26.75 (CH₂), 27.03 (Me), 31.15 (CH), 32.62 (N-Me), 34.45 (CH₂), 39.79 (C), 40.83 (CH), 40.85 (CH₂), 50.19 (N-CH₂), 50.32 (CH), 75.51 (CH), 107.23 (CH), 108.25 (CH), 109.00 (CH), 110.52 (C), 118.81 (CH), 119.12 (CH), 121.36 (CH), 121.81 (CH), 124.94 (2x CH), 125.41 (2x CH), 126.48 (2x CH), 126.92 (C), 127.12 (CH), 127.81 (2x CH), 128.33 (CH), 128.40 (2x CH), 129.88 (C), 136.76 (C), 138.10 (C), 151.01 (C), 170.97 (C=O) ppm.

(-)-8-Phenylmenthyl (N-benzyl-2-pyrrolyl)-(N-menthyl-3-indolyl)acetate

![Chemical structure of (-)-8-Phenylmenthyl (N-benzyl-2-pyrrolyl)-(N-menthyl-3-indolyl)acetate](image)
Pyrophosphorylchloride (0.049g, 0.20 mmol) was added dropwise to a stirred solution of (-)-8-phenylmenthyl (N-menthyl-3-indolyl)hydroxyacetate (49) (0.075g, 0.178 mmol) and 1,2-dimethylindole (0.051g, 0.356 mmol) in dichloromethane (30 cm³) at –83°C. The reaction mixture was then gradually allowed to warm to a temperature of –30°C over a period of 45 minutes before being quenched by the addition of a saturated aqueous solution of sodium hydrogencarbonate (30 cm³), extracted with dichloromethane (3x30 cm³), dried over (MgSO₄) and the solvent evaporated. Flash chromatography on silica gel eluting diethyl ether-light petroleum (b.p. 40-60°C) (1:4) gave (-)-8-phenylmenthyl (N-methyl-3-indolyl)-(1,2-dimethyl-3-indolyl)acetate (51) as colourless needle-like crystals, (0.084g, 68%); mp=186-187°C; (Found: C, 81.25; H, 7.75; N, 5.29, C₃₇H₄₂N₂O₂ requires C, 81.32; H, 7.69; N, 5.13 %); Found: M⁺, 546.3298, C₃₇H₄₂N₂O₂ requires 546.3246; v_max/cm⁻¹ 1721 (ester C=O); δH (400 MHz; CDCl₃) 0.58 (1H, q, J=12.16 Hz), 0.71 (3H, d, J=6.48), 0.83 (2H, m), 1.07 (1H, dq, J=2.92 and 12.78 Hz), 1.24 (3H, s), 1.33 (3H, s), 1.54-1.68 (3H, m), 1.96 (1H, dt, J=3.32 and 12.27 Hz), 2.25 (3H, s), 3.61 (3H, s), 3.72 (3H, s), 4.72 (1H, s), 4.83 (1H, dt, J=4.42 and 10.68 Hz), 6.99-7.30 (12H, m), 7.35 (1H, d, J=7.92 Hz), 7.55 (1H, d, J=7.92 Hz); δC (62.9; CDCl₃) 10.39 (Me), 21.55 (Me), 25.25 (Me), 26.50 (CH₂), 27.41 (Me), 29.34 (N-Me), 31.02 (CH), 32.61 (N-Me), 34.39 (CH₂), 39.49 (CH), 39.57 (C), 40.65 (CH₂), 50.14 (CH), 74.67 (CH), 108.09 (CH), 108.17 (C), 108.89 (CH), 112.07 (C), 118.42 (CH), 118.55 (CH), 119.12 (CH), 119.26 (CH), 120.13 (CH), 121.09 (CH), 124.87 (CH), 125.34 (2 x CH), 126.80 (C), 127.36 (C), 127.81 (CH), 127.86 (2 x CH), 133.69 (C), 136.30 (C), 136.80 (C), 151.71 (C), 172.13 (C=O) ppm.
Pyrophosphorylchloride (0.049g, 0.20 mmol) was added dropwise to a stirred solution of (-)-8-phenylmenthyl (N-menthyl-3-indolyl)hydroxyacetate (49) (0.075g, 0.178 mmol) and (R)-N-(1-phenethyl)pyrrole (0.050g, 0.267 mmol) in dichloromethane (30 cm$^3$) at -83°C. The reaction mixture was then gradually allowed to warm to a temperature of -50°C over a period of 30 minutes, before being quenched by the addition of a saturated aqueous solution of sodium hydrogencarbonate (30 cm$^3$), extracted with dichloromethane (3x30 cm$^3$), dried over (MgSO$_4$) and the solvent evaporated. Flash chromatography on silica gel eluting with diethyl ether-light petroleum (b.p. 40-60°C) (1:4) gave (-)-8-phenylmenthyl N-(1-phenylethyl)-2-pyrrolyl-(N-methyl-3-indolyl)acetate (52) as a light yellow oil, (0.097g, 93%); Found: M$^+$ 572.3415, C$_{39}$H$_{44}$N$_2$O$_2$ requires 572.34026; $\nu_{\text{max/cm}^{-1}}$ 1724 (ester C=O); $\delta$H (400 MHz; CDCl$_3$) 0.82-1.09 (3H, m), 0.85 (3H, d, J=6.48 Hz), 1.16 (3H, s), 1.19 (3H, s), 1.53-1.63 (3H, m), 1.71 (3H, d, J=7.04 Hz), 1.88-1.93 (1H, m), 1.97-2.04 (1H, m), 3.65 (3H, s), 4.55 (1H, s), 4.82 (1H, dt, J=4.24 and 10.72 Hz), 5.29 (1H, q, J=7 Hz), 5.93 (1H, m), 6.07 (1H, t, J=3.24 Hz), 6.77 (1H, m), 6.80-6.92 (4H, m), 6.99-7.03 (3H, m), 7.09-7.13 (3H, m), 7.17-7.25 (7H, m); $\delta$C(62.9; CDCI$_3$) 21.70 (CH$_3$), 22.42 (CH$_3$), 26.18 (CH$_3$), 26.58 (CH$_3$), 26.72 (CH$_2$), 31.18 (CH), 32.55 (CH), 34.49 (CH$_2$), 39.70 (C), 40.72 (N-Me), 41.10 (CH$_2$), 50.53 (CH), 54.30 (CH), 75.46 (CH), 107.02 (CH), 108.52 (CH), 108.78 (CH), 110.17 (C), 117.94 (CH), 118.58 (CH), 119.16 (CH), 121.19 (CH), 124.93 (CH), 125.38 (2 x CH), 125.67 (2 x CH), 126.82 (CH), 126.92 (C), 127.81 (2 x CH), 128.24 (2 x CH), 128.29 (CH), 128.47 (C), 130.11 (C), 136.61 (C), 143.39 (C), 151.21 (C), 171.07 (C=O, ester) ppm.
Sodium borohydride (0.25g, 6.75 mmol) was added portionwise to a solution of (-)-8-phenylmenthyl (N-benzyl-2-pyrrolyl)glyoxylate\textsuperscript{118} (1.0g, 2.25 mmol) in methanol (40 cm\textsuperscript{3}) at 0°C. The solution was then stirred at room temperature for 20 minutes before the reaction was quenched by the addition of water (20 cm\textsuperscript{3}). The crude product was then extracted with dichloromethane (3x30 cm\textsuperscript{3}), dried (MgSO\textsubscript{4}) and the solvent evaporated. Flash chromatography on silica gel eluting with diethyl ether-light petroleum (1:19) gave \textit{(-)-8-phenylmenthyl (N-benzyl-2-pyrrolyl)hydroxyacetate} \textsuperscript{(53)} as a viscous yellow oil (0.49g, 49 %), Found M\textsuperscript{+} 445.2619 C\textsubscript{29}H\textsubscript{35}N\textsubscript{3}O\textsubscript{3} requires 445.26168; $\nu_{\text{max}}$/cm\textsuperscript{1} 1731 (ester C=O); $\delta_{\text{H}}$ (250 MHz; CDCl\textsubscript{3}) 0.84 (3H, d, $J$=6.46 Hz), 0.88-2.04 (8H, m), 1.12 (3H, s), 1.15 (3H, s), 1.42 (broad OH), 4.76 (1H, d, $J$=5.51 Hz), 4.85 (1H, dt, $J$=4.4 and 10.7 Hz), 5.09 (2H, d, $J$=5.35), 6.10 (2H, m), 6.57 (1H, m), 7.03-7.32 (10H, m) ppm; $\delta_{\text{C}}$\textsubscript{62.9; CCDl3} 21.71 (CH\textsubscript{3}), 25.80 (CH\textsubscript{3}), 26.77 (CH\textsubscript{2}), 26.86 (CH\textsubscript{3}), 31.32 (CH), 34.39 (CH\textsubscript{2}), 39.79 (C), 41.29 (CH\textsubscript{2}), 50.29 (CH), 50.59 (CH\textsubscript{2}), 67.15 (CH), 76.93 (CH), 107.71 (CH), 109.11 (CH), 123.26 (CH), 125.36 (CH), 125.47 (2 x CH), 126.78 (2 x CH), 127.52 (CH), 127.97 (C), 128.46 (2 x CH), 128.69 (2 x CH), 137.96 (C), 151.40 (C), 170.76 (ester C=O) ppm.
Methyl (N-benzyl-2-pyrrolyl)-(N-methyl-3-indolyl)acetate

![Chemical Structure](image)

**Procedure 1**

Pyrophosphoryl chloride (110 mg, 0.44 mmol) was added to a solution of methyl (N-benzyl-2-pyrrolyl)hydroxyacetate (100 mg, 0.40 mmol) and N-methylindole (105 mg, 0.8 mmol) in dichloromethane (25 cm³) at 0°C. After 45 minutes the reaction was quenched with a saturated aqueous solution of sodium hydrogencarbonate (30 cm³). Flash chromatography on silica gel eluting with diethyl ether-light petroleum (bp 40-60°C) (3:7) gave methyl (N-benzyl-2-pyrrolyl)-(N-methyl-3-indolyl)acetate (54) as a light yellow oil, (99 mg, 80%); Found M⁺ 358.16812 C₂₃H₂₂N₂O₂ requires 358.16812; v_max/cm⁻¹ 1740.3 (C=O, ester); δ_H (250 MHz; CDCl₃) 3.62 (3H, s), 3.68 (3H, s), 5.00 (2H, s), 5.13 (1H, s), 6.14-6.21 (2H, m), 6.67 (1H, m), 6.81-7.23 (10H, m); δ_C (62.9; CDCl₃) 32.69 (N-Me), 41.01 (CH), 50.57 (CH₂), 52.27 (OMe), 107.35 (CH), 108.81 (CH), 109.27 (CH), 110.84 (C), 118.94 (CH), 119.22 (CH), 121.71 (CH), 122.44 (CH), 126.42 (2 x CH), 126.83 (C), 127.30 (CH), 128.19 (CH), 128.57 (2 x CH), 129.33 (C), 136.95 (C), 138.03 (C), 172.40 (C=O ester) ppm.

**Procedure 2**

FSA (0.057 cm³, 1.0 mmol) was added dropwise to a solution of BSA (0.407 g, 2.0 mmol) in dichloromethane (25 cm³) and the resulting solution stirred at 25°C for 30 minutes. The reaction mixture was then cooled to -78°C and solutions of methyl (N-methyl-3-indolyl)hydroxyacetate (1.54 g, 7.0 mmol) and N-benzylpyrrole (1.57 g, 10.0 mmol) in dichloromethane (40 cm³) were added sequentially. The reaction was quenched after 45 minutes with the addition of a saturated aqueous solution of sodium hydrogencarbonate (20 cm³). The crude product was extracted into dichloromethane (3 × 30 cm³) dried over (MgSO₄) and the solvent evaporated. Flash chromatography on silica gel eluting with light petroleum (bp 40-60°C)-ethyl acetate (4:1) gave the product as a light yellow oil (1.84 g, 73%).
Procedure 3

FSA (0.057 cm$^3$, 1.0 mmol) was added dropwise to a solution of BSU (0.41 g, 2.0 mmol) in dichloromethane (25 cm$^3$) and the resulting solution stirred at 25°C for 30 minutes. The solution was then cooled to -78°C and solutions of methyl (N-methyl-3-indolyl)hydroxyacetate (0.22 g, 1.0 mmol) and N-benzylpyrrole (0.236 g, 1.5 mmol) in dichloromethane (20 cm$^3$) were added sequentially. The reaction was quenched after 30 minutes with the addition of a saturated aqueous solution of sodium hydrogen carbonate (20 cm$^3$). The crude product was extracted into dichloromethane (3 x 30 cm$^3$) dried over (MgSO$_4$) and the solvent evaporated. Flash chromatography on silica gel eluting with light petroleum (bp 40-60°C)-ethyl acetate (4:1) gave the product as a light yellow oil (0.31 g, 86%).

2-CN-benzyl-2-pyrrolyn-2-CN-methyl-3-indolynethanol

(55 / 56)

Procedure 1

Lithium aluminium hydride (0.015 g, 0.4 mmol) was added gradually at 0°C to a stirred solution of (-)-8-phenylmenthyl (N-benzyl-2-pyrrolyl)-(N-methyl-3-indolyl)acetate (50) (0.139 g, 0.25 mmol) in diethyl ether (30 cm$^3$). The solution was then gently heated under reflux for 2 hours before the reaction was quenched by the addition of water (1.7 cm$^3$), 15% NaOH (1.7 cm$^3$) then water again (5.1 cm$^3$). The resultant precipitate was removed by filtration through a bed of celite. The filtrate was then dried (MgSO$_4$) filtered and solvent evaporated to give 2-(N-benzyl-2-pyrrolyl)-2-(N-methyl-3-indolyl)ethanol (55) as a light brown oil (0.0799 g, 97%); Found: M$^+$ 330.1735 C$_{22}$H$_{22}$N$_2$O requires 330.1732; $\nu_{\text{max}}$ /cm$^{-1}$ 3457 (O-H); $\delta$H (250 MHz; CDCl$_3$) 1.84 (1H, broad O-H), 3.64 (3H, s), 4.04 (2H, d, J=6.9 Hz), 6.67 (1H, m), 6.84 (2H, m), 7.05 (1H, m), 7.16-7.29 (6H, m), 7.43 (1H, d, J=7.5 Hz) ppm; $\delta$C (62.9 MHz; CDCl$_3$) 32.63 (N-Me), 37.33 (CH), 50.36 (CH$_2$), 65.78 (CH$_2$), 105.71 (CH), 107.15 (CH), 109.29 (CH), 113.53 (C), 118.97 (CH), 119.11 (CH), 121.74 (CH), 102
121.99 (CH), 126.34 (2 x CH), 126.93 (C), 127.19 (CH), 127.64 (CH), 128.50 (2 x CH), 132.49 (C), 136.94 (C), 138.24 (C) ppm.

Procedure 2

To a suspension of lithium aluminium hydride (0.042 g, 1.1 mmol), in tetrahydrofuran (10 cm$^3$) a solution of methyl (N-benzyl-2-pyrrolyl)-(N-methyl-3-indolyl)acetate (54) (0.197 g, 0.55 mmol) in tetrahydrofuran (15 cm$^3$) was added gradually and the solution stirred at 25$^\circ$C for 30 minutes. The reaction was quenched by the addition of water (1.7 cm$^3$), 15% NaOH (1.7 cm$^3$) then water again (5.1 cm$^3$). The resultant precipitate was removed by filtration through a bed of celite. The filtrate was then dried (MgSO$_4$) filtered and the solvent evaporated to give 2-(N-benzyl-2-pyrrolyl)-2-(N-methyl-3-indolyl)ethanol (56) as a light brown oil (0.174 g, 96%)

3,5-Dinitrophenyl-[2-(N-benzyl-2-pyrrolyl)-2-(N-methyl-3-indolyl)ethanoate$^{119}$(57)

A solution of 2-(N-benzyl-2-pyrrolyl)-2-(N-methyl-3-indolyl)ethanol (55) (0.1 g, 0.3 mmol) in dichloromethane (25 cm$^3$) was treated with triethylamine (0.045 cm$^3$, 0.45 mmol) at 0$^\circ$C and stirred for 15 minutes. A solution of 3,5-dinitrobenzoylchloide in dichloromethane (30 cm$^3$) was then added dropwise, the reaction mixture was gradually warmed to room temperature and allowed to react until esterification was complete (TLC analysis). The reaction was quenched with the addition of a saturated aqueous solution of sodium hydrogencarbonate (20 cm$^3$). The crude product was extracted into dichloromethane (3x30 cm$^3$) dried over (MgSO$_4$) and the solvent evaporated. Flash chromatography on silica gel eluting with light petroleum (bp 40-60$^\circ$C)-ethyl acetate (1:1) gave 3,5-dinitrophenyl-[2-(N-benzyl-2-pyrrolyl)-2-(N-methyl-3-indolyl)ethanoate (57) as a brown crystalline solid (0.135 g, 85%) mp 135-137$^\circ$C; (Found C, 66.49; H, 4.58; N, 10.40 C$_{29}$H$_{24}$N$_4$O$_6$ requires C, 66.41 H, 4.58;
N, 10.69); Found M+ 524.1692 C29H24N4O6 requires 524.16957; v_max/cm⁻¹ 1731 (ester C=O), 1545, 1344 (nitro); δ_H (250MHz; CDCl₃) 3.68 (3H, s), 4.64 (1H, t, J=7.25 Hz) 4.87-4.99 (4H, m), 6.25 (2H, m), 6.66-6.83 (4H, m), 7.04-7.27 (6H, m), 7.51 (1H, m), 8.91 (1H, s), 8.93 (1H, s), 9.13 (1H, s) ppm. δ_C(62.9; CDCl₃) 32.73 (N-Me), 33.61 (CH), 50.51 (CH₂), 68.90 (CH₂), 106.25 (CH), 107.18 (CH), 109.48 (CH), 113.00 (C), 118.60 (CH), 119.40 (CH), 121.90 (CH), 122.16 (CH), 122.28 (CH), 126.20 (2 x CH), 126.86 (C), 127.25 (CH), 127.77 (CH), 128.55 (2 x CH), 129.40 (2 x CH), 131.24 (C), 133.87 (C), 137.87 (C), 138.28 (C), 142.47 (2 x C), 162.42 (ester C=O) ppm.

(+)-trans-2-(α-cumyl)cyclohexyl (N-methyl-3-indolyl)glyoxylate

[Image]

Oxalyl chloride (0.23g, 1.8 mmol) was added dropwise to a solution of N-methylindo1e (0.1979, 1.5 mmol) at 0°C in dichloromethane (30 cm³). The reaction mixture was stirred at 25°C for 3h before the reaction was quenched by the addition of a solution of (+)-trans-2-(α-cumyl)cyclohexanol (0.392g, 1.8 mmol) and triethylamine (0.364g, 3.6 mmol) in dichloromethane (30 cm³). The resulting solution was stirred at 25°C for 24h before the addition of a saturated aqueous solution of sodium hydrogen carbonate (20 cm³), the crude product was then extracted into dichloromethane (3x30 cm³) dried over (MgSO₄), filtered and the solvent evaporate. Flash chromatography on silica gel eluting with diethyl ether-light petroleum (bp 40-60°C) (1:4) gave (+)-trans-2-(α-cumyl)cyclohexyl (N-methyl-3-indolyl)glyoxylate (61) as a viscous light yellow oil (0.315g, 52%); Found M+ 403.2135 C₂₆H₂₉N₂O₃ requires 403.21473; v_max/cm⁻¹ 1645(C=O, ketone), 1717 (C=O, ester); δ_H (250MHz; CDCl₃) 0.85-1.29 (5H, m), 1.35 (3H, s), 1.40 (3H, s), 1.41-1.79 (2H, m), 2.04-2.16 (2H, m), 3.87 (3H, s), 4.92 (1H, m), 6.96-7.36 (8H, m), 8.19 (1H, s), 8.41 (1H, m) ppm; δ_C (62.9; CDCl₃) 24.67 (CH₂), 25.74 (CH₂), 25.89 (CH₃), 27.43 (CH₂), 28.09 (CH₃), 33.01 (CH₂), 33.71 (CH), 40.26 (C), 51.04 (N-Me), 77.18 (CH), 109.69 (CH), 112.92 (C), 122.79 (CH), 123.34 (CH), 123.95 (CH), 125.17 (CH), 125.61 (2 x CH), 127.08 (C), 127.89 (2 x CH), 137.51 (C), 139.93 (CH), 150.14 (C), 161.67 (C), 177.51 (C) ppm.
Sodium borohydride (23mg, 0.6 mmol) was added portionwise to a solution of (+)-trans-2-(α-cumyl)cyclohexyl (N-methyl-3-indolyl)glyoxylate (61) (81mg, 0.2 mmol) in methanol (20 cm³) with cooling (ice bath). The reaction mixture was then stirred at 25°C for 0.5h and treated with a saturated aqueous solution of sodium hydrogen carbonate (20 cm³). The crude product was then extracted into dichloromethane (3x30 cm³) dried over (MgSO₄), filtered and the solvent evaporated. Flash chromatography on silica gel eluting with diethyl ether-light petroleum (bp 40-60°C) (1:4) gave (+)-trans-2-(α-cumyl)cyclohexyl (N-methyl-3-indolyl)hydroxyacetate (62) as a light yellow oil (46mg, 79%); Found M⁺ 405.2314 C₂₆H₃₁N⁰₃ requires 405.23038; νmax/cm⁻¹ 1720 (C=O, ester), 3467 (O-H); δH (250MHz; CDCl₃) [Note: two diastereomers are present (38% de.)] (major diastereomer) 0.85-2.15 (9H, m), 0.89 (3H, s), 0.98 (3H, s), 2.38 (1H, s, br), 3.70 (3H, s), 4.82 (1H, dt, J=4.35, 10.26 Hz), 5.14 (1H, s), 7.06-7.36 (9H, m), 7.65 (1H, m) ppm; δC (62.9; CDCl₃) (major diastereomer) 23.14 (Me), 24.54 (CH₂), 25.70 (CH₂), 26.15 (Me), 27.17 (CH₂), 32.64 (N-Me), 33.07 (CH₂), 39.80 (C), 50.67 (CH), 68.04 (CH), 77.48 (CH), 109.22 (CH), 111.67 (C), 119.25 (CH), 119.58 (CH), 119.83 (CH), 121.95 (CH), 125.27 (CH), 125.45 (2 x CH), 126.25 (C), 128.01 (2 x CH), 137.31 (C), 151.01 (C), 172.17 (C=O, ester) ppm.
(+)-trans-2-(α-cumyl)cyclohexyl (N-methyl-3-indolyl)-(1,2-dimethyl-3-indolyl)acetate

FSA (0.029 cm³, 0.5 mmol) was added dropwise to a solution of BSA (0.203g, 1.0 mmol) in dichloromethane (30 cm³) and the resulting solution stirred for 0.5h at 25°C. The solution was then cooled to -78°C before the addition of (+)-trans-2-(α-cumyl)cyclohexyl (N-methyl-3-indolyl)hydroxyacetate (62) (20mg, 0.05 mmol) 1,2-dimethylindole (15mg, 0.06 mmol) and stirred for a further hour at this temperature. The solution was then treated with a saturated aqueous solution of sodium hydrogen carbonate (20 cm³). The crude product was then extracted into dichloromethane (3x30 cm³) dried over (MgSO₄), filtered and the solvent evaporated. Flash chromatography on silica gel eluting with ethyl acetate and light petroleum (bp 40-60°C) (1:4) gave (+)-trans-2-(α-cumyl)cyclohexyl (N-methyl-3-indolyl)-(1,2-dimethyl-3-indolyl)acetate (63) as a viscous light yellow oil (24 mg, 92 %); Found M⁺ 532.3090, C₃₆H₄₀N₂O₂ requires 532.30896; νmax/cm⁻¹ 1728 (C=O); δH (250MHz; CDCl₃) (major diastereomer, 65% de) 0.79-1.60 (9H, m), 1.23 (3H, s), 1.34 (3H, s), 2.23 (3H, s), 3.60 (3H, s), 3.70 (3H, s), 4.73 (1H, s), 4.74-4.80 (1H, m), 6.99-7.56 (14H, m) ppm; δc (62.9; CDCl₃) (major diastereomer) 10.93 (Me), 23.17 (Me), 24.28 (Me), 24.40 (CH₂), 24.52 (CH₂), 25.67 (CH₂), 29.22 (N-Me), 32.51 (CH₂), 32.68 (N-Me), 39.98 (C), 50.62 (CH), 57.41 (CH), 76.10 (CH), 109.11 (CH), 112.58 (C), 119.25 (CH), 119.58 (CH), 119.82 (CH), 121.73 (CH), 121.94 (CH), 125.13 (CH), 125.35 (CH), 125.45 (CH), 126.66 (CH), 126.83 (CH), 126.92 (CH), 127.41 (C), 127.87 (C), 128.00 (CH), 128.11 (CH), 134.25 (C), 137.34 (C), 150.61 (C), 151.75 (C), 162.42 (C), 172.59 (C=O, ester) ppm.
**N-3,4-Dimethoxybenzylpyrrole**

![Structural formula of N-3,4-Dimethoxybenzylpyrrole (65)](image)

A stirred solution of veratrylamine (8.36g, 50.0 mmol) and 2,5-dimethoxytetrahydrofuran (7.93g, 60.0 mmol) in a mixed solvent system of toluene (100 cm³) and glacial acetic acid (100 cm³) was heated for 19 h at 80°C. The crude product was extracted into dichloromethane (3x30 cm³), washed with a saturated aqueous solution of sodium hydrogencarbonate (20 cm³), dried over (MgSO₄), filtered and the solvent evaporated. Flash chromatography on silica gel eluting with ethyl acetate-light petroleum (bp 40-60°C) (1:1) gave N-3,4-dimethoxybenzylpyrrole (65) as a viscous colourless oil (8.85g, 81%); Found M⁺ 217.1111 C₁₃H₁₅NO₂ requires 217.1102; νmax/cm⁻¹ 2836 (OMe); δH (250MHz; CDCl₃) 3.81 (3H, s), 3.84 (3H, s), 4.98 (2H, s), 6.16-6.18 (2H, m), 6.51-6.62 (5H, m) ppm; δC (62.9 MHz; CDCl₃) 53.04 (CH₂), 55.77 (OMe), 55.87 (OMe), 108.36 (CH), 110.36 (CH), 111.15 (CH), 119.50 (2 x CH), 120.93 (2 x CH), 130.53 (C), 148.52 (C), 149.15 (C) ppm.

**Methyl (N-3,4-dimethoxybenzyl-2-pyrrolylglyoxylate**

![Structural formula of Methyl (N-3,4-dimethoxybenzyl-2-pyrrolylglyoxylate (66)](image)

Oxalyl chloride (1.26g, 9.9 mmol) was added dropwise over a period of 0.5h to a solution of N-3,4-dimethoxybenzylpyrrole (65) (1.95g, 9.0 mmol) in diethyl ether (50 cm³) cooled to 0°C (ice bath). The reaction mixture was stirred for 1h at 25°C before the addition of a solution of triethylamine (2.75 cm³) in methanol (20 cm³). Stirring was then continued for a further 3h before the reaction was quenched by the
addition of water (20 cm$^3$). The crude product was then extracted into dichloromethane (3x30 cm$^3$), dried over (MgSO$_4$) filtered and the solvent evaporated. Flash chromatography on silica gel eluting with ethyl acetate-light petroleum (bp 40-60°C) (1:1) gave methyl (N-3,4-dimethoxybenzyl-2-pyrrolyl)glyoxylate (66) as a bright yellow oil (2.18g, 80%); Found M$^+$ 303.1097 C$_{16}$H$_{17}$NO$_5$ requires 303.11066; $\nu_{\text{max}}$/cm$^{-1}$ 1642 (C=O, ketone), 1737 (C=O, ester), 2836 (OMe); $\delta$H (250MHz; CDCl$_3$) 3.82 (3H, s), 3.84 (3H, s), 3.90 (3H, s), 5.50 (CH$_2$), 6.24-6.27 (1H, m), 6.70-6.81 (3H, m), 7.06-7.08 (1H, m), 7.33-7.35 (1H, m) ppm; $\delta$C (62.9MHz; CDCl$_3$) 52.58 (CH$_2$), 52.63 (OMe), 55.75 (OMe), 55.78 (OMe), 110.22 (CH), 110.77 (CH), 111.08 (CH), 119.92 (CH), 125.73 (CH), 126.98 (C), 129.46 (C), 133.48 (CH), 148.58 (C), 149.02 (C), 163.58 (C), 173.66 (C=O, ester) ppm.

Methyl (N-3,4-dimethoxybenzyl-2-pyrrolyl)hydroxyacetate

Sodium borohydride (68mg, 1.8 mmol) was added portionwise to a solution of methyl (N-3,4-dimethoxybenzyl-2-pyrrolyl)glyoxylate (66) (1.10g, 3.6 mmol) in methanol (30 cm$^3$) with cooling (ice bath). The resulting solution was stirred at 20°C over a period of 15 minutes. The reaction was then quenched by the addition of water (20 cm$^3$) and extracted with dichloromethane (3x30 cm$^3$), dried over (MgSO$_4$), filtered and the excess solvent evaporated. Flash chromatography on silica gel eluting with ethyl acetate-light petroleum (bp 40-60°C) (1:1) gave methyl (N-3,4-dimethoxybenzyl-2-pyrrolyl)hydroxyacetate (64) (0.87g, 79%) as a yellow oil; Found M$^+$ 305.1258, C$_{16}$H$_{19}$NO$_5$ requires 305.12631; $\nu_{\text{max}}$/cm$^{-1}$ 1746 (C=O, ester), 2836 (OMe), 3482(O-H); $\delta$H (250MHz; CDCl$_3$) 3.11 (1H, s, br), 3.67 (3H, s), 3.83 (3H, s), 3.85 (3H, s), 5.12 (2H, s), 5.18 (1H, s), 6.11-6.14 (2H, m), 6.64-6.69 (3H, m), 6.78-6.82 (1H, m) ppm; $\delta$C (62.9 MHz; CDCl$_3$) 50.38 (CH$_2$), 52.78 (OMe), 55.79 (OMe), 55.91 (OMe), 66.30 (CH), 107.49 (CH), 109.49 (CH), 109.01 (CH), 108
109.79 (CH), 11.17 (CH), 118.76 (CH), 123.75 (CH), 129.06 (C), 130.22 (C), 148.43 (C), 149.21 (C), 173.22 (C=O, ester) ppm.

\textit{N-3.5-dimethoxybenzylpyrrole}

\includegraphics{68}

\textbf{Procedure 1}^{66}

Freshly prepared 1,4-dichloro-1,4-dimethoxybutane (6.17g, 33 mmol) was added dropwise to a solution of 3,5-dimethoxybenzylamine (4.6g, 27.5 mmol) in dichloromethane (150 cm$^3$) at 0°C. To this, Amberlyst A21 ion exchange resin (20g) was added and the solution was then allowed to warm to 25°C and stirred for 20 h. The Amberlyst A21 ion exchange resin was then removed by filtration and the reaction quenched by the addition of a saturated aqueous solution of sodium hydrogen carbonate (20 cm$^3$) and extracted with dichloromethane (3x50 cm$^3$), dried over (MgSO$_4$), filtered and the excess solvent evaporated. Flash chromatography on silica gel eluting with diethyl ether-light petroleum (bp 40-60°C) (1:4) gave \textit{N-3.5-dimethoxybenzylpyrrole} (68) as a white crystalline solid (1.00g, 17%); mp=79-81°C, (Found: C, 71.97; H, 7.00; N, 6.42; C$_{13}$H$_{15}$NO$_2$ requires C, 71.89; H, 6.91; N, 6.45 %); Found M$^+$ 217.11027 C$_{13}$H$_{15}$NO$_2$ requires 217.1105; $\delta_{\text{max}}$/cm$^{-1}$ 2836 (OMe); $\delta_H$ (250MHz; CDCl$_3$) 3.74 (2 x OMe), 4.99 (CH$_2$), 6.18 (2H, t, $J$=2.08 Hz), 6.25 (2H, d, $J$=2.24 Hz), 6.36 (1H, t, $J$=2.24 Hz), 6.68 (2H, t, $J$=2.09 Hz) ppm; $\delta_C$ (62.9MHz; CDCl$_3$) 53.30 (CH$_2$), 55.23 (2 x OMe), 99.29 (2 x CH), 104.96 (2 x CH), 108.45 (2 x CH), 121.14 (CH), 140.51 (C), 161.04 (2 x C) ppm.

\textbf{Procedure 2}^{67}

A suspension of crushed potassium hydroxide (2.81g, 50 mmol) DMSO (50 cm$^3$) was stirred for 0.5h. Pyrrole (1.68g, 25 mmol) and 3,5-dimethoxybenzylbromide (5.77g, 25 mmol) were then added and the resulting mixture was stirred for 12h at 25°C. The reaction was quenched with water (20 cm$^3$) and extracted with dichloromethane (3x50 cm$^3$), dried over (MgSO$_4$), filtered and the excess solvent evaporated. Flash
chromatography on silica gel eluting with diethyl ether-light petroleum (bp 40-60°C) (1:4) gave the title compound as a white crystalline solid, (5.38g, 99%).

3,5-Dimethoxybenzyl alcohol

To a suspension of lithium aluminium hydride (2.28g, 60 mmol) in diethyl ether (50 cm$^3$) a solution of 3,5-dimethoxybenzaldehyde (9.97g, 60 mmol) in diethyl ether (75 cm$^3$) was added dropwise over a period of 15 minutes. The suspension was stirred for 16h before the reaction was quenched by the addition of ethyl acetate (75 cm$^3$) to decompose the remaining lithium aluminium hydride before filtration over a bed of celite. The ethereal solution was then washed with water (3x30 cm$^3$), dried (MgSO$_4$), filtered and the excess solvent evaporated. Flash chromatography on silica gel eluting with diethyl ether-light petroleum (bp 40-60°C) (3:7) gave 3,5-dimethoxybenzyl alcohol (69) as a white crystalline solid, (7.54g, 75%); mp=48.5 0 C; Found M$^+$ 168.0790 C$_9$H$_{12}$O$_3$ requires 168.07864); $\nu_{\text{max}}$/cm$^{-1}$ 2836 (OMe), 3534 (O-H); $\delta$H (250MHz; CDCl$_3$) 2.57 (1H, br, s), 3.76 (3H, s), 4.58 (2H, s), 6.36 (1H, m), 6.48 (2H, d, $J=2.2$ Hz) ppm; $\delta$C (62.9; CDC$_3$) 55.22 (2 x OMe), 65.02 (CH$_2$), 99.48 (CH), 104.48 (2 x CH), 143.43 (C), 160.84 (2 x C) ppm.

3,5-Dimethoxybenzyl bromide

Phosphorus tribromide (4.33g, 16 mmol) was added dropwise to a solution of 3,5-dimethoxybenzyl alcohol (69) (5.04g, 30 mmol) in diethyl ether (50 cm$^3$) at -10°C (ice / salt bath). The reaction mixture was then allowed to warm to ambient temperature and the resulting solution stirred for 48h. The reaction was quenched by the addition of ice (20g), washed with a saturated aqueous solution of sodium chloride (3x30 cm$^3$) extracted into dichloromethane (3x30 cm$^3$), dried over (MgSO$_4$), filtered and the excess solvent evaporated to give 3,5-dimethoxybenzyl bromide (70) as a light pink crystalline solid, (6.33g, 91%); mp=75°C; Found M$^+$

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229.9957 C₉H₁₁O₂Br requires 229.99428; ν_max/cm⁻¹ 2838 (OMe), 699 (C-Br); δ_H (250MHz; CDCl₃) 3.79 (2 x 3H, s), 4.41 (2H, s), 6.39 (1H, m), 6.53 (2H, d, J=2.22 Hz) ppm; δ_C (62.9; CDCl₃) 33.57 (CH₂), 55.33 (2 x OMe), 100.52 (CH), 106.88 (2 x CH), 139.67 (C), 160.83 (2 x C) ppm.

**Methyl (N-3,5-dimethoxybenzyl-2-pyrrolyl)glyoxylate**

\[
\text{Me} \quad \begin{array}{c}
\text{N} \\
\text{O} \\
\text{OMe} \\
\text{OMe} \\
\end{array}
\]

(71)

Oxalyl chloride (105mg, 0.83 mmol) in diethyl ether (20 cm³) was added dropwise at 0°C to a solution of 3,5-dimethoxybenzylpyrrole (68) (150mg, 0.69 mmol) in diethyl ether (10 cm³). The solution was then allowed to warm to room temperature and stirring continued for 2h before a solution of triethylamine (0.14g, 1.4 mmol) in methanol (10 cm³) was added, and stirring continued for a further 12h. The reaction was then quenched by the addition of a saturated aqueous solution of sodium hydrogen carbonate (20 cm³) and extracted with diethyl ether (3x50 cm³), dried over (MgSO₄), filtered and the excess solvent evaporated. Flash chromatography on silica gel eluting with diethyl ether-light petroleum (bp 40-60°C) (2:3) gave methyl (N-3,5-dimethoxybenzyl-2-pyrrolyl)glyoxylate (71) as a yellow oil, (0.199g, 96%); Found M⁺ 303.1111 C₁₆H₁₇NO₅ requires 303.11066; ν_max/cm⁻¹ 2840 (OMe), 1737 (C=O, ester), 1650 (C=O); δ_H (250MHz; CDCl₃) 3.74 (2 x 3H, s), 3.89 (3H, s), 5.51 (2H, s), 6.25-6.27 (2H, m), 6.35 (1H, m), 7.07 (2H, m), 7.43 (1H, m) ppm; δ_C (62.9; CDCl₃) 52.67 (OMe), 52.86 (CH₂), 55.29 (2 x OMe), 99.52 (CH), 105.29 (2 x CH), 110.36 (CH), 125.73 (CH), 127.12 (C), 133.79 (CH), 139.49 (C), 161.01 (2 x C), 163.51 (C), 173.59 (C=O, ester) ppm.
Methyl (N-3,5-dimethoxybenzyl-2-pyrrolyl)hydroxyacetate

Sodium borohydride (0.30g, 8.0 mmol) was added portionwise to a solution of methyl (N-3,5-dimethoxybenzyl-2-pyrrolyl)glyoxylate (71) (1.21g, 4.0 mmol) in methanol (40 cm³) with cooling (ice bath). The resulting solution was stirred at 20°C over a period of 1h. The reaction was then quenched by the addition of water (20 cm³) and extracted with dichloromethane (3x30 cm³), dried over (MgSO₄), filtered and the excess solvent evaporated. Flash chromatography on silica gel eluting with ethyl acetate-light petroleum (bp 40-60°C) (1:1) gave methyl (N-3,5-dimethoxybenzyl-2-pyrrolyl)hydroxyacetate (67) as a yellow oil, (0.79g, 65%); Found M+ 305.1258 C₁₆H₁₉NO₅ requires 305.12631; ν max/cm⁻¹ 1747 (C=O, ester), 2836 (OMe), 3484 (O-H); ¹H (250MHz; CDCl₃) 3.04 (OW, OH), d, J=6,68 Hz), 3.67 (3H, s), 3.73 (2 x 3H, s), 5.12 (2H, s), 5.15 (1H, d, J=6.58 Hz), 6.11-6.12 (2H, m), 6.18-6.19 (2H, m), 6.34-6.35 (1H, m), 6.62-6.68 (1H, m) ppm; δC (62.9; CDCl₃) 50.56 (CH₂), 52.65 (OMe), 55.20 (2 x OMe), 66.25 (CH), 99.26 (CH), 104.45 (2 x CH), 107.66 (CH), 108.99 (CH), 119.25 (CH), 123.88 (CH), 140.35 (C), 161.06 (2 x C), 173.17 (C=O, ester) ppm.
Oxalyl chloride (5.10g, 40 mmol) in diethyl ether (20 cm³) was added dropwise at 0°C over a period of 15 minutes to a solution of N-(3',4'-dimethoxyphenyl)ethyl pyrrole (7.62g, 33 mmol) in diethyl ether (30 cm³). The solution was then stirred at 25°C for 3h. The reaction was then quenched by the addition of an ethereal solution of triethylamine (8.10g, 80mmol) and methanol (20 cm³) and left to stir for 12h. The reaction was quenched with a saturated aqueous solution of sodium hydrogen carbonate and the product extracted with diethyl ether (3x30 cm³), dried over (MgSO₄), filtered and the excess solvent evaporated. Flash chromatography on silica gel using an eluant of ethyl acetate and light petroleum (bp 40-60°C) (3:7) gave methyl (N-3',4'-dimethoxy-2-phenylethyl)-2-pyrrolylglyoxylate (73) as a light yellow oil, (10.04g, 96%); Found M⁺ 317.1283 C₁₇H₁₉N₀₅ requires 317.1263; νmax/cm⁻¹ 1646 (C=O, ketone) 1737 (C=O, ester) 2836 (OMe); δH (250MHz; CDCl₃) 2.97 (2H, t, J=7.09Hz), 3.81 (3H, s), 3.85 (3H, s), 3.94 (3H, s), 4.50 (2H, t, J=7.30Hz), 6.12-6.15 (1H, m), 6.55-6.79 (4H, m), 7.31-7.33 (1H, m); δC(62.9; CDCl₃) 37.16 (CH₂), 51.97 (CH₂), 52.64 (OMe), 55.72 (OMe), 55.79 (OMe), 109.61 (CH), 111.20 (CH), 112.00 (CH), 120.82 (CH), 125.76 (CH), 126.54 (C), 130.41 (2 x C), 134.06 (CH), 147.68 (CH), 148.77 (CH), 163.73 (C=O ester).
Methyl \((N\text{-}3',4'\text{-dimethoxy-2-phenylethyl})\text{-}2\text{-pyrrolylhydroxyacetate}\)

\[
\begin{array}{c}
\text{\begin{tikzpicture}
\begin{scope}[scale=0.8]
\node[inner sep=0pt] (methyl) at (0,0) {
  \begin{tikzpicture}[every node/.style={draw,shape=circle,fill=black,minimum size=2pt,inner sep=0pt}]
  \node (n1) at (0,0) {};
  \node (n2) at (1,0.5) {};
  \node (n3) at (1,-0.5) {};
  \node (n4) at (0.5,1) {};
  \node (n5) at (0.5,-1) {};
  \node (n6) at (1,0) {};
  \node (n7) at (0,1) {};
  \node (n8) at (0,-1) {};
  \node (n9) at (0.5,0) {};
  \draw (n1) -- (n2);
  \draw (n2) -- (n3);
  \draw (n3) -- (n4);
  \draw (n4) -- (n5);
  \draw (n5) -- (n6);
  \draw (n6) -- (n7);
  \draw (n7) -- (n8);
  \draw (n8) -- (n9);
  \draw (n9) -- (n1);
\end{tikzpicture}};
\end{scope}
\end{tikzpicture}}
\end{array}
\]

Natrium borohydrid (0.64 g, 17.0 mmol) was added portionwise to a solution of methyl \((N\text{-}3',4'\text{-dimethoxy-2-phenylethyl})\text{-}2\text{-pyrrolylglyoxylate}\) (73) (3.48 g, 11.0 mmol) in methanol (30 cm\(^3\)) with cooling (ice bath). The resulting solution was stirred at 20°C over a period of 15 minutes. The reaction was then quenched by the addition of water (20 cm\(^3\)) and extracted with dichloromethane (3x30 cm\(^3\)), dried over (MgSO\(_4\)), filtered and the excess solvent evaporated. Flash chromatography on silica gel using an eluant of ethyl acetate-light petroleum (bp 40-60°C) (3:7) gave methyl \((N\text{-}3',4'\text{-dimethoxy-2-phenylethyl})\text{-}2\text{-pyrrolylhydroxyacetate}\) (74) as a white crystalline solid, (2.08 g, 66%); mp=85-86°C; Found M\(^+\) 319.1426 \text{C}_{17}\text{H}_{21}\text{NO}_{5} \text{ requires } 319.1419; \nu_{max}/\text{cm}^{-1} 1746 (\text{C=O, ester}), 2836 (\text{OMe}), 3481(\text{O-H}); \delta_{H} (250\text{MHz}; \text{CDCl}_3) 2.87 (1H, d, J=7.19 Hz), 2.97 (2H, t, J=7.21 Hz), 3.78 (3H, s), 3.79 (3H, s), 3.85 (3H, s), 4.14 (2H, t, J=7.27 Hz), 5.03 (1H, d, J=7.27 Hz), 6.00-6.07 (2H, m), 6.44 (1H, d, J=1.89 Hz), 6.57-6.59 (1H, m), 6.65-6.69 (1H, m), 6.78 (1H, d, J=8.18 Hz) ppm; \delta_{c} (62.9; \text{CDCl}_3) 37.66 (\text{CH}_2), 48.77 (\text{CH}_2), 52.71 (\text{OMe}), 55.64 (\text{OMe}), 55.82 (\text{OMe}), 66.00 (\text{CH}), 107.32 (\text{CH}), 108.17 (\text{CH}), 111.20 (\text{CH}), 111.91 (\text{CH}), 120.57 (\text{CH}), 122.64 (\text{CH}), 128.80 (\text{C}), 130.74 (\text{C}), 131.34 (\text{C}), 147.77 (\text{C}), 173.27 (\text{C=O, ester}) ppm.
6.3 Experimental for Chapter 3

2-Methoxybenzylcyclohexanone\textsuperscript{80}

\[ \text{Procedure 1} \]

To a stirred solution of BSA (0.1 g, 0.5 mmol) in dichloromethane (50 cm\textsuperscript{3}) at -78\textdegree C TfoH (0.038 g, 0.25 mmol) was added. After the solution was stirred for 15 minutes, 1-trimethylsilyloxy cyclohexanone (0.85 g, 5.0 mmol) and benzaldehyde dimethyl acetal (0.761 g, 5 mmol) were added sequentially and the solution stirred for a further 15 minutes before the reaction was quenched by the addition of a saturated aqueous solution of sodium hydrogencarbonate (20 cm\textsuperscript{3}). The crude product was extracted with dichloromethane (3x30 cm\textsuperscript{3}), dried over (MgSO\textsubscript{4}) and the solvent evaporated. Flash chromatography on silica gel with an eluant system of light petroleum (bp 40-60\textdegree C) and diethyl ether (4:1) gave 2-methoxybenzylcyclohexanone (79) as a light colourless oil, (0.98 g, 90\%); Found M\textsuperscript{+} 218.1310 C\textsubscript{14}H\textsubscript{18}O\textsubscript{2} requires 218.13067; \( \nu_{\text{max}} / \text{cm}^{-1} \) 1709 (ketone C=O); \( \delta_{\text{H}} \) (250 MHz; CDCl\textsubscript{3}) Note (79\% de from NMR) 1.22-2.44 (9H, m), 3.26 (3H, s), 4.78 (1H, d, \( J=9.15 \text{ Hz} \)), 7.29 (5H, s); \( \delta_{\text{C}} \) (62.9 MHz; CDCl\textsubscript{3}) 24.57 (CH\textsubscript{2}), 26.37 (CH\textsubscript{2}), 27.01 (CH\textsubscript{2}), 42.23 (CH\textsubscript{2}), 57.25 (OMe), 57.38 (CH), 60.01 (CH), 126.89 (2 x CH), 127.25 (CH), 128.34 (CH), 140.91 (C), 210.45 (ketone C=O) ppm.

\[ \text{Procedure 2} \]

To a stirred solution of BSU (0.1 g, 0.5 mmol) in dichloromethane (50 cm\textsuperscript{3}) at -78\textdegree C TfoH (0.038 g, 0.25 mmol) was added. After the solution was stirred for 15 minutes 1-trimethylsilyloxy cyclohexanone (0.34 g, 2.0 mmol) and benzaldehyde dimethyl acetal (0.30 g, 2.0 mmol) were added sequentially and the solution stirred for a further 15 minutes before the reaction was quenched by the addition of a saturated aqueous solution of sodium hydrogencarbonate (20 cm\textsuperscript{3}). The crude product was extracted with dichloromethane (3x30 cm\textsuperscript{3}), dried over (MgSO\textsubscript{4}) and the solvent evaporated. Flash chromatography on silica gel with an eluant system of light petroleum...
(bp 40-60°C) and diethyl ether (4:1) gave 2-methoxybenzylicyclohexanone (79) as a light colourless oil (0.38g, 88%), 70% de.

Procedure 3

To a stirred solution of BSA (0.41g, 2.0 mmol) in dichloromethane (50 cm³) at -78°C FSA (0.1g, 1.0 mmol) was added. After the solution was stirred for 15 minutes 1-trimethylsilyloxy cyclohexanone (0.85g, 5.0 mmol) and benzaldehyde dimethyl acetal (0.76g, 5.0 mmol) were added sequentially and the solution stirred for a further 15 minutes before the reaction was quenched by the addition of a saturated aqueous solution of sodium hydrogencarbonate (20 cm³). The crude product was extracted with dichloromethane (3x30 cm³), dried over (MgSO₄) and the solvent evaporated. Flash chromatography on silica gel with an eluant system of light petroleum (bp 40-60°C) and diethyl ether (4:1) gave 2-methoxybenzylicyclohexanone (79) as a light colourless oil (0.88g, 80%), 83% de.

2-Methoxypropylcyclohexanone 80

FSA (0.1g, 1.0 mmol) was added dropwise to a solution of BSA (0.41g, 2.0 mmol) in dichloromethane (25 cm³) at 0°C and stirred for 15 minutes. The solution was then cooled to -78°C before 1-trimethylsilyloxy cyclohexanone (0.85g, 5.0 mmol) and 2,2-dimethoxy propane (0.52Ig, 5.0 mmol) were added sequentially and the solution stirred for 1h. The reaction was then quenched by the addition of a saturated aqueous solution of sodium hydrogencarbonate (20 cm³). The crude product was extracted with dichloromethane (3x30 cm³), dried over (MgSO₄) and the solvent evaporated. Flash chromatography on silica gel with an eluant system of light petroleum (bp 40-60°C) and diethyl ether (19: 1) gave 2-methoxypropylcyclohexanone (80) as a light colourless oil (0.69g, 81%); Found M⁺ 170.1294 C₁₀H₁₈O₂ requires 170.13067; νmax / cm⁻¹ 1710 (ketone C=O); δH (250 MHz; CDCl₃) 1.21 (3H, s), 1.29 (3H, s), 1.61-1.69 (3H, m), 1.91 (2H, m), 2.29-2.36 (3H, m), 2.55 1H, dd, J=4.61 and J=11.77 Hz), 3.16 (3H, s); δC (62.9; CDCl₃) 21.04 (Me), 23.23 (Me), 25.45 (CH₂), 28.52 (CH₂), 28.94 (CH₂), 43.90 (CH₂), 48.29 (OMe), 58.28 (CH), 75.11 (C), 211.67 (ketone C=O) ppm.
2-Furaldehyde ethoxy cyclohexanone

![Chemical Structure](image)

FSA (0.1g, 1.0 mmol) was added dropwise to a solution of BSU (0.41g, 2.0 mmol) in dichloromethane (100 cm³) at 0°C and stirred for 15 minutes. The solution was cooled to -78°C before 1-trimethylsilyloxy cyclohexanone (0.85g, 5.0 mmol) and 2-furaldehyde diethyl acetal (0.851 g, 5.0 mmol) were added sequentially and the solution stirred for 0.75h. The reaction was then quenched by the addition of a saturated aqueous solution of sodium hydrogencarbonate (20 cm³). The crude product was extracted with dichloromethane (3x30 cm³), dried over (MgSO₄) and the solvent evaporated. Flash chromatography on silica gel with an eluant system of light petroleum (bp 40-60°C) and diethyl ether (4:1) gave 2-furaldehyde ethoxy cyclohexanone (81) as a light red/brown oil, (0.21g, 19%); Found M⁺ 222.1261 C₁₃H₁₈O₃ requires 222.12559; ν max / cm⁻¹ 1713 (ketone C=O); δH (250MHz; CDCl₃) 1.13 (3H, t, J=7.02 Hz), 1.60-1.87 (5H, m), 2.32-2.49 (3H, m), 2.95 (1H, m), 3.43 (2H, m), 4.69 (1H, d, J=8.64 ), 6.27-6.34 (2H, m), 7.39 (1H, m); δc (62.9MHz; CDCl₃) 15.04 (Me), 22.87 (CH₂), 28.50 (CH₂), 30.48 (CH₂), 42.25 (CH₂), 55.14 (CH), 64.39 (CH₂), 73.16 (CH), 109.07 (CH), 109.76 (CH), 142.39 (CH), 152.86 (C), 210.72 (ketone C=O) ppm.

4-Benzyl oxy-4-phenyl-1-butene 82

![Chemical Structure](image)

**Procedure 1**

TfOH (0.075g, 0.5 mmol) was added to a stirred solution of BSA (0.203g, 1.0 mmol) in tetrachloromethane (30 cm³) at room temperature. The solution was stirred for 15 minutes and then benzaldehyde (0.318g, 3.0 mmol), allyl trimethylsilane (0.343g, 3.0 mmol) was added dropwise to a solution of BSU (0.41g, 2.0 mmol) in dichloromethane (100 cm³) at 0°C and stirred for 15 minutes. The solution was cooled to -78°C before 1-trimethylsilyloxy cyclohexanone (0.85g, 5.0 mmol) and 2-furaldehyde diethyl acetal (0.851 g, 5.0 mmol) were added sequentially and the solution stirred for 0.75h. The reaction was then quenched by the addition of a saturated aqueous solution of sodium hydrogencarbonate (20 cm³). The crude product was extracted with dichloromethane (3x30 cm³), dried over (MgSO₄) and the solvent evaporated. Flash chromatography on silica gel with an eluant system of light petroleum (bp 40-60°C) and diethyl ether (4:1) gave 2-furaldehyde ethoxy cyclohexanone (81) as a light red/brown oil, (0.21g, 19%); Found M⁺ 222.1261 C₁₃H₁₈O₃ requires 222.12559; ν max / cm⁻¹ 1713 (ketone C=O); δH (250MHz; CDCl₃) 1.13 (3H, t, J=7.02 Hz), 1.60-1.87 (5H, m), 2.32-2.49 (3H, m), 2.95 (1H, m), 3.43 (2H, m), 4.69 (1H, d, J=8.64 ), 6.27-6.34 (2H, m), 7.39 (1H, m); δc (62.9MHz; CDCl₃) 15.04 (Me), 22.87 (CH₂), 28.50 (CH₂), 30.48 (CH₂), 42.25 (CH₂), 55.14 (CH), 64.39 (CH₂), 73.16 (CH), 109.07 (CH), 109.76 (CH), 142.39 (CH), 152.86 (C), 210.72 (ketone C=O) ppm.

4-Benzyl oxy-4-phenyl-1-butene 82

![Chemical Structure](image)

**Procedure 1**

TfOH (0.075g, 0.5 mmol) was added to a stirred solution of BSA (0.203g, 1.0 mmol) in tetrachloromethane (30 cm³) at room temperature. The solution was stirred for 15 minutes and then benzaldehyde (0.318g, 3.0 mmol), allyl trimethylsilane (0.343g, 3.0 mmol) was added dropwise to a solution of BSU (0.41g, 2.0 mmol) in dichloromethane (100 cm³) at 0°C and stirred for 15 minutes. The solution was cooled to -78°C before 1-trimethylsilyloxy cyclohexanone (0.85g, 5.0 mmol) and 2-furaldehyde diethyl acetal (0.851 g, 5.0 mmol) were added sequentially and the solution stirred for 0.75h. The reaction was then quenched by the addition of a saturated aqueous solution of sodium hydrogencarbonate (20 cm³). The crude product was extracted with dichloromethane (3x30 cm³), dried over (MgSO₄) and the solvent evaporated. Flash chromatography on silica gel with an eluant system of light petroleum (bp 40-60°C) and diethyl ether (4:1) gave 2-furaldehyde ethoxy cyclohexanone (81) as a light red/brown oil, (0.21g, 19%); Found M⁺ 222.1261 C₁₃H₁₈O₃ requires 222.12559; ν max / cm⁻¹ 1713 (ketone C=O); δH (250MHz; CDCl₃) 1.13 (3H, t, J=7.02 Hz), 1.60-1.87 (5H, m), 2.32-2.49 (3H, m), 2.95 (1H, m), 3.43 (2H, m), 4.69 (1H, d, J=8.64 ), 6.27-6.34 (2H, m), 7.39 (1H, m); δc (62.9MHz; CDCl₃) 15.04 (Me), 22.87 (CH₂), 28.50 (CH₂), 30.48 (CH₂), 42.25 (CH₂), 55.14 (CH), 64.39 (CH₂), 73.16 (CH), 109.07 (CH), 109.76 (CH), 142.39 (CH), 152.86 (C), 210.72 (ketone C=O) ppm.
mmol), and benzylxytrimethylsilane (0.541g, 3.0 mmol) were added dropwise at room temperature. The reaction was quenched after 30 minutes by the addition of a saturated aqueous solution of sodium hydrogencarbonate (25 cm$^3$). The crude product was extracted into dichloromethane (3x30 cm$^3$), dried over (MgSO$_4$), filtered and the solvent evaporated. Flash chromatography on silica gel, eluting with light petroleum (bp 40-60°C) and diethyl ether (9.5:0.5) gave 4-benzyloxy-4-phenyl-1-butene (82) as a colourless oil (0.641g, 90%); $\nu_{\text{max}}$ cm$^{-1}$ 1069, 1092 (C-O); $\delta_H$ (250 MHz; CDCl$_3$) 2.0-2.6 (2H, m), 4.27 and 4.44 (2H, AB, $J$=12.5Hz), 4.36 (1H, X of ABX), 5.01 (1H, m), and 7.29 (10H, m) ppm; $\delta_C$ (62.9; CDCl$_3$) 42.65, 70.36, 81.20, 116.83, 126.85, 127.43, 127.63, 127.66, 128.88, 128.39, 134.85, 138.5, and 141.89 ppm.

**Procedure 2**

TfOH (0.075g, 0.5 mmol) was added to a stirred solution of BSU (0.204g, 1.0 mmol) in tetrachloromethane (50 cm$^3$) at room temperature. The solution was stirred for 15 minutes and then benzaldehyde (0.318g, 3.0 mmol), allyl trimethylsilane (0.343g, 3.0 mmol), and benzylxytrimethylsilane (0.541g, 3.0 mmol) were added dropwise at room temperature. The reaction mixture was quenched after 30 minutes by the addition of a saturated aqueous solution of sodium hydrogencarbonate (25 cm$^3$). The crude product was extracted into dichloromethane (3x30 cm$^3$), dried over (MgSO$_4$), filtered and the solvent evaporated. Flash chromatography on silica gel, eluting with light petroleum (bp 40-60°C) and diethyl ether (9.5:0.5) gave 4-benzyloxy-4-phenyl-1-butene (82) as a colourless oil, (0.654g, 92%).

**Procedure 3**

FSA (0.05g, 0.5 mmol) was added to a stirred solution of BSA (0.203g, 1.0 mmol) in dichloromethane (30 cm$^3$) at room temperature. The solution was stirred for 15 minutes and then benzaldehyde (0.318g, 3.0 mmol), allyl trimethylsilane (0.343g, 3.0 mmol), and benzylxytrimethylsilane (0.541g, 3.0 mmol) were added dropwise also at room temperature. The reaction was quenched after 30 minutes by the addition of a saturated aqueous solution of sodium hydrogencarbonate (25 cm$^3$). The crude product was extracted into dichloromethane (3x30 cm$^3$), dried over (MgSO$_4$) filtered and the solvent evaporated. Flash chromatography on silica gel, eluting with light petroleum (bp 40-60°C) and diethyl ether (9.5:0.5) gave 4-benzyloxy-4-phenyl-1-butene (82) as a colourless oil, (0.68g, 95%).

118
Procedure 4

FSA (0.05g, 0.5 mmol) was added to a stirred solution of BSU (0.204g, 1.0 mmol) in dichloromethane (100 cm³) at 0°C. The solution was stirred for 15 minutes and then benzaldehyde (0.318g, 3.0 mmol), allyl trimethylsilane (0.343g, 3.0 mmol), and benzyloxytrimethylsilane (0.541g, 3.0 mmol) were added dropwise at -78°C and gradually allowed to warm to room temperature over a period of 4h. The reaction mixture was then quenched by the addition of a saturated aqueous solution of sodium hydrogencarbonate (25 cm³). The crude product was extracted into dichloromethane (3x30 cm³), dried over (MgSO₄), filtered and the solvent evaporated. Flash chromatography on silica gel, eluting with light petroleum (bp 40-60°C) and diethyl ether (9.5:0.5) gave 4-benzyloxy-4-phenyl-1-butene (82) as a colourless oil, (0.65g, 91%).

Procedure 5

To a stirred solution of benzaldehyde (0.318g, 3.0 mmol), allyl trimethylsilane (0.343g, 3.0 mmol), and benzyloxytrimethylsilane (0.541g, 3.0 mmol) in dichloromethane (50 cm³) at -78°C Fluorosulfonic acid (0.05g, 0.5 mmol) was added dropwise and gradually allowed to warm to room temperature over a period of 4h. The reaction mixture was quenched by the addition of a saturated aqueous solution of sodium hydrogencarbonate (25 cm³). The crude product was extracted into dichloromethane (3x30 cm³), dried over (MgSO₄), filtered and the solvent evaporated. Flash chromatography on silica gel, eluting with light petroleum (bp 40-60°C) and diethyl ether (9:1) gave 4-benzyloxy-4-phenyl-1-butene (82) as a colourless oil, (0.36g, 50%).
8-Methyl-1,4-dioxaspirodecane$^{83}$

![Chemical Structure](attachment:83.png)

**Procedure 1**

FSA (0.1g, 1.0 mmol) was added dropwise to a solution of BSU (0.41g, 2.0 mmol) in dichloromethane (100 cm$^3$) at -78° C and allowed to stir for 15 minutes before 1,2-bis(trimethylsilyloxy)ethane (0.83g, 4.0 mmol) and 4-methylcyclohexanone (0.34g, 3.0 mmol) were added. The reaction mixture was stirred at -78° C and after 2h pyridine (1.0 cm$^3$) was added and the mixture was poured into a saturated aqueous solution of sodium hydrogencarbonate (50 cm$^3$). The crude product was extracted into dichloromethane (3x30 cm$^3$), washed with a saturated aqueous solution of copper sulphate (3x30 cm$^3$), dried over (MgSO$_4$), and filtered. The solvent was removed and the product purified by flash chromatography on silica gel, eluting with (1:4) diethyl ether light-petroleum (bp 40-60° C) to afford 8-methyl-1,4-dioxaspirodecane (83) as a colourless oil (0.55g, 97%); Found M$^+$ 156.1156 C$_9$H$_{16}$O$_2$ requires 156.11502; $\nu$ max / cm$^{-1}$ 1082, 1109 (C-O); $\delta$H(250MHz; CDCl$_3$) 0.91 (3H, d, $J$=6.25Hz), 1.21-1.88 (9H, m), and 3.93 (4H, s) ppm; $\delta$C (62.9MHz; CDCl$_3$) 21.69 (CH$_3$), 31.40 (CH), 32.29 (CH$_2$), 34.56 (CH$_2$), 64.16 (CH$_2$), and 109.03 (C) ppm.

**Procedure 2**

FSA (0.1g, 1.0 mmol) was added dropwise to a solution of BSA (0.41g, 2.0 mmol) in dichloromethane (100 cm$^3$) at -78° C and allowed to stir for 30 minutes before 1,2-bis(trimethylsilyloxy)ethane (27.45g, 133 mmol) and 4-methylcyclohexanone (11.22g, 100 mmol) were added. The reaction mixture was stirred at -78° C for 5h and then left to stir for a further 12h at room temperature. The reaction was then quenched by the addition of a saturated aqueous solution of sodium hydrogencarbonate (50 cm$^3$). The crude product was extracted into dichloromethane (3x50 cm$^3$), dried over (MgSO$_4$) and filtered. The solvent was removed and the
product purified by flash chromatography on silica gel, eluting with (1:4) diethyl ether-light-petroleum (bp 40-60°C) to afford 8-methyl-1,4-dioxaspirodecane (83) as a colourless oil, (13.1g, 84%).

Procedure 3

To a stirred solution of 4-methylcyclohexanone (0.34g, 3.0 mmol) and 1,2-bis(trimethylsilyloxy)ethane (0.83g, 4.0 mmol) in dichloromethane (50 cm³) at -78°C FSA (0.1g, 1.0 mmol) was added dropwise and stirred for 3h before the reaction was quenched by the addition of pyridine (1.0 cm³). The reaction mixture was poured into a saturated aqueous solution of sodium hydrogencarbonate (50 cm³) and the crude product was extracted into dichloromethane (3×30 cm³), washed with a saturated aqueous solution of copper sulphate (3×30 cm³), dried over (MgSO₄) and filtered. The solvent was removed and the product purified by flash chromatography on silica gel, eluting with (1:9) diethyl ether-light-petroleum (bp 40-60°C) to afford 8-methyl-1,4-dioxaspirodecane (83) as a colourless oil, (0.023g, 5%).

1,4-dioxaspirodecane\textsuperscript{83}

\[ \text{O} \quad \text{O} \]

(84)

Procedure 1

TfOH (0.075g, 0.5 mmol) was added dropwise to a solution of BSA (0.203g, 1.0 mmol) in dichloromethane (50 cm³) at room temperature and allowed to stir for 20 minutes. The reaction mixture was then cooled to -78°C before the addition of 1,2-bis(trimethylsilyloxy)ethane (0.52g, 2.5 mmol) and cyclohexanone (0.245g, 2.5 mmol) were added. The solution was quenched after 3.5h with pyridine (1 cm³) and the solution was poured into a saturated aqueous solution of sodium hydrogencarbonate (50 cm³). The crude product was extracted into dichloromethane (3×30 cm³), washed with a saturated aqueous solution of copper sulphate (3×30 cm³), dried over (MgSO₄) and filtered. The solvent was removed to afford 1,4-dioxaspirodecane (84) as a colourless oil, (0.27g, 76%); ν\text{max}/ cm\textsuperscript{-1}1082, 1109 (C=O); δ\text{H}(250 MHz; CDCl₃) 1.41(2H, m), 1.58 (4H, s), 1.59 (4H, s), 3.93 (4H, s) ppm;
\[ \delta_c (62.9 \text{ MHz}; \text{CDCl}_3) 24.03 (2 \times \text{CH}_2), \ 25.23 (\text{CH}_2), \ 35.25 (2 \times \text{CH}_2), \ 64.19(2 \times \text{CH}_2), \text{ and } 109.06 (\text{C}) \text{ ppm.} \]

**Procedure 2**

TfOH (0.15g, 1.0 mmol) was added dropwise to a solution of BSU (0.41g, 2.0 mmol) in dichloromethane (100 cm\(^3\)) at room temperature and allowed to stir for 15 minutes. The solution was then cooled to -78\(^\circ\)C before the addition of 1,2-bis(trimethylsilyloxy)ethane (0.83g, 4.0 mmol) and cyclohexanone (0.29g, 3.0 mmol) were added. The solution was quenched after 3.5h with pyridine (1 cm\(^3\)) and the solution was poured into a saturated aqueous solution of sodium hydroncarbonate (50 cm\(^3\)). The product was extracted into dichloromethane (3x30 cm\(^3\)), washed with a saturated aqueous solution of copper sulphate (3x30 cm\(^3\)), dried over (MgSO\(_4\)) and filtered. The solvent was removed to afford 1,4-dioxaspirodecane (84) as a colourless oil, (0.35g, 82%).

**4-Methoxy-4-phenyl-1-butene\(^84\)**

\[
\begin{array}{c}
\text{OMe}^{} \\
\text{(85)}
\end{array}
\]

**Procedure 1**

TfOH (0.075g, 0.5 mmol) was added to a stirred solution of BSA (0.203g, 1.0 mmol) in dichloromethane (30 cm\(^3\)) at room temperature. The reaction mixture was stirred for 15 minutes and then cooled to -78\(^\circ\)C before the addition of solutions of benzaldehyde dimethyl acetal (0.31g, 2.0 mmol) and allyl trimethylsilane (0.25g, 2.2 mmol) in dichloromethane (25 cm\(^3\)). The reaction mixture was quenched after 1 h by the addition of a saturated aqueous solution of sodium hydroncarbonate (25 cm\(^3\)). The crude product was extracted into dichloromethane (3x30 cm\(^3\)), dried over (MgSO\(_4\)), filtered and the solvent evaporated. Flash chromatography on silica gel, eluting with light petroleum (bp 40-60\(^\circ\)C) and diethyl ether (4:1) gave 4-methoxy-4-phenyl-1-butene (85) as a colourless oil, (0.27g, 83%); \(\nu_{\max} \text{ /cm}^{-1} 1069, 1092\) (C-O); \(\delta_H(250 \text{ MHz}; \text{CDCl}_3) 2.7-2.52 (2H, m), 3.14 (3H, s), 4.09 (1H, m), 4.96 (2H, m), 5.68 (1H, m) \text{ and } 7.22 (5H, m) \text{ ppm; } \delta_c (62.9; \text{CDCl}_3) 40.58 (\text{CH}_2), 54.67 \]
Procedure 2

TfOH (0.075g, 0.5 mmol) was added to a stirred solution of BSU (0.204g, 1.0 mmol) in dichloromethane (50 cm³) at room temperature. The solution was stirred for 15 minutes and then cooled to -78°C before the addition of solutions of benzaldehyde dimethyl acetal (0.76g, 5.0 mmol) and allyl trimethylsilane (0.63g, 5.5 mmol) in dichloromethane (25 cm³). The reaction was quenched after 1 h by the addition of a saturated aqueous solution of sodium hydrogencarbonate (25 cm³). The crude product was extracted into dichloromethane (3x30 cm³), dried over (MgSO₄), filtered and the solvent evaporated. Flash chromatography on silica gel, eluting with light petroleum (bp 40-60°C) and diethyl ether (4:1) to afford 4-methoxy-4-phenyl-1-butene (85) as a colourless oil, (0.80g, 99%).

Procedure 3

FSA (0.1g, 1.0 mmol) was added to a stirred solution of BSU (0.41g, 2.0 mmol) in dichloromethane (100 cm³) at room temperature. The solution was stirred for 10 minutes and then cooled to -78°C before the addition of solutions of benzaldehyde dimethyl acetal (0.61g, 4.0 mmol) and allyl trimethylsilane (0.50g, 4.4 mmol) in dichloromethane (25 cm³). The reaction was quenched after 2 h by the addition of a saturated aqueous solution of sodium hydrogencarbonate (25 cm³). The crude product was extracted into dichloromethane (3x30 cm³), dried over (MgSO₄) filtered, and the solvent evaporated to afford 4-methoxy-4-phenyl-1-butene (85) as a colourless oil, (0.65g, 100%).

I-Ethoxymethylnapthalene \(^{85}\)

\[
\text{\includegraphics[width=0.2\textwidth]{image.png}}
\]

(86)
Procedure 1

To a solution of BSU (0.41g, 2.0 mmol) in dichloromethane (50 cm³), FSA (0.1g, 1.0 mmol), was added dropwise and allowed to stir for 0.5h at room temperature. The solution was then cooled to -78°C and solutions of triethylsilane (0.66g, 5.7 mmol) and 1-naphthaldehyde diethyl acetal (1.17g, 5.1 mmol) in dichloromethane (20 cm³) were added sequentially and stirred for 2h before the reaction was quenched with the addition of a saturated aqueous solution of sodium hydrogen carbonate (25 cm³). The crude product was extracted into dichloromethane (3x30 cm³), dried over (MgSO₄) filtered, and the solvent evaporated. Flash chromatography on silica gel, eluting with light petroleum (bp 40-60°C) and diethyl ether (4:1) gave 1-ethoxymethylnaphthalene (86) as a colourless oil, (0.68g, 83%); Found M⁺ 186.1039, C₁₃H₁₄O requires 186.10446; δH(250 MHz; CDCl₃) 1.24 (3H, t, J=7.01 Hz), 3.57 (2H, q, J=6.99 Hz), 4.90 (2H, s), 7.35-7.52 (4H, m), 7.53-7.83 (2H, m), 8.08 (1H, d, J=8.1 Hz), ppm; δC(62.9; CDCl₃) 15.34 (Me), 65.85 (CH₂), 71.20 (CH₂), 124.04 (CH), 125.25 (CH), 125.74 (CH), 126.14 (CH), 126.29 (CH), 128.51 (CH), 128.53 (CH), 131.80 (C), 133.81 (C), 134.05 (C) ppm.

Procedure 2

To a stirred solution of triethylsilane (0.26g, 2.2 mmol) and 1-naphthaldehyde diethyl acetal (0.46g, 2.0 mmol) in dichloromethane (50 cm³) at -78°C FSA (0.1g, 1.0 mmol) was added dropwise. The solution was stirred for 3h before being quenched by the addition of a saturated aqueous solution of sodium hydrogen carbonate (25 cm³). The crude product was extracted into dichloromethane (3x30 cm³), dried over (MgSO₄), filtered and the solvent evaporated. Flash chromatography on silica gel, eluting with light petroleum (bp 40-60°C) and diethyl ether (9:1) gave 1-ethoxymethylnaphthalene (86) as a colourless oil, (0.32g, 87%).
Benzylmethylether

![Benzylmethylether](image)

(87)

### Procedure 1

To a solution of BSA (0.61g, 3.0 mmol) in dichloromethane (50 cm$^3$), TfOH (0.23g, 1.5 mmol), was added dropwise and allowed to stir for 0.5h at room temperature. The solution was then cooled to -78°C and solutions of triethylsilane (0.66g, 5.7 mmol) and benzaldehyde dimethyl acetal (0.78g, 5.1 mmol) in dichloromethane (20 cm$^3$), were added sequentially and stirred for 2h before the reaction was quenched with the addition of a saturated aqueous solution of sodium hydrogen carbonate (25 cm$^3$). The crude product was extracted into dichloromethane (3x30 cm$^3$), dried over (MgSO$_4$), filtered and the solvent evaporated. Flash chromatography on silica gel, eluting with light petroleum (bp 40-60°C) and diethyl ether (4:1) gave benzylmethylether (87) as a colourless oil, (0.55g, 88%); δ$^H$(250 MHz; CDCl$_3$) 3.37 (3H, s), 4.45 (2H, s), 7.33 (5H, s); δ$^C$(62.9; CDCl$_3$) 44.53 (OMe), 74.71 (CH$_2$), 128.16 (CH), 128.31(2 x CH), 128.41 (2 x CH) ppm.

### Procedure 2

To a solution of BSU (0.20g, 1.0 mmol) in dichloromethane (100 cm$^3$), TfOH (0.075g, 0.5 mmol), was added dropwise and allowed to stir for 0.5h at room temperature. The solution was then cooled to 0°C and solutions of triethylsilane (0.23g, 2.0 mmol) and benzaldehyde dimethyl acetal (0.27g, 1.8 mmol) in dichloromethane (20 cm$^3$), were added sequentially and stirred for 2h at room temperature before the reaction was quenched with the addition of a saturated aqueous solution of sodium hydrogen carbonate (25 cm$^3$). The crude product was extracted into dichloromethane (3x30 cm$^3$), dried over (MgSO$_4$), filtered and the solvent evaporated. Flash chromatography on silica gel, eluting with light petroleum (bp 40-60°C) and diethyl ether (4:1) gave benzylmethylether (87) as a colourless oil, (0.19g, 85%).
Procedure 3

To a solution of BSA (0.41g, 2.0 mmol) in dichloromethane (50 cm³), FSA (0.1g, 1.0 mmol), was added dropwise and allowed to stir for 10 minutes at 0°C. Triethylsilane (0.663g, 5.7 mmol) and benzaldehyde dimethyl acetal (0.75g, 5.1 mmol) in dichloromethane (20 cm³), were added sequentially and stirred for 2h at room temperature before the reaction was quenched with the addition of a saturated aqueous solution of sodium hydrogencarbonate (25 cm³). The crude product was extracted into dichloromethane (3x30 cm³), dried over (MgSO₄), filtered and the solvent evaporated. Flash chromatography on silica gel, eluting with light petroleum (bp 40-60°C) and diethyl ether (4:1) gave benzylmethylether (87) as a colourless oil, (0.47g, 76%)

1-Methoxy-1-cyclohexylmethane

\[ \text{OMe} \]

To a solution of BSU (0.41g, 2.0 mmol) in dichloromethane (100 cm³), FSA (0.1g, 1.0 mmol), was added dropwise and allowed to stir for 10 minutes at -83°C. Triethylsilane (0.66g, 5.7 mmol) and cyclohexylaldehyde dimethyl acetal (0.81g, 5.1 mmol) in dichloromethane (20 cm³), were added sequentially and stirred for 2h at -83°C before the reaction was quenched by the addition of a saturated aqueous solution of sodium hydrogencarbonate (25 cm³). The crude product was extracted into dichloromethane (3x30 cm³), dried over (MgSO₄), filtered and the solvent evaporated. Flash chromatography on silica gel, eluting with light petroleum (bp 40-60°C) and diethyl ether (4:1) gave 1-methoxy-1-cyclohexylmethane (88) as a colourless oil, (0.54g, 82%); δH(250MHz; CDCl₃) 1.01-1.26 (5H, m), 1.62-1.79 (6H, m), 3.10 (2H, d, J=6.44 Hz), 3.24 (3H, m); δC(62.9MHz; CDCl₃) 23.85 (2 x CH₂), 24.71 (CH₂), 28.16 (2 x CH₂), 36.12 (CH), 56.83 (3H, m), 76.98 (CH₂) ppm.
6.4 Experimental for Chapter 4

**1,2-Dimethylindole**

![1,2-Dimethylindole](image)

A suspension of crushed potassium hydroxide pellets (4.49g, 80.0 mmol) in dimethylsulfoxide (75 cm$^3$) was stirred for 30 minutes. 2-Methylindole (5.25g, 40.0 mmol) was then added to this reaction mixture and stirred for a further 30 minutes. Methyl iodide (5.68g, 40.0 mmol) was then added and the reaction mixture stirred for a further 12h at room temperature. The reaction mixture was quenched by the addition of water (30 cm$^3$) and the crude product extracted into diethyl ether (3x30 cm$^3$), dried over (MgSO$_4$), filtered and the solvent evaporated. Flash chromatography on silica gel using an eluant of diethyl ether and light petroleum (bp 40-60°C) (1:5) gave 1,2-dimethylindole (90) (5.41 g, 93%) as colourless needles mp=56-57°C; Found M$^+$ 145.0751 C$_{10}$H$_{11}$N requires 145.08914; $\delta_H$ (250MHz; CDCl$_3$) 2.93 (3H, s), 3.61 (3H, s), 6.23 (CH), 7.05-7.24 (3H, m), 7.50 (1H, d, $J$=7.55) ppm; $\delta_C$ (62.9MHz; CDCl$_3$) 12.71 (Me), 29.30 (N-Me), 99.52 (CH), 108.67 (CH), 119.19 (CH), 119.57 (CH), 120.38 (CH), 127.92 (CH), 136.75 (C), 137.28 (C) ppm.

**Methyl (N-methyl-3-indolyl)hydroxyacetate**

![Methyl (N-methyl-3-indolyl)hydroxyacetate](image)

Sodium borohydride (0.34g, 18.0 mmol) was added portionwise to a stirred solution of methyl (N-methyl-3-indolyl)glyoxylate (3.93g, 9.0 mmol) in methanol (30 cm$^3$) at 0°C. The solution was then stirred at 25°C for 1 hour before being quenched by the addition of water (25 cm$^3$). The crude product was extracted with dichloromethane (3x30 cm$^3$), dried over (MgSO$_4$) and the solvent evaporated. Flash chromatography on silica gel with an eluant system of light petroleum (bp 40-60°C) and ethyl acetate (17:3) gave methyl (N-methyl-3-indolyl)hydroxyacetate (91) as a crystalline yellow solid, (2.5g, 63%); mp=95-97°C; (Found: C, 66.02; H, 5.89; N, 6.37, C$_{12}$H$_{13}$NO$_3$ 127
requires C, 65.75; H, 5.94; N, 6.45%); Found M+ 219.0909 C_{12}H_{13}NO_{3} requires 219.08954; v_{max}/cm^{-1} 3531 (OH), 1735 (ester C=O), \delta_H (250MHz; CDCl_3) 3.24 (H, broad O-H), 3.74 (3H, s), 3.75 (3H, s), 5.46 (1H, s), 7.13-7.31 (4H, m), 7.67 (1H, m) ppm; \delta_C (62.9MHz; CDCl_3) 32.80 (N-CH_3), 52.79 (OMe), 67.05 (CH), 109.52 (CH), 112.13 (C), 119.42 (CH), 119.82 (CH), 122.17 (CH), 125.85 (C), 127.62 (CH), 137.26 (C), 174.56 (C) ppm.

Methyl (1,2-dimethyl-3-indolyl)-(N-methyl-3-indolyl)acetate

\[
\begin{align*}
\text{MeCO}_2H & \quad \text{H} \\
\text{N} & \quad \text{Me}
\end{align*}
\]

(93)

Procedure I

To a solution of methyl (N-methyl-3-indolyl)hydroxyacetate (91) (0.11 g, 0.5 mmol) and 1,2-dimethylindole (0.08 g, 0.55 mmol) in dichloromethane (30 cm³) at ambient temperature Sc(OTf)₃ (0.049 g, 0.1 mmol) was added. The reaction mixture was then stirred for 30 minutes before being quenched by the addition of de-ionised water (10 cm³). The Sc(OTf)₃ was recovered from the aqueous phase while the product was extracted into dichloromethane (3 x 20 cm³), dried over (MgSO₄), filtered and the solvent evaporated under vacuo to yield the crude product. Flash chromatography on silica gel using an eluent of ethyl acetate and light petroleum (bp 40-60°C) (3.5 : 6.5) gave methyl (1,2-dimethyl-3-indolyl)-(N-methyl-3-indolyl)acetate (93) as a colourless crystalline solid, (0.153 g, 88%); m.p=170-172°C; \nu_{max}/cm^{-1} 1736 (C=O, ester); Found M+ 346.1682 C_{22}H_{22}N_{2}O_{2} requires 346.16812 \delta_H (250MHz; CDCl_3) 2.41 (3H, s), 3.66 (3H, s), 3.67 (3H, s), 3.70 (3H, s), 5.48 (1H, s), 6.92-7.28 (7H, m), 7.42 (1H, d, J=7.28 Hz), 7.70 (1H, d, J=7.82 Hz) ppm; \delta_C (62.9MHz; CDCl_3) 10.57 (CH₃), 29.55 (N-Me), 32.66 (N-Me), 40.03 (OMe), 52.05 (CH), 107.76 (C), 108.56 (CH), 109.21 (CH), 112.17 (C), 118.89 (CH), 118.94 (CH), 119.06 (CH), 119.46 (CH), 120.56 (CH), 121.51 (CH), 126.86 (C), 127.29 (C), 127.98 (CH), 134.25 (C), 136.58 (C), 137.01 (C), 173.72 (C=O, ester) ppm.
Procedure 2

To a solution of methyl (N-methyl-3-indolyl)hydroxyacetate (91) (44mg, 0.2 mmol) and 1,2-dimethylindole (29mg, 0.2 mmol) in dichloromethane (10 cm³) at ambient temperature Cu(OTf)₂ (7.0mg, 0.04 mmol) was added. The solution was then stirred for 5 minutes before the reaction was quenched by the addition of de-ionised water (10 cm³). The crude product was extracted into dichloromethane (3x20 cm³) dried over (MgSO₄), filtered and the solvent evaporated. Flash chromatography on silica gel using an eluant of ethyl acetate and light petroleum (bp 40-60°C) (3.5:6.5) gave methyl (1,2-dimethyl-3-indolyl)-(N-methyl-3-indolyl)acetate (93) as a colourless crystalline solid, (64mg, 92%).

Methyl (phenyl)-(N-methyl-3-indolyl)acetate

Procedure 1

To a solution of racemic methyl mandelate (0.332g, 2.0 mmol) and N-methylindole (0.29g, 2.2 mmol) in dichloromethane (30 cm³), Sc(OTf)₃ (100mg, 0.2 mmol) was added. The solution was heated under reflux for 48h and the reaction mixture quenched by the addition of water (10 cm³) and the product extracted into dichloromethane (3x30 cm³), dried over (MgSO₄), filtered and the solvent evaporated under vacuo. Flash chromatography on silica gel using an eluant of diethyl ether and light petroleum (bp 40-60°C) (1:4) gave methyl (phenyl)-(N-methyl-3-indolyl)acetate (95) as a light brown oil, (0.24 g, 42%); Found M⁺ 279.1098, C₁₈H₁₇NO₂ requires 279.12592; νmax/cm⁻¹ 1737 (C=O, ester); δH (250MHz; CDCl₃) 3.74 (3H, s), 3.75 (3H, s), 5.25 (1H, s), 7.03-7.41 (10H, m) ppm; δC (62.9MHz; CDCl₃) 32.74 (N-Me), 48.76 (OMe), 52.28 (CH), 109.31 (CH), 111.87 (C), 119.96 (2 x CH), 120.16 (CH), 122.27 (C), 127.18 (CH), 127.84 (CH), 128.36 (2 x CH), 128.51 (CH), 137.58 (C), 139.01 (C), 173.79 (C=O, ester) ppm.

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Procedure 2

To a solution of (S)-methyl mandelate (83 mg, 0.5 mmol) and N-methylindole (72 mg, 0.55 mmol) in dichloromethane (30 cm³), Sc(OTf)₃ (74 mg, 0.15 mmol) was added. The solution was heated under reflux for 28 h and the reaction quenched by the addition of water (10 cm³) and the crude product extracted into dichloromethane (3 x 30 cm³), dried over (MgSO₄), filtered and the solvent evaporated under vacuo. Flash chromatography on silica gel using an eluant of diethyl ether and light petroleum (bp 40-60°C) (1:4) gave methyl (phenyl)-(N-methyl-3-indolyl)acetate (95) as a light brown oil, (18 mg, 13%).

(-)-α-methylbenzyl-(N-methyl-3-indolyl)glyoxamide

![Chemical Structure](image)

To a solution of N-methylindole (2.75 g, 20 mmol) in diethyl ether (40 cm³) at 0°C a solution of oxalyl chloride (3.17 g, 25 mmol) in diethyl ether (35 cm³) was added dropwise over a period of 15 minutes. The reaction mixture was then stirred at room temperature for 1 h before the careful addition, over a period of 0.5 h, of a solution (-)-α-methylbenzylamine (3.03 g, 25 mmol) and triethylamine (5.06 g, 40 mmol) dissolved in dichloromethane (75 cm³). The solution was then stirred for 12 h before the reaction was quenched by the addition of a saturated aqueous solution of sodium hydrogen carbonate (40 cm³). The crude product was then extracted into dichloromethane (3 x 40 cm³), dried over (MgSO₄), filtered and the solvent evaporated. Flash chromatography on silica gel using an eluant of diethyl ether and light petroleum (bp 40-60°C) (1:4) gave (-)-α-methylbenzyl-(N-methyl-3-indolyl)glyoxamide (97) (5.99 g, 89%) as a yellow crystalline solid mp = 98°C; Found M⁺ 306.1380 C₁₉H₁₈N₂O₂ requires 306.1368; νmax/cm⁻¹ 1620, 1670, 3307 (N-H); δH (250 MHz; CDCl₃) 1.52 (3H, d, J = 6.91 Hz), 3.55 (3H, s), 5.12 (1H, q, J = 7.39 Hz), 7.15-7.36 (8H, m), 8.06 (1H, d, J = 8.22 Hz), 8.37-8.41 (1H, m), 8.82 (1H, s) ppm; δC (62.9 MHz; CDCl₃) 21.99 (Me), 33.41 (N-Me), 48.92 (CH), 109.95 (CH), 11.77 (C), 122.47 (CH), 123.31 (CH), 123.75 (CH), 126.13 (2 x CH), 127.35 (CH), 128.67 (2 x CH), 136.92 (C), 142.22 (CH), 143.03 (C), 159.16 (C), 161.86 (C=O), 180.08 (C=O) ppm.
128.67 (2 x CH), 136.92 (C), 142.22 (CH), 143.03 (C), 159.16 (C), 161.86 (C=O), 180.08 (C=O) ppm.

(-)-α-methylbenzyl-[(N-methyl-3-indolyl)hydroxyamide

![Chemical structure](https://example.com/structure.png)

(98)

To a solution of (-)-α-methylbenzyl-(N-methyl-3-indolyl)glyoxamide (3.06g, 10.00 mmol) in a mixed solvent system of dichloromethane (30 cm³) and methanol (30 cm³) at 0°C sodium borohydride (0.57g, 15.00 mmol) was added and the solution was stirred for 1h before the reaction was quenched by the addition of a saturated aqueous solution of sodium hydrogencarbonate (40 cm³). The crude product was then extracted into dichloromethane (3x40 cm³), dried over (MgSO₄), filtered and the solvent evaporated. Flash chromatography on silica gel using an eluant of ethyl acetate and light petroleum (bp 40-60°C) (1:4) gave (-)-α-methylbenzyl-(N-methyl-3-indolyl)hydroxyamide (98) as a white crystalline solid, (2.64g, 86%); mp=248°C; Found M⁺ 308.1507 C₁₉H₂₀N₂O₂ requires 308.15247; v_max/cm⁻¹ 3397 (N-H), 3154 (O-H); δ_H (250MHz; CDCl₃) 1.39 (3H, d, J=6.76 Hz), 1.62 (1H, s, br), 3.68 (3H, s), 5.24 (1H, quin. J=7.55 Hz), 5.36 (1H, s), 6.22 (1H, d, br, J=8.24 Hz), 6.83-6.84 (2H, m), 6.99-7.31 (6H, m), 7.46-7.56 (2H, m) ppm. δ_c (62.9MHz; CDCl₃) 21.80 (CH₃), 32.87 (N-Me), 48.77 (CH), 67.97 (CH), 109.47 (CH), 113.02 (C), 119.41 (CH), 119.53 (CH), 122.14 (CH), 125.99 (CH), 126.20 (CH), 127.22 (CH), 127.36 (CH), 128.41 (CH), 128.47 (CH), 137.22 (C), 138.73 (C), 143.88 (C), 172.04 (C=O) ppm.

(-)-α-methylbenzyl-(1,2-dimethyl-3-indolyl)-(N-methyl-3-indolyl)amide

![Chemical structure](https://example.com/structure.png)

(99)

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Procedure 1

To a solution of (-)-α-methylbenzyl-(N-methyl-3-indolynhydroxyamide (0.154g, 0.5 mmol) and 1,2-dimethylindole (0.80g, 0.55 mmol) in dichloromethane (30 cm$^3$) at 25°C, Cu(OTf)$_2$ (36mg, 0.1 mmol) was added. The solution was stirred for 0.5h before the reaction was quenched by the addition of a saturated solution of sodium hydrogencarbonate (40 cm$^3$). The crude product was then extracted into dichloromethane (3x20 cm$^3$), dried over (MgSO$_4$), filtered and the solvent evaporated. Flash chromatography on silica gel using an eluant of ethyl acetate and light petroleum (bp 40-60°C) (1:1) gave (-)-α-methylbenzyl-(1,2-dimethyl-3-indolyl)-(N-methyl-3-indolynamide(99), as a light grey crystalline solid, (0.154g, 71%); mp=187°C; Found M$^+ 435.2311$ C$_{29}$H$_{29}$N$_3$O requires 435.2305; $\nu_{max}$/cm$^{-1}$ 1654 (C=O), 3298, 3393 (N-H); $\delta_H$ (250MHz; CDCl$_3$) 1.38 (3H, d, J=6.89), 2.34 (3H, s), 3.63 (3H, s), 3.66 (3H, s), 5.15-5.31(1H, m), 5.35 (1H, s), 6.30-6.35 (1H, s, br), 6.74-7.54(28H, m) ppm; $\delta_C$ (100.64MHz; CDCl$_3$) 11.01 (CH$_3$), 21.40 (CH$_3$), 30.00 (N-Me), 33.09 (N-Me), 42.48 (CH), 49.08 (CH), 109.09 (CH), 109.74 (CH), 112.36 (C), 119.31 (CH), 119.43 (C), 119.54 (CH), 119.64 (C), 119.73 (CH), 121.06 (CH), 122.15 (CH), 126.61 (CH), 126.85 (CH), 127.38 (CH), 127.53 (CH), 128.72 (CH), 128.83 (CH), 128.99 (CH), 134.82 (C), 137.59 (C), 137.82 (C), 143.41 (C), 143.91 (C), 172.19 (C=O) ppm.

Procedure 2

To a solution of (-)-α-methylbenzyl-(N-methyl-3-indolynhydroxyamide (98) (0.154g, 0.5 mmol) and 1,2-dimethylindole (0.80g, 0.55 mmol) in dichloromethane (30 cm$^3$) at 25°C Sc(OTf)$_3$ (49mg, 0.1 mmol) was added. The solution was stirred for 0.5h before the reaction was quenched by the addition of a saturated aqueous solution of sodium hydrogencarbonate (40 cm$^3$). The crude product was then extracted into dichloromethane (3x20 cm$^3$), dried over (MgSO$_4$), filtered and the solvent evaporated. Flash chromatography on silica gel using an eluant of ethyl acetate and light petroleum (bp 40-60°C) (1:1) gave (-)-α-methylbenzyl-(1,2-dimethyl-3-indolyl)-(N-methyl-3-indolynamide (99), (0.128g, 59%).
1,2-dimethyl-3-indolyl-(3-indolyl)methane

(103)

Procedure 1

To a solution of 3-methyl(hydroxy)indole (0.147g, 1.0 mmol), and 1,2-dimethylindole (0.145g, 1.0 mmol) in dichloromethane (30 cm³), Sc(OTf)₃ (49mg, 0.1 mmol), was added and the solution stirred for 2h. The reaction was quenched by the addition of water (20 cm³) and the product extracted into dichloromethane (3x25 cm³), dried over (MgSO₄), filtered and the solvent evaporated. Flash chromatography on silica gel using an eluant of diethyl ether and light petroleum (bp 40-60°C) (1:4) gave 1,2-dimethyl-3-indolyl-(3-indolyl)methane (103), as light brown solid, (0.128g, 49%); mp=145-146°C; Found M⁺ 274.1482 CI₉H₁₈N₂ requires 274.1469; νmax/cm⁻¹ 3395 (N-H); δH (400MHz; CDCl₃) 2.39 (3H, s), 3.68 (3H, s), 4.18 (2H, s), 7.01-7.33 (7H, m), 7.47 (1H, d, J=7.68 Hz), 7.66 (1H, m), 7.79 (1H, s, br ) ppm; δC (100.64MHz; CDCl₃) 9.66 (Me), 19.55 (CH₂), 28.84 (N-Me), 107.73 (CH), 108.90 (C), 110.29 (CH), 115.93 (C), 117.80 (CH), 117.95 (CH), 118.24 (CH), 118.47 (CH), 119.72 (CH), 121.15 (CH), 121.36 (CH), 126.81 (C), 127.38 (C), 132.49 (C), 135.85 (C), 136.00 (C) ppm.

Procedure 2

To a solution of 3-methyl(hydroxy)indole (0.147g, 1.0 mmol) and 1,2-dimethylindole (0.145g, 1.0 mmol) in dichloromethane (30 cm³), Cu(OTf)₂ (36mg, 0.1 mmol), 10mol %, was added and the solution stirred for 2h. The reaction was quenched by the addition of water (20 cm³) and the crude product extracted into dichloromethane (3x25 cm³), dried over (MgSO₄), filtered and the solvent evaporated. Flash chromatography on silica gel using an eluant of diethyl ether and light petroleum (bp 40-60°C) (1:4) gave 1,2-dimethyl-3-indolyl-(3-indolyl)methane (103), (0.139g, 53%).

Procedure 3

To a solution of 3-methyl(hydroxy)indole (0.147g, 1.0 mmol), and 1,2-dimethylindole (0.145g, 1.0 mmol) in dichloromethane (30 cm³), Sc(OTf)₃ (0.1 mmol, 49mg), recovered from aqueous phase, was added and the solution stirred for
2h. The reaction was quenched by the addition of water (20 cm$^3$) and the crude product extracted into dichloromethane (3x25 cm$^3$), dried over (MgSO$_4$), filtered and the solvent evaporated. Flash chromatography on silica gel using an eluant of diethyl ether and light petroleum (bp 40-60°C) (1:4) gave 1,2-dimethyl-3-indoly1-(3-indoly1)methane (103), (0.136g, 52%).

\[ N\text{-methyl-3-indoly1-(3-indoly1)methane} \]

\[
\begin{array}{c}
\text{Me} \\
N \\
\end{array}
\]

(104)

Procedure 1

To a solution of 3-methyl(hydroxy)indole (85mg, 0.58 mmol), and N-methylindole (76mg, 0.85 mmol) in dichloromethane (30 cm$^3$), Sc(OTf)$_3$ (49mg, 0.1 mmol), was added and the solution stirred for 2h. The reaction was quenched by the addition of water (20 cm$^3$) and the crude product extracted into dichloromethane (3x25 cm$^3$), dried over (MgSO$_4$), filtered and the solvent evaporated. Flash chromatography on silica gel using an eluant of diethyl ether and light petroleum (bp 40-60°C) (1:4) gave \( N\text{-methyl-3-indoly1-(3-indoly1)methane} \) (104) as a light brown solid, (84mg, 56%); mp=125°C; Found M$^+$ 260.1126 C$_{18}$H$_{16}$N$_2$ requires 260.1314; \( \nu_{\text{max}}/\text{cm}^{-1} \) 3395 (N-H); \( \delta_H \) (250MHz; CDCl$_3$) 3.68 (3H, s), 4.22 (2H, s), 6.77-7.63 (10H, m), 7.78 (1H, s, broad) ppm; \( \delta_C \) (62.9MHz; CDCl$_3$) 21.00 (CH$_2$), 32.50 (N-Me), 109.04 (CH), 110.31 (C), 110.96 (CH), 117.10 (C), 118.52 (CH), 119.17 (CH), 119.22 (CH), 121.15 (CH), 121.80 (2 x CH), 122.10 (CH), 126.92 (CH), 128.13 (C), 129.81 (C), 138.04 (C), 139.89 (CH) ppm.

Procedure 2

To a solution of 3-methyl(hydroxy)indole (85mg, 0.58 mmol), and N-methylindole (76mg, 0.85 mmol) in dichloromethane (30 cm$^3$), Cu(OTf)$_2$ (36mg, 0.1 mmol), was added and the solution stirred for 2h. The reaction was quenched by the addition of water (20 cm$^3$) and the crude product extracted into dichloromethane (3x25 cm$^3$), dried over (MgSO$_4$), filtered and the solvent evaporated. Flash chromatography on
silica gel using an eluant of diethyl ether and light petroleum (bp 40-60°C) (1:4) gave
N-methyl-3-indolyl-(3-indolyl)methane (104) (87mg, 58%).

1-Methoxy-N-2-(3-indolyl)-ethyl-isoindol-3[H]-one

A solution of N-2'-carbomethoxybenzylidene-2-indolethylamine (1.00g, 3.26 mmol)
in methanol (70 cm³) and a catalytic amount of sodium was stirred for 48h. The crude
product was then extracted into dichloromethane (3x25 cm³), washed with water
(2x20 cm³) dried over (MgSO₄), filtered and the solvent evaporated. The crude
product was then purified by recrystallization from ethyl acetate and light petroleum
(bp 40-60°C) (1:1) giving 1-methoxy-N-2-(3-indolyl)-ethyl-isoindol-3[H]-one (110)
as colourless needles (0.98g, 98%); mp=153-155°C; (Found: C, 74.41; H, 5.66; N,
9.18% C₁₉H₁₈N₂O₂ requires C, 74.50; H, 5.88; N, 9.15 %); Found M⁺ 306.1346
C₁₉H₁₈N₂O₂ requires 306.1368; v_max/cm⁻¹ 3508 (N-H), 1689 (C=O); δ_H
(250MHz; CDCl₃) 2.86 (3H, s), 3.12-3.20 (2H, m), 3.53-3.65 (1H, m), 4.00-4.17 (1H,
m), 5.75 (1H, s), 7.03 (1H, s), 7.04-7.16 (3H, m), 7.31-7.34 (1H, m), 7.46-7.52 (3H,
m), 7.52-7.68 (1H, m), 8.35 (broad N-H) ppm; δ_C (62.9MHz; CDCl₃) 23.98 (CH₂),
39.90 (CH₂), 49.27 (Ome), 86.55 (CH), 111.19 (CH), 112.62 (C), 118.64 (2 x CH),
119.30 (CH), 121.94 (CH), 123.32 (CH), 123.36 (CH), 127.31 (C), 129.87 (CH),
131.91 (CH), 133.10 (C), 136.29 (C), 140.40 (C), 167.86 (C=O) ppm.

1-Methoxy-2-(3-methoxy-phenoxy)-N-ethylisoindol-3[1H]-one

A solution of N-2'-carbomethoxybenzylidene-2-(3-methoxy-phenoxy)-ethylamine
(1.80g, 5.75 mmol) in methanol (50 cm³) and a catalytic amount of sodium was
stirred for 48h. The crude product was then extracted into dichloromethane (3x25 cm³), washed with water (2x20 cm³) dried over (MgSO₄), filtered and the solvent evaporated. Flash chromatography on silica gel using an eluant of ethyl acetate and light petroleum (bp 40-60°C) (1:1) gave 1-methoxy-2-(3-methoxy-phenoxyl)-N-ethylisoindol-3[H]one (111) as a yellow oil, (1.8g, 100%); Found M⁺ 313.1320 C₁₈H₁₉N₀₄ requires 313.1314; νmax/cm⁻¹ 1705 (C=O); δH (250MHz; CDCl₃) 2.93 (3H, s), 3.73 (1H, m), 3.76 (3H, s), 4.10-4.26 (3H, m), 6.09 (1H, s), 6.45-6.51 (3H, m), 7.11-7.14 (1H, m), 7.51-7.56 (3H, m), 7.82 (1H, m) ppm; δC (62.9MHz; CDCl₃) 39.35 (CH₂), 49.87 (OMe), 55.67 (OMe), 66.59 (CH₂), 87.92 (CH), 101.32 (CH), 106.92 (CH), 107.10 (CH), 123.72 (CH), 123.89 (CH), 130.34 (CH), 130.46 (CH), 132.54 (CH), 133.16 (C), 141.13 (C), 160.0 (C), 161.30 (C), 168.32 (C=O) ppm.

1-Methoxy-N-2-(3,4-dimethoxyphenyl)-ethyl-isoindol-3[H]one

A solution of N-2'-carbomethoxybenzylidene-2-(3,4-dimethoxyphenyl)-ethylamine (1.5g, 4.58 mmol) in methanol (50 cm³) and a catalytic amount of sodium was stirred for 48h. The crude product was then extracted into dichloromethane (3x25 cm³), washed with water (2x20 cm³) dried over (MgSO₄), filtered and the solvent evaporated. Flash chromatography on silica gel using an eluant of ethyl acetate and light petroleum (bp 40-60°C) (2:3) gave 1-methoxy-N-2-(3,4-dimethoxyphenyl)-ethyl-isoindol-3[H]one (112) as a yellow oil, (1.42g, 95%); Found M⁺ 327.1443 C₁₉H₂₁N₀₄ requires 327.1470; νmax/cm⁻¹ 1702 (C=O); δH (250MHz; CDCl₃) 2.84 (3H, s), 2.94-3.0 (2H, m), 3.40-3.47 (1H, m), 3.79 (3H, s), 3.84 (3H, s), 3.97-4.08 (1H, m), 5.60 (1H, s), 6.76-6.79 (3H, m), 7.45-7.57 (3H, m), 7.81-7.84 (1H, m) ppm; δC (62.9MHz; CDCl₃) 33.76 (CH₂), 40.91 (CH₂), 49.08 (OMe), 55.69 (OMe), 55.76 (OMe), 86.52 (CH), 111.26 (CH), 111.81 (CH), 120.58 (CH), 123.33 (CH), 123.41 (CH), 129.83 (CH), 131.17 (C), 131.89 (CH), 132.97 (C), 140.25 (C), 147.53 (C), 148.84 (C), 167.40 (C=O) ppm.

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A solution of N-2'-carbomethoxybenzylidene-2-(3,4-dimethoxyphenyl)propylamine (2.46 g, 7.21 mmol) in methanol (70 cm³) and a catalytic amount of sodium was stirred for 48 h. The crude product was then extracted into dichloromethane (3 x 25 cm³), washed with water (2 x 20 cm³) dried over (MgSO₄), filtered and the solvent evaporated. Flash chromatography on silica gel using an eluant of ethyl acetate and light petroleum (bp 40-60°C) (1:1) gave 1-methoxy-N-2-(3,4-dimethoxyphenyl)propylisoindol-3H-one (113) as a yellow oil, (2.46 g, 100%); Found M⁺ 341.1638, requires 341.1627; vmax/cm⁻¹ 1702 (C=O); δH (250 MHz, CDCl₃) 0.96-2.0 (2H, m), 2.62-2.68 (2H, m), 2.87 (3H, s), 3.27-3.33 (1H, m), 3.84 (3H, s), 3.85 (1H, m), 3.86 (3H, s), 5.85 (1H, s), 6.75-6.79 (3H, m), 7.49-7.53 (3H, m), 7.80-7.84 (1H, m) ppm; δC (62.9 MHz, CDCl₃) 30.25 (CH₂), 33.33 (CH₂), 39.69 (CH₂), 49.53 (OMe), 56.20 (OMe), 56.28 (OMe), 86.65 (CH), 111.63 (CH), 112.04 (CH), 120.45 (CH), 123.77(CH), 123.82 (CH), 130.35 (CH), 132.36 (C), 133.52 (C), 134.36 (C), 140.65 (C), 147.60 (C), 149.20 (C), 168.16 (C=O) ppm.

To a solution of 1-methoxy-N-2-(3-indolyl)-ethyl-isoindol-3H-one (110) (0.073 g, 0.25 mmol) in dichloromethane (20 cm³), Cu(O Tf)₂ (10 mg, 0.025 mmol) was added and the solution was stirred for 3 h. The reaction was quenched by the addition of water (20 cm³) and the product extracted into dichloromethane (3 x 25 cm³), dried over (MgSO₄), filtered and the solvent evaporated. The crude product was purified by recrystallization from ethyl acetate to give 1,2-isoindolono-1,3,4-trihydro-β-carboline as colourless needles, (63 mg, 94%); mp=246-248°C; (Found C, 78.75; H, 4.83; N,
10.14 \( \text{C}_{18}\text{H}_{14}\text{N}_{2}\text{O} \) requires C, 78.83; H, 5.10; N, 10.21; Found \( M^+ \) 274.1061
\( \text{C}_{18}\text{H}_{14}\text{N}_{2}\text{O} \) requires 274.1106; \( \nu_{\text{max}}/\text{cm}^{-1} \) 3412 (N-H), 1700 (C=O); \( \delta \text{H} \) (250MHz; CDCl\(_3\)) 2.65-2.84 (2H, m), 3.28-3.40 (1H, m), 4.57-4.65 (1H, m), 6.02 (1H, s), 6.95-7.01 (1H, m), 7.07-7.14 (1H, m), 7.38-7.44 (2H, m), 7.49-7.55 (1H, m), 7.66-7.73 (1H, m), 7.74-7.77 (1H, m), 8.30-8.33 (1H, m) ppm; \( \delta \text{C} \) (62.9MHz; CDCl\(_3\)) 26.53 (CH\(_2\)), 42.85 (CH\(_2\)), 61.80 (CH), 112.32 (C), 116.42 (CH), 123.28 (CH), 124.02 (CH), 126.68 (CH), 128.28 (CH), 128.92 (CH), 131.32 (C), 133.74 (CH), 136.02 (C), 136.86 (C), 136.99 (CH), 141.62 (C), 148.80 (C), 172.32 (C=O) ppm.

Procedure 2

To a solution of \( 1\)-methoxy-\( N\)-2-(3-indolyl)-ethyl-isoindol-3[H]-one (110) (0.073g, 0.25 mmol) in dichloromethane (20 cm\(^3\)), Sc(OTf\(_3\)) (12mg, 0.025 mmol) was added and the solution was stirred for 3h. The reaction was quenched by the addition of water (20 cm\(^3\)) and the crude product extracted into dichloromethane (3x25 cm\(^3\)), dried over (MgSO\(_4\)), filtered and the solvent evaporated. The crude product was purified by recrystallization from ethyl acetate giving \( 1,2\)-isoindolono-1,3,4-trihydro-\( \beta \)-carboline (114), (37mg, 56%).

3-Methoxy-(1,2-isoindolono)benzoxazepine

![Diagram](image)

Procedure 1

To a solution of 1-methoxy-2-(3-methoxy-phenoxy)-\( N \)-ethylisoindol-3[H]-one (111) (0.100g, 0.325 mmol) in dichloromethane (20 cm\(^3\)), Cu(OTf\(_2\)) (12mg, 0.0325 mmol) was heated under reflux, 40\(^\circ\)C, for 12h. The reaction was quenched by the addition of water (20 cm\(^3\)) and the crude product extracted into dichloromethane (3x25 cm\(^3\)), dried over (MgSO\(_4\)), filtered and the solvent evaporated. Flash chromatography on silica gel using an eluant of ethyl acetate and light petroleum (bp 40-60\(^\circ\)C) (3:7) gave 3-methoxy-(1,2-isoindolono)benzoxazepine (115) as colourless needles, (51mg, 56%); mp 114-118\(^\circ\)C; Found \( M^+ \) 281.1052 \( \text{C}_{17}\text{H}_{15}\text{NO}_3 \) requires 281.1049;
Procedure 2

To a solution of 1-methoxy-2-(3-methoxy-phenoxy)-N-ethylisoindol-3[1H]one (111) (0.155g, 0.5 mmol) in dichloromethane (20 cm³), Sc(OTf)3 (54mg, 0.11 mmol), was heated under reflux, 40°C, for 12h. The reaction was quenched by the addition of water (20 cm³) and the crude product extracted into dichloromethane (3x25 cm³), dried over (MgSO4) filtered and the solvent evaporated. Flash chromatography on silica gel using an eluant of ethyl acetate and light petroleum (bp 40-60°C) (3:7) gave 3-methoxy-(1,2-isoindolono)benzoxazepine (115) as colourless needles, (76mg, 54%).

6,7-Dimethoxy-(1,2-isoindolono)tetrahydroisoquinoline

![Chemical Structure](image)

Procedure 1

To a solution of 1-methoxy-N-2-(3,4-dimethoxyphenyl)-ethyl-isoindol-3[1H]-one (112) (98mg, 0.30 mmol) in dichloromethane (30 cm³), Cu(OTf)2 (110mg, 0.3 mmol) was added and the solution stirred for 12h. The reaction was quenched by the addition of water (20 cm³) and the crude product extracted into dichloromethane (3x25 cm³), dried over (MgSO4), filtered and the solvent evaporated. Flash chromatography on silica gel using an eluant of ethyl acetate and light petroleum (bp 40-60°C) (2:3) gave 6,7-dimethoxy-(1,2-isoindolono)tetrahydroisoquinoline (116) as colourless needles, (64mg, 73%); mp 172-173°C; Found M+ 295.1208 C18H17N03 requires 295.1215; \( \nu \text{max/cm}^{-1} \) 1692 (C=O); \( \delta_H \) (250MHz; CDCl3) 3.66-3.74 (1H, m), 3.77 (3H, s), 3.83-3.93 (1H, m), 4.44-4.56 (2H, m), 5.74 (1H, s), 6.51-6.66 (1H, dd, \( J=2.61 \) and 8.53 Hz), 6.70 (1H, d, \( J=2.61 \) Hz), 7.0 (1H, d, \( J=8.53 \) Hz), 7.53-7.69 (3H, m), 7.90 (1H, d, \( J=7.51 \) Hz) ppm; \( \delta_C \) (62.9MHz; CDCl3) 44.23 (CH2), 55.35 (OMe), 61.13 (CH), 71.93 (CH2), 107.88 (CH), 109.29 (CH), 121.86 (C), 124.37 (CH), 124.72 (CH), 127.62 (CH), 128.59 (CH), 131.05 (CH), 131.80 (C), 142.30 (C), 160.58 (C), 160.85 (C), 167.91 (C=O) ppm.
m), 2.95-3.07 (1H, m), 3.36-3.47 (1H, m), 3.85 (3H, s), 3.93 (3H, s), 4.46-4.55 (1H, m), 5.60 (1H, s), 6.66 (1H, s), 7.12 (1H, s), 7.46-7.52 (1H, m), 7.57-7.64 (1H, m), 7.81-7.87 (1H, m) ppm; δC (62.9MHz; CDCl3) 28.97 (CH2), 38.12 (CH2), 55.87 (OMe), 56.15 (OMe), 58.93 (CH), 108.68 (CH), 111.94 (CH), 122.96 (CH), 123.90 (CH), 127.52 (C), 128.38 (CH), 129.34 (C), 131.50 (CH), 132.33 (C), 144.56 (C), 147.82 (C), 148.31 (C), 167.80 (C=O) ppm.

Procedure 2

To a solution of 1-methoxy-N-2-(3,4-dimethoxyphenyl)-ethyl-isodiol-3[1H]-one (112) (98mg, 0.30 mmol) in dichloromethane (30 cm³), Sc(OTf)3 (147mg, 0.3 mmol), was added and the solution stirred for 18h. The reaction was quenched by the addition of water (20 cm³) and the crude product extracted into dichloromethane (3x25 cm³), dried over (MgSO4), filtered and the solvent evaporated. Flash chromatography on silica gel using an eluant of ethyl acetate and light petroleum (bp 40-60°C) (2:3) gave 6,7-dimethoxy-(1,2-isodiolono)tetrahydroisoquinoline (116) as colourless crystalline needles, (67mg, 76%).

7,8-Dimethoxy-(1,2-isodiolono)benzazepine

Procedure 1

To a solution of 1-methoxy-N-2-(3,4-dimethoxyphenyl)-propyl-isodiol-3[1H]-one (113) (0.102g, 0.3 mmol) in dichloromethane (20 cm³), Cu(OTf)2 (11.0mg, 0.03 mmol), was heated under reflux, 40°C, for 12h. The reaction was quenched by the addition of water (20 cm³) and the crude product extracted into dichloromethane (3x25 cm³), dried over (MgSO4), filtered and the solvent evaporated. Flash chromatography on silica gel using an eluant of ethyl acetate and light petroleum (bp 40-60°C) (1:1) gave 7,8-dimethoxy-(1,2-isodiolono)benzazepine (117) (60mg, 64%) as colourless needles; mp=145-147°C; (Found C, 73.78; H, 6.14; N, 4.53; C19H19NO3 requires C, 73.75; H, 6.19; N, 4.53); Found M+ 309.1376 C19H19NO3 requires 309.1365; v_max/cm⁻¹ 1697 (C=O); δH (250MHz; CDCl3) 1.77-1.96 (1H,
m), 2.06-2.30 (1H, m), 2.63-2.68 (2H, m), 3.27-3.41 (1H, m), 3.83 (3H, s), 3.85 (3H, s), 4.26-4.35 (1H, m), 6.64 (1H, s), 6.81 (1H, s), 7.45-7.55 (3H, m), 7.85 (1H, m) ppm; $\delta_c$ (62.9MHz; CDCl$_3$) 25.47 (CH$_2$), 30.95 (CH$_2$), 40.85 (CH$_2$), 55.74 (OMe), 55.86 (OMe), 64.45 (CH), 111.37 (CH), 113.88 (CH), 123.02 (CH), 123.79 (CH), 126.64 (C), 128.33 (CH), 128.84 (C), 131.31 (CH), 132.38 (C), 144.19 (C), 147.34 (C), 148.36 (C), 168.77 (C=O) ppm.

**Procedure 2**

To a solution of 1-methoxy-N-2-(3,4-dimethoxyphenyl)-propyl-isoindol-3[H]-one (113) (0.102g, 0.3 mmol) in dichloromethane (20 cm$^3$) Sc(OTf)$_3$ (15.0mg, 0.03 mmol) was heated under reflux, 40$^\circ$C, for 12h. The reaction was quenched by the addition of water (20 cm$^3$) and the crude product extracted into dichloromethane (3x25 cm$^3$), dried over (MgSO$_4$), filtered and the solvent evaporated. Flash chromatography on silica gel using an eluant of ethyl acetate and light petroleum (bp 40-60$^\circ$C) (1:1) gave 7,8-dimethoxy-(1,2-isoindolono)benzazepine (117) (57mg, 61%).
A solution of paraformaldehyde (0.30 g, 10.0 mmol) in water (5 cm$^3$) with a catalytic amount of sodium hydroxide (1 M) was warmed gently until the solution became clear. This solution was then added to a solution of C-methylcalix[4]resorcinarene (0.544 g, 1.0 mmol) and (R)-α-methylbenzylamine (0.61 g, 5.0 mmol) in ethanol (100 cm$^3$). The stirred solution was then heated under reflux at 80°C for 20 h. The solvent was then evaporated under vacuo to yield the crude product which was then washed with cold methanol (30 cm$^3$) before being dried over P$_4$O$_{10}$ at 70°C and 10 mmHg for 12 h, giving compound (124) as an amorphous light pink solid, (0.639 g, 57%). $[\alpha]_D^{25} +132$, c=0.05, CHCl$_3$; mp, decomposed at 90°C; $\nu_{\text{max}}$/cm$^{-1}$ 3358 (OH); $\delta_H$ (250 MHz; CDCl$_3$) 1.29 (4 x 3H, d, $J=5.95$ Hz), 1.75 (4 x 3H, m), 3.74 (4 x 1H, d, $J=17.75$ Hz), 3.80-3.83 (4 x 1H, m), 3.97 (4 x 1H, d, $J=17.41$ Hz), 4.48 (4 x 1H, m), 4.92 (4 x 1H, d, $J=10.06$ Hz), 5.15 (4 x 1H, d, $J=9.79$ Hz), 6.94-7.27 (4 x 6H, m), 7.75 (4 x 1H, s) ppm; $\delta_C$ (62.9 MHz; CDCl$_3$) 19.83 (Me), 21.44 (Me), 26.98 (CH), 44.42 (CH$_2$), 57.97 (CH), 80.99 (CH$_2$), 108.95 (C), 120.70 (CH), 124.48 (C), 125.11 (C), 126.95 (CH), 127.01 (CH), 128.19 (CH), 144.44 (C), 148.29 (C), 149.25 (C) ppm.
(0.544g, 1.0 mmol) and (S)-α-methylbenzylamine (0.61g, 5.0 mmol) in ethanol (100 cm\textsuperscript{3}). The stirred solution was then heated under reflux at 80°C for 20h. The solvent was then evaporated under vacuo to yield the crude product which was then washed with cold methanol (30 cm\textsuperscript{3}) before being dried over P\textsubscript{2}O\textsubscript{5} at 70°C and 10 mmHg for 12h, giving compound (125) as an amorphous light yellow solid, (0.716g, 64%). [\alpha]D\textsuperscript{25} -130, c=0.05, CHCl\textsubscript{3}; mp, decomposes at 90°C; \nu\textsubscript{max}/cm\textsuperscript{-1} 3358(O-H); \delta\textsubscript{H} (250MHz; CDCl\textsubscript{3}) 1.29 (4 x 3H, d, J=5.95 Hz), 1.75 (4 x 3H, m), 3.74 (4 x 1H, d, J=17.75 Hz), 3.80-3.83 (4 x 1H, m), 3.97 (4 x 1H, d, J=17.41 Hz), 4.48 (4 x 1H, m), 4.92 (4 x 1H, d, J=10.06 Hz), 5.15 (4 x 1H, d, J=9.79 Hz), 6.94-7.27 (4 x 6H, m), 7.75 (4 x 1H, s) ppm; \delta\textsubscript{C} (62.9MHz; CDCl\textsubscript{3}) 19.83 (Me), 21.44 (Me), 26.98 (CH), 44.42 (CH\textsubscript{2}), 57.97 (CH), 80.99 (CH\textsubscript{2}), 108.95 (C), 120.70 (CH), 124.48 (C), 125.11 (C), 126.95 (CH), 127.01 (CH), 128.19 (CH), 144.44 (C), 148.29 (C), 149.25 (C) ppm.

![Diagram](126)

A solution of paraformaldehyde (0.30g, 10.0 mmol) in water (5 cm\textsuperscript{3}) with a catalytic amount of sodium hydroxide (1M) was warmed gently until the solution became clear. This solution was then added to a solution of C-hexanalcalix[4]resorcinarene (0.768g, 1.0 mmol) and (R)-α-methylbenzylamine (0.61g, 5.0 mmol) in a mixed solvent system of ethanol / toluene (1:1, 100cm\textsuperscript{3}). The stirred solution was then heated at 110°C for 18h. The solvent was then evaporated under vacuo to yield the crude product which was then washed with cold methanol (50 cm\textsuperscript{3}) giving compound (126) as an amorphous light pink solid, (1.07g, 79%). [\alpha]D\textsuperscript{25} +118, c=0.05, CHCl\textsubscript{3}; mp=185-187°C; \nu\textsubscript{max}/cm\textsuperscript{-1}; \delta\textsubscript{H} (400MHz; CDCl\textsubscript{3}) 0.94 (4 x 3H, t, J=6.9 Hz), 1.32 (4 x 3H d, J=6.5 Hz), 1.38 (4 x 6H, m), 2.18 (4 x 2H, m), 3.77 (4 x 1H, d, J=17.4 Hz), 3.83 (4 x 1H, q, J=6.5 Hz), 3.99 (4 x 1H, d, J=17.4 Hz), 4.22 (4 x 1H, t, J=7.7 Hz), 4.96 (4 x 1H, d, J=10.2 Hz), 5.15 (4 x 1H, d, J=10.2 Hz), 6.95-7.22 (4 x 6H, m), 7.68 (4 x 1H, s) ppm; \delta\textsubscript{C}(100.64MHz; CDCl\textsubscript{3}) 14.57 (Me), 21.80 (Me), 23.09 (CH\textsubscript{2}), 28.22 (CH\textsubscript{2}), 32.37 (CH\textsubscript{2}), 33.17 (CH), 34.12 (CH\textsubscript{2}), 44.95 (CH\textsubscript{2}), 58.47 (CH), 81.35 (CH\textsubscript{2}), 109.33 (C), 121.48 (CH), 123.88 (C), 124.72 (C), 127.42 (2 x CH), 128.60 (CH), 144.90 (C), 149.13(C), and 149.98 (C) ppm.
A solution of paraformaldehyde (0.30g, 10.0 mmol) in water (5 cm³) with a catalytic amount of sodium hydroxide (1M) was warmed gently until the solution became clear. This solution was then added to a solution of C-hexanalcalfresorcinarene (0.768g, 1.0 mmol) and (S)-α-methylbenzylamine (0.61g, 5.0 mmol) in a mixed solvent system of ethanol / toluene (1:1, 100 cm³). The stirred solution was then heated at 110°C for 18h. The solvent was then evaporated under vacuo to yield the crude product which was then washed with cold methanol (30 cm³) before being dried over P₄O₁₀ at 100°C and 10 mmHg for 12h, giving compound (127) as an amorphous light pink solid, (0.99g, 74%). [α]D²⁵ ⁰ 118, c=0.05, CHCl₃; mp=186-187°C; νmax/cm⁻¹: δH (400MHz; CDCl₃) 0.94 (4 x 3H, t, J=6.9 Hz), 1.32 (4 x 3H d, J=6.5 Hz), 1.38 (4 x 6H, m), 2.18 (4 x 2H, m), 3.77 (4 x 1H, d, J=17.4 Hz), 3.83 (4 x 1H, q, J=6.5 Hz), 3.99 (4 x 1H, d, J=17.4 Hz), 4.22 (4 x 1H, t, J=7.7 Hz), 4.96 (4 x 1H, d, J=10.2 Hz), 5.15 (4 x 1H, d, J=10.2 Hz), 6.95-7.22 (4 x 6H, m), 7.68 (4 x 1H, s) ppm; δC (100.64MHz; CDCl₃) 14.57 (Me), 21.80 (Me), 23.09 (CH₂), 28.22 (CH₂), 32.37 (CH₂), 33.17 (CH), 34.12 (CH₂), 44.95 (CH₂), 58.47 (CH), 81.35 (CH₂), 109.33 (C), 121.48 (CH), 123.88 (C), 124.72 (C), 127.42 (2 x CH), 128.60 (CH), 144.90 (C), 149.13(C), and 149.98 (C) ppm.

A solution of paraformaldehyde (0.30g, 10.0 mmol) in water (5 cm³) with a catalytic amount of sodium hydroxide (1M) was warmed gently until the solution became
clear. This solution was then added to a solution of C-phenylethylcalix[4]resorcinarene (0.904g, 1.0 mmol) and (R)-α-methylbenzylamine (0.61g, 5.0 mmol) in ethanol (150 cm³). The stirred solution was then heated under reflux at 100°C for 14h. The solvent was then evaporated under vacuo to yield the crude product which was then washed with cold methanol (50 cm³) before being dried over P₄O₁₀ at 100°C and 10 mmHg for 12h, giving compound (128), as an amorphous light pink solid, (1.20g, 81%). [α]D²⁵ +122, c=0.05, CHCl₃; mp=190-192 °C; vmax/cm⁻¹ 3359 (O-H); δH (250MHz; CDCl₃) 1.29 (4 x 3H, d, J=6.49 Hz), 1.58 (4 x 2H, m), 2.54-2.61 (4 x 2H, m), 3.75 (4 x 1H; d, J=18.19 Hz), 3.83 (4 x 1H, m), 3.99 (4 x 1H, d, J=17.48 Hz), 4.27 (4 x 1H, J=6.71 Hz), 4.93 (4 x 1H, d, J=10.18 Hz), 5.13 (4 x 1H, d, J=10.44 Hz), 6.93-7.25 (4 x 1H, m), 7.66 (4 x 1H, s) ppm; δC (100.64MHz; CDCl₃) 21.44 (Me), 32.68 (CH), 34.65 (CH2), 36.13 (CH2), 44.65 (CH2), 58.10 (CH), 81.04 (CH2), 109.26 (C), 120.91 (CH), 123.26 (C), 124.06 (C), 125.88 (2 x CH), 127.02 (2 x CH), 128.25 (2 x CH), 128.46 (2 x CH), 128.59 (2 x CH), 141.93 (C), 144.45 (C), 148.98 (C), 149.85 (C) ppm.

A solution of paraformaldehyde (0.30g, 10.0 mmol) in water (5 cm³) with a catalytic amount of sodium hydroxide (1M) was warmed gently until the solution became clear. This solution was then added to a solution of C-phenylethylcalix[4]resorcinarene (0.904g, 1.0 mmol) and (S)-α-methylbenzylamine (0.61g, 5.0 mmol) in ethanol (150 cm³). The stirred solution was then heated under reflux at 100°C for 14h. The solvent was then evaporated under vacuo to yield the crude product which was then washed with cold methanol (50 cm³) before being dried over P₄O₁₀ at 100°C and 10 mmHg for 12h, giving compound (129) as an amorphous light pink solid, (1.08g, 73%). [α]D²⁵ -124, c=0.05, CHCl₃; mp=191-192 °C; vmax/cm⁻¹ 3359 (O-H); δH (250MHz; CDCl₃) 1.29 (4 x 3H, d, J=6.49 Hz), 1.58 (4 x 2H, m), 2.54-2.61 (4 x 2H, m), 3.75 (4 x 1H; d, J=18.19 Hz), 3.83 (4 x 1H, m), 3.99 (4 x 1H, d, J=17.48 Hz), 4.27 (4 x 1H, J=6.71 Hz), 4.93 (4 x 1H, d, J=10.18 Hz), 5.13 (4 x 1H, d, J=10.44 Hz), 6.93-7.25 (4 x 1H, m), 7.66 (4 x 1H, s) ppm; δC (100.64MHz; CDCl₃) 21.44 (Me), 32.68 (CH), 34.65 (CH2), 36.13 (CH2), 44.65 (CH2), 58.10 (CH), 81.04 (CH2), 109.26 (C), 120.91 (CH), 123.26 (C), 124.06 (C), 125.88 (2 x CH), 127.02 (2 x CH), 128.25 (2 x CH), 128.46 (2 x CH), 128.59 (2 x CH), 141.93 (C), 144.45 (C), 148.98 (C), 149.85 (C) ppm.
A solution of paraformaldehyde (0.30g, 10.0 mmol) in water (5 cm³) with a catalytic amount of sodium hydroxide (1M) was warmed gently until the solution became clear. This solution was then added to a solution of C-undecylcalix[4]resorcinarene (1.104g 1.0 mmol) and (R)-α-methylbenzylamine (0.61g, 5.0 mmol) in ethanol (100 cm³). The stirred solution was then heated under reflux at 90°C for 24h. The solvent was then evaporated under vacuo to yield the crude product which was then washed with cold methanol (50 cm³) before being dried over P₄O₁₀ at 60°C and 10 mmHg for 12h, giving compound (130) as an amorphous light yellow solid, (L33g, 79%). [α]D25 +112, c=0.05, CHCl₃; mp=74-76°C; νmax/cm⁻¹ 3358 (O-H); δH (250 MHz; CDCl₃) 0.88 (4 x 3H, t, J=6.85 Hz), 1.27 (4 x 21H, m), 2.17 (4 x 2H, m), 3.73 (4 x 1H, d, J=17.64), 3.78 (4 x 1H, q, J=6.55), 4.20 (4 x 1H, t, J=7.52 Hz), 4.93 (4 x 1H, d, J=10.25 Hz), 5.14 (4 x 1H, d, J=10.01), 7.01-7.26 (4 x 6H, m), 7.65 (4 x 1H, s) ppm; δC (62.9MHz; CDCl₃) 14.13 (Me), 21.45 (Me), 22.72 (CH₂), 28.16 (CH₂), 29.38 (CH₂), 29.44 (CH₂), 29.70 (2 x CH₂), 29.77 (CH₂), 29.81 (CH₂), 31.98 (CH₂), 32.72 (CH), 33.76 (CH₂), 44.59 (CH₂), 58.06 (CH), 80.95 (CH), 108.94 (C), 121.12 (CH), 123.46 (C), 124.32 (C), 127.04 (4 x CH), 128.22 (CH), 144.53 (C), 148.74 (C), 149.59 (C) ppm.
A solution of paraformaldehyde (0.30 g, 10.0 mmol) in water (5 cm³) with a catalytic amount of sodium hydroxide (1M) was warmed gently until the solution became clear. This solution was then added to a solution of C-undecylcalix[4]resorcinarene (1.104 g, 1.0 mmol) and (S)-α-methylbenzylamine (0.61 g, 5.0 mmol) in ethanol (100 cm³). The stirred solution was then heated under reflux at 90°C for 18 h. The solvent was then evaporated under vacuo to yield the crude product which was then washed with cold methanol (50 cm³), before being dried over P₄O₁₀ at 65°C and 10 mmHg for 12 h, giving compound (131) as an amorphous light yellow solid, (1.15 g, 68%). [α]D²⁵ -110, c=0.05, CHCl₃; mp=74-76°C; νmax/cm⁻¹ 3358 (O-H); δH (250 MHz; CDCl₃) 0.88 (4 x 3H, t, J=6.85 Hz), 1.27 (4 x 21H, m), 2.17 (4 x 2H, m), 3.73 (4 x 1H, d, J=17.64), 3.78 (4 x 1H, q, J=6.55), 4.20 (4 x 1H, t, J=7.52 Hz), 4.93 (4 x 1H, d, J=10.25 Hz), 5.14 (4 x 1H, d, J=10.01), 7.01-7.26 (4 x 6H, m), 7.65 (4 x 1H, s) ppm; δC (62.9 MHz; CDCl₃) 14.13 (Me), 21.45 (Me), 22.72 (CH₂), 28.16 (CH₂), 29.38 (CH₂), 29.44 (CH₂), 29.70 (2 x CH₂), 29.77 (CH₂), 29.81 (CH₂), 31.98 (CH₂), 32.72 (CH), 33.76 (CH₂), 44.59 (CH₂), 58.06 (CH), 80.95 (CH₂), 108.94 (C), 121.12 (CH), 123.46 (C), 124.32 (C), 127.04 (4 x CH), 128.22 (CH), 144.53 (C), 148.74 (C), 149.59 (C) ppm.
References and Notes


102. Carried out in collaboration with Dr Khamis F. Shuhaibar.
(b) Högberg, A.G.S. J. Am. Chem. Soc. 1980, 102, 6046-6050
117. Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited with the Cambridge data Centre.

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Appendix 1

Chiral HPLC Results

Both the chiral 3,5 dinitrobenzoate and the racemic esters (57) and (58) were analysed by chiral HPLC.

Enantiomeric separation of these derivatives was undertaken using the following HPLC parameters:

- **HPLC Column**: HP1090M
- **Chromatographic Column**: Chiralpak AD
- **Mobile phase**: iso-propanol:hexane (25:75, v/v)
- **Flow rate**: 1 ml/min
- **Oven temperature**: Ambient
- **Run time**: 40 minutes
- **Injection volume**: 10μl
- **Wavelength**: 254 nm

Using this method chromatograms for the racemic material and the chiral material were obtained **Figures 19**. The racemic material (58) was found to contain two peaks, with retention times of 16.7 and 31.9 minutes, with the ratio of these two peaks being 1.02, **Figures 19** (a). Analysis of the chiral material (57) revealed the ratio of these two peaks, with retention times of 16.7 and 31.9 minutes, to be 1:3.9 **Figure 19** (b).

![Chemical Structures](images/structures.png)

(58)  
(57)