To my Mother
Too often we are scared.
Scared of what we might not be able to do.
Scared of what people might think if we tried.
We let our fears stand in the way of our hopes.
We say no when we want to say yes.
We sit quietly when we want to scream.
And we shout with the others,
when we should keep our mouths shut.
Why?
After all,
we do only go around once.
There's really no time to be afraid.
So stop.
Try something you've never tried.
Risk it.
Enter a triathlon.
Write a letter to the editor.
Demand a raise.
Call winners at the toughest court.
Throw away your television.
Bicycle across the United States.
Try bobsledding.
Try anything.
Speak out against the designated hitter.
Travel to a country where you don't speak the language.
Patent something.
Call her.
You have nothing to lose
and everything
everything
everything to gain.
JUST DO IT.

NIKE Advertisement 1991
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I would first like to thank my supervisor, Dr Steve Davies, for giving me the opportunity to work under his guidance, and for his enthusiasm and advice over the last three years. I am also grateful to Roussel Laboratories for providing me with a studentship and Dr Charles Hedgecock for his interest in the project.

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Finally and most importantly, I would like to thank my family for their undying support and encouragement throughout my many years of studying.
Synthetic Applications of Arene Chromium Tricarbonyl Complexes

P. L. Dolan
St. Peter's College

Abstract
This thesis investigates the use of arene chromium complexes as phenyl cation synthons in the synthesis of homochiral N-phenylamino esters, and the dianion formation of a series of complexed aryl ethers.

Chapter 1 reviews the properties of arene chromium tricarbonyl complexes and discusses in detail the ability of some of these complexes to undergo nucleophilic aromatic substitution.

Chapter 2 outlines the biological importance of homochiral N-phenylamino esters. The N-phenylation of a series of amino alcohols are first investigated both by direct reaction of haloarene complexes with amino alcohols and also via a Smiles rearrangement of an aryl ether derivative. In addition, methodology is developed for the synthesis of a series of homochiral N-phenyl-α-amino esters and N-phenyl-β-amino esters. The synthetic strategy is then applied to the synthesis of some N-phenyl-β-lactams, in particular (+)-SCH 48461.

Chapter 3 reviews the directed metallation of complexed and uncomplexed arene compounds and discusses the mechanism involved. The generation of dianions in a series of complexed aryl ethers is investigated. Regioselective deprotonation is observed using different alkyllithium bases and the degree of dianion formation is confirmed by electrophilic quench of the dianionic intermediates with CD₃OD and TMSCl.
### ABBREVIATIONS

#### General

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>Ar</td>
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<td>Pr</td>
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</tr>
<tr>
<td>Bu</td>
<td>butyl</td>
</tr>
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</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>X</td>
<td>leaving group</td>
</tr>
<tr>
<td>Nu</td>
<td>nucleophile</td>
</tr>
<tr>
<td>E</td>
<td>electrophile</td>
</tr>
<tr>
<td>m.p.</td>
<td>melting point</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>MNDO</td>
<td>modified neglect of diatomic overlap</td>
</tr>
<tr>
<td>mol</td>
<td>Moles(s)</td>
</tr>
<tr>
<td>L</td>
<td>ligand</td>
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#### Reagents

<table>
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<tr>
<td>LDA</td>
<td>lithium diisopropylamine</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
</tr>
<tr>
<td>TMEDA</td>
<td>N,N,N',N'-tetramethylethylene diamine</td>
</tr>
<tr>
<td>Dioxane</td>
<td>1,4-dioxane</td>
</tr>
<tr>
<td>n-BuLi</td>
<td>n-butyllithium</td>
</tr>
<tr>
<td>t-BuLi</td>
<td>t-butyllithium</td>
</tr>
<tr>
<td>MeLi</td>
<td>methylolithium</td>
</tr>
<tr>
<td>MeMgBr</td>
<td>methylmagnesium bromide</td>
</tr>
<tr>
<td>DMF</td>
<td>dimethylformamide</td>
</tr>
<tr>
<td>DMG</td>
<td>directing metallation group</td>
</tr>
<tr>
<td>HMDS</td>
<td>hexamethyldisilazane</td>
</tr>
<tr>
<td>LHMDS</td>
<td>lithium hexamethyldisilazide</td>
</tr>
<tr>
<td>KHMDS</td>
<td>potassium hexamethyldisilazide</td>
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</tbody>
</table>
DABCO  1,4-diazabicyclo[2.2.2]octane

**Spectroscopy**

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<td>nmr</td>
<td>nuclear magnetic resonance spectroscopy</td>
</tr>
<tr>
<td>UV</td>
<td>ultraviolet</td>
</tr>
<tr>
<td>IR</td>
<td>infrared</td>
</tr>
<tr>
<td>nOe</td>
<td>nuclear Overhauser effect</td>
</tr>
<tr>
<td>$J$</td>
<td>nmr coupling constant</td>
</tr>
<tr>
<td>m/z</td>
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<td>CI</td>
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<td>EI</td>
<td>electron impact</td>
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<td>molecular ion</td>
</tr>
<tr>
<td>$MH^+$</td>
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</tr>
<tr>
<td>$v_{max}$</td>
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</tr>
<tr>
<td>$\delta$</td>
<td>chemical shift in parts per million downfield from tetramethylsilane</td>
</tr>
<tr>
<td>$s$</td>
<td>singlet</td>
</tr>
<tr>
<td>$d$</td>
<td>doublet</td>
</tr>
<tr>
<td>$dd$</td>
<td>double of doublets</td>
</tr>
<tr>
<td>$t$</td>
<td>triplet</td>
</tr>
<tr>
<td>$q$</td>
<td>quartet</td>
</tr>
<tr>
<td>$m$</td>
<td>multiplet</td>
</tr>
<tr>
<td>de</td>
<td>diastereomeric excess</td>
</tr>
<tr>
<td>ee</td>
<td>enantiomeric excess</td>
</tr>
</tbody>
</table>
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Chapter 1
1 Introduction to Arene Chromium Tricarbonyl Chemistry

Arene chromium tricarbonyl complexes \((\eta^6(\text{arene})\text{Cr(CO)}_3)^*\) are moderately air stable compounds and are usually bright yellow in colour. These complexes consists of a chromium tricarbonyl unit bonded to one face of the arene ring, in which the arene ligand is capable of donating 6-electrons to the chromium metal atom in order to achieve a stable 18 electron metal-centred complex. X-ray crystallographic studies have shown that these complexes are generally pseudo-octahedral in geometry, with the arene ligand occupying three of the coordination sites and the three carbonyl ligands occupying the three remaining coordination sites.\(^1\) Thus in the solid stated the complex is said to resemble a "piano stool" (Figure 1).

![Figure 1]

Each carbon of the arene ring is considered to be bonded to the chromium metal via a d-p \(\pi\)-type bond. Due to the strong \(\pi\)-accepting carbon monoxide ligands bonded to the metal, the \(\text{Cr(CO)}_3\) moiety exerts a net electron withdrawing effect on the coordinated arene ring, which causes the ring to be electron deficient.

The characteristic spectroscopic properties of these complexed arenes include two strong carbonyl stretching absorption bands between 2000-1800 cm\(^{-1}\) in the IR spectrum and an upfield shift of the arene ring protons to 6.0-5.0 ppm in the \(^1\text{H}\) nmr spectrum.

1.0 Synthesis of Arene Chromium Tricarbonyl Complexes

Arene chromium tricarbonyl complexes 1 are generally synthesised by the thermolysis of the relevant arene with chromium hexacarbonyl in a refluxing solution of a 10:1 mixture of dibutyl ether and THF (Scheme 1).\(^2\) Other milder methods of complexation involve thermolysis of the arene with chromium tricarbonyl complexes

\(^*\) \(\eta^N\): \(N\) represents the number of carbon atoms of the arene ligand bonded to the metal; henceforth, the prefix \(\eta^6\) is omitted for clarity, except when it is necessary to identify between complexed and uncomplexed arenes in a molecule
containing ligands which are more labile than CO, e.g. Cr(CO)\(_3\)L\(_3\) (L=NH\(_3\), CH\(_3\)CN, or pyridine\(^5\)).

\[
\begin{align*}
\begin{array}{c}
\text{R} \\
\text{arene complex}
\end{array}
\rightarrow
\begin{array}{c}
\text{R} \\
\text{Cr(CO)\(_3\)}
\end{array}
+ 3 \text{CO}
\end{align*}
\]

Scheme 1: Reagents: i) Cr(CO)\(_6\), Bu\(_2\)O/THF, 150°C

The arene chromium tricarbonyl complexes can also readily undergo decomplexation by treating the arene complex with an oxidising agent such as iodine, cerium(IV), or by leaving an ether solution of the complex in sunlight and air (whereby peroxides are generated \emph{in situ}), which oxidises chromium(0) to chromium(III) (Scheme 2). The green chromium(III) salts are then easily removed by filtration through celite or alumina (grade (V)), followed by removal of the solvent to afford the uncomplexed arene.

\[
\begin{align*}
\begin{array}{c}
\text{R} \\
\text{arene complex}
\end{array}
\rightarrow
\begin{array}{c}
\text{R} \\
\text{arene}
\end{array}
\end{align*}
\]

Scheme 2

2.0 Arene Chromium Tricarbonyl Complexes in Organic Synthesis

The ease which a chromium tricarbonyl moiety can be attached to, and detached from, an arene ligand and the changes in its properties upon complexation, gives arene chromium tricarbonyl complexes enormous potential in the field of synthetic organic chemistry. The synthetic applications of these complexes have been thoroughly investigated and are extensively reviewed.\(^8, 34\) A summary of some of these properties are briefly discussed in the following text and summarised in Figure 2.
2.1 Increased Stabilisation of Benzylic Carbocations

The stabilisation of benzylic carbocations of chromium tricarbonyl complexes is due to the back donation of the electron density from filled d-orbitals on the chromium metal to vacant p-orbitals on the benzylic carbon atom. The most stable resonance structure of the intermediate contains exocyclic double bond character, which causes restricted rotation about the Cα-Cipso bond.

An illustrated example of benzylic carbocation stabilisation by the chromium tricarbonyl moiety can be seen in the synthesis of (S)-(−)-(N-acyl-α-methylbenzylamine)Cr(CO)₃ 4, carried out by Jaouen and Top (Scheme 3). On reaction of (S)-(+)-(1-phenethyl alcohol)Cr(CO)₃ 2 with acid in acetonitrile, the chromium tricarbonyl moiety assists, via neighbouring group participation, in the departure of the protonated hydroxyl species from the exo-face, to give the benzylic carbocation intermediate 3. This intermediate is then trapped from the least hindered exo-face by the nitrile to give (S)-(−)-4, with overall retention of configuration.
2.2 Steric Effect of the Chromium Tricarbonyl Unit

The complexation of the bulky chromium tricarbonyl unit to one face of the arene ring, effectively shields this face of the molecule from attack by reagents. An illustrated example of this is seen in the nucleophilic attack of methyl magnesium bromide on the carbonyl group of (1-tetralone)Cr(CO)\textsubscript{3} 5, (Scheme 4). The Grignard reagent exclusively attacks the least hindered exo-face of the carbonyl group, to give (endo-1-hydroxy-exo-1-methyltetralin)Cr(CO)\textsubscript{3} 6.\textsuperscript{11}

2.3 Chirality upon Complexation of an Arene to a Chromium Tricarbonyl Unit

Since a chromium tricarbonyl unit can complex to either face of an arene, a racemic mixture is formed when the unit attaches itself to either enantiotopic face of an unsymmetrical 1,2 or 1,3 disubstituted arene (Scheme 5).
Several of these type of complexes can be resolved by classical methods; for example by enzymatic resolution, crystallisation of diastereomeric ammonium salts formed with homochiral amines or homochiral acids, and chemical resolution (i.e. the separation of diastereomers formed by the reaction of the racemate with an enantiomerically pure reagent).

When a substituted arene ring containing a stereogenic centre 'X' is complexed with a chromium tricarbonyl unit, the ortho protons HS and HR become diastereotopic (Figure 3). A number of research groups have now investigated the transferral of asymmetry from the chiral substituent X onto the axially dissymmetric arene ring via stereoselective deprotonation reactions.

### 2.4 Enhanced Acidity of Benzylic Protons

The acidity of benzylic protons are greatly enhanced upon complexation of an alkyl substituted arene with a chromium tricarbonyl moiety, due to resonance stabilisation. $^1$H NMR spectroscopy has shown that the anion intermediate has a high degree of exocyclic
double bond character.\textsuperscript{16} The benzylic anion is thermodynamically more stable than that of the arene anion and therefore by varying the base used it is possible to selectively remove either an arene or benzylic proton. An illustrative example shows the benzylic deprotonation of (toluene)\textit{Cr}(CO)\textsubscript{3} \textit{7} with \textit{t}-butoxide (Scheme 6).\textsuperscript{17}

\begin{equation}
\text{Cr} \quad \text{(CO)}_3 \quad \text{7}
\end{equation}

\begin{equation}
\text{Scheme 6: Reagents: i) tBuOK; ii) PhCH}_2\text{Br}
\end{equation}

\subsection{2.5 Enhanced Acidity of Arene Protons}

The coordination of the arene ring to the chromium tricarbonyl unit enhances the acidity of the arene protons relative to the uncomplexed arene.\textsuperscript{18} The increase in acidity is due to the inductive withdrawal of electron density by the chromium tricarbonyl unit which stabilises the aryl anion. An illustrative example of the ease of deprotonation of arene complexes can be seen in the work carried out by Widdowson,\textsuperscript{19} whereby a series of 4-substituted indoles \textit{10} were synthesised by the regioselective C-4 deprotonation of the 1-triisopropylsilylindole complex \textit{9} with \textit{n}-BuLi at low temperatures (Scheme 7).

\begin{equation}
\text{Scheme 7: Reagents : i) \textit{n}-BuLi, TMEDA; ii) E}^+}
\end{equation}
2.6 Nucleophilic Aromatic Substitution

The strong electron withdrawing ability of a Cr(CO)₃ moiety on a complexed arene unit as well as its reversibility of attachment, makes it a powerful tool in synthetic organic chemistry. The reversal of polarity in the complexed ring by the Cr(CO)₃ unit makes it susceptible to nucleophilic substitution to an extent similar to nitro substituents on a haloarene ring.

Following the initial discovery by Nichols and Whiting in 1959 of the nucleophilic substitution of (chlorobenzene)Cr(CO)₃ with sodium methoxide, numerous other nucleophiles have been examined, for example alkoxides, sulfides, carbanions and amines (Scheme 8).

The enhanced ability of appropriately substituted arene chromium tricarbonyl compounds towards nucleophilic substitution, is seen in the conversion of (chlorobenzene)Cr(CO)₃ to 12, in comparison to the lack of reactivity between 13 and the anion under similar conditions (Scheme 9).

A plausible mechanism for the reaction is seen in (Scheme 10). The exo attack of the nucleophile on the arene ring to form a π-(cyclohexadienyl) chromium tricarbonyl anion...
14 is followed by irreversible loss of the halide anion to give the resulting substituted benzene complex 15. The formation of the cyclohexadienyl intermediate as well as the order of reactivity of the leaving groups are similar to that of classical nucleophilic aromatic substitution. However, the mechanism for the complexed arene case is more complicated, with nucleophilic addition as well as nucleophilic substitution occurring.

Evidence for the existence of the π-(cyclohexadienyl) chromium tricarbonyl intermediate 14 has been proven by the isolation and X-ray crystal structure of the intermediate (Figure 14) formed by the nucleophilic addition of 2-lithio-1,3-dithiane with (benzene)Cr(CO)3 in THF at 0°C (Scheme 11). The X-ray structure shows the carbon at the site of addition to be 38.6° out of the pentadienyl plane.
The reactivity of the haloarene chromium tricarbonyl complexes towards nucleophilic substitution is of the order F»Cl=Br»I and kinetic measurements\textsuperscript{31} have shown that the fluorobenzene complex is 2,000 times more reactive than the chloro derivative, which suggests the rate limiting step in the reaction to be the initial attack of the nucleophile. The greater reactivity of the fluorine derivative is usually explained on the basis of the greater electronegativity of fluorine with respect to other halogens, which increases the positive charge of the ipso centre, thus favouring nucleophilic attack. However, oxygen leaving groups such as p-toluenesulfonate do not undergo nucleophilic substitution readily due to the unfavourable steric effects between the chromium tricarbonyl moiety and the bulky endo leaving group.\textsuperscript{21} The order of reactivity of haloarene complexes can be seen in the reaction of sodium diethylmalonate with various (halorene)Cr(CO)\textsubscript{3} complexes (Scheme 12) under similar conditions.

\begin{equation}
\begin{array}{c}
\text{Scheme 12: Reagents : i) NaCH(CO}_2\text{Et)}_2, 50^\circ\text{C, 24h} \\
\end{array}
\end{equation}

<table>
<thead>
<tr>
<th>X</th>
<th>Product %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl</td>
<td>5</td>
</tr>
<tr>
<td>I</td>
<td>0</td>
</tr>
<tr>
<td>F</td>
<td>63</td>
</tr>
</tbody>
</table>
Substitution for halogen is a somewhat limited process and depends upon the nature of the nucleophile. Very reactive carbanions add to the unsubstituted positions, which is kinetically favoured and often slowly isomerises to the ipso position where substitution of the halide occurs. A good illustration of this is in the reaction of 2-lithio-2-methylpropionitrile with (chlorobenzene)Cr(CO)₃ 18 (Scheme 13).²⁵ At -78°C the carbanion adds predominantly at the meta position at -78°C and if oxidised with I₂ at this temperature, the addition product 20 is formed. However, if the reaction is allowed to warm to room temperature, the intermediate 19 isomerises to 21, irreversible loss of the chloride ion then occurs to give the ipso substituted product 22.

![Scheme 13: Reagents: i) C(CH₃)₂CN](image)

This isomerisation is possibly due to intermolecular transfer of the nucleophile,⁶ ³²⁻³³ however hydrogen migration via the chromium metal 23 cannot be ruled out (Scheme 14).³⁴
Less reactive nucleophiles however, only undergo direct ipso substitution, for example, the reaction of (2-fluoroanisole)Cr(CO)$_3$ with pyrrolidine (Scheme 15).$^{35}$

In the case of carbanions containing a second acidic proton, substitution for the halide doesn't occur because it has been proposed that after addition, the newly formed chromium anion removes the second acidic proton to give a stable chromium species 25, which is protonated on the metal (Scheme 16).$^{34, 36}$
As discussed above, nucleophilic aromatic substitution may occur through a variety of pathways depending on the nature of the substrate and the identity of the nucleophile. However in the next part, amine nucleophiles will be discussed in more detail.

### 3.0 Nucleophilic Aromatic Substitution with Amines

Even though there is a great demand for N-phenylated nitrogen containing functional groups for commercial as well as medicinal use, very little reference has been made to the reaction of π-haloarene complexes with amine nucleophiles.\(^{21, 28, 35}\) It was first discovered by Whiting\(^{29}\) in 1967 in the reaction of a range of amine nucleophiles with (fluorobenzene)\(\text{Cr(CO)}_3\) in polar aprotic solvents (Scheme 17).

<table>
<thead>
<tr>
<th>(\text{NHR}_1\text{R}_2)</th>
<th>Yield %</th>
</tr>
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<tbody>
<tr>
<td>(\text{MeNH}_2)</td>
<td>84%</td>
</tr>
<tr>
<td>(\text{Me}_2\text{NH})</td>
<td>84%</td>
</tr>
<tr>
<td>(\text{PhNH}_2)</td>
<td>87%</td>
</tr>
<tr>
<td>(\text{t-BuNH}_2)</td>
<td>88%</td>
</tr>
</tbody>
</table>

---

\(\text{Scheme 16: Reagents : i) } \text{CH(}\text{Me}\text{)CO}_2\text{R, THF, -78 to 0°C; ii) oxidative step}\)

\(\text{Scheme 17: Reagents : i) NHR}_1\text{R}_2, \text{rt}\)
More recently, Widdowson has reacted pyrrolidine with a variety of fluoroanisole chromium tricarbonyl complexes 26 to give the subsequent substituted products in high yields (Scheme 18).  

![Scheme 18: Reagents: i) pyrrolidine, CH₃CN, rt]

3.1 Kinetic Studies

Kinetic studies on the nucleophilic aromatic substitution of (haloarene)Cr(CO)₃ with amine nucleophiles has been studied by Bunnet and Olienik. The order of reactivity of haloarene complexes has been observed as being F > Cl > Br > I and a cyclohexadienyl intermediate is formed which suggests a mechanism analogous to that seen in aromatic nucleophilic substitution.

In the reaction of (fluorobenzene)Cr(CO)₃ complexes with secondary amines (Scheme 19), the expulsion of fluorine from the chromium complex intermediate 29 in step (3) is seen to be rate determining and the reaction is base catalysed. The defluorination step is rate limiting due to the fluorine-arene bond being more polarised and thus making fluorine a poor leaving group. The catalyst 'B' can either be the reacting amine (e.g. piperidine) or an "external" amine such as quinuclidine. In the case of less nucleophilic primary amines, it is thought that both steps (1) and (3) are somewhat rate limiting.
The catalytic amine 'B' is thought to act as a bifunctional catalyst in that it removes the amine proton from the chromium complex intermediate 28 after the addition step (2) and then its conjugate acid helps in the electrophilic removal of the fluoride ion from the chromium complex intermediate 29 in step (3). This defluorination step from the endo side of the ring is quite sterically demanding and the size of the reacting amine and the catalytic amine can thus have an effect on the overall rate limiting step of the reaction. The lack of base catalysis by Et$_3$N, observed by Bunnet$^{21}$ may be due to the steric hindrance of the quaternary ammonium salt on it's approach to the endo side of the arene ring (Figure 5).

In the case of chlorobenzene and bromobenzene complexes,$^{28}$ the first step is determined as being rate limiting and base catalysis is not observed.

$N$-phenylated compounds can also be synthesised via a Smiles rearrangement of a β-aminoalkyl aryl ether chromium tricarbonyl complex, recently reported in our laboratory.$^{38}$ This rearrangement usually occurs in arene rings containing ortho and para electron
withdrawing substituents, however the inductive effects of the Cr(CO)₃ moiety facilitates this reaction at -78°C.

This rearrangement occurs through the intramolecular ipso substitution of the alkyl aryl ether by the generated lithium amide. This is clearly illustrated in the rearrangement of the 4-methoxy phenyl ephedrine derivative 30 (Scheme 20). Generation of the lithium amide of 30 with n-BuLi at -78°C caused it to undergo intramolecular exo attack at the ipso carbon to form the η⁵-intermediate 31, which slowly fragments via endo elimination of the alkoxide to afford the N-phenylated product 32 in 97% yield, upon quenching with methanol.

![Scheme 20: Reagents: i) n-BuLi, THF, -78°C](image)

4.0 Nucleophilic Aromatic Substitution of Arene(Cr(CO)₃ Complexes in Synthesis

The ability of (arene)Cr(CO)₃ complexes to act as a phenyl cation synthon has allowed for the synthesis of a wide variety of phenylated compounds. With metallation of a substrate and quenching with an electrophile such as (fluorobenzene)Cr(CO)₃, phenyl substituents can be incorporated into a wide range of compounds.

A good illustration of this is in the synthesis of Demerol 35 (Scheme 21). The reaction of (fluorobenzene)Cr(CO)₃ 33 with 34 at room temperature, gave the desired phenylated product 35 in 85% yield.
Also research by Blagg\textsuperscript{39} has shown the ease of incorporation of a phenyl group both regioselectively and stereoselectively (Scheme 22). Deprotonation of the Tetrahydroisoquinone complex \(36\) with n-BuLi and addition of a THF solution of (fluorobenzene)Cr(CO)\(_3\) \(37\) at -40°C generated the 4-exo-complex \(38\). Decomplexation gave the 4-phenyl Tetrahydroisoquinoline derivative \(39\), which is a known dopamine agonist, in 15% yield.\textsuperscript{40}

Widdowson has reacted \textit{ortho} lithiated (fluorobenzene)Cr(CO)\(_3\) \(40\) (which in effect is a 1,2-dipolar synthon) with a wide variety difunctional electrophiles, to give benzo-fused compounds.\textsuperscript{41}
Thus the reaction of the lithiated species 40 with a bifunctional electrophile 41 will generate a nucleophile (Y) which will then displace the fluorine atom to generate a benzofused heterocycle 42 (Scheme 23).

![Scheme 23](image)

A good illustration of this is seen in the reaction of (2-lithiofluorobenzene)Cr(CO)$_3$ 43 with γ-butyrolactone which afforded the bicyclic compound 44 in 73% yield (Scheme 24).$^{41}$

![Scheme 24: Reagents](image)
5.0 References


Chapter 2
2 Asymmetric Synthesis of N-Phenyl Amino Acids

1.0 Introduction

Derivatives of N-phenyl amino acids are important in both the agrochemical and pharmaceutical industry. For example, (±) 45, which is a N-phenylvaline derivative, is a known insecticide against *Musca domestica* (Figure 6).²

![Figure 6](image)

It has also been envisaged that N-phenyl amino acids could play a role in neuropeptide research,³ and the potent analgesic (R)-Phenampromide 46 has been synthesised from (R)-N-phenyl alanine 47 (Scheme 25).⁴

![Scheme 25](image)

Racemic N-phenyl-β-amino acids have also been investigated as potential hypotensive agents⁵ and are widely used as starting materials in the synthesis of N-phenyl β-lactams.⁶
2.0 Asymmetric Synthesis of N-Phenyl α- and β- Amino Acids

There has been few reports in the literature of the asymmetric synthesis of N-phenyl-α-amino acids and no report of an asymmetric synthesis of N-phenyl-β-amino acids could be found (except through the resolution of racemates). 10

Two methods have been employed for the synthesis of N-phenyl α-amino acids. Phenylation of an α-amino acid derivative by SNAr displacement of an activated aromatic compound or by nucleophilic substitution of an appropriately α-substituted carboxylic ester with an aniline derivative. 8, 9, 11, 12

2.1 N-Arylation of α-Amino Acid Derivatives

This approach usually involves the use of nitro substituted haloarene derivatives. The nitro substituents render the arene ring to be very electron deficient and undergo nucleophilic aromatic substitution under mild conditions. This method was first used by Sanger to identify the free amino groups in insulin and later a modified procedure was published by Levy (Scheme 26) in the synthesis of (5)-2,4-dinitrophenyl leucine 49 from 2,4 dinitrofluorobenzene and (S)-leucine. 7 However, this method limits the range of substituents which can be placed on the N-aryl group.

![Scheme 26: Reagents: i) (S)-leucine, NaCO3, H2O, 40°C, 0.5h]

2.2 Displacement of α-Substituted Esters

Nucleophilic substitution reactions of homochiral α-substituted carboxylic ester 50 with aniline nucleophiles have been thoroughly studied by Effenberger (Scheme 27). 8, 9
He concluded that the reaction proceeded by an amine underwent $S_N2$ mechanism at the $\alpha$-carbon, with Walden inversion to give the chiral $\alpha$-amino esters 51.

\[
\begin{align*}
\text{Scheme 27: Reagents: i) NHR}_1R_2, \text{ rt, CH}_2\text{Cl}_2
\end{align*}
\]

The rate of nucleophilic substitution decreased in the following order of $\alpha$-substituents (X):

\[
\text{triflate} \gg \text{bromide} > \text{mesylate} \geq \text{tosylate} > \text{chloride}
\]

The less reactive substituents requiring harsher conditions which led to increased racemisation and elimination. A good illustration of this method is seen in the synthesis of the herbicide Ridomil® 55 (Scheme 28). However this method is limited to the availability of homochiral $\alpha$-substituted esters 50.

\[
\begin{align*}
\text{Scheme 28: Reagents: i) Tf}_2\text{O Pyridine; ii) 2,6-dimethylaniline, rt, 17h, CH}_2\text{Cl}_2; \\
\hspace{1cm} \text{iii) MeOCH}_2\text{COCl, NaHCO}_3
\end{align*}
\]
In Scheme 28, the starting (S)-α-hydroxy ester 52 is converted to the triflate derivative 53 in 70% yield with retention of configuration. The triflate derivative then undergoes nucleophilic substitution with 2,6-dimethylaniline, to afford the (R)-N-arylated product 54 in 90% yield with complete inversion of configuration, this is then acylated to give 55 in 80% yield.

3.0 Aims

It was envisaged that a new method of synthesising N-phenyl β-amino acids in their homochiral form would open up a new route to the synthesis of chiral N-phenyl β-lactams of pharmaceutical interest. For example (-) SCH 48461 (Figure 7), which is a known cholesterol reuptake inhibitor developed by Schering Plough.

Therefore, the aim of this project was to develop a new flexible method of synthesising N-phenyl α- and β-amino acid derivatives in their homochiral form with a wide range of functionality on both the arene ring and the amino acid. It was envisaged that this could be achieved by using a haloarene chromium tricarbonyl complex as a phenyl cation synthon, since nucleophilic displacements using such complexes occur under mild conditions and thus would be less likely to cause racemisation. In this method, the chirality would be fixed in the amino ester 56, before the arylation step and after nucleophilic
substitution, the chromium tricarbonyl moiety would be easily removed from 57 by oxidative decomplexation, to afford the chiral N-phenyl amino derivative 58 (Figure 29).

\[
\begin{align*}
\text{Cr} & \quad \text{X} \\
\text{i} & \quad \rightarrow \\
\text{Cr} & \quad \text{NR}_1\text{R}_2^* \\
\text{57} & \quad \text{ii} \\
\text{NR}_1\text{R}_2^* & \quad \text{58}
\end{align*}
\]

\text{Scheme 29: Reagents: i) 56; ii) h\textsubscript{2}O, Et\textsubscript{2}O}

This chapter describes the N-phenylation of naturally occurring \(\alpha\)-amino alcohols, and \(\alpha\) and \(\beta\)-amino esters and the use of N-phenyl \(\beta\)-amino esters in the synthesis of homochiral \(\beta\)-lactams.

4.0 Asymmetric Synthesis of N-Phenyl \(\alpha\)-Amino Alcohols

4.1 Asymmetric Synthesis of \((S)-[\eta^6\text{N-Phenylphenylalalinol}]\text{Cr(CO)}_3\)

The reaction of \((S)\)-phenylalaninol 60 with (fluorobenzene)\text{CrCO}_3 59 was first examined. Compound 60 was obtained in 95% yield from the reduction of \((S)\)-phenylalanine with sodium borohydride-sulphuric acid, according to the literature procedure.\textsuperscript{15} The (fluorobenzene)\text{Cr(CO)}_3 59 was obtained in 50% yield by complexation of the arene with chromium hexacarbonyl, under standard conditions.\textsuperscript{16} An excess of the amino alcohol 60 was then stirred with 59 in a small amount of DMF in the dark at room temperature. The reaction was monitored by thin layer chromatography and was worked up after two days, as the reaction began to turn green, indicating decomplexation of the chromium tricarbonyl complex. Flash chromatography gave two yellow fractions, the less polar fraction was shown to be 59 in 33% yield and the second fraction was the \(N\)-phenyl product 61 in 48% yield (Scheme 30)
The $^1$H spectrum of 61 exhibited a 0.67 ppm downfield shift of the proton at the stereogenic centre, relative to the starting material and the appearance of a NH doublet at 3.99 ppm, which both indicate phenylation at the nitrogen atom, also the $^{13}$C spectrum showed the six inequivalent carbon resonances of the complexed arene ring indicative of the replacement of the flourine atom with the chiral amino alcohol, making the two ortho protons diastereotopic. Infrared analysis showed an OH stretch at 3626 cm$^{-1}$ and the carbonyl stretches of the Cr(CO)$_3$ moiety at 1959 and 1878 cm$^{-1}$. This together with the correct molecular ion peak $m/z= 364$ (MH$^+$) and microanalysis confirmed the structure of 61.

4.2 Asymmetric Synthesis of (S)-[$\eta^6$N-Phenylprolinol]Cr(CO)$_3$

Similarly, an excess of (S)-prolinol 62 was stirred with 59 under the same conditions for 2 days and upon work-up and column chromatography, afforded 63 in 78% yield and a small amount of starting material 59 (2%) (Scheme 31).
Analysis of the $^1$H nmr spectrum of (S)-63 indicated phenylation at the nitrogen atom by a downfield shift of the proton at the stereogenic centre by 0.28 ppm and the methylene protons α to the nitrogen atom of the prolinol ring are also shifted downfield, relative to the starting (S)-prolinol. The five inequivalent proton resonances of the complexed arene ring in the $^1$H nmr spectrum, are also indicative of the presence of a stereogenic centre in the arene substituent, making the two ortho protons diastereotopic. Examination of the infrared spectrum also shows an OH stretch at 3398 cm$^{-1}$ as well as the carbonyl stretches of the Cr(CO)$_3$ moiety at 1929 and 1849 cm$^{-1}$. This together with a molecular ion peak $m/z=313$ (M$^+$) and the correct microanalysis, confirmed the structure of 63.

4.3 N-Phenyl Amino Alcohols Via the Smiles Rearrangement

It has been recently been discovered by Hume$^{17}$ that the ephedrine derivative 64 undergoes a Smiles rearrangement on reaction with n-BuLi at -78°C to afford the N-phenyl derivative 65 in excellent yield 96%, (Scheme 32). It was hoped that this methodology could be developed as a general approach to the synthesis of N-phenyl amino alcohols.

![Scheme 32: Reagents : i) n-BuLi, THF, -78°C](image)

The chromium complex of (S)-phenylalaninol phenyl ether 66 was synthesised by generation of the alkoxide of (S)-60 with NaH in THF at room temperature and after stirring the solution for 2 hours, a THF solution of 59 was added dropwise. The reaction was left to stir overnight whereupon ipso substitution of the fluoride ion by the alkoxide
occurred (Scheme 33). Work-up and column chromatography afforded the o-phenyl ether species (66) in good yield (71%) as a yellow solid (m.p. 82-83°C).

![Scheme 33: Reagents: i) (S)-60, THF, 0°C](image)

Analysis of the \(^1\)H nmr spectrum (S)-66 confirmed the phenylation of the alkoxide by a downfield shift of 0.26 ppm of the methylene protons α to the oxygen atom, relative to the starting (S)-phenylalaninol and the appearance of the chromium complexed arene signals at 4.89, 5.14 and 5.55 ppm. This together with the correct molecular ion peak \(m/z=364\) (MH\(^+\)) and microanalysis, confirmed the structure of (S)-66.

The phenyl ether derivative (S)-66 was then taken up in THF, cooled to -78°C and 2 equivalents of \(n\)-BuLi added. The generated lithium amide then underwent \textit{ipso} attack at the \textit{exo} face of the carbon bearing the fluorine atom, to give a 5-membered intermediate 67, which \textit{endo} elimination of the alkoxide, generated the \(N\)-phenyl phenylalaninol derivative (S)-61 (Scheme 34). Upon quenching the reaction with a saturated ammonium chloride solution, work-up and column chromatography led to the isolation of (S)-61 in excellent yield (90%) as a yellow oil.

![Scheme 34: Reagents: i) 2 equiv. \(n\)-BuLi, THF, -78°C](image)
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The $^1$H nmr spectrum of this Smiles rearranged product (S)-61 was identical to the $^1$H nmr spectrum of the N-phenyl compound (S)-61 derived from the direct N-phenylation of 59 with (S)-phenyl alaninol 60 in DMF, described previously.

5.0 Asymmetric Synthesis of N-Phenyl $\alpha$-Amino Esters

The synthesis of N-phenyl $\alpha$-amino esters was first attempted using the same conditions as for the synthesis of the N-phenyl $\alpha$-amino alcohols.

5.1 Asymmetric Synthesis of (S)-[N-Phenylvaline $\tau$-butyl ester]Cr(CO)$_3$

The reaction of (fluorobenzene)Cr(CO)$_3$ 59 with (S)-valine $\tau$-butyl ester (S)-68 was first examined. Compound (S)-68 was obtained in high yield (74%) from (S)-valine, according to the literature procedure. An excess of (S)-68 was then stirred with 59 in a small amount of DMF in the dark at room temperature (Scheme 35). The reaction was monitored by thin layer chromatography and after 37 days there was still some starting material present, however the reaction was then worked up. Purification by column chromatography afforded the N-phenylated product 69 as a yellow solid (18% yield), some decomplexed product 70 (14% yield), as well as some starting materials 68 (74%) and 59 (24%) (Table 1, Entry 1).

![Scheme 35: Reagents : i) (S)-68, DMF, rt](image)

Analysis of the $^1$H nmr spectrum of (S)-69 showed a downfield shift of 0.42 ppm for the proton at the stereogenic centre, relative to the starting material, as well as a NH
doublet at 4.35 ppm. The infrared spectrum also showed a carbonyl stretch at 1714 cm\(^{-1}\) indicative of the \(t\)-butyl ester, as well as carbonyl stretches at 1947 and 1860 cm\(^{-1}\), representative of the chromium tricarbonyl moiety. The presence of the complexed phenyl ring was determined by the characteristic 5 upfield CH resonances at 4.72, 4.77, 5.56 ppm. A molecular ion peak of m/z=386 (MH\(^+\)) and microanalysis further confirmed the structure.

Compound (S)-70 was isolated as a white crystalline solid (m.p. 77-79°C) and both the \(^1\)H, \(^{13}\)C nmr spectra, as well as analyses of the infra-red spectrum, confirmed the removal of the chromium tricarbonyl unit. This together with a parent ion of m/z=298 (MH\(^+\)) and microanalysis confirmed the structure of (S)-70.

However this reaction was very sluggish, requiring stirring for 37 days, before affording the product (S)-69 in poor yield. Bunnett \textit{et al} \textsuperscript{18} observed that nucleophilic substitution of (fluorobenzene)Cr(CO)\(_3\) with amines was base catalysed either by the reacting amine or by an external amine and that the rate limiting step was the expulsion of fluoride from the cyclohexadienyl intermediate. In order to enhance the rate of nucleophilic substitution and subsequently the yields of N-phenyl derivatives, a series of external amines were next examined for their catalytic ability. These results are also summarised in Table 1.

The sterically encumbered amine, \(t\)-butylamine 71, was first examined as an amine catalyst in the reaction. An excess of (S)-68 was then stirred with 59 in a small amount of DMF in the presence of 71, under the standard conditions (Scheme 36). After 11 days the reaction was worked up and column chromatography afforded the N-phenylated product (S)-69 as a yellow solid (15% yield), a small amount of decomplexed product (S)-70 (1% yield), as well as some starting materials 68 (73%) and 59 (48%) (Table 1, Entry 2). However, the \(t\)-butylamine had also underwent nucleophilic substitution with 59 at a similar rate, to afford 72 (10%), which was fully characterised.
Quinuclidine 73 was next examined as an amine catalyst. An excess of (S)-68 was stirred with 58 and 73 in a small amount of DMF, under standard conditions (Scheme 37). The reaction was monitored by thin layer chromatography and after 14 days there was still some starting material present, however the reaction was then worked up. Purification by column chromatography afforded the N-phenylated product (S)-69 as a yellow solid (69% yield), as well as some starting materials 68 (74%) and 59 (28%). No decomplexed product 70 was isolated (Table 1, Entry 3).

It was observed that the rate of nucleophilic substitution was increased dramatically in the presence of quinuclidine. It is thought that the alkyl structure of 73 is far enough removed from the nitrogen atom so that the conjugate acid can fit into the endo face of the complex and hydrogen bond to the fluoride atom, thus assisting in its expulsion (Figure 8).
Since the α-amino alcohols reacted without an external amine to give N-phenylated amino alcohols in high yields and at a faster rate than their ester derivatives, it was thought that the alcohol functionality maybe assisting in the electrophilic expulsion of the fluoride ion. With this in mind, 3-quinuclidinol was examined next as an external catalytic base.

An excess of (S)-68 was stirred with 59 and 3-quinuclidinol 74 in a small amount of DMF, under standard conditions (Scheme 38). The reaction was monitored by thin layer chromatography and after 19 days there was still some starting material present, however the reaction was worked up. Purification by column chromatography afforded the N-phenylated product (S)-69 as a yellow solid (37%) and some decomplexed product (S)-70 (17%), as well as starting materials (S)-68 (72%) and 59 (45%) (Table 1, Entry 4).

Attempts at increasing the rate of the reaction by heating were also investigated. An excess of (S)-68 was stirred with 59 and quinucline 73 in a small amount of DMF, and was heated to 50°C, under standard conditions (Scheme 39). The reaction was monitored by thin layer chromatography and after 2 days the reaction was worked up. Purification by column chromatography afforded the N-phenylated product (S)-69 as a yellow solid (19%),
as well as starting materials (S)-68 (87%) and 59 (24%) (Table 1, Entry 5). No decomplexed product 70 was isolated. It was concluded that at higher temperatures a rate enhancement was observed, however this was thwarted by increased decomposition of the (fluorobenzene)Cr(CO)3.

Scheme 39: Reagents: i) (S)-68, quinuclidine, DMF, 50°C

As can be seen from Table 1, the optimum conditions for the synthesis of N-phenyl α-amino esters with (fluorobenzene)Cr(CO)3 seems to be in the presence of quinuclidine at room temperatures (Entry 3)

Table 1

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Days</th>
<th>Product (%)</th>
<th>Recovered Material (%)</th>
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<td></td>
<td></td>
<td></td>
<td>complexed</td>
<td>decomplexed</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>69</td>
<td>70</td>
</tr>
<tr>
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<td>none</td>
<td>37 (rt)</td>
<td>18</td>
<td>14</td>
</tr>
<tr>
<td>2</td>
<td>t-butylamine</td>
<td>11 (rt)</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>(71)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>quinuclidine</td>
<td>14 (rt)</td>
<td>69</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>(73)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>3-quinuclidinol</td>
<td>19 (rt)</td>
<td>37</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>(74)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>quinuclidine</td>
<td>2 (50°C)</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>(73)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
5.2 Asymmetric Synthesis of (S)-N-Phenylvaline

 Compound 69 was then subjected to oxidative decomplexation by exposure to air and direct sunlight for two days, after which the resulting mixture was filtered through deactivated alumina and the solvent was removed in vacuo, to afford the free arene 70 as a white crystalline solid (m.p. 77-79°C), in quantitative yield (Scheme 38). Both $^1$H and $^{13}$C and infra-red analyses confirmed the removal of the chromium tricarbonyl unit. This together with a parent ion of m/z=298 (MH$^+$) and microanalysis confirmed the assignment of 70.

\[ \text{Scheme 38: Reagents : i) h}_2\text{O, Et}_2\text{O} \]

$N$-Phenyl valine 75 was formed by acid hydrolysis of the $t$-butyl ester 70 in TFA (Scheme 40). Isolation was achieved by removing the TFA in vacuo and taking up the crude solid in 1N NaOH. Following extraction with CHCl$_3$, the aqueous phase was adjusted to pH 4 whereupon the acid 75 precipitated out and was recrystallised from EtOH/H$_2$O to afford a white crystalline solid, in excellent yield (92%) (m.p. 123-124°C).
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Analysis of the $^1$H and $^{13}$C spectra confirmed the removal of the $t$-butyl group. Comparison of the specific rotation of $(S)$-75 with the literature value,$^{11}$ strongly suggests that no racemisation took place during the arylation process $^{(S)}$-75 $\left[\alpha\right]_D^{22}$ -86.77, (C 0.31, EtOH); lit$^{11}$ $\left[\alpha\right]_D^{25}$ -86.0, (C 1.2, EtOH}).

5.3 Asymmetric Synthesis of $(S)$-[$N$-Phenylproline $t$-butyl ester]$Cr(CO)_3$

$(S)$-$t$-Butyl proline 76 was isolated as a yellow oil in 64% yield from $(S)$-proline 77, according to the literature procedure.$^{19}$ $N$-Phenylation occurred by stirring an excess of 76 in a small amount of DMF with 59 and quinuclidine for 6 days at room temperature (Scheme 41). Upon work-up, column chromatography afforded $(S)$-78 in good yield (70%) with no starting material 59 being recovered.

$^{1}$H nmr spectroscopic analysis showed a downfield shift of 0.35 ppm for the proton at the stereogenic centre. The infrared spectrum exhibited the carbonyl stretch of the $t$-butyl ester at 1736 cm$^{-1}$ and two carbonyl stretches as 1946 and 1849 cm$^{-1}$, indicative of
the chromium tricarbonyl moiety. The molecular ion peak m/z = 384 (MH⁺) from the mass spectrum and elemental analysis also confirmed the structure.

5.4 Asymmetric Synthesis of (S)-N-Phenylproline t-butyl ester

With (S)-78 in hand, an ether solution of the compound (S)-78 underwent oxidative decomplexation by exposure to air and direct sunlight (Scheme 42). The solution was then filtered through deactivated alumina and the solvent removed in vacuo, to give the decomplexed product (S)-79 as an oil.

\[
\begin{align*}
\text{(S)-78} & \quad \xrightarrow{\text{i) } h\nu, \text{Et}_2\text{O}} \quad \text{(S)-79} \\
\end{align*}
\]

Scheme 42: Reagents : i) hν, Et₂O

\(^1\)H, \(^13\)C and infra-red spectral analysis confirmed the removal of the chromium tricarbonyl unit and this together with a molecular ion of m/z=248 (MH⁺) confirmed the structure (S)-79.

5.5 Asymmetric Synthesis of (S)-[\(\eta^6\)-N-Phenylphenylalanine t-butyl ester] Cr(CO)₃

The (S)-phenylalanine t-butyl ester (S)-81 was synthesised in good yield (69%) from (S)-phenylalanine (S)-80 using the standard procedure. An excess of (S)-81 was stirred in a small amount of DMF with 59 and quinuclidine at room temperature for 5 days (Scheme 43). Upon work-up of the green solution and purification by column chromatography the N-phenyl derivative 82 was isolated in 43% yield as a yellow solid (m.p. 109-110°C), with some recovered starting material 59 (25%).
Investigation of the $^1$H nmr spectrum showed the 5 non-equivalent protons of the complexed arene ring and a downfield shift of 0.36 ppm, with respect to the starting material, for the proton at the stereogenic centre and a broad singlet at 4.3 ppm representative of the NH proton. The infrared spectrum also showed a carbonyl stretch at 1729 cm$^{-1}$ for the $t$-butyl ester group and two strong carbonyl bands at 1961 and 1882 cm$^{-1}$, from the chromium tricarbonyl moiety. This together with a molecular ion peak of $m/z=434$ (MH$^+$) and elemental analysis confirm this structure.

5.6 Asymmetric Synthesis of (S)-N-Phenylphenylalanine $t$-butyl ester

With (S)-82 in hand, an ether solution of the compound underwent oxidative decomplexation by exposure to air and direct sunlight (Scheme 44). The solution was then filtered through deactivated alumina and the solvent removed in vacuo, to give the decomplexed product 83 a white solid m.p. 81-82°C.
\(^1\)H spectroscopic analysis confirmed the removal of the chromium tricarbonyl unit by the disappearance of the proton resonances of the complexed arene ring between 5.52-4.45 ppm. Similarly, the \(^{13}\)C showed the disappearance of the carbon resonance of the chromium tricarbonyl group at 234.18 ppm. This together with a parent ion of m/z=298 (MH\(^+\)) confirmed the structure 83.

5.7 Asymmetric Symmetric of (S)-[N-Phenylalanine methyl ester]Cr(CO)\(_3\)

The (S)-phenylalanine methyl ester 85 was formed by stirring (S’)-phenylalanine (S)-84 in acidic methanol overnight in 85% yield.

The (S)-N-phenyl derivative 86 was then synthesised by stirring an excess of 85 in a small amount of DMF with 59 and quinuclidine at room temperature for 5 days (Scheme 45). After work-up, column chromatography lead to the isolation of 86 in 38% yield as a yellow solid (m.p. 88-90\(^\circ\)C) and some starting material 59 (30%).

Examination of the \(^1\)H nmr spectrum, shows a downfield shift of 0.61 ppm for the proton at the stereogenic centre also the appearance of a doublet at 4.18 ppm representing the proton of the secondary amine. Analysis of the infrared spectrum also shows the carbonyl stretch of the methyl ester at 1723 cm\(^{-1}\) as well as the carbonyl stretching bands of the chromium tricarbonyl moiety at 1942 cm\(^{-1}\) and 1855 cm\(^{-1}\). This together with a parent ion of m/z=391 (M\(^+\)) from the mass spectrum, confirmed the structure.
5.8 Attempted Synthesis of Ridomil®

A new route to the synthesis of the herbicide Ridomil® 87 was next investigated. It was envisaged that 87 could be synthesised by reacting (2,6-dimethyl fluorobenzene)Cr(CO)₃ 89 with (R)-alanine methyl ester 90 (Scheme 46).

![Scheme 46]

Compound 89 was synthesised by refluxing 2-fluoro-m-xylene with chromium hexacarbonyl in a refluxing solution of THF/dibutyl ether under nitrogen for two days in the dark. Upon column chromatography 89 was isolated as a yellow crystalline solid in 32% yield (m.p. 63-65°C) and was characterised by analysis of the ¹H, ¹³C and infrared spectra.

Stirring 89 and 90 in a small amount of DMF, with one equivalent of quinuclidine for two weeks afforded only starting material (Scheme 47). It is thought that the 89 was probably too sterically hindered to undergo nucleophilic substitution.

![Scheme 47: Reagents : i) (R)-90 quinuclidine, rt, DMF]
6.0 Asymmetric Synthesis of β Amino Acids

6.1 Introduction

Recently, a novel method of synthesising β-amino acids in their homochiral form was discovered in this laboratory. This entails a stereoselective Michael addition of chiral lithium amides \( \text{(S)}-92 \) to \( \alpha,\beta \)-unsaturated esters \( 93 \) (Scheme 48), to afford the Michael addition product \( 94 \) in high yield and with high diastereoselectivity.

![Scheme 48: Reagents: i) (S)-92, THF, -78°C](image)

This high diastereoselectivity has been postulated as being due to the transition state shown (Figure 9a and 9b).

![Fig 9a: disfavoured](image)

![Fig 9b: favoured](image)

The addition of the lithium amide \( 92 \) to the \( \alpha,\beta \)-unsaturated ester \( 93 \) is anticipated to occur via a six membered chelated transition state, with the ester in a \( s\text{-cis} \) conformation, however this hypothesis has yet to be fully validated. If a six membered
transition state is assumed then molecular modelling suggest that the phenyl rings become partially eclipsed with one another. If we consider attack of the \((R)\)-lithium amide on the \(Si\) face of the enoate (Figure 9A), the six membered transition state would cause a severe non-bonding interaction between the \(\alpha\)-methyl of the benzylic group and the \(R\) group of the unsaturated ester making addition unfavourable. On the other hand, if we examine the attack of the \((S)\)-lithium amide on the same face of the acceptor (Figure 9b), the six membered chelation state would place the \(\alpha\)-methyl of the benzylic substituent distal to the \(R\) group of the acceptor, thus avoiding the non-bonding interactions and so favour in the Michael addition to this face.

From a practical point of view the chiral amines 95 is are readily prepared as either enantiomer from homochiral \(\alpha\)-methyl benzylamine. After formation of the Michael adduct 96 the benzyl groups can be removed by catalytic hydrogenolysis (Scheme 49), to form the \(\beta\)-amino ester 97, without racemisation.

\[
\begin{align*}
\text{Ph} & \quad \text{N} \quad \text{O} \\
\text{R} & \quad \text{OR'}
\end{align*}
\]

\((S,S)\)-96 \[\text{Ph} \quad \text{N} \quad \text{O} \quad \text{R} \quad \text{OR'} \] \[\text{Ph} \quad \text{N} \quad \text{O} \quad \text{R} \quad \text{OR'} \] \\

\[(S)\)-97 \[\text{NH}_2 \quad \text{O} \quad \text{R} \quad \text{OR'} \] \\

85-100% 

\text{Scheme 49: Reagents: } i) \text{Pd(OH)}_2/C/H_2 (5\text{atm})

Using this methodology and the (fluorobenzene)\(\text{Cr(CO)}_3\) complex as a phenyl cation synthon, it was envisaged that \(N\)-phenyl \(\beta\)-amino esters could be synthesised stereoselectively and be used as chiral starting materials for the asymmetric synthesis of \(N\)-phenyl \(\beta\)-lactams.

6.2 Asymmetric Synthesis of \((S)\)-\(\beta\)-Amino Butyric Ester 101

The chiral secondary amine 95 was prepared by condensation of \((S)\)-\(\alpha\)-methylbenzylamine \((S)\)-94 with benzaldehyde in ethanol, followed by reduction of the
imine intermediate with sodium borohydride (Scheme 50). The crude product formed was purified by crystallisation of its hydrochloride salt and on converting back to the free amine afforded (S)-95 as a colourless oil in good yield (77%) \([\alpha]_D^{25} -53.8\) (c 3.2, EtOH); lit\(^{22}\) \([\alpha]_D^{25} -53.6\) (c 3.8, EtOH)).

\[
\begin{align*}
\text{Ph} & \quad \text{NH}_2 \\
94 & \quad \text{i, ii} \quad 76\% \\
\text{Ph} & \quad \text{NH} \\
95 &
\end{align*}
\]

Scheme 50: Reagents: i) PhCHO, EtOH, reflux; ii) NaBH\(_4\)

(E)-\(\text{-Bu}\) crotonate 99 was prepared by the esterification of crotonic acid 98 with isobutylene, under acidic conditions (Scheme 51). Flash chromatography afforded 99 as a colourless oil in 66% yield.

\[
\begin{align*}
\text{CH}_2\text{CO}_2 & \quad \text{OH} \\
98 & \quad \text{i, ii} \quad 66\% \\
\text{CH}_2\text{CO}_2 & \quad \text{OBu}^t \\
99 &
\end{align*}
\]

Scheme 51: Reagents: i) isobutylene, CH\(_2\)Cl\(_2\), H\(_2\)SO\(_4\), ii) NaHCO\(_3\)

Addition of \(n\)-BuLi to the amine at \(-78^\circ\text{C}\) afforded a pink solution of the lithium amide 92. Subsequent addition of a THF solution of the \(\text{-Bu}\) crotonate 99 to the lithium amide solution, afforded an orange solution, presumably of the \(\text{-Bu}\) amino enolate. (Scheme 52). Upon quenching the reaction with saturated ammonium chloride and aqueous work-up, analysis of the crude \(^1\text{H}\) nmr spectrum indicated a distinctive eight line pattern in the region 2.28-1.97 ppm arising from the AB part of an ABX system. This system was attributed to the diastereotopic methylene protons vicinal to the carbonyl moiety coupling to the protons at the \(\beta\)-stereogenic centre (CHCH\(_2\)CO\(_2\)). Analysis of the crude \(^1\text{H}\) nmr spectrum showed the reaction occurred with excellent diastereoselectivity.
Column chromatography allowed isolation of **100** in high yield (78\%) \([\alpha]_D^{25} +4.36 (c 0.90, \text{CHCl}_3)\); lit\(^2\) for **(R,R)-100** \([\alpha]_D^{25} -4.3(c 1.06, \text{CH}_2\text{Cl}_2)\).

![Scheme 52: Reagents: i) (S)-92, -78°C, THF](image)

In order to remove the benzylic nitrogen substituents, **100** was submitted to catalytic hydrogenolysis over Pearlman's catalyst at 50°C and under 5 atmospheres of hydrogen (Scheme 53). Upon work-up and column chromatography the \(\beta\)-amino ester **101** was isolated in 83\% yield \([\alpha]_D^{22} -35.03 (c 1.73, \text{CHCl}_3)\). \(^1\)H nmr spectrum analysis of the product showed the disappearance of the methylene protons of the benzylic group at 3.78-3.59 ppm, which indicated debenzylation of this group took place.

![Scheme 53: Reagents: i) Pd(OH)\(_2\)/C](image)

### 6.3 Asymmetric Synthesis of (3S)-[N-(t-butyl 3-butoanoate)aniline]Cr(CO)\(_3\) (S)-102

With the (S)-101 in hand, \(N\)-phenylation was attempted. An excess of the \(\beta\)-amino ester (S)-101 in a small amount of DMF and 59 with 1 equivalent of quinuclidine was stirred at room temperature in the dark (Scheme 54). The reaction was sluggish and after 2
weeks it was worked up and purification by column chromatography brought about the isolation of 102 in 81% yield.

\[
\begin{align*}
\text{Scheme 54: Reagents: } & i) (S)-101, \text{ quinuclidine, DMF, rt} \\
\end{align*}
\]

\[
\begin{align*}
\text{Scheme 54: Reagents: } & i) (S)-101, \text{ quinuclidine, DMF, rt} \\
\end{align*}
\]

\[
\begin{align*}
\text{Scheme 54: Reagents: } & i) (S)-101, \text{ quinuclidine, DMF, rt} \\
\end{align*}
\]

1H nmr spectroscopic analysis of (S)-102 indicated a downfield shift of 0.31 ppm for the proton at the stereogenic centre, relative to the starting β-amino ester and the appearance of a secondary amine doublet at 4.10 ppm. Infra red analysis showed an ester carbonyl stretch at 1703 cm\(^{-1}\) as well as two strong carbonyl bands at 1963 cm\(^{-1}\) and 1823 cm\(^{-1}\) due to the Cr(CO)\(_3\) moiety. This together with a molecular ion of m/z=372 (MH\(^+\)) and microanalysis confirmed the proposed structure of this novel chromium tricarbonyl complex.

6.4 Asymmetric Synthesis of (3S)-N-(t-butyl 3-butanoate)aniline (S)-103

An ether solution of (S)-102 was allowed to stand in air and direct sunlight for two days, after which the resulting mixture was filtered through deactivated alumina and the solvent was removed \textit{in vacuo}, to give the product (S)-103 as a colourless oil (Scheme 55). Both \(^{13}\)C and infra-red analysis confirmed the removal of the chromium tricarbonyl unit. This together with a parent ion of m/z=237 (MH\(^+\)) and high resolution mass spectrometry, confirmed the structure of (S)-103.
7.0 Asymmetric Synthesis of (S)-4-Methyl Azetidin-2-one (S)-107

Sakaki recently synthesised 4-methyl azetidin-2-one (S)-107 in its homochiral form (Scheme 56), however this synthesis was limited in the fact that only the (R)-enantiomer could be made. This limitation was due to the availability of the only the (S)-β-hydroxy ester 105, obtained from the stereoselective reduction of the β-ketoester 104 by Baker’s yeast. Attempts to from the opposite enantiomer by bromination of the mesylate 106 only led to racemisation.

However using the aforementioned stereoselective synthesis of N-phenyl β-amino esters, it is envisaged that either enantiomer of 107 could be formed.
With the (S)-N-phenyl β-amino ester 103 in hand, a strategy was developed to synthesise the β-lactam 107 in its homochiral (S)-enantiomer. Transesterification of the N-phenyl amino ester 103 occurred smoothly upon stirring in acidic methanol overnight (Scheme 57) and upon work-up, the methyl ester derivative (S)-108 was obtained in good yield (79%). Analysis of the $^1$H nmr spectrum showed the disappearance of the singlet resonance of the t-butyl group at 1.46 ppm and the appearance of a singlet resonance at 3.69 ppm, which integrates for three protons and is indicative of the methyl ester. Comparison of the specific rotation of (S)-(108) with that of the known (R)-enantiomer (R)-108 {((S)-(108)[$\alpha$]$_D^{22}$ +7.51, ($c$ 0.95, CHCl$_3$); lit$^{10}$ (R)-108 [$\alpha$]$_D$ -7.0 ($c$ 2.0, CHCl$_3$)} confirmed the absolute stereochemistry to be (S) and provided evidence that the N-phenylation process occurred with little or no racemisation.

Next, cyclisation of (S)-108 was induced by the Breckpot reaction with CH$_3$MgBr (Scheme 58), to afford the N-phenyl β-lactam (R)-107 in 94% yield after work-up and column chromatography. The $^1$H nmr spectrum and the specific rotation obtained were in excellent agreement with the literature data for (R)-107 {((S)-107 [$\alpha$]$_D^{22}$ +113.9 ($c$ 0.61, CHCl$_3$), for lit$^{24}$ [(R)-107 [$\alpha$]$_D^{25}$ -117 ($c$ 1.34, CHCl$_3$)}
8.0 Asymmetric Synthesis of (-)-SCH 48461

(-)-SCH 48461 109 has recently been synthesised by Scherring Plough (Figure 10) and has been shown to be a potent inhibitor of acyl-CoA: cholesterol acyltransferase, an enzyme which is involved in the reabsorption of cholesterol in the large intestine.²⁵

The synthesis of this compound by Burnett et al²⁵ involves an imine condensation with the chiral ester 110 (Scheme 59) to afford the desired stereochemistry at C-4 111, with a 93% e.e. and in moderate yield (55%). However this synthesis was inefficient as it gave a mixture of the β-lactam product 111 as its cis/trans isomers (18:1), in favour of the wrong selectivity. After epimerisation of this mixture the desired trans β-lactam (3R,4S) was isolated by chromatography and further purified by Chiralcel OD column, to give 109 in its homochiral form (3R,4S).¹⁴
In the next section, the asymmetric synthesis of the opposite enantiomer \((3S,4R)-(+)-\text{SCH 48461}\) is attempted using methodology previously described for the asymmetric synthesis of \(\beta\)-amino acids and \(N\)-phenylation using \((4\text{-fluoroanisole})\text{Cr(CO)}_3\), with a view to its general use in forming either enantiomer.

### 8.1 Synthetic Strategy of \((+)-(3S, 4R)-\text{SCH 48461 109}\)

A simple retrosynthetic analysis of 109 shows two alternative starting materials, either the \((R)\)-\(N\)-phenyl \(\beta\)-amino ester 112 or the \((R)\)-\(\beta\)-lactam 113 (Scheme 60).
The first approach in this section will involve the asymmetric synthesis of the β-lactam \( \text{113} \) with a view to using (4-fluoroanisole)\( \text{Cr(CO)}_3 \) as an aryl cation synthon to arylate \( \text{113} \).

### 8.2 Asymmetric Synthesis of \((4R)-4-(4\text{-Methoxyphenyl})\text{-2-azetidinone}\)

The \( \alpha,\beta \)-unsaturated ester \( \text{115} \) is readily synthesised from reacting 4-methoxy cinnamic acid \( \text{114} \) with isobutylene in acidic \( \text{CH}_2\text{Cl}_2 \) (69% yield, m.p. 44-45°C) (Scheme 61).
With 115 in hand, an asymmetric Michael addition with the lithium amide (S)-92 was carried out (Scheme 62) using the standard procedure. Upon work up, the $^1$H nmr spectrum of the crude reaction product, showed the formation of the Michael adduct (S,R)-116 in $>95\%$ d.e..

After purification by column chromatography the desired product (S,R)-116 was isolated in 96% yield and fully characterised ($\left[\alpha\right]_{D}^{22} -2.69$ (c 1.41, CHCl$_3$)). $^1$H nmr analysis showed a distinctive eight line pattern at 2.53-2.47 ppm arising from the AB part of an ABX system of the diastereotopic methylene protons vicinal to the carbonyl moiety coupling to the protons at the $\beta$-stereogenic centre (CHCH$_2$CO$_2$) and a multiplet at 3.99 ppm representing the proton at the $\beta$-stereogenic centre.

Catalytic hydrogenolysis of the Michael adduct (S,R)-116 using Pearlman's catalyst under 5 atm of hydrogen at 50°C (Scheme 63), afforded after work-up, the (R)-$\beta$-amino ester (R)-117 in 78% yield ($\left[\alpha\right]_{D}^{22} +10.41$ (c 0.73, CHCl$_3$)). The $^1$H and $^{13}$C nmr spectra of (R)-117 showed that the desired debenzylation took place, since the characteristic
signals arising from the benzyl and α-methylbenzyl groups had disappeared, while the methoxy peak was still present. Further evidence was obtained by identification of a molecular ion peak of m/z= 252 and the correct elemental analysis.

![Scheme 63: Reagents: i) Pd(OH)$_2$/C](image)

The β-amino ester (R)-117 was then transesterified in acidic methanol to give the known (R)-117 in 84% yield (Scheme 64). This structure was confirmed by $^1$H and $^{13}$C nmr analysis and had a molecular ion peak of m/z=210 (MH$^+$). Comparison of the specific rotation of the HCl salt of (R)-118 with the literature data$^{26}$ allowed the unambiguous assignment of the absolute configuration of 118 as (R) {[$\alpha$]$_D^{22}$ -90.2 (c 1.4, MeOH); lit$^{26}$ [$\alpha$]$_D^{25}$ -91.5 (c 1.42, MeOH)}.

![Scheme 64: Reagents: i) MeOH, H$^+$](image)

The β-amino ester (R)-(118) was then cyclised on reaction with Al(Me)$_3$ at 0°C, to afford the β-lactam (R)-113 in 75% yield {[$\alpha$]$_D^{22}$ +131.3, (c 0.115, CHC1$_3$)} (Scheme 65).
8.3 N-Phenylation of (4R)-4-(4-Methoxyphenyl)-2-azetidinone

With the β-lactam (R)-113 in hand, N-arylation was attempted with the hope of synthesising 120, the main precursor in the total synthesis of (+)-SCH48461. (4-fluoroanisole)Cr(CO)₃ 119 was synthesised in 34% yield under normal complexation procedures. However formation of the anion of the β-lactam 113 with KHMDS and stirring with 119 in THF, resulted in only recovery of starting materials (Scheme 66).

This is thought to be due to either steric effects inhibiting ipso substitution of the fluoride group by the amide or by reversible addition-elimination of the β-lactam with (4-fluoroanisole)Cr(CO)₃.
8.4 Asymmetric Synthesis of \((3R)-N-(\text{methyl 3-propanoate-3-(4-methoxybenzene)})-4\text{-methoxyaniline (R)}-112\)

Consequently, attention was turned to the asymmetric synthesis of \((R)-112\) via a stereoselective Michael addition of the chiral lithium amide 125 with the \(t\)-butyl ester of 4-methoxycinnamate 121. The Michael acceptor 121 was readily made as described previously. The chiral amine 123 was synthesised by stirring \((S)\)-\(\alpha\)-methylbenzylamine 94 with 119 in DMF at room temperature (Scheme 67). The reaction was very sluggish, possibly due to the para methoxyl substituent making the ring less electrophilic. After 10 days the reaction was worked up and purification by column chromatography brought about the isolation of \((S)-123\) in 36% yield as a yellow solid (m.p. 108-110°C), \([\alpha]_D^{22} -275.21\ (c\ 0.48, \text{CHCl}_3)\) and 26% starting material 119.

\[
\begin{array}{c}
\text{MeO} \quad \text{Cr} \quad \text{F} \\
119 \quad i \quad 36% \\
\text{MeO} \quad \text{Cr} \quad \text{N} \quad \text{Ph} \\
(S)-123
\end{array}
\]

Scheme 67: Reagents: i) \((S)-94, \text{rt, DMF}\)

\(^1\text{H}\) nmr spectroscopic analysis of \((S)-123\) showed the characteristic four upfield resonances at 4.45, 4.93, 5.17, 5.37 ppm of the complexed phenyl ring and a multiplet at 4.19 ppm representing the proton at the stereogenic centre. Also the extremely strong carbonyl stretch at 1943 and 1839 cm\(^{-1}\) of the Cr(CO)\(_3\) moiety as well as the molecular ion of m/z=363 (M\(^+\)) further confirmed the structure.

Oxidative decomplexation of \((S)-123\) afforded \((S)-124\) in quantitative yield \([\alpha]_D^{22} -8.83\ (c\ 1.67, \text{CH}_3\text{OH})\) (Scheme 68). Analysis of the \(^{13}\text{C}\) and infra-red spectra confirmed the removal of the chromium tricarbonyl unit and the \(^1\text{H}\) nmr spectrum was identical in all respects to the known racemic compound.\(^{27}\)
Next, an attempt was made at the synthesis of 126 via the asymmetric Michael addition of the lithium amide 125 with the acceptor 121. The α,β-unsaturated ester 121 was added to the lithium amide 125 at -78°C and stirred for 3 hours (Scheme 69). Work-up and examination of the crude ¹H nmr showed only starting material. Repeating the reaction at 0°C also failed to give any product.

The softer nucleophile 127 (Scheme 72) was also investigated to see if addition could be induced. Compound 128 was made by stirring (fluorobenzene)Cr(CO)₃ in (S)-α-methylbenzylamine 94 for three days at room temperature (Scheme 70) to yield (S)-(128) (83%) as a yellow solid and 10% starting material 59 after work-up and column chromatography. ¹H nmr spectroscopic analysis of 128 showed the characteristic five upfield resonances at 4.47, 4.75, 4.85, 5.41 and 5.54 ppm of the complexed arene ring in which the arene substituent has a stereogenic centre, thus making the two ortho protons diastereotopic. The presence of the Cr(CO)₃ unit was identified by the extremely strong
carbonyl stretch at 1941 cm\(^{-1}\) and 1844 cm\(^{-1}\) in the infra-red spectrum. This together with a molecular ion peak of \(m/z=334\) (MH\(^+\)) and the correct microanalysis, confirmed the structure of (S)-128. It should be noted here that this reaction was less sluggish and afforded the product in higher yield than the less electrophilic (S)-123.

Scheme 70: Reagents: i) (S)-94, rt, DMF

An ether solution of (S)-128 was then allowed to stand in air and direct sunlight for two days, after which the resulting mixture was filtered through deactivated alumina and the solvent removed in vacuo to afford (S)-129 quantitatively, as a white crystalline solid m.p. 43-45°C. (Scheme 71).

Scheme 71: Reagents: i) hv, Et\(_2\)O

Both \(^1\text{H}\) and infra-red analysis confirmed the removal of the Cr(CO)\(_3\) unit. This together with the correct microanalysis and a specific rotation, which was similar but of opposite sign, to that of the known (R)-enantiomer ((S)-(129) [\(\alpha\])\(_D\)=+20.9 \((c\ 1, \text{MeOH})\); lit\(^\text{28}\) (R)-(129) [\(\alpha\])\(_D\)=-19.5 \((c\ 1, \text{MeOH})\)), confirmed the structure of (S)-(129).

Attempted Michael addition of the lithium amide 127 to 121, under standard conditions, was also unsuccessful and only starting material was recovered (Scheme 72). It was
postulated that the addition reaction did occur but was followed by concurrent elimination of the amide, due to its good leaving group ability.

![Scheme 72: Reagents: i) (S)-127, -78°C to 0°C, THF](image)

8.5 Asymmetric synthesis of (3R)-[η⁶-N-(t-butyl 3-propanoate-3-(4-methoxybenzene))-4-methoxyaniline]Cr(CO)₃

An alternative route to the synthesis of 112 was then chosen. This involved the N-arylation of the β-amino ester 117 by stirring an excess of 117 with 119 in DMF with quinuclidine at room temperature (Scheme 73). This reaction was also very sluggish and after 14 days afforded the compound 131 in 14% yield and recovered ester 117 in 66% yield.

![Scheme 73: Reagents: i) 119, quinuclidine, rt, DMF](image)

¹H nmr spectroscopic analysis of 131 showed an NH doublet at 4.63 ppm, also the presence of the stereogenic centre in the arene substituent caused the complexed arene
protons to become inequivalent and appear as four upfield resonances at 4.65, 4.95, 5.15 and 5.26 ppm.

8.6 Synthesis of (3R)-N-(t-butyl 3-propanoate-3-(4-methoxybenzene))-4-methoxyaniline

Oxidative decomplexation of 131 in an ether solution and in direct sunlight afforded, after workup, the free arene 132 in quantitative yield $[[\alpha]_D^{22} +16.25 (c 0.72$ in CHCl$_3$) as a white solid mp 95-96°C (Scheme 74).

![Scheme 74: Reagents: i) hν, Et$_2$O](image)

$^1$H and $^{13}$C spectral analysis indicates a shift of 0.34 ppm of the proton at the stereogenic centre and the appearance of two doublet of doublets at 6.53 and 6.70 ppm are indicative of the 4-methoxyaniline ring system. Also a molecular ion peak of m/z = 210 (MH$^+$) helped confirm the structure.

8.7 Asymmetric Synthesis of (4R)-1,4-bis(4-methoxyphenyl)-2-azetidinone

Transesterification of (R)-131 in acidic methanol overnight (Scheme 75) afforded the methyl ester (R)-133 quantitatively $[[\alpha]_D^{22} 11.78 (c 0.28$, CHCl$_3$).
This was confirmed by analysis of the $^1$H nmr spectrum in which the $r$-butyl singlet resonance had disappeared and a singlet resonance integrating for three protons appeared at 3.65 ppm, indicative of the methyl ester. Cyclisation of 133 by the Breckpot reaction with CH$_3$MgBr in Et$_2$O at 0°C (Scheme 76) gave the $\beta$-lactam (4$R$)-(134) $\left([\alpha]_D^{22} +98.46, (c 0.65, \text{CHCl}_3)\right)$ in 89% yield, upon work-up and column chromatography.

Analysis of the $^1$H nmr spectrum, together with a molecular ion peak of $m/z=284$ (MH$^+$), confirmed the formation of the (4$R$)-$\beta$-lactam 134.

8.8 Attempted Alkylation of (4$R$)-1,4-bis(4-methoxyphenyl)-2-azetidinone

To complete the total synthesis of (+)-SCH48461, alkylation of (4$R$)-134 at the $\alpha$-position with alkyl halide 135 had to be investigated. It was envisaged that alkylation at this $\alpha$-position would occur with some degree of stereoselectivity, owing to the stereogenic
centre at the β-position disfavouring electrophilic quench by the alkyl halide from the cis face.

The anion at the α-position of the β-lactam was generated at -78°C using 1.3 equivalents of LHMDS and the reaction stirred for 2 hours at this temperature (Scheme 77), 3 equivalents of 3-phenyl bromopropane 135 was added and the reaction allowed to slowly warm to room temperature overnight. On quenching the reaction with phosphate buffer (pH 7) and work-up, a crude 1H nmr spectrum showed an intractable mixture which did not contain the starting β-lactam 134 or the alkylated product 109. This reaction was repeated again using KHMDS to generate a more nucleophilic anion but still no alkylated product 109 was isolated.

Scheme 77: Reagents: i) (Li or)KHMDS; ii) 135

The unsuccessful alkylation of the β-lactam (4R)-134 has recently been substantiated by researchers29 whose attempts to alkylate (4R)-134 with a variety of alkyl halides (Br, I) and bases also failed, except in the case of methyl iodide (88%, LDA, -78°C). This is thought to be due to the alkyl halide 135 being unreactive at temperatures below -30°C, regardless of base (LDA, LiCA or LHMDS) and temperatures above -30°C lead to decomposition of the β-lactam anion.
9.0 Conclusion

The use of arene chromium tricarbonyl complexes as phenyl cation synthons has allowed the \(N\)-phenylation of a variety of homochiral amines without fear of racemisation (Scheme 78). When electron donating groups e.g. methoxyl groups are present on the complexed arene ring, the \(N\)-phenylation reaction appear to be more sluggish due to the decrease in electrophilicity of the complexed arene ring. With the synthesis of the subsequent complexed \(N\)-phenyl product, removal of the chromium tricarbonyl unit under mild conditions, gave the desired \(N\)-phenyl product in its homochiral form.

This methodology thus offers mild reaction conditions for amines containing sensitive functional groups.

\[\text{Scheme 78}\]
10.0 References


Chapter 3
3 Introduction to Directed Metallation Chemistry

1.0 Regioselective Deprotonation in Electron Rich Aromatic Systems

Since the initial independent discovery by Gilman and Wittig of ortho deprotonation of anisole (Scheme 79) and the commercial availability of alkylolithium in the 1970s, metallation chemistry has become a significant fundamental methodology for the regiospecific construction of polysubstituted aromatic and heteroaromatic compounds of synthetic interest.

![Scheme 79: Reagents: i) n-BuLi, Et2O, rt, 20h; ii) CO2]

The characteristics of directed metallation reactions are the regioselectivity and increased rate of the reaction. A good illustration of this is shown in the competitive metallation of an equimolar mixture of benzene and anisole with n-BuLi/TMEDA (Scheme 80), whereupon the 52% yield of the mixed ester product consisted of 99% of the ortho esterified anisole derivative 137 and 0.5% of the benzene esterified product 138. This showed that the methoxyl directing group enhanced the rate of ortho metallation of anisole 10^2 times more than that of benzene.

![Scheme 80: Reagents: i) n-BuLi/TMEDA, Et2O, 2h; ii) CO2, H2SO4, MeOH]

Since the initial identification of methoxyl groups as ortho metallation directors, over 30 different ortho directing groups have been discovered and this area has been extensively reviewed.
The following discussion will summarise the theory of directed ortho metallation (DoM) reactions both in the free arene and in arene chromium tricarbonyl complexes and the generation of dianions in both systems, with examples to highlight the advantages of DoM chemistry.

1.1 General Characteristics of DoM Chemistry

The directed ortho metallation reaction consists of deprotonation of a site ortho to a directed metallation group (DMG) by a strong base, to form a lithiated species which is reacted with an electrophile to yield a 1,2-disubstituted derivative. The important factors which determine the effectiveness of a DoM reaction are, the DMG itself, the nature of the base and the aggregation states of the organolithium intermediate, the solvent used and the size and reactivity of the electrophile employed.

1.2 Mechanism

DMGs facilitate regioselective deprotonation by increasing the kinetic acidity of the ortho protons by inductive effects and/or by co-ordination with the lithium ion of the alkyllithium reagent. These distinct mechanisms are (i) coordination mechanism and (ii) inductive mechanism.

1.2.1. Coordination Mechanism

The 3 steps involved in coordinated ortho metallation are:

1) Co-ordination
2) Deprotonation
3) Reaction with electrophiles

It was first proposed by Roberts⁵ that the lithium cation of the metallation agent coordinates with the lone pair of electrons on the DMG 139. Upon co-ordination, the ionic bond between the metal and the carbanion weakens and the inductive effect of the DMG increases. This causes the adjacent C-H bond to weaken, enabling the removal of the ortho hydrogen by the coordinated alkyllithium or perhaps by a separate non-complexed
alkyllithium. The stability of the ortho lithiated species 140 has been confirmed by thermochemical data, where the pKa of ortho protons have been measured\textsuperscript{6} and the enthalpies of 2-lithiated aryl ethers are calculated as being ca.20 KJ/(mol RLi) lower than their 4-lithiated isomers.\textsuperscript{7}

\[
\begin{align*}
\text{DMG} \quad (\text{RLi})_n \\
\end{align*}
\]

\[
\begin{align*}
-\text{(RH)}_n & \quad \text{DMG} \\
\end{align*}
\]

Scheme 81

It has been proposed\textsuperscript{8} that in the case of anisole, the availability of the pair of electrons on the methoxyl group is decreased due to the ground state resonance of the molecule, thus making it a less effective DMG. This ground state resonance also serves to decrease the inductive effect of the methoxyl group and so make the two ortho protons less acidic (Figure 11). As a result the rate determining step is the initial coordination of the alkyllithium to the methoxyl group. Once complexed the resonance deactivation is decreased and the ortho hydrogens become amenable to deprotonation by the co-ordinating alkyllithium or perhaps by a separate alkyllithium.
In order to discover the role that coordination plays in the deprotonation of anisole, Slocum et al performed metallation studies on an anisole derivative whose ability to chelate to the alkyl lithium was reduced. \( \alpha-t \)-Butylanisole 141 was examined, as models showed that the methoxyl substituent is positioned distal to the large \( t \)-butyl group (Figure 12) resulting in the coordinating site being sterically hindered.

![Figure 11](image)

**Figure 11**

In order to discover the role that coordination plays in the deprotonation of anisole, Slocum et al performed metallation studies on an anisole derivative whose ability to chelate to the alkyl lithium was reduced. \( \alpha-t \)-Butylanisole 141 was examined, as models showed that the methoxyl substituent is positioned distal to the large \( t \)-butyl group (Figure 12) resulting in the coordinating site being sterically hindered.

![Figure 12](image)

**Figure 12**

Competition studies were carried out on the rate of metallation of 2-\( t \)-butyl anisole 141 and anisole 142 (Scheme 82). On reacting 141 with \( n \)-BuLi followed by addition of Dry ice, only starting material (91.5%) was recovered. This was in stark contrast to 142 which afforded 143 in 65% yield under the same conditions. On repeating the attempted metallation of 141 with \( n \)-BuLi/TMEDA and condensation with benzophenone afforded 144 in 25% yield.

It was conclude from this that deprotonation didn't occur with \( n \)-BuLi due to the failure of the alkyl lithium to coordinate. Only when TMEDA was added to form the highly reactive base was deprotonation observed in 141. It is thought that deprotonation with the
more basic TMEDA/n-BuLi oligomer occurs via inductive effects rather than coordination to the methoxyl group.

![Image of chemical structures with reactions and yields]

**Scheme 82: Reagents**: i) n-BuLi; ii) CO₂; iii) H⁺, H₂O; iv) n-BuLi/TMEDA

### 1.2.2 Inductive Mechanism

This is considered to occur through the inductive withdrawal of electron density from the carbons ortho to an electronegative DMG e.g. fluorine. This net withdrawal weakens the C-H bond and consequently makes the ortho protons more acidic and so enables subsequent removal with strong bases.

A prime example of deprotonation by an inductive mechanism can be seen in the work carried out by Bauer on the ortho deprotonation of fluorobenzene 145 (Scheme 83). When 145 is treated with 1 equiv. of n-BuLi in toluene-d₈, ⁶Li, ¹H Hoesy experiments and the ¹³C nmr spectrum show no co-ordination of the alkyl lithium to fluorobenzene. On addition of 1 equiv. of TMEDA to the reaction, ¹H and ¹³C nmr spectra still showed no co-ordination of the alkyl lithium to the fluorine atom, however deprotonation occurs slowly to form the 0-lithiated intermediate 146. This suggests that metallation occurs without prior coordination to the fluorine group and only on addition of TMEDA does n-BuLi become a strong enough base to cause metallation.
Scheme 83: Reagents: i) n-BuLi/TMEDA, toluene-dg; ii) n-BuLi, toluene-dg

1.3 DMG

The ability of substituents on aromatic ring systems to act as directed metallation groups have been thoroughly investigated. Nearly always, the DMG possesses a heteroatom containing an unshared pair of electrons which can coordinate to the organolithium oligomer as a prelude to the deprotonation step. Jennings and Slocum have determined the relative strength of a range of DMGs by intramolecular competition reactions using 4-methoxyphenyl derivatives (Figure 13). The order of the directing ability was determined as:

\[ X = \text{SO}_2\text{NR}_2, \text{SO}_2\text{N-R}, \text{CON-R}, \text{CH}_2\text{NR}_2 > \text{OCH}_3, \text{CH}_2\text{CH}_2\text{NR}, \text{NR}_2, \text{CF}_3, \text{F} \]

Figure 13

It should be noted here that the relative significance of the co-ordination effects and the inductive effects of DMGs has not been systematically correlated and generally metallation reactions occur by a combination of both effects.
1.4 Bases

Ever since the discovery of the metallation of fluorenes with ethyl lithium in 1928 by Schlenk and Bergman, alkyllithiums have proven to be of great importance in metallation reactions due to their high solubility in organic solvents and strong basicity. In solution, alkyllithiums associate into aggregates which are bridged structures consisting of weak C-Li bonds and vary in size depending on the alkyllithium, temperature and the basicity of the solvent used. For example $n$-BuLi is known to exist as a hexameric species in cyclohexane, however on addition of THF, this is converted into an equilibrating mixture of solvated tetramer 148 and dimer forms 149 (Figure 14). The proportion of the dimer structure is said to increase with a decrease in temperature and is readily distinguished below -60°C by $^6$Li, $^1$H nmr studies.\(^{14,15}\)

\[
(BuLi)_6 + THF \rightarrow \frac{3}{2}(BuLi)_4 \cdot 4THF + 4THF \rightleftharpoons 2(BuLi)_2 \cdot 4THF
\]

Addition of bidentate ligands such as TMEDA to solutions of alkyllithiums, effectively break down these complex aggregates to form dimers or monomers, which greatly enhances their basicity.\(^ {16,17}\) A good illustration of this is the seen in the ortho deprotonation of anisole (Scheme 84). Metallation studies have shown that only 50% ortho deprotonation of anisole occurs with 1 equivalent of $n$-BuLi at room temperature after 24 hours. However on repeating the reaction in the presence of TMEDA, a dramatic acceleration in rate is observed, with 95% metallation occurring after a half hour.\(^8\)
This can be explained by the breaking up of the \( n \)-BuLi/anisole tetramer 150 and formation of the \( n \)-BuLi/TMEDA dimer 151, a more reactive base, which rapidly removes the most acidic ortho proton.

Investigation of this mechanism has been carried out by Bauer et al\textsuperscript{10} using nmr and MNDO calculations. Analysis of the \( ^6\)Li, \( ^1\)H two dimensional Hoesy spectrum for a 1:1 mixture of \( n \)-BuLi and anisole in toluene d_8, shows cross peaks between the Li atom and the methoxyl group, suggesting that the butyllithium is tightly bound to the anisole molecule 150. \( ^{13}\)C, Li coupling nmr data indicates that this complex is tetrameric in form. However no deprotonation is observed. On addition of TMEDA, the former tetramer aggregate 150 breaks up and \( ^1\)H nmr shows anisole as being uncomplexed. \( ^6\)Li, \( ^1\)H Hoesy now shows only aggregation between TMEDA and butyllithium and rapid deprotonation occurs.

\[ \text{Scheme 84} \]

The proposed mechanism for this is the opening of a \( n \)-BuLi/TMEDA dimer 151 and loss of a mono hapto ligand to form a highly reactive oligomer 152, containing two co-
ordination sites on the lithium atom (Scheme 84). It is hypothesized that the Li ion's two new vacant coordination sites are occupied by the oxygen of the methoxyl group and agostic Li-H interactions 153. Rapid metallation then occurs to afford ortho metallated anisole 154. This proposed chelated intermediate 153 has been supported by MNDO calculations, which show an increased positive charge on the hydrogen atom chelated to the Li ion and a shorter Li-H distance. Therefore the proposal that the reactive species is not the butyllithium tetramer but the dimer species, agrees with the observation's by Slocum.8

1.5 Steric Effects

The steric effects of the co-ordination of the alkyllithium to the substrate has also been thoroughly investigated. It has been widely proposed that the slow step in the reaction is the initial co-ordination of the organolithium to the DMG8 and accordingly the size of the oligomer could have a profound effect on the regioselectivity of metallation reactions. In Shirley's18 investigation of the regioselective deprotonation of 3-methylanisole 155 (Scheme 85), he found that the regioselective deprotonation of the two non-equivalent ortho protons next to the methoxyl substituent were not only effected by the deactivation of the adjacent alkyl group but also influenced by the steric effects of the RLi oligomers (Table 1).

![Scheme 85: Reagents: i) RLi; ii) CO2; iii) diazomethane](image)

**Table 1**

<table>
<thead>
<tr>
<th>entry</th>
<th>RLi</th>
<th>Solvent</th>
<th>oligomer</th>
<th>(156) %</th>
<th>(157) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n-BuLi</td>
<td>cyclohexane</td>
<td>hexamer</td>
<td>09</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>n-BuLi</td>
<td>Et2O</td>
<td>dimer/ tetramer</td>
<td>39</td>
<td>61</td>
</tr>
<tr>
<td>3</td>
<td>t-BuLi</td>
<td>cyclohexane</td>
<td>tetramer</td>
<td>30</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>nBuLi/TMEDA</td>
<td>Et2O</td>
<td>monomeric</td>
<td>47</td>
<td>53</td>
</tr>
</tbody>
</table>
Shirley suggested that since the alkylolithiums are found in different forms, depending on the solvent, it was possible to alter the regioselectivity of the deprotonation by changing the solvent used or by the addition of a co-solvent, such as TMEDA. For example $n$-BuLi forms large hexamer aggregates in hydrocarbon solvents$^{19,20}$ and so chelation to the methoxyl group followed by deprotonation and reaction with diazomethane occurs at the less hindered site C-6 to a greater extent $157(91\%)$ than that of the more sterically encumbered C-2 position, $156\ (9\%)$ (Table 1, Entry 1). However on repeating the reaction in ether, the alkylolithium is found in its smaller tetramer and dimer form$^{14,19,21}$ and is able to deprotonate the C-2 site more readily $156\ (39\%)$ (Table 1, Entry 2).

In comparing the deprotonation rates of $t$-BuLi and $n$-BuLi at the more hindered C-2 site, it is noted that $t$-BuLi deprotonates to a greater extent, $156\ (30\%)$ (Table 1, Entry 3) than that of $n$-BuLi $156\ (9\%)$ (Table 1, Entry 1). This is in contrast to what you would expect as $t$-BuLi is thought as being bigger than $n$-BuLi. However looking at their aggregation state in cyclohexane, $n$-BuLi is found as the larger hexamer oligomer as opposed to $t$-BuLi which is found in its tetramer state.$^{19,22}$ A similar observation is seen in comparing the tetrameric aggregate of $n$-BuLi (Table 1, Entry 2) and the tetramer aggregate of $t$-BuLi (Table 1, Entry 3), which both deprotonate at the C-2 site to a similar extent.

On examination of the monomer$^{23}$ of $n$-BuLi/TMEDA little discrimination is observed between either the proton at C-6 and C-2, and both are deprotonated to a similar extent (Table 1, Entry 4).

2.0 Regioselective Deprotonation in Chromium Tricarbonyl Chemistry

Over the past three decades there has been considerable interest in the novel properties imparted on arene systems complexed to the electron withdrawing chromium tricarbonyl unit. This moiety activates the ring system towards nucleophilic addition and metallation by alkylolithiums.$^{24}$ It is the ease at which these chromium tricarbonyl complexes can be formed and oxidatively removed in quantitative yields that makes them a useful tool in the synthesis of substituted benzene derivatives.$^{25}$ For example Semmelhack has used the
mild ortho deprotonation ability of (anisole)Cr(CO)$_3$ 158 to synthesise the tetralin derivative 159 in 50% yield (Scheme 86).$^{26}$

![Scheme 86: Reagents : i) n-BuLi; ii) CH$_3$CO(CH$_2$)$_3$CN; iii) CH$_3$I, iv) LiNR$_2$; v) I$_2$](image)

Considerable interest has been shown in the ease with which the system undergoes both ring$^{27}$ and benzylic deprotonation in comparison to the free arene.$^{28}$ The electron withdrawing metal moiety renders the ring protons more acidic via inductive stabilisation of the carbanion formed on deprotonation. This is quite evident in the ortho deprotonation of anisole. Facile metallation reactions are therefore possible, for example on reacting (anisole)Cr(CO)$_3$ 159 with n-BuLi for thirty minutes at $-35^\circ$C and subsequent electrophilic quench with TMSCl, 70% of the monosilylated compound 160 is formed (Scheme 87).$^{27}$ However in the uncomplexed species, when anisole 161 is deprotonated with n-BuLi for 24 hours at room temperature and quenched with TMSCl, 50% of the mono silylated species (162) was formed$^{8}$ (Scheme 88).

![Scheme 87: Reagents : i) n-BuLi, Et$_2$O, 0.5h, -35°C; ii) TMSCl](image)

![Scheme 88: Reagents : i) n-BuLi, Et$_2$O, 24h, 25°C; ii) TMSCl](image)
In the free arene, the benzylic protons are kinetically 150 times more acidic than the arene protons,\(^3\) thus making the metallation of ring protons on alkyl substituted arenes inefficient. However, co-ordination of the Cr(CO)\(_3\) unit to an alkyl substituted arene causes the arene protons to become more kinetically acidic\(^29\) while the benzylic protons are thermodynamically more acidic due to resonance stabilisation of the benzylic anion.\(^30\) For example, treatment of (ethylbenzene)Cr(CO)\(_3\) 163 with 8 equiv. of \(n\)-BuLi at -20°C gives predominantly arene metallation 164 (80%) and a small amount of benzylic metallation 165 (<1%)\(^29\) whereas the use of \(t\)-BuOK in DMSO at room temperature gives rise to exclusive benzylic deprotonation to afford 166 (55%) upon electrophilic quench with (CD\(_3\))\(_2\)CO(Scheme 89).\(^31\) Thus enabling the selective deprotonation of protons on alkyl substituted arenes by altering the conditions and bases used.

![Scheme 89](image)

**Scheme 89: Reagents**:  i) \(t\)-BuOK, DMSO, rt; ii) (CD\(_3\))\(_2\)CO

iii) 8 equiv \(n\)-BuLi, THF, -20°C; iv) MeI

Widdowson has investigated the ortho directing ability of a number of heteroatoms on substituted arene complexes. However, the sequence of their ortho directing abilities has been shown to be different from those on the free parent molecule.\(^{32,33,34,35}\) The general order\(^4,16,36\) of ortho directing ability of some arene substituents on the uncomplexed arene ring are shown as:
Uncomplexed

\[ \text{CONR}_2 > \text{CONHR} > \text{NHCO}^t\text{Bu} > \text{CH}_2\text{NMe}_2 > \text{OMe} > \text{F} > \text{NR}_2 = \text{SR} \]

However on complexation of the arene to a chromium tricarbonyl moiety the order is changed:

Complexed

\[ \text{F} > \text{NHCO}^t\text{Bu} > \text{OMe} = \text{CH}_2\text{NMe}_2 > \text{CH}_2\text{OMe} (> \text{NR}_2, \text{SR}) \]

Further light can be shone on this unusual alteration of ortho directing ability regioselectivity by looking at deprotonation studies of (4-fluoroanisole)Cr(CO)\(_3\)\(\text{167}\). It was revealed that in the deprotonation of \(\text{167}\) with \(n\)-BuLi, deprotonation occurred exclusively ortho to the fluorine atom, not ortho to the methoxyl group as observed in the free arene \(\text{168}\) (Scheme 90).

![Scheme 90: Reagents: i) 1 eq. \(n\)-BuLi, THF, -78°C, 0.75 h; ii) TMSCl iii) \(s\)-BuLi, THF, -78°C, 1.5h;]

From X-ray analysis of (4-fluoroanisole)Cr(CO)\(_3\)\(\text{167}\), it is observed that the aryl-oxygen bond becomes shorter, upon complexation, and double bond characteristics develop, due to the mesomeric donation of the lone pair of electrons on oxygen into the arene ring.\(^{33}\) A slight positive charge develops on the oxygen atom and reduces the co-
ordination ability of the methoxyl group. This increased electron density in the arene ring due to the back donation will cause the sigma framework to increase the inductive effect more, leading to a push-pull effect of electron density which has been termed the "Chromium effect". Thus, this two fold modification of reactivity of the directing group on the arene ring causes the chelation characteristics of the ortho directing groups to be minimised, leaving the directing ability to be due mainly to inductive effects.

Similar changes in regioselectivity were observed in other (fluoroanisole)Cr(CO)₃ isomers 169 and 170, with metallation always occurring ortho to the fluorine atom (Scheme 91) and (Scheme 92).

Scheme 91: Reagents: i) n-BuLi, THF, -78°C; ii) TMSCl

Scheme 92: Reagents: i) n-BuLi, THF, -78°C; ii) TMSCl; iii) MeI
3.0 Introduction to Dimetallation Chemistry

3.1 Dianions in Electron Rich Aromatic Systems

Since the late 1920’s the generation of monometallated aromatics has been thoroughly investigated. However the generation of dilithiated species constituted until recently, a relatively unknown and underdeveloped methodology in the core area of metallation chemistry except through their generation via halogen-metal and metal-metal exchange.

One of the first discoveries of dilithiation of aromatic systems was reported by Bryce-Smith. On refluxing phenyllithium with 0.5 equiv. n-BuLi for 20h in benzene, it was observed that the aryl lithiated product was formed (5%) consisting of a ration of 2:1 meta and para dianions.

The dilithiation of aromatic ethers was first discovered by Pring in the reaction of veratrole 171 with 2.5 equiv. of n-BuLi/TMEDA and upon electrophilic quench with I2, afforded the di-iodo derivative 172 in only 2% yield (Scheme 93).

Further research was carried out by Crowther and Cabiddu, who noted that a series of aryl ethers gave dianions after stirring in excess alkyllithium over long periods of time. For example 4-methoxyanisole 173, as well as 3,5-dimethoxyanisole 174 generated dilithiated species under a variety of conditions which often required long reaction times and activated bases (Scheme 94 and Scheme 95) and when reacted with TMSCl, generated the disilylated compounds 175 (94%) and 176 (86%) respectively.
The high yielding dilithiation of 173 and 174 can be looked upon as being due to a kinetic phenomena, where the alkyllithium is able to coordinate freely with each of the methoxyl groups and so generate the dilithiated species. However no dilithiation was observed in the reaction of anisole 177 (Scheme 96) or 1,3-dimethoxybenzene 179 (Scheme 97), which only afforded the monosilylated products 178 and 180 upon reaction with TMSCl.

The exclusive monometallation of anisole 177 maybe due to deactivation of the other ortho position by the generation of the first metallated species which diminishes the effectiveness of the methoxyl group to chelate to the second alkyllithium for the formation
of a dilithiated species. In the case of the 1,3-dimethoxy species 179, metallation only occurs at C-2, the most acidic site.

![Scheme 97: Reagents: i) 2.1 eq. n-BuLi/TMEDA, rt, 11h; ii) TMSCl](image)

Semi-empirical MNDO calculations\textsuperscript{45} for the regioselective deprotonation of 179 by CH\textsubscript{3}Li indicates that deprotonation occurs by a tweezer mechanism, whereby both methoxyl groups chelate to the alkyl lithium and direct the deprotonation to the C-2 site 181 (Scheme 98). The failure to generate a dilithiated species of 179 may be due to the inability of the second alkyl lithium to coordinate to the methoxyl groups as they are already involved in chelation at the first lithiated site.

![Scheme 98: Reagents: i) CH\textsubscript{3}Li](image)

Snieckus\textsuperscript{41} investigated the dilithiation of the strong ortho directing group N,N-diethyl benzamides 182, but failed to generate a dilithiated species directly. On reacting 182 with excess s-BuLi/TMEDA and quenching with an electrophile, only the mono-substituted product 183 was obtained, (Scheme 99). Failure to generate the dilithiated species of 182 could once again, stem from the reduced inductive effects and coordination effects of the DoM group after the generation of the first anion.
However, it was only Snieckus's investigation of the dimetallation of $O,O'$-aryl dicarbamates 184 that generated dilithiated products in substantial yield,\textsuperscript{41} from direct deprotonation with s-BuLi (Scheme 100). The reason for this was that the first alkyl lithium deprotonated ortho to the carbamate and deactivated it from further deprotonation thus forcing the second site to occur ortho to the other carbamate.

It seems from these results that for dimetallation to occur in substantial yield, at least two DoM groups need to be available to activate the aryl ring sufficiently.

Transmetallation has also been used in the formation of dilithiated species either by halogen-metal or metal-metal exchange.\textsuperscript{42} Eaton\textsuperscript{46} overcame the problem of generating 186 by reverse transmetallation of the dimercuric chloride species 185 with excess $n$-BuLi, and quenching with MeI to afford the 2,6-dimethylated product 187 in 61% yield (Scheme 101)
3.2 Dianions in Chromium Tricarbonyl Complexes

Considerable attention has been shown by research groups towards the monometallation of arene chromium tricarbonyl complexes. However a few references to the formation of small amounts of o-disubstituted compounds in the presence of excess base, may suggest the formation of dianions.27, 29, 32, 47

The first suggestion that dianions may occur was seen in the work carried out by Semmelhack in his investigation of the metallation of a series of mono-substituted benzene chromium tricarbonyl complexes.27 On reacting (anisole)Cr(CO)₃ 188, (fluorobenzene)Cr(CO)₃ 189 and (chlorobenzene)Cr(CO)₃ 190 with n-BuLi in ether at -78°C and subsequent quenching with TMSCl, the mono-silylated products 191 were formed, as well as the 2,6-disilylated species 192 in 10-20% yield (Table 2). However it was thought by Semmelhack that some of the 2,6-disubstituted compounds were formed by rapid proton transfer between the starting material and some of the mono-lithiated species.

Table 2

<table>
<thead>
<tr>
<th></th>
<th>191 (%)</th>
<th>192 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>188 OCH₃</td>
<td>70</td>
<td>10-20</td>
</tr>
<tr>
<td>189 F</td>
<td>46</td>
<td>10-20</td>
</tr>
<tr>
<td>190 Cl</td>
<td>49</td>
<td>10-20</td>
</tr>
</tbody>
</table>
Card and Trahanovsky\textsuperscript{29} also observed the formation of the 2,6-disubstituted species 195 in the metallation of (anisole)Cr(CO)\textsubscript{3} 193 with 4 equivalents of \(t\)-BuLi at -40\(^\circ\)C, which afforded the monomethylated species 194 (14\%) and the 2,6-dimethylated species 195 (66\%) being formed on treatment with MeI (Scheme 104).

\[ \text{Scheme 103: Reagents: i) 4.0 equiv n-BuLi, -40\(^\circ\)C; ii) CH}_3\text{I; iii) } \text{hv} \]

Also Widdowson's metallation studies of (4-fluoropivanyl)Cr(CO)\textsubscript{3} 196 with excess \(n\)-butyllithium led to the generation of a small amount of 2,6-disubstituted product 197.\textsuperscript{32} When the arene chromium tricarbonyl complex 196 was treated with 2.2 equivalents of \(n\)-BuLi in THF at -78\(^\circ\)C and then quenched with MeI, 3,5-dimethyl-4-fluoropivanyl was obtained 197 in 7\% yield after decomplexation as well as the two monomethylated isomers 198 and 199 (Scheme 104).

\[ \text{Scheme 104: Reagents: i) 2.2 equiv n-BuLi; ii)CH}_3\text{I; iii) } \text{hv} \]
However, recent research in our group has unequivocally established the formation of dianions on diphenylsulfoxide chromium tricarbonyl complexes under mild conditions (Scheme 105). On reacting the (S)-(diphenylsulfoxide)Cr(CO)$_3$ with two equivalents of LDA, followed by electrophilic quench with CD$_3$OD, the dimetallated species 201 was obtained in 92% yield. This confirms that dianions had been formed here, since the instantaneous electrophilic quench with CD$_3$OD of the excess alkylithium and aryl anion eliminates the possibility of rapid proton transfer or further deprotonation occurring after addition of the electrophile.

\[
\begin{align*}
  \text{Scheme 105: Reagents: i) LDA, -78°C, THF; ii) CD$_3$OD}
\end{align*}
\]

Transmetallation has also been used recently in the formation of dianions of arene chromium tricarbonyls. These were formed by the transmetallation of (1,4-bis-tributylstannylbenzene)Cr(CO)$_3$ 202 with excess n-BuLi at -78°C, to generate the dilithiated species 203, which upon electrophilic quench with a variety of electrophiles, gave the disubstituted derivatives in high yields (Scheme 106).
This offers a new route to the synthesis of arene chromium tricarbonyl complexes containing electron withdrawing substituents which generally have been synthesised in poor yields by direct complexation.50

3.2.1 Aims

It was envisaged that the electron withdrawing ability of the chromium tricarbonyl moiety, together with the inductive and chelation effects of a DoM group, would enhance dianion formation by increasing the acidity of the arene protons.

A methodical approach to the study of dianion formation was carried out in order to define the parameters required for their formation. Initially a MOM group which has two co-ordination sites was used to investigate 2,6-dianion formation. This was followed by the use of a methoxyl group, which has only one co-ordination site, and finally regio-isomers of meta and para substituted anisole were also investigated.

3.2.2 Metallation studies of (Methoxy methyl phenol)Cr(CO)3 207

Dianion studies were first investigated using the MOM protected chromium tricarbonyl complex 207 shown in Scheme 107. It was thought that the strong ortho directing ability of the MOM group, as well as the availability of two heteroatoms which
could chelate to the metallation sites 204, would assist in the generation of the dianion at the 2,6-positions (Scheme 107).

\[
\begin{align*}
\text{OMe} & \quad \text{RLi} \\
\text{207} \\
\end{align*}
\]

\[
\begin{align*}
\text{204} & \quad \text{Me} \\
\text{Li-O} \\
\text{E} & \quad \text{OMe} \\
\text{E} \\
\end{align*}
\]

Scheme 107

206 Was made by the deprotonation of phenol 205 with NaH at 0°C, followed by the addition of chloromethyl methyl ether. The reaction was allowed to warm to room temperature overnight and after aqueous work-up and column chromatography, 206 was isolated as a colourless oil in 47% yield (Scheme 108).

\[
\begin{align*}
\text{OH} & \quad \text{OMe} \\
\text{205} \\
\end{align*}
\]

\[
\begin{align*}
\text{i, ii} & \quad \text{47\%} \\
\text{205} \\
\end{align*}
\]

\[
\begin{align*}
\text{206} \\
\end{align*}
\]

Scheme 108: Reagents: i) NaH, 0°C, THF; ii) MOMCl

With the protected phenol in hand 206, this was then heated with chromium hexacarbonyl in a solution of dibutyl ether-THF at reflux for 2 days, in the absence of light. Purification by column chromatography brought about the isolation of 207 as a yellow crystalline solid (m.p. 77-79°C) in 35% yield (Scheme 109)

\[
\begin{align*}
\text{OMe} & \quad \text{OMe} \\
\text{206} \\
\end{align*}
\]

\[
\begin{align*}
\text{i} & \quad \text{35\%} \\
\text{206} \\
\end{align*}
\]

\[
\begin{align*}
\text{207} \\
\end{align*}
\]

Scheme 109: Reagents: i) Cr(CO)\text{6}, dibutyl ether-THF

Examination of a stepwise deprotonation was undertaken first to generate the 2,6-disilylated product 209. The monosilylated compound 208 was readily formed by
reaction of 207 with 1.0 equivalents of $n$-BuLi at -78°C followed by electrophilic quench. After work-up and column chromatography 208 was isolated as a yellow solid (m.p. 64-65°C) in 65% yield (Scheme 110).

Treatment of the monosilylated compound 208 with 1.0 equivalents of $n$-BuLi at -78°C, followed by electrophilic quench with TMSCl afforded after work-up and column chromatography, the desired 2,6-disilylated compound 209 in 73% yield (Scheme 111).

Subsequently, the possible formation of 209 by generation of the 2,6-dianion with excess alkyllithium and electrophilic quench with TMSCl was examined. On reacting 207 with 3.0 equivalents of $n$-BuLi at -42°C for 3 hours and subsequent quenching with TMSCl, the 2,6-disilylated compound 209 was isolated in 55% yield (Scheme 112). The spectroscopic data of 209 was identical in all respects to the compound formed by the stepwise route.
In interpreting the results of the derivatisation experiment described above (Scheme 112), it was important to know whether 209 resulted from the quenching of a dilithiated species or from stepwise metatllation during silylation. To prove unequivocally the formation of the 2,6-dianion, the metatllation reaction was repeated under similar conditions as before, but was quenched with CD$_3$OD, which instantaneously quenches both the aryl anions and excess alkylolithiums in the reaction mixture.

Treatment of 207 with 3.0 equivalents of $n$-BuLi at -78°C for 3 hours affected complete dianion formation, which upon quenching with CD$_3$OD gave 210 in 99% yield (Scheme 113). The $^1$H nmr spectrum was identical to that of the starting material, except for a decrease in the resonance peak at 5.52 ppm, due to deuterium incorporation at the 2,6-positions (Table 3, entry 1) and this was confirmed by a molecular ion of m/z=276 (M$^+$). Similar results were observed in the reaction of 207 with 5.0 equivalents of $t$-BuLi under the same conditions (Scheme 113), which afforded 210 in 98% yield and 96% dideuterium incorporation at the 2,6-positions (Table 3, entry 2).

![Scheme 113](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>RLi (equiv.)</th>
<th>2,6-deuterium incorp. (210)</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$n$-BuLi (3.0)</td>
<td>97%</td>
<td>99%</td>
</tr>
<tr>
<td>2</td>
<td>$t$-BuLi (5.0)</td>
<td>96%</td>
<td>98%</td>
</tr>
</tbody>
</table>

3.3.3 Metallation Studies of (Anisole)Cr(CO)$_3$ (212)

Studies to date have offered inconclusive evidence concerning the formation of dianions in the 2,6-positions.$^{29}$ Although $o$-disubstituted products were observed when (anisole)Cr(CO)$_3$ was treated with excess alkylolithium followed by electrophilic quench
with either TMSCl or MeI, the possibility of a stepwise deprotonation during the electrophilic quench was not eliminated.

Accordingly, the metallation studies analogous to those described above were performed on (anisole)Cr(CO)₃, to unequivocally prove the generation of dianions on (anisole)Cr(CO)₃.

(Anisole)Cr(CO)₃ 212 was formed by heating anisole 211 with chromium hexacarbonyl in a solution of dibutyl ether/THF, at reflux, for two days to afford 212 as a yellow crystalline solid in 35% yield (Scheme 114). 48

![Scheme 114: Reagents: i) Cr(CO)₃, dibutyl ether-THF](image)

On reacting 212 with 3 equivalents of n-BuLi at -78°C for 3 hours and subsequent quenching with CD₃OD (Scheme 115) afforded, after work-up, 213 in 95% yield (Table 4, entry 1).

![Scheme 115](image)

<table>
<thead>
<tr>
<th>Table 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Entry</strong></td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
</tbody>
</table>
Analysis of the crude $^1$H nmr spectrum showed 95% dideuterium incorporation at the 2,6-positions. This value was attained by comparison of the integrals of the *ortho* protons at 5.11 ppm with that of the two *meta* protons at 5.58 ppm appearing now as a doublet.

Similar results were observed using 5.0 equivalents of $t$-BuLi at -78°C. After electrophilic quench of the reaction with CD$_3$OD (Scheme 115), 213 was isolated in 94% yield (Table 4, entry 2) and upon examination of the crude $^1$H nmr spectrum, a 97% incorporation of deuterium was observed at the 2,6-positions.

It can therefore be concluded from the above studies that o-dianions of (anisole)Cr(CO)$_3$ are readily formed at low temperature and in high yield. It is also worth noting here that although the methoxyl group is involved in co-ordination of the first anion, a second deprotonation can still occur at the other *ortho* site, this seems to indicate that the second site of deprotonation is controlled by inductive effects more than chelation.

Metallation studies with the weaker base, LDA, was next examined to investigate the acidity of the second *ortho* proton that is removed in the formation of the dianion. Treatment of a LDA solution (5 equiv.) with 212 in THF at -78°C for 3 hours, followed by electrophilic quench with CD$_3$OD, afforded 214 in 99% yield after work-up (Scheme 116).

On examination of the crude $^1$H nmr spectrum, 95% deuterium incorporation was observed at the C-2 position, indicative of the generation of only the mono-anion with LDA also a mass peak of m/z=245 (M$^+$), helped confirm the above structure. In
comparison with the reaction with \(n\)-BuLi (Table 3, entry 1), it is concluded that the second acidic site in the generation of dianions on (anisole)Cr(CO)\(_3\) is not acidic enough to be removed by LDA.

Having discovered that dianion formation of (anisole)Cr(CO)\(_3\) occurs readily with excess alkyl lithium at low temperature, and to further expand on the synthetic scope of the reactions, a series of anisole derivatives were next examined.

### 3.3.4 Metallation Studies of (4-Methylanisole)Cr(CO)\(_3\) (215)

The formation of dianions with disubstituted compounds was next investigated. (4-methylanisole)Cr(CO)\(_3\) 216 was formed by refluxing 4-methylanisole 215 with chromium hexacarbonyl in a dibutyl ether-THF solution for 2 days in the dark. After column chromatography 216 was isolated as a yellow crystalline solid (m.p. 46-48°C) in 60% yield (Scheme 117).

\[
\begin{align*}
\text{Scheme 117: Reagents:} & \quad i) \text{Cr(CO)}_6, \text{dibutyl ether-THF} \\
215 \quad \text{OMe} \quad \text{Cr} \quad \text{OMe} \\
\text{60%} \\
\end{align*}
\]

\(^1\text{H} \text{nmr} \text{analysis} \text{showed two doublets at 5.13 and 5.14 ppm indicative of the four arene protons. These protons were assigned with the aid of nOe studies.}

Compound 216 was treated with 5.0 equivalents of \(n\)-BuLi at -78°C for 4 hours, followed by electrophilic quench with CD\(_3\)OD (Scheme 118). Upon work-up, the \(^1\text{H} \text{nmr} \text{spectrum of} \ 219 \text{was observed to be identical to} \ 216 \text{except for a decrease in the resonance peak at 5.13 ppm, which indicated 76% deuterium incorporation at the 2,6-positions} \ 219. \text{No deuterium incorporation was observed at any other position in the molecule, indicating regiospecific dianion formation at only the 2,6-positions.}
The reaction of 216 with electrophiles other than deuterium was also examined. On repeating the reaction with n-BuLi at -78°C, an excess of TMSCl was added to the reaction mixture and was slowly warmed to room temperature overnight (Scheme 119). After work-up, column chromatography led to the isolation of the 2,6-disilylated compound 217 in 49% yield and a small amount of the monosilylated derivative 218 (10%).

3.3.5 Metallation Studies of (3-Methylanisole)Cr(CO)$_3$ (220)

Further metallation studies were carried out on the unsymmetrical (3-methylanisole)Cr(CO)$_3$ 220 to investigate the extent of dianion formation at the C-2 and C-6 positions since these were now inequivalent.

The compound (3-methylanisole)Cr(CO)$_3$ 220 was formed by heating 3-methylanisole 219 with chromium hexacarbonyl in a solution of dibutyl ether-THF at reflux, for 2 days under standard conditions (Scheme 120), to afford 220 as a yellow crystalline solid (m.p. 77-78°C) in 35% yield.
Scheme 120: Reagents: \( \text{i) Cr(CO)\textsubscript{6}, dibutyl ether-THF} \)

Generation of the dianion of 220 with excess alkyl lithium followed by electrophilic quench was next examined and the results are shown in Table 5.

On reacting 220 with 4.4 equivalents of \( n\)-BuLi at \(-78^\circ\text{C} \) and subsequent quenching with \( \text{CD}_3\text{OD} \) (Scheme 121), a mixture of deuteriated products were formed (Table 5, entry 1). \(^1\text{H} \) nmr spectroscopic analysis of the crude reaction product revealed the spectrum to be identical to 220, except for a decrease of 43% in the resonance peaks at 4.41 ppm, indicative of deuterium incorporation at the 2-position, and a decrease of 89% in the resonance peak at 4.39 ppm due to deuterium incorporation at the 6-position. This was confirmed by investigation of the \(^2\text{H} \) nmr, which showed two deuterium peaks at 4.19 ppm and 4.40 ppm. Investigation of the mass spectrum, showed a 1:1 ratio of the molecular ion peaks (\( \text{M}^+ \)) 260 and 259, which confirm the formation of a mixture of dideuteriated and monodeuteriated compounds. Therefore from the \(^1\text{H} \) nmr spectrum, it was calculated that the deuteriated reaction product mixture contained 48% of the dideuteriated species 221 and 52% of the monodeuteriated species 222.

<table>
<thead>
<tr>
<th>Entry</th>
<th>RLi (equiv.)</th>
<th>( \text{E}^+ )</th>
<th>221</th>
<th>222</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( n)-BuLi (4.4)</td>
<td>( \text{CD}_3\text{OD} )</td>
<td>48</td>
<td>52</td>
</tr>
<tr>
<td>2</td>
<td>( t)-BuLi (4.0)</td>
<td>( \text{CD}_3\text{OD} )</td>
<td>33</td>
<td>67</td>
</tr>
</tbody>
</table>
The removal of the two inequivalent protons at C-2 and C-6 to generate the dianion is assumed to occur stepwise by chelation of the alkyllithium to the unshared pair of electrons on the methoxyl group and removal of the kinetically more acidic ortho proton at C-6 followed by removal of the next most acidic proton at the C-2 position.

Similar results were observed when 220 was reacted with t-BuLi (Scheme 122). Upon quenching of the dianion with CD$_3$OD a mixture of deuteriated products were obtained. The $^1$H nmr spectrum of the crude product mixture was identical to 220, except for a 31% decrease in the resonance peak at 4.41 ppm, due to deuterium incorporation at the C-2 position and a 93% decrease in the resonance peak at 4.20 ppm, due to deuterium incorporation at the C-6 position. Analysis of the mass spectrum showed a 2:1 ratio of the molecular ion peaks (M+) 259 and 260, which was consistent with a mixture of the mono and dideuteriated compounds. Therefore from the $^1$H nmr spectrum it was calculated that the deuteriated reaction product mixture contained 33% of the dideuteriated species 221 and 67% of the monodeuteriated species 222 (Table 5, Entry 2).

Incomplete dianion formation in both of the above metallation experiments is thought to be due to a slow deprotonation at the C-2 position, owing to severe steric hindrance about this site.

The relative acidity of these protons was examined by reacting 1.2 equivalents of n-BuLi with 220 at -78°C and subsequent quenching with TMSCl. TMS incorporation was observed solely at the C-6 position, affording 223 in 73% yield (Table 5, entry 1). Similar results were also observed with t-BuLi (Table 6, entry 2).

\[ \text{Scheme 122} \]
Table 6

<table>
<thead>
<tr>
<th>Entry</th>
<th>RLi (equiv.)</th>
<th>223</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n-BuLi (1.2)</td>
<td>73%</td>
</tr>
<tr>
<td>2</td>
<td>t-BuLi (1.1)</td>
<td>60%</td>
</tr>
</tbody>
</table>

Subsequently the reaction of the dianion of 220 with TMSCl as an electrophile was examined. Interestingly, on generation of the dianion with an excess of n-BuLi (5.0 equiv.) and subsequent quenching of the reaction mixture with TMSCl (Scheme 123), the major product isolated was the 6-monosilylated derivative 223 (55%) with a small amount of 2,6-disilylated material 224 (1%) being formed.

![Scheme 123: Reagents: i) 5.0 equiv. n-BuLi; TMSCl](image)

This was thought to be due to generation of the dianion at the 2,6-positions as proven previously (Table 4, Entry 1) but reaction of the anion at C-2 with the bulky TMSCl is very slow due to the steric hindrance at the C-2 site. It is postulated that upon chelation of n-BuLi to the lone pair of electrons on the methoxyl group and subsequent deprotonation at C-6, the methoxyl group sits distal to the anionic site and so partially blocks the site at C-2 (Figure 15). Similar observations have been seen in the X-ray structure of the 2-lithio anisole tetrameric oligomer.51 The proton at C-2 is therefore positioned in a small pocket which is still accessible enough to be deprotonated by n-BuLi, however, the anion formed it is too sterically hindered to react with TMSCl at an appreciable rate. This result is in contrast with the reaction of the dianion with the smaller electrophile D+, whereby deuterium quench is rapid (Table 3, Entry 1).
Interestingly, on repeating the reaction with excess tert-BuLi at -78°C and quenching with TMSCl, three reaction products were obtained (Scheme 124). The monosilylated compound 223 (21%), the disilylated compound 225 (72%) and a small amount of the trisilylated compound (2%), assigned tentatively as 226.

![Scheme 124: Reagents: i) 4.0 equiv. tert-BuLi, TMSCl](image)

It is now known from the preceding deprotonation experiments (Schemes 121 and 123) that the generation of the dianion at the 2,6-position in 220 is incomplete (Table 5). Therefore it is postulated (Scheme 125) that upon reacting 220 with an excess of tert-BuLi, the reaction mixture consist of both the dianionic species 227, the mono-anionic species 228. Upon addition of TMSCl, the anion at C-6 is quenched rapidly but the sterically hindered anion at C-2 reacts very slowly with TMSCl to give the 2,6-disilylated compound 224. At the same time, the mono-anion 228 was quenched with TMSCl in the reaction mixture, to form the 6-silylated compound 223. However, the majority of the anion at C-2 229 is only quenched upon protic work-up, to afford the monosilylated derivative 223 in 21% yield.
Also, a second deprotonation step occurs in the reaction mixture due to the excess \( \text{t-BuLi} \) still present. The 6-silylated compound 223 and the 2,6-disilylated compound 224 both undergo deprotonation again, and \textit{in situ} quench with TMSCl, affords the 225 (72\%) and 226 (2\%). This observation is not seen in the previous reaction with \( \text{n-BuLi} \) (Scheme 123) as the excess \( \text{n-BuLi} \) reacts faster with excess TMSCl relative to \( \text{t-BuLi} \)\textsuperscript{52} and is essentially removed from the reaction mixture.
Scheme 125
With the aim to verify the postulated reaction pathway shown above, a series of metallation studies were carried out on the monosilylated compound 223, using different electrophiles.

Compound 223 was treated with 1.1 equivalent of n-BuLi and subsequently quenched with CD$_3$OD, to afford a mixture of deuteriated products (Scheme 126). Analysis of the crude $^1$H nmr spectrum showed it to have 50% deuterium incorporation at the C-2 site and 19% deuterium incorporation at the benzylic site. This has also been confirmed by $^2$H nmr spectroscopy, which shows two deuterium peaks at 4.95 ppm and 2.31 ppm. However, analysis of the mass spectrum, after correction for the naturally occurring $^{29}$Si and $^{30}$Si isotopes, shows only a mass peak of m/z=331, which suggests only monodeuterium incorporation. Therefore it is tentatively assigned that two monodeuteriated compounds 230 and 231 are formed in the reaction.

These results can be postulated as being due to competitive kinetic deprotonation at the two sites. The acidity of the benzylic groups are known to be greatly enhanced upon introduction of a silyl group into the para position of the arene ring.\textsuperscript{53} This enhanced acidity is thought to be due to back donation of the $\pi$-electrons from the arene ring into the 3d orbitals of the silicon atom (2p\textpi-3d\textsigma bonding), stabilising the resultant benzylic anion (Figure 16).
Since the proton at C-2 is quite hindered, deprotonation here is somewhat slow (as seen in (Scheme 121), and concurrent deprotonation at the next most acidic site, the benzylic group, occurs.

Repeating this reaction with 1.1 equiv. of $t$-BuLi and 223 (Scheme 127), the $t$-BuLi is much too sterically encumbered to allow deprotonate at the C-2 site and therefore deprotonation only occurs at the next most acidic site, the benzylic group. Analysis of the $^1$H nmr spectrum showed the benzylic peak to integrate for only two protons, indicating 100% incorporation of a single deuterium atom at the benzylic position 230. The $^2$H nmr spectrum showed a broad singlet at 2.31 ppm. Examination of the mass spectrum, taking into account the relative Si isotopes, shows a mass peak m/z=331, which confirms the monodeuterated species 230. The reason that 100% benzylic deprotonation occurs with $t$-BuLi, as opposed to only 19% with $n$-BuLi, is possibly due to $t$-BuLi being a stronger base.

![Scheme 127: Reagents: i) 1.1 equiv. $t$-BuLi; ii) CD$_3$OD](image)

On treatment of 223 with 1.1 equivalent of $t$-BuLi at -78°C and quenching with TMSCl, 225 was isolated in excellent yield (95%) with TMS incorporation only at the benzylic site (Scheme 128)

![Scheme 128 Reagents: i) 1.1 equiv. $t$-BuLi; ii) TMSCl](image)
These monometallation studies of the monosilylated compound 223 and their products, help confirm the postulated reaction pathway in Scheme 125.

### 3.3.6 Metallation Studies of (1,4-Dimethoxybenzene)Cr(CO)₃ (233)

Similar metallation studies were next carried out on (1,4-dimethoxybenzene)Cr(CO)₃ 233, which has two DoM groups para to one another. The compound 233 was readily made by heating 1,4-dimethoxybenzene 232 with chromium hexacarbonyl in a solution of dibutyl ether-THF at reflux for two days under standard conditions, to afford 233 as a yellow crystalline solid (m.p. 96-99°C) in 47% yield (Scheme 129).

![Scheme 129: Reagents: i) Cr(CO)_6, dibutyl ether-THF](image)

1H nmr spectroscopic analysis showed two singlets at 3.63 and 5.26 ppm indicative of the two equivalent methoxyl groups and the four equivalent arene protons respectively.

The compound 233 was deprotonated using 2.2 equivalents of n-BuLi and after 3 hours at -78°C was quenched with CD₃OD (Scheme 130). Work-up afforded the deuteriated species 234, in 82% yield and analysis of the 1H nmr spectrum of the crude reaction product showed it to be identical to 233, except that the resonance at 5.26 ppm now only integrated for two hydrogen atoms (92% dideuteriated), this was confirmed by a mass peak m/z=277 (MH⁺).

![Scheme 130](image)
However, it was unclear as to the regioselectivity of the deprotonation since all the arene protons are equivalent and appear as a singlet at 5.26 ppm in the $^1$H nmr spectrum. The results of the deuterium incorporation experiment was partially confirmed by using TMSCl as the electrophile.

The compound 233 was treated with 2.2 equivalents of $n$-BuLi at -78°C followed by electrophilic quench with TMSCl (Scheme 131). Work-up and subsequent purification by column chromatography, resulted in the isolation of two silylated products. Analysis of the $^1$H nmr spectrum revealed the reaction products as the 2,5-disilylated compound 235 (28%) and the 2,6-disilylated compound 236 (25%) (Table 7, entry 1). The ratio of the two disilylated compounds was 1:1.

![Scheme 131](image)

**Table 7**

<table>
<thead>
<tr>
<th>Entry</th>
<th>RLi (equiv.)</th>
<th>235</th>
<th>236</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$n$-BuLi (2.0)</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>$t$-BuLi (3.0)</td>
<td>7</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Repeating the metallation reaction of 233 with 3.0 equivalents of $t$-BuLi and quenching with TMSCl overnight, afforded upon work-up and column chromatography the 2,5-disilylated compound 235 (27%) and the 2,6-disilylated derivative 236 (4%) (Table 7, entry 2) in a ratio of 7:1.

Interestingly, it was observed that changing the base from $n$-BuLi to $t$-BuLi to generate the dianion of 233 and subsequent reaction with TMSCl, the ratio of the 2,5-disilylated compound increased (Table 7). Upon deprotonation at the C-2 position, the
methoxyl group at the C-1 position sits distal to the anionic site and so makes the deprotonation site at the C-6 position more hindered. The second equivalent of t-BuLi now has two sites which it can deprotonate, either at C-5 or C-6 (since deprotonation at C-3 would be unfavourable due to charge repulsion). Since the C-6 position is slightly hindered and the methoxyl group ortho to it is already involved in chelation at C-2, it is clear that deprotonation occurs at the C-5 position at a faster rate than at C-6. The fact that some deprotonation occurs at the C-6 position, shows that chelation is not a prerequisite to deprotonation of the second proton. This has also been observed in the case of the 2,6-dimetallation of (anisole)Cr(CO)₃ \( 212 \) (Scheme 115).

In interpreting the results of the silylation experiments described above, it is important to know whether the silyl derivatives formed accurately reflect the position of the lithiation of \( 233 \), or whether some of the products arise from lithiation during silylation. To investigate this possibility deprotonation studies were carried out on the monosilylated compound \( 237 \) to simulate a stepwise deprotonation sequence.

The compound \( 237 \) was afforded as a yellow crystalline solid (m.p. 119-120°C) in 59% yield by subjecting (1,4-dimethoxybenzene)Cr(CO)₃ \( 233 \) to deprotonation with 1 equivalent of n-BuLi and upon electrophilic quench with TMSCl (Scheme 132).

\[
\text{MeO} \text{Cr} \text{MeO} \quad \text{i, ii} \quad 59\% \quad \text{MeO} \text{Cr} \text{MeO}
\]

\( \text{Scheme 132: Reagents: i) 1.0 equiv n-BuLi; ii) TMSCl} \)

With \( 237 \) in hand, this was deprotonated at -78°C with 1.0 equivalent of n-BuLi and stirred for 2 hours at this temperature before being quenched with TMSCl (Scheme 133). Upon work-up, examination of the crude \(^1\)H nmr spectrum showed two structures, namely the 2,5-disilylated compound \( 235 \) and the 2,6-disilylated compound \( 236 \), in a ratio of 2:1 respectively (Table 8, Entry 1). Repeating the reaction using 1.0 equivalent of t-
BuLi, the same ratio of products were observed by crude $^1$H nmr analysis (Table 8, Entry 2).

![Scheme 133: Reagents : i) 1.0 equiv RLi; ii) TMSCI](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>RLi (equiv.)</th>
<th>235</th>
<th>236</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n-BuLi (1.0)</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>t-BuLi (1.0)</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

This ratio shows that the kinetic acidity of the proton at C-5 is greater than that at C-6. This is possibly due to the methoxyl group sitting distal to the bulky silyl group at C-2 causing increased steric hindrance at the C-6 site. Therefore, one would expect a faster rate of deprotonation at C-5 due to the lower steric requirements. Also in observing a change in the ratio of the two disilylated products 235 and 236 (Table 8) with those generated via the dianion (Table 7), indicates that a stepwise deprotonation did not occur.

### 3.3.7 Metallation Studies of (1,3-Dimethoxybenzene)Cr(CO)$_3$ (239)

Similar metallation studies were carried out on (1,3-dimethoxybenzene)Cr(CO)$_3$ 239 to investigate what the effect of changing the position of the two DoM groups with respect to one another would have on the generation of dianions.

The compound 239 was formed by refluxing 1,3-dimethoxybenzene 238 with Cr(CO)$_6$ in a solution of dibutyl ether-THF for two days (Scheme 134), to afford upon
work-up and column chromatography, the desired product 239 was isolated as a yellow crystalline solid (m.p. 121-123°C) in 48% yield.

\[
\begin{align*}
\text{Scheme 134: Reagents: i) Cr(CO)_3, dibutyl ether-THF}
\end{align*}
\]

Formation of the mono-anion was first examined. On reacting 239 with 1.1 equivalents of \( n \)-BuLi at -78°C for 3 hours followed by electrophilic quench with CD\(_3\)OD, the deuteriated compound 240 was isolated quantitatively (Scheme 135). \(^1\)H nmr spectroscopic analysis showed deuterium incorporation (94%) at the most acidic C-2 position. This was confirmed by a mass peak m/z=275 (M\(^+\)).

\[
\begin{align*}
\text{Scheme 135: Reagents: i) 1.1 equiv. \( n \)-BuLi; ii) CD\(_3\)OD}
\end{align*}
\]

However incomplete dianion formation resulted when 239 was treated with 4.0 equivalents of \( n \)-BuLi at -78°C for 3 hours followed by electrophilic quench with CD\(_3\)OD, afforded a mixture of deuteriated products (Scheme 136). The \(^1\)H nmr of the crude reaction mixture was identical with 239 except that the resonance at 5.18 ppm was decreased in area by 93% and the area of the resonance peak at 4.82 ppm decreased by 16%, due to deuterium incorporation at the 2-position and 6-position respectively. Investigation of the mass spectrum showed the presence of the molecular ion peaks (M\(^+\)) 275 and 276, which confirmed the formation of the monodeuteriated and dideuteriated
species. Therefore from the $^1$H nmr spectrum it was calculated that the deuteriated reaction products consisted of 83% of 240 and 17% of 241.

\begin{figure}
\centering
\includegraphics[width=0.8\textwidth]{scheme136.png}
\caption{Scheme 136: Reagents: i) 4.0 equiv. n-BuLi; ii) CD$_3$OD}
\end{figure}

The low proportion of 241 in Scheme 136 is thought to be due to the slow deprotonation of at the 6-position with n-BuLi. This reduced rate of deprotonation is thought to be due to the lone pair of electrons on the methoxyl group already involved in chelation of the lithiated species at C-2 (as in the free arene case) and the fact that the proton is less acidic at C-6 than at C-2.

The dianion of 239 was generated again, by the treatment of 239 with 4.0 equivalents of $t$-BuLi at -78°C for three hours. Electrophilic quench with CD$_3$OD afforded the dideuteriated species 241 with 100% deuterium incorporation at both the C-2 and C-6 positions (Scheme 137).

\begin{figure}
\centering
\includegraphics[width=0.8\textwidth]{scheme137.png}
\caption{Scheme 137: Reagents: i) 4.0 equiv. $t$-BuLi; ii) CD$_3$OD}
\end{figure}

$^1$H nmr spectroscopic analysis confirmed the identity of 241 by disappearance of the singlet at 5.30 ppm and integration of the doublet at 4.82 ppm for only one proton. This was also confirmed by the $^2$H nmr spectrum showing two deuterium peaks at 4.87 and 5.21 ppm, as well as a molecular ion peak, m/z=276 (M$^+$) in the mass spectrum.
corresponding to the incorporation of the two deuterium atoms. The high amount of dianion formation when using \( t\)-BuLi is thought to arise from the increased basicity of \( t\)-BuLi over \( n\)-BuLi.

Subsequently, the reaction of the dianion of \( \text{239} \) with TMSCl as the electrophile was studied (Scheme 138).

![Scheme 138](image)

The compound \( \text{239} \) was treated with 4.0 equivalents of \( t\)-BuLi for 3 hours at -78°C, an excess of TMSCl was added and the reaction mixture allowed to warm to room temperature overnight. Upon work-up and column chromatography \( \text{242} \) was isolated in 75% yield as a yellow crystalline solid (m.p. 134-136°C). It is interesting to compare this result with the poor yield in the disilylation of (3-methylanisole)Cr(CO)\(_3\) using excess \( t\)-BuLi (Scheme 138). In this case the dianion formation is complete, indicating the increased acidity of the proton at the C-2 position, and electrophilic quench with TMSCl is fast owing to less steric hindrance at C-2, since the methoxyl group has a smaller van der Waals radius than the methyl group and is electron withdrawing.\(^{54}\)

4.0 Conclusion

From the deprotonation and deuterium studies of the series of (arylether)Cr(CO)\(_3\) complexes with excess alkyl lithium, it can be seen that dianion formation occurs readily at low temperature.

It was also observed from the dimetallation studies of (anisole)Cr(CO)\(_3\) \( \text{212} \), (4-methylanisole)Cr(CO)\(_3\) \( \text{216} \) and (3-methylanisole)Cr(CO)\(_3\) \( \text{223} \), that only one DMG was required for dianion formation to occur at the C-2 and C-6 positions. The fact that 2,6-dianion formation can occur suggests that the second deprotonation occurs mainly by an
inductive mechanism, since the DMG is already involved in chelation to the first anionic site. However, using a weaker base such as LDA, only the mono-anion is generated.

Since direct dianion formation with uncomplexed compounds containing only one DMG is not observed, the ability of these arene chromium complexes to undergo dianion formation is due to the inductive electron withdrawing ability of the chromium tricarbonyl moiety. This unit merely increases the acidity of the arene protons and stabilises the dianions formed.
5.0 References


Chapter 4
General Experimental

1. General

All reactions involving (arene)Cr(CO)$_3$ complexes and organometallic or air sensitive reagents were performed under an atmosphere of dry nitrogen using standard vacuum line and Schlenk tube techniques, with all solvents being degassed before use. Reactions which were moisture sensitive were carried out with flame-dried glassware which had been cooled 
\textit{in vacuo} before use. The diastereoselectivities cited were determined by peak integration of the crude reaction products' $^1$H nmr spectrum. The percentage of deuterium incorporation was calculated by measurement of the respective peak heights in the $^1$H nmr spectrum and deuteriation was also confirmed by mass spectroscopy.

2. Solvents

All solvents were distilled under a nitrogen atmosphere. Tetrahydrofuran, diethyl ether and 1,4-dioxane were distilled from sodium benzophenone ketyl, dichloromethane was distilled from calcium hydride, dimethyl formamide was distilled under reduced pressure from sodium hydride and stored over Linde type 4A molecular sieves. Petrol refers to the fraction which distils between 40 and 60°C and was redistilled before use.

3. Reagents

Chromium hexacarbonyl was sublimed prior to use under reduced pressure. Trimethylsilyl chloride were distilled immediately prior to use from calcium hydride. Sodium hydride was used as a 60% dispersion in mineral oil and was washed twice with petrol prior to use. Lithium hexamethyldisilazide (LHMDS) and lithium diisopropylamide (LDA) were prepared \textit{in situ}. $n$-Butyllithium was used as a 1.30-1.60M solution in hexanes, $t$-butyllithium as a 1.7M solution in pentane, potassium hexamethyldisilylilamide (KHMDS) as a 0.65M solution in toluene, methylmagnesium bromide as a 3.0M solution in diethyl ether and trimethylaluminium as a 2.0M in toluene.

4. Chromatography

Flash chromatography was performed on silica gel (Kieselgel 60) under a positive pressure of nitrogen. Thin layer chromatography was carried out using glass-backed plates coated with GF$_{254}$ blend silica gel; visualisation generally being effected with both UV light and iodine.

5. Melting Points

All melting points were carried out on a Gallenkamp hot stage apparatus and are uncorrected.
6. **Infrared spectroscopy**

Infrared spectra were recorded on a Perkin-Elmer 781 FT spectrophotometer either as chloroform solutions in 1 cm NaCl cells or as KBr disks, and were referenced against polystyrene (1601 cm⁻¹).

7. **Nmr spectroscopy**

Nmr spectra were recorded on Bruker WH300 (¹H; 300.13 MHz), AM500 (¹H; 500.13 MHz and ¹³C; 125.7 MHz; ²H 76.75 MHz) or Varian Gemini 200 (¹H; 200 MHz) instruments; ¹³C nmr being obtained with DEPT editing. All chemical shifts are quoted in parts per million relative to trimethylsilane (δ 0.00 pp) and coupling constants are measures in Hertz. The 500 MHz ¹H and ¹³C nmr spectra were recorded by Mrs. E. McGuinness. The 500MHz ²H nmr spectra were recorded by Mrs. E. McGuinness and Miss T. Jackson.

8. **Mass Spectroscopy**

Mass spectra were obtained by Dr. R. T. Aplin and Mr. Robin R. Proctor of the Dyson Perrins analytical department, generally using chemical ionisation (CI) techniques on a VG Masslab VG 20-250. Fast atom bombardment (FAB) spectra were obtained using a VG Micromass ZAB-1F. Gas chromatography mass spectra (GCMS) were recorded on a VG Trio 1 spectrometer.

9. **Polarimetry**

Optical rotations were recorded on a Perkin-Elmer 241 polarimeter.

10. **Elemental Analysis**

Elemental analyses were obtained by Mrs. V. Lamburn of the Dyson Perrins analytical department on a Carla Erba 1106 elemental analyser.

11. **Yields**

All quoted yields refer to isolated material unless otherwise indicated.
Experimental: Chapter 2
Preparation of [fluorobenzene] chromium tricarbonyl\(^1\) 59

\[
\begin{align*}
\text{F} & \quad \text{Cr(CO)}_3 \quad \text{Bu}_2\text{O}/\text{THF} \\
& \quad \text{50\%}
\end{align*}
\]

To a solution of fluorobenzene (15 cm\(^3\), 15.98 mmol) in \(\text{Bu}_2\text{O}:\text{THF}\) (10:1, 110 cm\(^3\)) was added chromium hexacarbonyl (4.0 g, 18.2 mmol) and the reaction mixture refluxed under nitrogen for 48 h. The reaction was then cooled and filtered under nitrogen, through a short column of active alumina, washed with petrol to remove all the \(\text{Bu}_2\text{O}\) then subsequently eluted with dichloromethane and the yellow solution was removed \textit{in vacuo} to afford 59 as a yellow solid (1.84 g, 50%); \(\delta_{\text{H}}\) (200 MHz; CDCl\(_3\)) 5.51 (2H, dt, \(\delta = 6.5, 3.1\), ArCr(CO\(_3\))), 5.33 (2H, m, ArCr(CO\(_3\))), 4.86 (1H, dt, \(\delta = 6.2, 2.9\), ArCr(CO\(_3\))).

Preparation of (S)-phenylalaninol\(^2\) 60

\[
\begin{align*}
\text{Ph} & \quad \text{H}_2\text{N} & \quad \text{OH} \\
\text{(s)} & \quad \text{H}_2\text{N} & \quad \text{OH} \\
\text{(s)-60}
\end{align*}
\]

To a stirred suspension of sodium borohydride in 100 cm\(^3\) of THF was added (S)-(−) phenylalanine (4.0 g, 24.2 mmol). The flask was then cooled to 0°C and a concentrated solution of H\(_2\)SO\(_4\) (15 cm\(^3\), 30.25 mmol) in THF (10 cm\(^3\)) was added slowly, keeping the temperature below 20°C. The reaction mixture was then allowed to stir overnight at room temperature. MeOH (20 cm\(^3\)) was added and the reaction mixture concentrated to 30 cm\(^3\). A solution of 5N Sodium hydroxide (100 cm\(^3\)) was added and the solvent which boiled below 100°C removed by distillation. The remaining mixture was heated at reflux for 3 h and after cooling, the mixture was filtered through Celite\(^\circledR\) then subsequently washed with water. The filtrate and washings were then combined, diluted with water (100 cm\(^3\)) and washed with CH\(_2\)Cl\(_2\) (4 x 50 cm\(^3\)) and then the solvent removed \textit{in vacuo} to yield (S)-60 (3.17 g, 87%) as a white solid, which was recrystallised from petrol/ethyl acetate; m.p. 91-93°C [lit.\(^3\), 92-94°C]; \([\alpha]_p^{22}\) -22.3 (c 1, 1N HCl)); [lit.\(^3\) \([\alpha]_p^{22}\) -22.8 (c 1.2, 1N HCl)); \(\delta_{\text{H}}\) (300 MHz; CDCl\(_3\)) 7.34-7.18 (5H, m, Ph), 3.63, 3.38 (2H, AB of ABX, \(J_{\text{AB}}\) 10.6, \(J_{\text{AX}}\) 7.2, \(J_{\text{BX}}\) 3.8, CH\(_2\)Ph), 3.12 (1H, m, CH\(_2\)CH), 2.70, 2.52 (2H, AB of ABX, \(J_{\text{AB}}\) 13.5, \(J_{\text{AX}}\) 8.6, \(J_{\text{BX}}\) 5.2, CH\(_2\)CH), 1.74 (3H, br s, NH\(_2\), OH).
Preparation of (S)-[η⁶-N-phenylphenylalaninol]chromium tricarbonyl (S)-61

To a DMF (0.5 cm³) solution of 59 (1.0 g, 4.31 mmol) was added (S)-(−)-phenylalaninol 60 (3.93 g, 28.62 mmol) and the reaction was allowed to stir at room temperature for 2 days. Dichloromethane was then added to the reaction mixture and it was then passed through a column of deactivated alumina and concentrated to give a crude yellow oil. Purification by column chromatography on silica gel [10% ethyl acetate/petrol], yielded some starting material 59 (33%) and (S)-61 as a yellow oil (0.75 g, 48%); [α]D²² +32.72 (c 1.75, CHCl₃); νmax (CHCl₃)/cm⁻¹ 3626 (O-H), 1959, 1878 (C=O), 1548 (N-H), 1320 (C-N), 798 (N-H); δH (300 MHz; CDCl₃) 7.34-7.19 (5H, m, Ph), 5.55 (2H, m, ArCr(CO)₃), 4.80 (2H, m, ArCr(CO)₃), 4.68 (1H, m, ArCr(CO)₃), 3.99 (1H, d, J 7.1, CHNH), 3.79 (1H, m, NHCH), 3.79 (1H, m, NHCH), 3.53 (2H, m, CH₂OH), 2.99-2.83 (2H, AB of ABX system, JAB 13.6, JAX 5.7, JBX 7.6, CH₂Ph), 1.88 (1H, br s, OCH₂); δC (125 MHz; CDCl₃) 234.83 (Cr(CO)₃), 137.26 (Ph: Ci₃SO), 132.83 (ArCr(CO)₃: Ci₃SO), 129.29, 128.73, 126.82 (Ph), 96.82, 96.68, 83.26, 76.29, 74.44 (ArCr(CO)₃: C), 62.39 (CH₂OH), 55.38 (NCH), 37.57 (CH₂Ph); m/z (CI) 364 (MH⁺, 68%), 228 (MH⁺-Cr(CO)₃, 100); (Found C, 59.22; H, 4.54. C₁₈H₁₇NO₄Cr requires C, 59.50; H, 4.72; N, 3.86%).

Preparation of (S)-[N-phenylprolinol] chromium tricarbonyl (S)-63

(S)-(−)-prolinol 62 (1.75 g, 17.30 mmol) was added to a DMF (0.5 cm³) solution of (fluorobenzene)Cr(CO)₃ (1.0 g, 4.31 mmol) and the reaction was allowed to stir at room temperature for 2 days. Dichloromethane was then added to the reaction mixture, it was passed through deactivated alumina, and concentrated to give a crude yellow solid. Purification by column chromatography on silica gel [50% ethyl acetate/petrol], yielded the product (S)-63 (1.05 g, 78%) as a yellow solid, which was recrystallised from petrol/ethyl acetate; m.p. 131-132°C; [α]D²⁵ 127.3 (c 0.58, CHCl₃); νmax (CHCl₃)/cm⁻¹ 3398 (O-H), 1936, 1849 (C≡O), 1364 (N-C); δH (300 MHz; CDCl₃) 5.62 (2H, m, ArCr(CO)₃), 4.88 (1H, m, ArCr(CO)₃), 4.83 (1H, m, ArCr(CO)₃), 4.76 (1H, m,
Ar(Cr(CO)₃), 3.79 (1H, m, NCH), 3.70-3.58 (2H, m, CH₂OH), 3.33, 3.10 (2H, m, NCH₂), 2.10-1.95 (4H, m, CH₂CH₂), 1.65 (1H, br s, OH); δC (125 MHz; CDCl₃) 234.74 (Cr(CO)₃, 133.47 (ArCr(CO)₃:Cipso), 97.27, 97.11, 82.63, 76.33, 75.33 (ArCr(CO)₃:C), 63.88 (CH₂OH), 60.35 (NCH), 49.27 (CHCH₂) 28.37 (NCHCH₂), 23.51 (NH₂CH₂); m/z (EI) 313 (M, 23%), 177 (M-Cr(CO)₃ - CH₂OH), 146 (M-Cr(CO)₃ - CH₂OH), 100; Found C, 53.67; H, 4.56; N, 4.58. C₁₄H₁₅NO₄Cr requires C, 53.67; H, 4.83; N, 4.47%.

Preparation of (2S)-[(2-amino-2-benzylethoxy)-η⁶-phenyl] chromium tricarbonyl (66)

![Chemical Structure](image)

To a solution of NaH (1.5 g, 6.46 mmol) in THF, was added a THF solution of (S)-phenylalaninol (S)-60 at 0°C. The reaction was stirred for 0.5h, after which (fluorobenzene)Cr(CO)₃ was added and the reaction was warmed to room temperature overnight. The solvent was removed in vacuo to give a yellow oil which was then dissolved in CH₂Cl₂, filtered through deactivated alumina and the CH₂Cl₂ was then removed in vacuo. The resulting yellow solid was purified by column chromatography on silica gel [petrol/ethyl acetate] to afford (S)-66 as a yellow solid (1.38 g, 71%) which was recrystallised from petrol/diethyl ether; m.p. 82-83°C; [α]D²² +5.45 (c 0.52, CHCl₃); νmax (KBr)/cm⁻¹ 1952, 1855 (C=O), 1368 (C-N), 1251 (C-O-C), 1085 (C-N), 1058 (C-O-C); δH (300 MHz; CDCl₃) 7.38-7.21 (5H, m, Ph), 5.55 (2H, t, J 6.4, ArCr(CO)₃), 5.14 (2H, d, J 6.8, ArCr(CO)₃), 4.89 (1H, t, J 6.1, ArCr(CO)₃), 3.84, 3.71 (2H, AB of ABX system, Jₐᵦ 8.6, Jₐₓ 6.6, Jₐₓ 4.2, OCH₂), 3.47 (1H, m, PhCH₂CH), 2.91, 2.68 (2H, AB of ABX system, Jₐᵦ 13.5, Jₐₓ 8.3, Jₐₓ 5.5, CH₂Ph), 2.18 (2H, s, NH₂); δC (125 MHz; CDCl₃) 223.11 (Cr(CO)₃), 142.26 (Ph:Cipso), 138.00 (ArCr(CO)₃:Cipso), 129.20, 128.66, 126.64 (Ph), 94.85, 85.45, 78.67, 78.41 (ArCr(CO)₃:C), 73.02 (CH₂O), 51.74 (CH₂Ph), 40.39 (CHNH₂); m/z (Cl) 364 (MH⁺, 100%), 228 (MH⁺-Cr(CO)₃), 76; (Found C, 59.83; H, 4.46; N, 3.68. C₁₈H₁₇NO₄Cr requires C, 59.50; H, 4.72; N, 3.86%).
Preparation of (S)-[η⁶-N-phenyl(phenylalaninol)] chromium tricarbonyl (S)-61 via Smiles rearrangement

To a THF solution of (S)-66 at -78°C was added 2 equivalents of n-BuLi (0.3 ml, 34.79 mmol) and the reaction stirred for 2 h. The reaction was then quenched with MeOH and concentrated to give a crude yellow oil. The oil was taken up in CH₂Cl₂ and passed through a small column of deactivated alumina and the solvent removed. The product (S)-61 was isolated by column chromatography on silica gel (50% petrol/ethyl acetate), as a yellow oil (0.78 g, 90%); [α]D²² +33.02 (c 1.81, CHCl₃) δH (300 MHz; CDCl₃) 7.38-7.15 (5H, m, Ph), 5.55 (2H, m, ArCr(CO)₃), 4.80 (2H, m, ArCr(CO)₃), 4.70 (1H, m, ArCr(CO)₃), 4.0 (1H, d, J 7.1, CHNH), 3.73 (1H, m, NHCH), 3.55 (2H, m, ClO₂H), 3.02-2.83 (2H, AB of ABX system, JAB 13.6, JAX 5.7, JBX 7.6, CH₂Ph), 1.92 (1H, br s, CH₂OH)

Preparation of (S)-valine t-butyI ester⁴ (S)-68

To a 500 cm³ round bottom flask containing a solution of (S)-valine (5.0 g, 42.7 mmol) in dioxane (80 cm³) and concentrated H₂SO₄ (8 cm³) at -78°C, was bubbled isobutylene gas (80 cm³). The reaction was then sealed with a rubber stopper and allowed to warm to room temperature overnight. The excess isobutylene gas was released from the reaction and the reaction mixture poured into a cold mixture of diethyl ether (200 cm³) and 1N NaOH (125 cm³). The aqueous phase was extracted with diethyl ether (3 x 50 cm³) and the organic phase was then dried over MgSO₄ and concentrated in vacuo to give an oil. Purification of the oil by column by column chromatography on silica gel (50% petrol/ethyl acetate) afforded (S)-68 as a yellow oil (5.5 g, 74%); [α]D²² +25.3 (neat), [lit.⁵ [α]D²⁰ +25.6]; δH (300 MHz; CDCl₃) 3.18 (1H, d, J 5.0, CH₂QD), 1.99 (1H, dq, J 4.9, 6.8, (CH₃)₂CH), 1.65 (2H, s, NH₂), 1.47 (9H, s, C(CH₃)₃), 0.96 (3H, d, J 7.0, CHCH₃), 0.90 (3H, d, J 7.0, CHCH₃).
Preparation of (S)-[N-phenylvaline t-butyl ester] chromium tricarbonyl (S)-69

A variety of conditions and external amines have been investigated. The experimental results are discussed below and the results summarised in Table 1.

**Table 1**

<table>
<thead>
<tr>
<th>Base</th>
<th>Days</th>
<th>Product (%)</th>
<th>Recovered Material (%)</th>
</tr>
</thead>
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<tr>
<td></td>
<td></td>
<td>complexed 69</td>
<td>decomplexed 70</td>
</tr>
<tr>
<td>none</td>
<td>37 (rt)</td>
<td>18</td>
<td>14</td>
</tr>
<tr>
<td>t-butylamine (71)</td>
<td>11 (rt)</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>quinuclidine (73)</td>
<td>14 (rt)</td>
<td>69</td>
<td>0</td>
</tr>
<tr>
<td>3-quinuclidinol (74)</td>
<td>19 (rt)</td>
<td>37</td>
<td>17</td>
</tr>
<tr>
<td>quinuclidine (73)</td>
<td>2 (50°C)</td>
<td>19</td>
<td>0</td>
</tr>
</tbody>
</table>
Preparation of (S)-[N-phenylvaline t-butyl ester] chromium tricarbonyl (S)-69.

To a DMF (0.5 cm³) solution of 59 (0.22 g, 0.95 mmol) was added (S)-(+)-valine t-butyl ester 68 (0.76 g, 4.4 mmol) and the reaction was allowed to stir at room temperature for 37 days. Dichloromethane was then added to the reaction mixture and solution was passed through deactivated alumina. The CH₂Cl₂ was then removed in vacuo and the resulting yellow oil purified by column chromatography on silica gel [10% dichloromethane/petrol] to yield (S)-69 (0.066 g, 18%) and decomplexed product (S)-70 (0.03 g, 14%).

The compound (S)-69 was recrystallised from petrol/diethyl ether; m.p. 76-78°C; [α]D²⁵ +7.12 (c 0.18, CHCl₃); νₘₐₓ (KBr)/cm⁻¹ 2974 (N-H), 1947, 1860 (C=O), 1714 (C=O), 1148 (CO₂); δH (300 MHz; CDCl₃) 5.56 (2H, t, J 6.6, ArCr(CO)₃), 4.77 (2H, m, ArCr(CO)₃), 4.72 (1H, m, ArCr(CO)₃), 4.35 (1H, d, J 6.7, CHNH), 3.60 (1H, dd, J 6.7, 4.4 NHCH), 1.47 (9H, s, C(CH₃)₃), 0.99 (3H, d, J 2.0, CHCH₃), 0.97 (3H, d, J 2.0, CHCH₃); δC (125 MHz; CDCl₃) 234.19 (Cr(CO)₃), 170.4 (C=O), 132.48 (ArCr(CO)₃:Cl₆), 96.47, 96.25, 83.06 (ArCr(CO)₃:Cl₆), 82.81 (C(CH₃)₃), 76.34, 74.85 (ArCr(CO)₃:Cl₆), 61.35 (NHCH), 31.64 (CH₃CH), 28.01 (C(CH₃)₃), 18.73 (CH₂CH₃), 18.27 (CH₂CH₃); m/z (CI) 386 (MH⁺, 56%), 330 (MH⁺-2(CO), 100), 250 (MH⁺-Cr(CO)₃, 17), 148 (MH⁺-Cr(CO)₃-C₅H₁₀O₂, 28); (Found C, 56.15; H, 5.85; N, 3.53. C₁₈H₂₃NO₅Cr requires C, 56.10; H, 6.02; N, 3.64%).

The compound (S)-70 was isolated as a white solid; m.p. 77-79°C. [α]D²² -54.4 (c 0.68, CHCl₃); νₘₐₓ (KBr)/cm⁻¹ 3383 (N-H), 1710 (C=O), 1369 (N-C), 1247 (C-N); δH (500 MHz; CDCl₃) 7.17 (2H, m, Ph), 6.72 (1H, m, Ph), 6.66 (2H, m, Ph), 6.14 (1H, br s, ArNH), 3.77 (1H, d, J 5.5, CHCO), 2.12 (1H, m, CH₃CH), 1.43 (9H, s, C(CH₃)₃), 1.06 (3H, d, J 4.4, CH₂CH₃) 1.03 (3H, d, J 4.4, CH₂CH₃); δC (125 MHz; CDCl₃) 172.75 (CO₂), 147.60 (Ph:Cl₆), 129.18, 117.91, 113.62 (Ph), 81.44 (C(CH₃)₃), 62.85 (NHCH), 31.47 (CH₂CH₃), 28.07 (C(CH₃)₃), 18.97 (CH₂CH₃) 18.65 (CH₂CH₃). m/z (El) 249 (M, 36), 150...
Preparation of (S)-[N-phenylvaline t-butyl ester] chromium tricarbonyl (S)-69 with t-butylamine as an amine catalyst

To a DMF (0.5 cm$^3$) solution of 59 (4.5 g, 19.23 mmol) and t-butylamine 71 (7.0 g, 96.2 mmol) was added (S)-68 (10.0 g, 57.72 mmol) and the reaction was allowed to stir at room temperature for 11 days. Dichloromethane was then added and the reaction mixture was passed through deactivated alumina. The CH$_2$Cl$_2$ was then removed in vacuo and the resulting yellow oil purified by column chromatography on silica gel [50% petrol/dichloromethane] to yield (S)-69 (1.1 g, 15%) and 72 (0.542 g, 10%) both as yellow solids and a small amount of the decomplexed product (S)-70 (1%).

The compound 72 was recrystallised from petrol/diethyl ether to afford the product as a yellow crystalline solid; m.p. 128-130°C; $\nu_{max}$ (KBr)/cm$^{-1}$ 1937, 1844 (C=O), 1504 (N-H), 1383 (C-H), 1372 (N-C), 1322 (C-N); $\delta$H (300 MHz; CDCl$_3$) 5.54 (2H, m, ArCr(CO)$_3$), 4.77 (3H, m, ArCr(CO)$_3$), 3.63 (1H, br s, NH), 1.37 (9H, s, C(CH$_3$)$_3$); $\delta$C (125 MHz; CDCl$_3$) 234.83 (Cr(CO)$_3$), 132.83 (ArCr(CO)$_3$:Cipso), 96.56, 82.45, 76.28 (ArCr(CO)$_3$:C), 51.65 (C(CH$_3$)$_3$), 29.19 (C(C$_2$H$_5$)$_3$); m/z (El) 285 (M, 23%), 229 (M-C$_4$H$_9$, 14), 149 (m-Cr(CO)$_3$, 6), 52 (Cr, 100); Found C, 54.68; H, 5.43; N, 4.93. C$_{13}$H$_{15}$NO$_3$Cr requires C, 54.74; H, 5.30; N, 4.91%).
Preparation of (S)-[N-phenylvaline t-butyl ester] chromium tricarbonyl (S)-69 with quinuclidine as an amine catalyst

To a DMF (0.5 cm\(^3\)) solution of 59 (2.0 g, 8.62 mmol) and quinuclidine 73 (0.958 g, 8.62 mmol) was added (S)-valine t-butyl ester 68 (7.5 g, 43.08 mmol) and the reaction was allowed to stir at room temperature for 14 days. Dichloromethane was then added to the reaction mixture which was then columned through deactivated alumina and concentrated to give a crude yellow oil. Purification by column chromatography yielded the product (S)-69. \(^1\)H nmr spectroscopic analysis was identical with that obtained earlier for this compound.

Preparation of (S)-[N-phenylvaline t-butyl ester] chromium tricarbonyl (S)-69 with 3-quinuclidinol as an amine catalyst

To a DMF (0.2 cm\(^3\)) solution of 59 (0.10 g, 0.43 mmol) and 3-quinuclidinol (0.06 g, 0.43 mmol) was added (S)-(+) valine t-butyl ester 68 (0.22 g, 1.29 mmol) and the reaction was allowed to stir at room temperature for 19 days. Dichloromethane was then added and the reaction mixture and solution was passed through deactivated alumina. The CH\(_2\)Cl\(_2\) was then removed \textit{in vacuo} and the resulting yellow oil purified by column chromatography on silica gel [50% petrol/dichloromethane] to yield (S)-69 (0.06 g, 37%) and the decomplexed product (S)-70 (0.02 g, 17%). \(^1\)H nmr spectroscopic analysis was identical with that obtained earlier for this compound.
Preparation of (S)-[N-phenylvaline t-butyl ester] chromium tricarbonyl (S)-69 at 50°C

To a DMF (0.5 cm³) solution of 59 (0.20 g, 0.86 mmol) and quinuclidine (0.11 g, 0.95 mmol) was added (S)-(−)-valine t-butyl ester 68 (0.75 g, 4.31 mmol) and the reaction was allowed to stir 50°C for 2 days. Dichloromethane was then added and the reaction mixture was passed through deactivated alumina. The CH₂Cl₂ was then removed in vacuo and the resulting yellow oil purified by column chromatography on silica gel [50% petrol/dichloromethane] to yield (S)-69 (0.06 g, 19%). ¹H nmr spectroscopic analysis was identical with that obtained earlier for this compound.

Preparation of (S)-N-phenylvaline t-butyl ester (S)-70

An ether solution of (S)-69 (0.91 g, 2.36 mmol) was allowed to stand in direct sunlight for 2 days, after which it was filtered through deactivated alumina, the solvent removed in vacuo to yield the product (S)-70 as a white crystalline solid (0.59 g, 100%); m.p. 77-79°C. ¹H nmr spectroscopic analysis was identical with that obtained earlier for this compound.

Preparation of (S)-N-phenylvaline (S)-75

(S)-N-Phenyl t-butyl valine 70 (0.114 g, 0.383 mmol) was dissolved in trifluoroacetic acid (2 ml) and stirred at room temperature overnight. The trifluoroacetic
acid was subsequently removed in vacuo and the resultant oil dissolved in a minimum amount of CHCl₃ and basified with 1 N NaOH. The aqueous solution was then extracted twice with CHCl₃ and then acidified with concentrated hydrochloric acid to pH 4. At this pH, the free acid crystallised out and was filtered. Recrystallisation from ethanol/water afforded the product as a white crystalline solid (S)-75 (0.680 g, 92% yield); m.p. 123-124°C; [α]D²² -86.77 (c 0.31, EtOH); (lit., [α]D²² -86.0 (1.2% EtOH)); δH (300 MHz; CD₃OD) 7.11 (2H, m, Ph), 6.65 (3H, m, Ph), 3.74 (1H, d, J 6.4, CHCO₂), 2.16 (1H, m, CH₂CH), 1.09 (3H, d, J 7.1, CHCH₃) 1.03 (3H, d, J 7.1, CHCH₃).

Preparation of (S)-proline l-buty1 ester⁴ (S)-76

![Diagram of (S)-77 and (S)-76]

To a 500 cm³ round bottom flask containing a solution of (S)-77 (5.09 g, 43.43 mmol) in dioxane (80 cm³) and concentrated H₂SO₄ (8 cm³) at -78°C, was bubbled isobutylene gas (85 cm³). The reaction was then sealed with a rubber stopper and allowed to warm to room temperature overnight. The excess isobutylene gas was released from the reaction and the reaction mixture poured into a cold mixture of diethyl ether (200 cm³) and 1N NaOH (125 cm³). The aqueous phase was extracted with diethyl ether (3 x 50 cm³) and the organic phase dried over MgSO₄ and concentrated in vacuo to give a crude oil. Purification of the oil by column chromatography on silica gel (50% petrol/ethyl acetate) afforded (S)-76 as a yellow oil (4.8 g, 65%); [α]D²² -40.8 (c 1.61, EtOH); (lit., [α]D²² -41.5 (c 1.8, EtOH)); δH (300 MHz; CDCl₃) 3.61 (1H, dd, J 4.8, 5.5, CHCO₂), 3.06-2.85 (2H, m, CH₂CH₂), 2.05 (2H, m, CH₂CH₂), 1.73 (2H, m, CH₂CH₂), 1.45 (9H, s, C(CH₃)₃).

Preparation of (S)-[N-phenylproline l-buty1 ester] chromium tricarbonyl (S)-78

![Diagram of 59, (S)-76, and (S)-78]

To a DMF (0.3 cm³) solution of 59 (0.25 g, 1.08 mmol) and quinuclidine 73 (0.131 g, 1.19 mmol) was added (S)-76 (0.92 g, 5.36 mmol) and the reaction was allowed to stir at room temperature for 6 days. Dichloromethane was then added to the reaction mixture and the solution passed through deactivated alumina. The solvent was removed in vacuo to afford a crude yellow oil. Purification by column chromatography yielded the product
(S)-78 (0.29 g, 70%), as a yellow solid, which was recrystallised from petrol/diethyl ether; m.p. 74-75°C. [α]D^25 -241.71 (c 0.70, CHCl₃); ν max (KBr/cm⁻¹ 2982 (N-H), 1946, 1849 (C=O), 1736 (C=O), 1370 (N-C); δH (300 MHz; CDCl₃) 5.57 (2H, m, ArCr(CO)₃), 4.77 (2H, m, ArCr(CO)₃), 4.55 (1H, m, ArCr(CO)₃), 3.96 (1H, dd, J 9.1, 2.4, CHNH), 3.48-3.24 (2H, m, NCH₂), 2.31-1.99 (4H, m, (CH₂)₂CH), 1.48 (9H, s, C(CH₃)₃); δC (125 MHz, CDCl₃) 234.61 (Cr(CO)₃), 171.62 (CO₂), 131.69 (ArCr(CO)₃-Cipso), 97.16, 96.96, 82.69 (ArCr(CO)₃-C), 82.13 (C(CH₃)₃), 75.67 (ArCr(CO)₃-C), 61.47 (NHCH), 48.73 (NCH₂), 30.62 (CHCH₂), 27.94 (C(CH₃)₃), 23.89 (NCH₂CH₂); m/z (Cl) 384 (MH+, 100%), 248 (MH⁺-Cr(CO)₃, 30), 146 (MH⁺-Cr(CO)₃-C₃H₁₀O₂, 53); Found C, 56.69; H, 5.22; N, 3.72. C₁₈H₂₁NO₅Cr requires C, 56.40; H, 5.52; N, 3.65%).

Preparation of (S)-N-phenylproline t-butyl ester (S)-79

An ether solution of (S)-78 (0.10 g, 0.26 mmol) was allowed to stand in direct sunlight for 2 days, after which it was filtered through deactivated alumina, the solvent removed in vacuo to yield (S)-79 as an oil (0.06 g, 93%); [α]D^22-132.31 (c 0.78, CHCl₃); ν max (CHCl₃/cm⁻¹ 1734 (C=O), 1369 (N-C), 1245 (C-N), 1216 (C=O); δH (500 MHz; CDCl₃) 7.22 (2H, m, Ph), 6.70 (1H, m, Ph), 6.57 (2H, m, Ph), 4.13 (1H, dd, J 8.5, 2.5, CHCO₂), 3.52, 3.40 (2H, m, CHCH₂), 2.20 (4H, m, CH₂CH₂), 1.43 (9H, s, C(CH₃)₃); δC (125 MHz, CDCl₃) 173.78 (CO₂), 146.85 (Ph:Cipso), 129.00, 116.36, 111.99 (Ph), 81.02 (C(CH₃)₃), 61.61 (NHCH), 48.18 (NCH₂), 30.74 (CHCH₂), 27.97 (C(CH₃)₃), 23.79 (NCH₂CH₂); Accurate mass (Cl) 248.165026. C₁₅H₂₂NO₂ (MH⁺) requires 248.165054; m/z (Cl) 248 (MH⁺, 73%), 192 (MH⁺-Bu¹, 30).

Preparation of (S)-phenylalanine t-butyl ester (S)-81

To a 250 cm³ round bottom flask containing a solution of (S)-80 (5.0 g, 30.27 mmol) in dioxane (80 cm³) and concentrated H₂SO₄ (5 cm³) at -78°C, was bubbled
isobutylene gas (50 cm$^3$). The reaction was then sealed with a rubber stopper and allowed to warm to room temperature overnight. The excess isobutylene gas was released from the reaction flask and the reaction mixture poured into a cold mixture of diethyl ether (200 cm$^3$) and 1N NaOH (125 cm$^3$) and the aqueous phase was extracted with diethyl ether (3 x 50 cm$^3$). The organic phase was then dried over MgSO$_4$ and concentrated in vacuo, to give an oil. Purification of the oil by column column chromatography on silica gel (50% petrol/ethyl acetate) afforded (S)-81 as a yellow oil (4.97 g, 74%); $[\alpha]_D^{22} +24.2$ (neat); (lit.$^7$, $[\alpha]_D^{25} +24.6$ (neat)); $\delta_H$ (300 MHz; CDCl$_3$) 7.35-7.21 (5H, m, Ph), 3.62 (1H, dd, $J_7.7, 5.7$, CH$_2$CH), 3.06, 2.85 (2H, AB of ABX system, $J_{AB} 13.5$, $J_{AX} 7.8$, $J_{BX} 5.6$, CH$_2$Ph), 1.57 (2H, s, NH$_2$), 1.43 (9H, s, C(CH$_3$)$_3$).

Preparation of (S)-[$\eta^6$-N-phenyl(phenylalanine $t$-butyl ester)] chromium tricarbonyl (S)-82

To a DMF (0.2 cm$^3$) solution of 59 (0.3 g, 1.29 mmol) and quinuclidine (0.143 g, 1.29 mmol) was added (S)-81 (1.43 g, 6.46 mmol) and the reaction was allowed to stir at room temperature for 5 days. Dichloromethane was then added to the reaction mixture and it was subsequently filtered through deactivated alumina. The solvent was then removed in vacuo to give a crude yellow oil. Purification by column chromatography yielded the product (S)-82 (0.24 g, 43%), as a yellow solid, which was recrystallised from petrol/diethyl ether; m.p. 109-110°C. $[\alpha]_D^{22} +75.12$ (c 1.17, CHCl$_3$); $\nu_{\text{max}}$ (KBr)/cm$^{-1}$ 3020 (N-H), 1611, 1882 (C=O), 1729 (CO$_2$); $\delta_H$ (500 MHz; CDCl$_3$) 7.31-7.19 (5H, m, Ph), 5.52 (1H, m, ArCr(CO)$_3$), 5.43 (1H, m, ArCr(CO)$_3$), 4.75 (2H, m, ArCr(CO)$_3$), 4.45 (1H, m, ArCr(CO)$_3$), 4.30 (1H, br s, NH), 3.98 (1H, dd, $J 6.3, 12.6$, CHCO$_2$), 3.05 (2H, AB of ABX system, $J_{AB} 13.9$, $J_{AX} 6.2$, $J_{BX} 6.5$, CH$_2$Ph), 1.40 (9H, s, C(CH$_3$)$_3$); $\delta_C$ (125 MHz; CDCl$_3$) 234.18 (Cr(CO)$_3$), 170.61 (CH$_2$CO$_2$), 135.83 (Ph), 131.50 (ArCr(CO)$_3$:Cipso), 129.56, 128.51, 127.12 (Ph), 96.44, 96.23, 83.15 (ArCr(CO)$_3$:C), 82.98 (C(CH$_3$)$_3$), 76.46, 74.82 (ArCr(CO)$_3$:C), 57.57 (NHCH), 39.13 (CH$_2$Ph), 27.80 (C(CH$_3$)$_3$); m/z (CI) 434 (MH$^+$, 59%), 298 (MH$^+$-Cr(CO)$_3$, 93), 293 (100), 196 (MH$^+$-Cr(CO)$_3$-C$_5$H$_{10}$O$_2$, 20); (Found C, 60.77; H, 5.12; N, 3.18. C$_{22}$H$_{23}$NO$_5$Cr requires C, 60.97; H, 5.35; N, 3.22%).
Preparation of (S)-N-phenylphenylalanine t-butyl ester (S)-83

An ether solution of (S)-82 (0.10 g, 0.23 mmol) was allowed to stand in direct sunlight for 2 days, after which it was filtered through deactivated alumina, the solvent removed in vacuo to yield the product (S)-83 as a white solid (0.67 g, 100%), m.p. 81-82°C. [α]D\textsuperscript{22} +21.43 (c 0.63, CHCl\textsubscript{3}); ν\textsubscript{max} (KBr)/cm\textsuperscript{-1} 3359 (N-H), 1705 (CO\textsubscript{2}), 1305 (N-H); δ\textsubscript{H} (500 MHz; CDCl\textsubscript{3}) 7.32-7.15 (7H, m, Ph), 6.74 (1H, t, J 7.3, Ph), 6.63 (2H, d, J 1.0, Ph), 4.25 (1H, t, J 6.4, CHCo\textsubscript{2}), 4.15 (1H, br s, NH), 3.11 (2H, d, J 6.4, PhCH\textsubscript{2}), 1.35 (9H, s, C(CH\textsubscript{3})\textsubscript{3}); δ\textsubscript{C} (125 MHz, CDCl\textsubscript{3}) 172.24 (CO\textsubscript{2}), 146.62 (Ph: Cipso), 136.70 (Ph: Cipso), 129.50, 129.25, 128.33, 126.81, 118.19, 113.63 (Ph), 81.73 (C(CH\textsubscript{3})\textsubscript{3}), 58.17 (NH\textsubscript{CH}), 38.66 (CH\textsubscript{2}Ph), 27.90 (C(CH\textsubscript{3})\textsubscript{3}); m/z (CI) 298 (MH\textsuperscript{+}, 100), 242 MH\textsuperscript{+}-t-Bu, 48; Accurate mass (CI) 298.1815. C\textsubscript{19}H\textsubscript{23}NO\textsubscript{2} (MH\textsuperscript{+}) requires 298.18070.

Preparation of (S)-[η\textsuperscript{6}-N-phenyl(phenylalanine methyl ester)] chromium tricarbonyl (S)-86

To a DMF (0.5 cm\textsuperscript{3}) solution of 59 (0.10 g, 0.43 mmol) and quinuclidine (0.048 g, 0.43 mmol) was added (S)-phenylalanine methyl ester (0.31 g, 1.72 mmol) and the reaction was allowed to stir at room temperature for 5 days. Dichloromethane was then added to the reaction mixture, it was columned through deactivated alumina and concentrated to give a crude yellow oil. Purification by column chromatography yielded the product (S)-86 as a yellow solid (0.58 g, 38%) which was recrystallised from petrol/diethyl ether; m.p. 88-90°C. [α]D\textsuperscript{22} +60.33 (c 0.31, CHCl\textsubscript{3}); ν\textsubscript{max} (KBr)/cm\textsuperscript{-1} 3027 (N-H), 1942, 1855 (Cr(CO)\textsubscript{3}), 1723 (C=O); δ\textsubscript{H} (500 MHz; CDCl\textsubscript{3}) 7.32-7.16 (5H, m, Ph), 5.47 (2H, m, ArCr(CO)\textsubscript{3}), 4.78 (2H, m, ArCr(CO)\textsubscript{3}), 4.53 (1H, m, ArCr(CO)\textsubscript{3}), 4.18 (1H, d, J 6.4, NH), 4.08 (2H, m, CHCo\textsubscript{2}), 3.74 (3H, s, OCH\textsubscript{3}), 3.13, 3.06, (2H, AB of ABX system, J\textsubscript{AB} 13.6, J\textsubscript{AX} 6.6, J\textsubscript{BX} 5.9, CH\textsubscript{2}Ph); δ\textsubscript{C} (125 MHz, CDCl\textsubscript{3}) 234.05 (Cr(CO)\textsubscript{3}), 172.07 (C=O), 135.49...
(ArCr(CO)₃:CpSO), 130.80 (ArCr(CO)₃:CpSO), 129.36, 128.77, 127.38 (Ph), 95.99, 95.83, 83.66 76.53, 75.23 (ArCr(CO)₃:C), 57.27 (NHCH), 52.65 (OCH₃), 39.07 (CH₂Ph); m/z (EI) 391 (M, 4%), 307 (M-(CO)₃, 100).

Preparation of [2,6-dimethylfluorobenzene]chromium tricarbonyl 89

To a solution of 88 (3 g, 24.16 mmol) in Bu₂O:THF (10:1, 110 cm³) was added chromium hexacarbonyl (8.0 g, 36.24 mmol) and the reaction mixture heated to reflux under nitrogen for 48 h. The reaction was then cooled and filtered under nitrogen, through a short column of active alumina and washed with petrol to remove all the Bu₂O and then subsequently eluted with dichloromethane. The yellow solution was concentrated in vacuo to afford the product 89 as a yellow solid (2.0 g, 32%); m.p. 63-65 °C; νmax (KBr)/cm⁻¹ 1951, 1855 Cr(CO)₃; δH (200 MHz; CDCl₃) 5.21 (2H, dd, 5.2, ArCr(CO)₃), 5.01 (1H, t, J 6.2, ArCr(CO)₃), 2.27 (6H, s, 2(CH₃)); m/z (EI) 260 (M, 17%), 176 (M-(CO)₃, 100); Found C, 51.10; H, 3.33. C₁₁H₉FO₃Cr requires C, 50.78; H, 3.49.

Attempted Synthesis of [(R)-N-(methyl 2-methylacetate)-2,6-dimethylbenzene] chromium tricarbonyl (R)-91

To a DMF (0.5 cm³) solution of 89 (0.25 g, 0.96 mmol) and quinuclidine (0.11 g, 0.96 mmol) was added (R)-aniline methyl ester (0.197 g, 1.92 mmol) and the reaction was allowed to stir at room temperature for 14 days. Dichloromethane was then added to the reaction and the reaction mixture was then filtered through basic alumina and concentrated to give a crude yellow oil. ¹H spectroscopic analysis of the crude reaction product indicated only starting material and purification by column chromatography yielded only starting materials.
Preparation of (S) -\((N\text{-benzyl}-N\text{-}\alpha\text{-methylbenzylamine (S)})-95\)

Freshly distilled benzaldehyde (8.94 g, 84.2 mmol) was added to a solution of (S)-94 (10 g, 82.52 mmol) in ethanol (500 cm³) and the mixture heated at reflux for 6h. The resultant solution was cooled to 0°C, sodium borohydride (2.4 g, 63.44 mmol) was added cautiously, and the resultant turbid solution stirred at room temperature for 48h. The solvent was subsequently evaporated under reduced pressure to afford a solid residue which was treated with water (500 cm³) and extracted with dichloromethane (3 x 100 cm³). The combined organic extracts were dried over magnesium sulphate, filtered, and the solvent evaporated under reduced pressure to afford a colourless oil which was then dissolved in diethyl ether (150 cm³). The solution was then slowly added to a boiling solution of 12% aqueous hydrochloric acid (200 cm³). The stirred mixture was then cooled to room temperature whereupon the product crystallised out as its hydrochloride salt. The crystals were then filtered and washed with diethyl ether and then dissolved in hot 4M sodium hydroxide (300 cm³). Upon cooling, the alkaline solution was extracted with dichloromethane (3 x 100 cm³). The combined organic extracts were dried over magnesium sulphate, filtered and the solvent evaporated under reduced pressure to afford the title compound (S)-95 as a colourless oil (13.5 g, 76%); \([\alpha]_D^{22} -53.8\) (c 3.2, EtOH); \([\alpha]_D^{22} -53.6\) (EtOH))\)); \(\delta_H\) (300 MHz; CDCl₃) 7.44-7.23 (10H, m, Ph), 3.84 (1H, q, J 6.6, NCHCH₃), 3.82, 3.85, (2H, AB system, JAB 13.1, NCH₂Ph), 1.69 (1H, br s, NH), 1.39 (3H, d, J 6.6, NCHCH₃).

Preparation of (E)-\(t\text{-butyl crotonate)99\)

To a stirred suspension of 98 (5.25 g, 60.10 mmol) in dichloromethane (50 cm³) at -78°C was added concentrated sulphuric acid (1 cm³). Isobutylene gas (20 cm³) was then bubbled though the solution and the resultant suspension allowed to warm to room temperature overnight, during which the solution turned clear. The acidic solution was then neutralised on addition of a saturated aqueous solution of sodium bicarbonate and extracted with dichloromethane. The organic extracts were then combined, dried over
magnesium sulphate, filtered and concentrated to give a crude oil which was purified by flash chromatography [silica; petrol/diethyl ether, 10:1] to give 99 as a colourless oil (5.6 g, 66%); δH (CDCl3; 300 MHz) 6.87 (1H, dq, J 15.5, 6.7, CH3CH) 5.75 (1H, dq, J 15.5, 1.7, CHCO2), 1.85 (3H, dd, J 6.7, 1.7, CH3CH), 1.50 (9H, s, C(CH3)2).

Preparation of (3S, αS)-t-butyl 3-(N-benzyl-N-α-methylbenzyl)aminobutanoate (3S,αS)-100

To a THF solution of (S)-95 (11.19 g, 52.95 mmol) at -78°C was added 1.6M butyllithium (31 cm3, 49.31 mmol) and the lithium amide (S)-92 the resulting pink solution was stirred at -78°C for 30 min. To this was added a THF solution of 99 (6.38 g, 44.83 mmol) at -78°C and the reaction mixture stirred at this temperature for 2 h. The reaction was then quenched by the addition of a saturated solution of aqueous ammonium chloride and extracted twice with diethyl ether. The organic extracts were combined, dried over magnesium sulphate and concentrated to give 16 g of a crude oil which was purified by flash chromatography on silica gel (10:1; petrol/ diethyl ether) to give (3S,αS)-100 as a colourless oil (14.6 g, 92%, > 95% d.e.); [α]D22 +4.36 (c 0.90, CHCl3), [lit.,8 [α]D25 -4.3 (c 1.06, CH2Cl2); δH (300 MHz; CDCl3) 7.41-7.18 (10H, m, Ph), 3.87 (1H, q, J 6.7, PhCHN), 3.75, 3.60 (2H, AB system, JAB 15.0, PhCH2N), 3.46-3.39 (1H, m, CH3CHN), 2.28, 1.97 (2H, AB of ABX system, JAB 14.1, JAX 4.7, JBX 9.1, CH2CO2), 1.39 (9H, s, C(CH3)3), 1.32 (3H, d, J 6.8, PhCHCH3), 1.12 (3H, d J 6.7, CHCH3).

Preparation of (3S)-t-butyl 3-aminobutanoate (3S)-101

To an ethanolic solution of the β-amino ester (S,S)-100 (2.0 g, 5.65 mmol) in a Fischer-Porter bottle, was added Pearlman's catalyst (1.0 g, 50% by weight) and the suspension stirred overnight at 50°C and under 5 atm of hydrogen. The reaction mixture
was then filtered through Celite® and the solvent removed in vacuo to give a crude oil which was purified by flash chromatography [methanol/ethyl acetate 10:1] giving (S)-101 as a colourless oil (0.75 g, 83%) \([\alpha]_D^{22} -35.03\) (c 1.73, CHCl₃) \(\delta_H\) (300 MHz; CDCl₃) 3.37 (1H, m, CH₃CH), 2.39-2.21 (2H, AB of ABX system, \(J_{AB}\) 15.7, \(J_{AX}\) 4.8, \(J_{BX}\) 8.2, CH₂CO₂), 2.04 (2H, br s, NH₂), 1.45 (9H, s, C(CH₃)₃), 1.13 (3H, d, \(J\) 6.5, CH₃CH).

Preparation of [(3S)-N-((t-butyl 3-butoanoate) aniline] chromium tricarbonyl (S)-102

![Diagram](image)

To a DMF (0.5 cm³) solution of 59 (1.5 g, 6.46 mmol) and quinuclidine (0.70 g, 6.30 mmol) was added (S)-101 (2.0 g, 12.56 mmol) and the reaction was allowed to stir at room temperature for 14 days. Dichloromethane was then added to the reaction and the reaction mixture was then filtered through basic alumina and concentrated to give a crude yellow oil. Purification by column chromatography yielded the product (S)-102 (1.95 g, 81%), as a yellow solid, which was recrystallised from petrol/diethyl ether; m.p. 79-81°C. \([\alpha]_D^{25} -9.23\) (c 0.46, CHCl₃); \(v_{max}\) (KBr)/cm⁻¹ 1963, 1823 (C=O), 1703 (CO₂), 1369 (N-C), 1309 (C-N); \(\delta_H\) (500 MHz; CDCl₃) 5.58-5.54 (2H, m, ArCr(CO)₃), 4.81-4.73 (3H, m, ArCr(CO)₃), 4.10 (1H, d, \(J\) 7.9, CHNH), 3.68 (CH₃CH), 2.52, 2.43 (2H, AB of ABX system, \(J_{AB}\) 15.1, \(J_{BX}\) 6.3, \(J_{AX}\) 5.1, CH₂CO₂), 1.46 (9H, s, C(CH₃)₃), 1.30 (3H, d, \(J\) 6.5, CH₂CH₃); \(\delta_C\) (125 MHz, CDCl₃) 234.59 (Cr(CO)₃), 171.19 (CH₂CO₂), 132.17 (ArCr(CO)₃:Cipso), 96.52, 82.99 (ArCr(CO)₃:C), 81.47 (C(CH₃)₃), 74.96, 74.63, (ArCr(CO)₃:C), 45.64 (NHCH), 41.68 (CHCH₂), 28.07 (C(CH₃)₃), 20.02 (CHCH₃); m/z (Cl) 372 (MH⁺, 100%), 236 (MH⁺-Cr(CO)₃, 54), 120 (MH⁺-Cr(CO)₃-C₆H₁₂O₂, 100); (Found C, 54.89; H, 5.57; N, 3.79. C₁₇H₂₁NO₅Cr requires C, 54.98; H, 5.70; N, 3.77%)

Preparation of (3S)-N-((t-butyl 3-butoanoate) aniline (S)-103

![Diagram](image)
An ether solution of \((S)-102\) (1.36 g, 3.66 mmol) was allowed to stand in direct sunlight for 2 days, after which it was filtered through deactivated alumina, the solvent was removed \textit{in vacuo} and purified by column chromatography [silica, petrol/diethyl ether, 10:1] to yield \((S)-103\) as a colourless oil (0.862 g, 100%). \([\alpha]_D^{25} + 4.38 \) (c 0.85, CHCl$_3$); \(\nu_{\text{max}}\) (CHCl$_3$)/cm$^{-1}$ 1718 (C=O), 1369 (N-C), 1303 (C-N); \(\delta_H\) (500 MHz; CDCl$_3$) 7.18 (2H, m, Ph), 6.71 (1H, m, Ph), 6.63 (2H, d, \(J\) 7.8, Ph), 3.90 (1H, d, \(J\) 5.3, NHCH), 3.79 (1H, m, CH$_3$CH), 2.56, 2.36 (AB of ABX system, \(J_{AB}\) 14.7, \(J_{AX}\) 5.2, \(J_{BX}\) 6.8, CH$_2$CO$_2$), 1.46 (9H, s, C(CH$_3$)$_3$), 1.29 (3H, d, \(J\) 6.4, CHCH$_3$); \(\delta_C\) (125 MHz, CDCl$_3$) 171.19 (CO$_2$), 146.90 (Ph: C$_{\text{ipso}}$), 129.29, 117.45, 113.47 (Ph), 80.71 (C(CH$_3$)$_3$), 46.12 (NHCH), 42.26 (CH$_2$CO$_2$), 28.07 (C(CH$_3$)$_3$), 20.46 (CHCH$_3$). m/z (CI) 236 (MH$^+$, 100), 180 (39), 120 (42); Accurate mass 236.1654. C$_{14}$H$_{21}$NO$_2$ requires 236.1651.

**Preparation of \((3S)\)-methyl 3-(N-phenyl)aminobutanoate \((S)-108\)**

\[
\begin{align*}
\text{NH} & \quad \text{O} \\
\text{(S)-103} & \quad \xrightarrow{\text{MeOH, H}^+} \quad \text{NH} \\
& \quad \text{(S)-108} \\
\end{align*}
\]

A methanolic solution of \((S)-103\) (0.71 g, 3.03 mmol) was allowed to stir at room temperature overnight. The next day the solvent was removed \textit{in vacuo} and the resulting solid was taken up in aqueous sodium bicarbonate (50 cm$^3$), extracted with dichloromethane (2 X 100 cm$^3$). The combined organic extracts were then dried over magnesium sulphate, filtered, and concentrated to give a crude oil. Purification by flash chromatography on silica gel (10:1; petrol/ethyl acetate) afforded the product \((S)-108\) as a yellow oil (0.46 g, 79%). \([\alpha]_D^{21} +7.51 \) (c 0.95, CHCl$_3$) [lit.$^4$ for \(R\) \([\alpha]_D^{21} -7.0 \) (c 2.0, CHCl$_3$)]; \(\nu_{\text{max}}\) (CHCl$_3$)/cm$^{-1}$ 1729 (C=O), 1504 (N-H), 1367 (N-C, 1299 (C-N); \(\delta_H\) (300 MHz; CDCl$_3$) 7.21-7.15 (2H, m, Ph), 6.74-6.68 (1H, m, Ph), 6.65-6.61 (2H, m, Ph), 4.01-3.90 (1H, m, NHCH), 3.76 (1H, br s, NH), 3.69 (3H, s, OCH$_3$), 2.67; 2.45 (2H, AB of ABX system, \(J_{AB}\) 15.1, \(J_{AX}\) 5.1, \(J_{BX}\) 6.9, CH$_2$CO$_2$), 3.87 (3H, d, \(J\) 6.3, CHCH$_3$); \(\delta_C\) (125 MHz, CDCl$_3$) 172.25 (CO$_2$), 146.70 (Ph: C$_{\text{ipso}}$), 129.36; 117.75; 113.64 (Ph), 51.62 (OCH$_3$), 46.01 (NHCH), 40.73 (CH$_2$CO$_2$), 20.62 (CHCH$_3$); m/z (CI) 194 (MH$^+$, 100), 120 (42).
Preparation of (S)-4-methyl-N-phenylazetidin-2-one (S)-107

3.0 M Methyl magnesium bromide (0.25 cm$^3$, 0.75 mmol) was added dropwise to a diethyl ether solution (2 cm$^3$) of (S)-108 (0.096 g, 0.497 mmol) at 0°C, whereupon a white precipitate formed. The reaction was stirred at 0°C for 1 h and then quenched with phosphate buffer (pH 7, 2 cm$^3$) and warmed to room temperature. The mixture was then extracted with brine (2 x 50 cm$^3$), dried over magnesium sulphate and concentrated to give a crude oil. Purification by flash chromatography yielded (S)-107 as a yellow oil (0.075 g, 94%); [$\alpha$]$_D$ 22 +113.9. (c 0.61, CHC$l_3$) [lit. for (*-107, [$\alpha$]$_D$ -117.5, (c 1.34, CHCl$_3$); \(\delta_H\) (300 MHz; CDCl$_3$) 7.40-7.31 (4H, m, Ph), 7.11-7.06 (1H, m, Ph), 4.22-4.13 (1H, m, CH$_3$CH), 3.27; 2.71 (2H, AB of ABX system, \(J_{AB}\) 15.1, \(J_{AX}\) 2.5, \(J_{BX}\) 5.5, CH$_2$CO), 1.53 (3H, d, \(J_{6.1}\), CH$_3$).

Preparation of (E)-/-butyl 4-methoxycinnamate 115

To a stirred suspension of 114 (5.0 g, 28.05 mmol) in dichloromethane (50 cm$^3$) at -78°C was added concentrated sulphuric acid (2 cm$^3$). Isobutylene gas (20 cm$^3$) was then bubbled through the solution and the resultant suspension allowed to warm to room temperature overnight. The acidic suspension was then neutralised on addition of a saturated aqueous solution of sodium bicarbonate and then extracted with dichloromethane. The organic extracts were then combined, dried over magnesium sulphate, filtered and concentrated to give a crude solid which was purified by flash chromatography on silica [petrol/ethyl acetate [10:1] to give 115 as a white solid (4.6 g, 69%); m.p. 44-45°C; \(\delta_H\) (300 MHz; CDCl$_3$) 7.52 (1H, d, \(J_{16.0}\), ArCH), 7.45 (2H, d, \(J_{8.7}\), Ar), 6.88 (2H, d, \(J_{8.7}\), Ar), 6.27 (1H, d, \(J_{16.0}\), CHCO$_2$), 3.84 (3H, s, OCH$_3$), 1.53 (9H, S, C(CH$_3$)$_3$).
Preparation of (3R,αS)-t-butyl 3-(N-benzyl-N-α-methylbenzyl)amino-3-(4-methoxyphenyl)propionate 116

To a THF solution (100 cm$^3$) of (S)-95 (5.38 g, 25.50 mmol) at -78°C was added 1.6M butyllithium (14.6 cm$^3$, 23.37 mmol) to generate the amide (S)-92 and the resulting pink solution was stirred at -78°C for 30 min. To this was added a THF solution of 115 (5.0 g, 21.25 mmol) at -78°C and the reaction mixture was stirred at this temperature for 2 h. The reaction was then quenched by the addition of a saturated solution of aqueous ammonium chloride (10 cm$^3$) and extracted twice with diethyl ether. The organic extracts were combined, dried over magnesium sulphate and concentrated to give 11.11 g of a crude oil which was purified by flash chromatography on silica gel [10:1; petrol/ethyl acetate] furnishing 116 as a colourless oil (9.04 g, 96%); [α]D$^22$ - 2.69 (c 1.41, CHCl$_3$); νmax (CHCl$_3$/cm$^{-1}$) 1716 (CO$_2$), 1369 (C-N); δ$_H$ (500 MHz; CDCl$_3$) 7.41 (2H, d, $\delta$ 8.5, AT), 7.33-7.23 (5H, m, Ph), 6.87 (2H, d, $\delta$ 8.5, Ar), 4.37-4.34 (1H, m, CH$_3$CH$_2$N), 3.99 (1H, q, J 6.8, CH$_3$CH$_2$), 3.81 (3H, s, OCH$_3$), 3.67 (2H, s, CH$_2$Ph), 2.53-2.47 (2H, AB of ABX system, $\delta_{AB}$ 14.5, $\delta_{AX}$ 5.0 and $\delta_{BX}$ 10.2, CH$_2$CO$_2$), 1.26 (3H, d, $\delta$ 6.8, CH$_3$CH$_2$), 1.24 (9H, s, C(CH$_3$)$_3$); δ$_C$ (125 MHz, CDCl$_3$) 171.19 (CO$_2$), 158.60; 144.30; 141.85; 133.86; (Ph: C$_p$s), 129.30; 128.07; 127.95; 127.83; 126.75; 126.44; 113.41 (Ph), 80.08 (C(CH$_3$)$_3$), 59.12; 57.06 (CH$_2$), 55.20 (OCH$_3$), 50.77 (CH$_2$N), 38.62 (CH$_2$CO$_2$), 27.83 (C(CH$_3$)$_3$), 16.46 (CH$_3$CH); m/z (CI) 446 (MH$^+$, 60%), 330 (40), 235 (58), 212 (100), 105 (25), 91 (33); (Found: C, 78.27; H, 7.67; N, 2.97. C$_{29}$H$_{35}$NO$_3$ requires C, 78.17; H, 7.92; N, 3.14%).

Preparation of (3R) 3-(4-methoxyphenyl)-3-aminopropionate (3R)117
To an ethanolic solution of the β-amino ester 116 (4.0 g, 8.98 mmol) in a Fischer-Porter bottle, was added palladium hydroxide on carbon (2.0 g, 50% by weight) and the suspension stirred overnight at 50°C and under 5 atm of hydrogen. The reaction mixture was then filtered through Celite® and the solvent removed in vacuo to give a crude oil which was purified by flash chromatography (10:1; methanol/ethyl acetate) affording (R)-117 as a colourless oil (1.75 g, 78%) \([\alpha]D^{22} +10.41 (c 0.73, CHCl_3)\); \(\nu_{\text{max}} (\text{CHCl}_3)/\text{cm}^{-1} 1718 (\text{CO}_2), 1612 (\text{N-H}), 1302 (\text{C-N})\); \(\delta_H (500 \text{ MHz}; \text{CDCl}_3) 7.27 (2H, d, J 8.7, Ar), 6.86 (2H, d, J 8.7, Ar), 4.35-4.32 (1H, m, NH_2CH), 3.80, (3H, s, OCH_3), 2.57-2.53 (2H, m, CH_2CO_2), 1.43 (9H, s, C(CH_3)_3); \(\delta_C (125 \text{ MHz, CDCl}_3) 171.42 (\text{CO}_2), 158.77; 136.96; (\text{Ar:Cipso}), 127.36; 113.85 (\text{Ph}), 80.66 (\text{C(CH}_3)_3), 55.27 (\text{NHCH}), 52.15 (\text{OCH}_3), 45.44 (\text{CH}_2CO_2), 28.07 (\text{C(CH}_3)_3); \text{m/z (Cl)} 252 (\text{MH}^+, 18%), 235 (46), 179 (27), 136 (100); (Found C, 66.79; H, 8.27; N, 5.39. C_{14}H_{21}NO_3 requires C, 66.91; H, 8.42; N, 5.57%).

**Preparation of (3R) methyl 3-(4-methoxyphenyl)aminopropionate (R)-118**

![Reaction Diagram]

A methanolic solution of (R)-117 (0.60 g, 2.38 mmol) was allowed to stir at room temperature overnight. The next day the solvent was removed in vacuo, the resulting solid was taken up in aqueous sodium bicarbonate (20 cm³) and this was extracted with dichloromethane (2 X 20 cm³). The combined organic extracts were then dried over magnesium sulphate, filtered, and concentrated to give the a crude oil which was purified by flash chromatography on silica (1:1; petrol/ethyl acetate) to afford (R)-118 as a yellow oil (0.42 g, 84%); \(\nu_{\text{max}} (\text{CHCl}_3)/\text{cm}^{-1} 1731 (\text{C=O}), 1520 (\text{N-H}), 1303 (\text{C-N}), 1251 (\text{C-O-C})\); \(\delta_H (500 \text{ MHz}; \text{CDCl}_3) 7.31 (2H, m, Ar), 6.89 (2H, m, Ar), 4.39 (1H, t, J 6.8, NH_2CH), 3.81, (3H, s, CH_3OAr), 3.69 (3H, s, CO_2CH_3), 2.65 (2H, d, J 6.9, CH_2CO_2), 1.71 (2H, br s, NH_2); \(\delta_C (125 \text{ MHz; CDCl}_3) 172.53 (\text{CO}_2), 158.86; 136.78; (\text{Ar:Cipso}), 127.23, 113.96, (\text{Ar}) 55.27 (\text{NHCH}), 51.99 (\text{ArOCH}_3), 51.63 (\text{CO}_2\text{CH}_3), 44.06 (\text{CH}_2\text{CO}_2); \text{m/z (Cl)} 210 (\text{MH}^+, 55%), 193 (100), 136 (83); (Found C, 63.49; H, 7.68; N, 6.66. C_{14}H_{15}NO_3 requires C, 63.14; H, 7.23; N, 6.69). The compound (R)-118 was converted to it's hydrochloric salt by dissolving the free amino ester (0.10 g) in acidic methanol (5 cm³) and the resultant solution allowed to stir at room temperature for 0.25 h. The solution was then concentrated in vacuo to afford the hydrochloric salt as an orange hygroscopic solid; \([\alpha]D^{22} -90.2 (c 1.40, \text{MeOH}) \text{ [lit.}^{11}, [\alpha]D^{24} -91.5 (c 1.42, \text{MeOH})].
Preparation of (4R)-4-(4-methoxyphenyl)-2-azetidinone (R)-113

2.0 M Trimethylaluminium (0.43 cm$^3$, 0.86 mmol) was added dropwise to a toluene solution (1 cm$^3$) of (R)-118 (0.09 g, 0.43 mmol) at 0°C. The reaction was stirred at 0°C for 1 h and then warmed to room temperature overnight. The solvent was then removed in vacuo and the crude solid taken up in Et$_2$O and washed with water (2 X 20 ml). The organic phase was dried over magnesium sulphate, the solvent removed in vacuo and the crude product then purified by flash chromatography on silica gel (10:1, petrol/diethyl ether). The product (R)-113 was isolated as a white solid (0.057 g, 75%); m.p. 130-132°C; [α]$_D$ +131.3 (c 0.12, CHCl$_3$); ν$_{max}$ (KBr)/cm$^{-1}$ 1750 (C=O) δ$_H$ (500 MHz; CDCl$_3$) 7.27 (2H, d, 8.7, Ph), 6.89 (2H, d, J 8.7, Ph), 6.37 (1H, br s, NH), 4.67 (1H, dd, J 5.1, 2.4, CH$_2$CH), 3.81 (3H, s, CH$_3$OAr), 3.41-2.81 (2H, AB of ABX system, J$_{AB}$ 15.0, J$_{AX}$ 2.4, J$_{BX}$ 5.2, CH$_2$CO); δ$_C$ (125 MHz, CDCl$_3$) 168.13 (CO$_2$), 159.55, 147.75 (AnQpso), 126.91, 114.18 (Ar), 55.33 (CH$_3$CH$_2$), 49.97 (CH$_3$OAr), 48.05 (CH$_2$CH); m/z (Cl) 178 (MH$^+$, 100%); Found C, 67.57; H, 6.57; N, 7.80. C$_{10}$H$_{11}$NO$_2$ requires C, 67.78; H, 6.26; N, 7.90%.

Preparation of (4-fluoroanisole) chromium tricarbonyl 119

To a solution of 4-fluoroanisole (4.2 g, 33.30 mmol) in Bu$_2$O:THF (10:1, 110 cm$^3$) was added chromium hexacarbonyl (4.0 g, 18.2 mmol) and the reaction mixture heated to reflux under nitrogen for 48 h. The reaction mixture was then cooled, filtered under nitrogen through a short column of active alumina and washed with petrol to remove all the Bu$_2$O and subsequent elution with dichloromethane gave a yellow solution, the solvent was then removed in vacuo to afford 119 as a yellow solid (1.59 g, 34%); m.p. 63-65 °C; δ$_H$ (200 MHz; CDCl$_3$) 5.57-5.52 (2H, dd, J 7.1, 3.9, ArCr(CO)$_3$), 5.23-5.18 (2H, dd, J 7.1, 2.1, ArCr(CO)$_3$), 3.64 (6H, s, 2(OCH$_3$)).
Attempted N-Phenylation of the β-Lactam (R)-113

To a THF solution of (R)-113 at 0°C was added KHMDS in toluene and the reaction stirred for 1 h. The compound 119 was then added in a solution and the reaction mixture was allowed to warm to room temperature overnight. The solvent was then removed in vacuo and the crude reaction mixture taken up in CH$_2$Cl$_2$ and filtered through deactivated alumina. The solution was then concentrated to give a crude yellow solid. $^1$H nmr spectroscopic analysis of the crude reaction product showed only starting material.

Preparation of (S)-[η$^6$-N-((α-phenylethyl)4-methoxyaniline] chromium tricarbonyl 123

To a DMF (0.5 cm$^3$) solution of 119 (0.94 g, 3.6 mmol) was added (S)-(−)-α-phenylethylamine (S)-94 (1.4 g, 11.55 mmol) and the reaction was allowed to stir at room temperature for 10 days. Dichloromethane was then added to the reaction and the reaction mixture was then filtered through basic alumina and concentrated to give a crude yellow oil. Purification by column chromatography yielded (S)-123 as a yellow solid (0.47 g, 36%), which was recrystallisation from petrol/diethyl ether; m.p. 108-110°C; [α]$_D^{25}$ -275.2 (c 0.48, CHCl$_3$); $\tilde{\nu}$$_{max}$ (KBr)/cm$^{-1}$ 1943, 1839 (C=O), 1514 (N-H), 1368 (N-C), 1321 (C-N), 1272 (C-N), 1243 (C-O-C), 1029 (C-O-C); $\delta_{H}$ (300 MHz; CDCl$_3$) 7.34-7.28 (5H, m, Ph), 5.37 (1H, dd, J 7.3, 2.4, ArCr(CO)$_3$), 5.17 (1H, dd, J 7.3, 2.4, ArCr(CO)$_3$), 4.93 (1H, dd, J 7.3, 2.5, ArCr(CO)$_3$), 4.54 (1H, dd, J 7.3, 2.4, ArCr(CO)$_3$), 4.19 (1H, m, CHCH$_3$), 4.15 (3H, s, OCH$_3$), 1.46 (3H, d, J 6.7, CHCH$_3$); $\delta_{C}$ (125 MHz, CDCl$_3$) 235.11 (Cr(CO)$_3$), 143.54 (Ar: C$_{ipso}$), 134.51 (ArCr(CO)$_3$: C$_{ipso}$), 128.99, 127.52 (Ph), 125.84
(ArCr(CO)$_3$:cipso), 125.58 (Ph), 82.93, 81.30, 78.07, 75.27 (ArCr(CO)$_3$), 56.45 (OCH$_3$), 54.88 (CHCH$_3$), 25.00 (CHCH$_3$); m/z (El) 363 (M, 100%), 279 (M-(CO)$_3$, 100), 227 (M-Cr(CO)$_3$); Found C, 59.77; H, 4.94; N, 3.93. C$_{18}$H$_{17}$NO$_4$Cr requires C, 59.50; H, 4.72; N, 3.86%.

**Preparation of (S)-η$^6$-N-(α-phenylethyl)4-methoxyaniline (S)-124**

An ether solution of (S)-123 (0.170 g, 0.468 mmol) was allowed to stand in direct sunlight for 2 days. The reaction mixture was then filtered through basic alumina and the solvent removed in vacuo to yield (S)-124 as a colourless oil (0.106 g, 100%); [α]$_D^{25}$ -8.83 (c 1.67, MeOH); ν$_{max}$ (CHCl$_3$)/cm$^{-1}$ 3426, 1513 (N-H), 1374 (N-C), 1236 (C-N), 1224 (C-O-C), 1039 (C-O-C); δ$_H$ (200 MHz; CDCl$_3$) 7.41-7.19 (5H, m, Ph), 6.67 (2H, m, ArCr(CO)$_3$), 6.50 (2H, m, ArCr(CO)$_3$), 4.45 (1H, q, $J$ 6.7, NHCH$_3$), 3.81 (1H, br s, NH), 3.71 (3H, s, OCH$_3$), 1.53 (3H, d, $J$ 6.7, CHCH$_3$); δ$_C$ (125 MHz, CDCl$_3$) 151.85 (Ar:Cipso), 145.46 (Ph:Cipso), 141.55 (Ar:Cipso), 128.58, 126.79, 125.86 (Ph), 114.72, 114.50 (Ar) 55.71 (CHCH$_3$), 54.21 (CH$_3$OA), 25.12 (CHCH$_3$); m/z (Cl) 228 (M$^+$, 100%), 124 (30), 105 (23).

**The Attempted Asymmetric Synthesis of N-Phenyl β-Amino Ester 126**

To a THF solution (10 cm$^3$) of (S)-124 (0.112 g, 0.49 mmol) at -78°C was added 1.6M butyllithium (0.27 cm$^3$, 0.43 mmol) to generate the lithium amide (S)-125 and the resulting red solution was stirred at -78°C for 1 hour. To this was added a THF solution of 121 (0.08 g, 0.33 mmol) at -78°C and the reaction mixture stirred at this temperature for 3 hr. The reaction was then quenched by the addition of a saturated solution of aqueous
ammonium chloride (10 cm³), whereupon the solution turned yellow. The reaction mixture was extracted twice with diethyl ether. The organic extracts were combined, dried over magnesium sulphate and concentrated to give a crude brown oil. \(^1\)H spectroscopic analysis of the crude reaction product indicated only starting material. The reaction was also repeated at a higher temperature (0°C), however only starting material was identified by analysis of the \(^1\)H nmr spectrum.

**Preparation of [(S)-η⁶–N–(α-phenylethyl)aniline] chromium tricarbonyl (S)-128**

![Chemical structure](image)

To a DMF (0.5 cm³) solution of 59 (2.0 g, 8.62 mmol) was added (S)-94 (5.2 g, 43.07 mmol) and the reaction was allowed to stir at room temperature for 3 days. Dichloromethane was then added to the reaction and the reaction mixture was filtered through basic alumina and concentrated to give a crude yellow oil. Purification by column chromatography yielded (S)-128 as a yellow solid (2.38 g, 83%) which was recrystallised from petrol/diethyl ether; m.p. 123-125°C; [α]D\(^{25}\) -369.04 (c 1.98, CHCl₃); \(\nu_{\text{max}}\) (KBr) cm⁻¹ 3410 (N-H), 1941, 1844 (Cr(CO)₃), 1493 (N-H), 1377 (N-C), 1320 (C-N), 1268 (C-N); \(\delta_{\text{H}}\) (300 MHz; CDCl₃) 7.38-7.27 (5H, m, Ph), 5.54 (1H, m, ArCr(CO)₃), 5.41 (1H, m, ArCr(CO)₃), 4.85 (1H, m, ArCr(CO)₃), 4.75 (1H, m, ArCr(CO)₃), 4.47 (1H, dd, J 6.7, 2.2, Ar(Cr(CO)₃), 4.37-4.29 (1H, dq, J 6.7, 3.4, CHCH₃), 3.81 (1H, m, ArCr(CO)₃), 1.52 (3H, d, J 6.8, CHCH₃); \(\delta_{\text{C}}\) (125 MHz; CDCl₃) 234.58 (Ph,Cipso), 131.85 (ArCr(CO)₃:Cipso), 129.00, 127.56, 125.57 (Ph), 96.70, 96.29, 83.29, 77.54, 75.11 (ArCr(CO)₃:C), 54.03 (CHCH₃), 24.89 (CHCH₃); m/z (CI) 334 (MH+, 100%), 198 (MH+–Cr(CO)₃, 22); Found C, 61.21; H, 4.37; N, 4.22. C₁₇H₁₅NO₃Cr requires C, 61.26; H, 4.54; N, 4.20%.

**Preparation of (S)-η⁶–N–(α-phenylethyl)aniline\(^{13}\) (S)-129**

![Chemical structure](image)

An ether solution of (S)-128 (0.60 g, 1.78 mmol) was allowed to stand in direct sunlight for 2 days, after which it was filtered through deactivated alumina to yield (S)-129.
as a white solid (0.35 g, 100%); m.p. 43-45°C; $[\alpha]_D^{25} +20.9$ (c 0.76, MeOH) (lit. $^{13}$, $[\alpha]_D^{24} +18.5$ (c 1, MeOH)); $\nu_{\max }$ (KBr)/cm$^{-1}$ 3410, 1503 (N-H), 1371 (N-C), 1279 (C-N); $\delta_H$ (200 MHz; CDCl$_3$) 7.39-7.23 (5H, m, Ph), 7.12 (2H, m, Ph), 6.66 (1H, m, Ph), 6.52 (2H, m, Ph), 4.52 (1H, q, $J$ 6.7, CH$_3$), 4.03 (1H, br s, NH), 1.55 (3H, d, $J$ 6.8, CH$_3$).

The Attempted Asymmetric Synthesis of N-Phenyl $\beta$-Amino Ester 130

To a THF solution (100 cm$^3$) of (S)-129 (4.58 g, 21.71 mmol) at -78°C was added 1.6M butyllithium (0.30 cm$^3$, 0.48 mmol) to generate the lithium amide (S)-127 and the resulting red solution was stirred at -78°C for 1 hour. A THF solution of 121 (3.65 g, 15.51 mmol) at -78°C was then added. The resulting reaction mixture was stirred at -78°C for 1.5 h. The reaction was then quenched by the addition of a saturated solution of aqueous ammonium chloride (10 cm$^3$), whereupon the reaction mixture turned from red to light orange in colour. The reaction mixture was then extracted twice with diethyl ether. The organic extracts were combined, dried over magnesium sulphate and concentrated to give a crude oil. $^1$H nmr spectroscopic analysis of the crude reaction product indicated only starting material. The reaction was also repeated at a higher temperature (0°C), however only starting material was identified by analysis of the $^1$H nmr spectrum.

Preparation of (3R)-[\(\eta^6\)-N-(t-buty 3-propanoate-3-p-methoxybenzene) p-methoxyaniline] chromium tricarbonyl (3R)-131

To a DMF (0.5 cm$^3$) solution of 119 (1.26 g, 4.81 mmol) and quinuclidine (0.27 g, 2.43 mmol) was added 117 (2.0 g, 12.56 mmol) and the reaction was allowed to stir at
room temperature for 14 days. Dichloromethane was then added to the reaction and the reaction mixture was then filtered through basic alumina and concentrated to give a crude yellow oil. Purification by column chromatography yielded 131 as a yellow solid (0.16 g, 14%). The compound rapidly decomposed and only satisfactory $^1$H nmr spectroscopy could be secured; $\delta_H$ (500 MHz; CDCl$_3$) 7.23 (2H, d, $J$ 8.8, Ph), 6.88 (2H, d, $J$ 8.8, Ph), 5.26 (1H, dd, $J$ 7.3, 2.4, ArCr(CO)$_3$), 5.15 (1H, dd, $J$ 7.3, 2.4, ArCr(CO)$_3$), 4.95 (1H, dd, $J$ 7.2, 2.6, ArCr(CO)$_3$), 4.65 (1H, m, ArCr(CO)$_3$), 4.63 (1H, d, $J$ 2.5, NH), 4.38 (1H, m, NHCH$_3$), 3.80 (3H, s, OCH$_3$), 3.56 (3H, s, OCH$_3$), 2.61 (2H, m, CH$_2$CO$_2$), 1.39 (9H, s, C(CH$_3$)$_3$).

Preparation of (3R)-$\eta^6$-N-(t-butyl 3-propanoate-3-$p$-methoxybenzene) $p$-methoxyaniline (3R)-132

An ether solution of (3R)-131 (0.15 g, 0.30 mmol) was allowed to stand in direct sunlight for 2 days, after which it was filtered through deactivated alumina to yield (3R)-132 as a colourless solid (0.108 g, 100%); m.p. 95-96°C. [$\alpha$]$_D^{22}$ + 16.25 (c 0.72, CHCl$_3$); $\nu_{\text{max}}$ (KBr)/cm$^{-1}$ 1708 (C=O), 1516 (N-H), 1368 (C-N), 1254 (C-O-C), 1093 (C-O-C); $\delta_H$ (500 MHz; CDCl$_3$) 7.29 (2H, dd, $J$ 8.7, 2.1, Ph), 6.85 (2H, dd, $J$ 8.7, 2.1, Ph), 6.70 (2H, dd, $J$ 8.7, 2.3, Ph), 6.53 (2H, dd, $J$ 8.7, 2.3, Ph), 4.66 (1H, t, $J$ 6.8, NHCH$_3$), 3.79 (3H, s, CH$_3$OC$_6$H$_4$), 3.71 (3H, s, CH$_3$OC$_6$H$_4$), 2.69 (2H, d, $J$ 7.4, CH$_2$CO$_2$), 1.39 (9H, s, C(CH$_3$)$_3$); $\delta_C$ (125 MHz; CDCl$_3$) 170.62 (CO$_2$), 158.74, 152.17, 141.26, 134.60 (Ph: Cipso), 127.46, 115.01, 114.73, 113.96 (Ph), 81.00 (C(CH$_3$)$_3$), 55.67, 55.58 (CH$_3$O), 55.20 (NHCH$_3$), 44.15 (CH$_2$CO$_2$), 28.00 (C(CH$_3$)$_3$). $m/z$ (Cl) 358 (MH$^+$, 28%), 242 (22), 235 (100), 179 (29), 124 (83); Accurate mass 358.2016. C$_{21}$H$_{27}$NO$_4$ (Cl, MH$^+$) requires 358.2018.
Preparation of (3R)-6-N-(methyl 3-propanoate-3-p-methoxybenzene) p-methoxyaniline (3R)-133

A methanolic solution of (3R)-132 (0.130 g, 0.364 mmol) was allowed to stir at room temperature overnight. The solvent was then removed in vacuo and the resulting solid was dissolved in aqueous sodium bicarbonate (10 cm³) and extracted with dichloromethane (2 X 10 cm³). The combined organic extracts were then dried over magnesium sulphate, filtered, and concentrated to give the crude oil which was purified by flash chromatography on silica gel (10:1; petrol/ethyl acetate) to afford (3R)-133 as a yellow oil (0.115 g, 100%). [α]D²² +11.78 (c 0.28, CHCl₃); νmax (CHCl₃)/cm⁻¹ 1733 (C=O), 1511 (N-H), 1261 (C-O-C); δH (500 MHz; CDCl₃) 7.28 (2H, dd, J 8.7, 2.1, Ph), 6.86 (2H, dd, J 8.7, 2.1, Ph), 6.71 (2H, dd, J 8.9, 2.3, Ph), 6.53 (2H, dd, J 8.9, 2.3, Ph), 4.72 (1H, t, J 6.5, NHCH), 3.79 (3H, s, CH₃OC₆H₄), 3.70 (3H, s, CH₃OC₆H₄), 3.65 (3H, s, CO₂CH₃), 2.78 (2H, AB of ABX system, JAB 7.4, JAX 1.21, JBX 2.5, CH₂CO₂); δC (125 MHz, CDCl₃) 171.14 (CO₂), 158.87, 152.39, 141.01, 134.41 (Ar:Cipso), 127.36, 115.28, 114.78, 114.13 (Ar), 55.71 (NHCH), 55.35, 55.22 (CH₃OC₆H₄), 51.77 (CO₂CH₃), 42.71 (CH₂CO₂); m/z (CI) 316 (MH⁺, 19%), 193 (100); accurate mass 316.1548 (CI, MH⁺). C₁₈H₂₂NO₄, requires 316.1548.

Preparation of (4R)-1,4-bis(4-methoxyphenyl)-2-azetidinone (4R)-134

3.0 M Methyl magnesium bromide (0.042 cm³, 0.127 mmol) was added dropwise to a diethyl ether solution (2 cm³) of (3R)-113 (0.02 g, 0.063 mmol) at 0°C, where-upon a white precipitate formed. The reaction was stirred at 0°C for 1 h and then it was quenched
with phosphate buffer (pH 7, 2 cm\(^3\)) and warmed to room temperature. The mixture was then extracted with brine (2 x 10 cm\(^3\)), dried over magnesium sulphate and concentrated to give a crude oil which was purified by flash chromatography on silica gel (10:1; petrol/diethyl ether) yielding (3R)-134 as an oil (0.016 g, 89%). Although pure by \(^1\)H nmr spectroscopy, satisfactory elemental analysis for (3R)-134 could not be secured; [\(\alpha\)]\(_D\)\(^{22}\) +98.46 (c 0.065, CHCl\(_3\)); \(\nu\)\(_{\text{max}}\) (CHCl\(_3\))/cm\(^{-1}\) 1737 (C=O) \(\delta\)\(_H\) (500 MHz; CDCl\(_3\)) 7.29 (2H, d, \(J\) 8.6, Ph), 7.23 (2H, dd, \(J\) 8.9, 2.1, Ph), 6.91 (2H, d, \(J\) 8.6, Ph), 6.79 (2H, dd, \(J\) 9.0, 2.1, Ph), 4.93 (1H, dd, \(J\) 5.5, 2.5, CH\(_2\)CH), 3.81, 3.75 (3H, s, \(\text{CH}_3\)OAr), 3.53, 2.90 (2H, AB of ABX system, \(J_{\text{AB}}\) 15.0, \(J_{\text{AX}}\) 2.5, \(J_{\text{BX}}\) 5.6, CH\(_2\)CO); \(\delta\)\(_C\) (125 MHz, CDCl\(_3\)) 164.18 (CO\(_2\)), 159.74, 155.94, 131.51, 130.20 (Ph:C\(_{\text{ipso}}\)), 127.22, 118.17, 114.54, 114.28 (Ph), 55.43 (CH\(_3\)OC\(_6\)H\(_4\)), 55.31 (CH\(_3\)OC\(_6\)H\(_4\)), 53.80 (NHCH), 47.07 (CH\(_2\)CH); \(m/z\) (CI) 284 (MH\(^+\), 72%), 149 (14), 134 (100).

**Attempted Alkylation of the \(\beta\)-Lactam (3R)-134**

A freshly prepared THF (1 cm\(^3\)) solution of (3R)-134 (0.019 g, 0.07 mmol) was added to a THF solution of LHMDS (0.09 mmol) and the reaction stirred at \(-78^\circ\text{C}\) for 2 hours. 3 equivalents of 3-bromopropane (0.04 g, 0.20 mmol) was then added and the reaction allowed to warm to room temperature overnight. The reaction was quenched with phosphate buffer (pH 7) and then extracted twice with diethyl ether, dried over magnesium sulphate and concentrated to give a crude brown oil. \(^1\)H nmr spectroscopic analysis showed disappearance of the \(\beta\)-lactam starting material (3R)-134, however no product 109 was observed. The reaction was repeated using KHMDS as a base, however still no product was observed.
References

8. Dr. A. J. Burke, personal communication.
Experimental: Chapter 3
General Procedures

General procedure for the silylation of (arene)chromium tricarbonyl complexes

To a THF solution of the (arene)chromium tricarbonyl complex at -78°C was added the required alkyl lithium base, under nitrogen. The reaction was stirred at -78°C for 3 hrs, after which 5 equivalents of trimethylsilyl chloride was added. The reaction mixture was then allowed to warm slowly to room temperature overnight. The solvent was removed in vacuo, the resulting oil dissolved in CH2Cl2 and then filtered through alumina (grade v). The CH2Cl2 was removed in vacuo and the resulting oil purified by column chromatography (silica gel), to yield the silylated products.

General procedure for the metallation of (arene)chromium tricarbonyl complexes

To a THF solution of the (arene)chromium tricarbonyl complex at -78°C was added the required base, under nitrogen. The reaction was stirred at -78°C for 3 hrs and CD3OD (5 equiv.) was then added. The reaction mixture was allowed to warm to room temperature and the solvent removed in vacuo. The resulting solid was dissolved in CH2Cl2 and filtered through alumina (grade v). The CH2Cl2 was removed in vacuo to afford a yellow solid. The reaction product was not further purified. The percentage of deuterium incorporation was calculated by measurement of the respective peak heights in the 1H nmr spectrum and deuteration was also confirmed by mass spectroscopy.

Preparation of methoxymethoxy benzene$^1$ 206

\[
\begin{array}{c}
\text{205} \\
\text{OH}
\end{array}
\xrightarrow{i) \text{NaH, THF, 0°C}}
\begin{array}{c}
\text{206} \\
\text{OMe}
\end{array}
\]

To a THF solution (10 cm³) of NaH (3.0 g, 76.51 mmol) at 0°C was added 205 (6.0 g, 63.76 mmol) and the solution allowed to stir at this temperature for 0.5 hour. Chloromethyl methyl ether (6.15 g, 76.51) was added dropwise and the reaction allowed to warm to room temperature overnight. The reaction was concentrated in vacuo and then taken up in CH2Cl2, washed with sodium bicarbonate, water, and brine and the organic phase dried over magnesium sulphate. The solution was then filtered and the solvent removed in vacuo to afford a crude oil. Purification by column chromatography [silica; petrol/ethyl acetate, 1:1] afforded the product 206 as a colourless oil (4.18 g, 47%); $\delta^1H$ (300 MHz; CDCl3) 7.36 - 7.28 (2H, m, Ph), 7.09 - 7.00 (3H, m, Ph), 5.21 (2H, s, OCH2O), 3.51 (3H, s, OCH3).
Preparation of (methoxymethoxy benzene)chromium tricarbonyl 207

\[
\text{206} \xrightarrow{\text{Cr(CO)}_6, \text{Bu}_2\text{O}/\text{THF}} \text{207}
\]

To a solution of 206 (3.56 g, 25.77 mmol) in \text{Bu}_2\text{O}:\text{THF} (10:1, 110 cm\textsuperscript{3}) was added chromium hexacarbonyl (7.36 g, 33.50 mmol) and the reaction mixture heated at reflux, under nitrogen, for 48 hr. The reaction was then cooled and filtered, under nitrogen, through a short column of alumina (grade v) and washed with petrol to remove all the \text{Bu}_2\text{O} and subsequently eluted with dichloromethane. The yellow solution was removed \textit{in vacuo} to afford 207 as a yellow solid (2.50 g, 35\%) and was then recrystallised from petrol/diethyl ether; m.p. 77-79°C; \nu_{\text{max}} (\text{KBr})/\text{cm}^{-1} 1960, 1885 (\text{C}=\text{O}), 1250, 1054 (\text{Ar-O-C}); \delta_H (300 \text{ MHz}; \text{CDCl}_3) 5.52 (2\text{H}, \text{m}, \text{ArCr(CO)}_3), 5.29 (2\text{H}, \text{d}, J 6.7, \text{ArCr(CO)}_3), 5.06 (2\text{H}, \text{s}, \text{OCH}_2\text{O}), 4.90 (1\text{H}, \text{m}, \text{ArCr(CO)}_3), 3.50 (3\text{H}, \text{s}, \text{OCH}_3); \delta_C (125.77 \text{ MHz}, \text{CDCl}_3) 233.70 (\text{Cr(CO)}_3), 140.70 (\text{ArCr(CO)}_3: \text{Cipso}), 95.0, 94.50, 85.80 (\text{ArCr(CO)}_3), 80.30 (\text{OCH}_2), 56.40 (\text{OCH}_3); m/z (\text{El}) 274 (M\textsuperscript{+}, 24\%), 190 (M\textsuperscript{+}-3(\text{CO}), 52 (\text{Cr}, 100); (Found C, 48.01; H, 3.64. \text{C}_{11}\text{H}_{10}\text{O}_5\text{Cr} requires C, 48.19; H, 3.68\%).

Monosilylation of (methoxymethoxy benzene)chromium tricarbonyl 207

\[
\text{207} \xrightarrow{i) 1.2 \text{ equiv. n-BuLi, ii) TMSCI}} \text{208}
\]

To a THF solution (8 cm\textsuperscript{3}) of 207 (0.23 g, 0.85 mmol) at -78°C, was added 1.2 equivalents of n-BuLi (1.3 M, 0.78 cm\textsuperscript{3}, 1.02 cm\textsuperscript{3}) and the reaction mixture stirred for 3 hours. Silylation was then carried out under the standard conditions for the silylation of (arene)chromium tricarbonyl complexes. Column chromatography [silica; petrol/diethyl ether, 10:1] afforded the monosilylated product 208 as a yellow solid (0.19 g, 65\%), which was recrystallised from n-pentane/diethyl ether, m.p. 64-65°C; \nu_{\text{max}} (\text{KBr})/\text{cm}^{-1} 1953, 1859 (\text{C}=\text{O}), 1249, 1074 (\text{Ar-O-C}); \delta_H (300 \text{ MHz}; \text{CDCl}_3) 5.66 (1\text{H}, \text{m}, \text{ArCr(CO)}_3), 5.57 (1\text{H}, \text{dd}, J 1.4, 6.2, \text{ArCr(CO)}_3), 5.30 (1\text{H}, \text{d}, J 6.9, \text{ArCr(CO)}_3), 5.16, 4.99 (2\text{H}, \text{AB system, } J_{\text{AB}} 7.1, \text{OCH}_2\text{O}), 4.80 (1\text{H}, \text{m}, \text{ArCr(CO)}_3), 3.49 (3\text{H}, \text{s}, \text{OCH}_3), 0.33 (9\text{H}, \text{s}, \text{TMS}); \delta_C (125.77 \text{ MHz}, \text{CDCl}_3) 234.1 (\text{Cr(CO)}_3), 145.0 (\text{ArCr(CO)}_3: \text{Cipso}), 101.20, 95.9, 94.4 (\text{ArCr(CO)}_3: \text{C}), 88.2 (\text{ArCr(CO)}_3: \text{Cipso}), 85.2 (\text{ArCr(CO)}_3: \text{C}), 77.3 (\text{OCH}_2), 56.40 (\text{OCH}_3), 0.6 (\text{TMS}); m/z (\text{El}) 346 (M\textsuperscript{+}, 18\%), 262 (M\textsuperscript{+}-3(\text{CO}), 100); (Found C, 48.70; H, 4.95. \text{C}_{14}\text{H}_{18}\text{O}_5\text{CrSi} requires C, 48.55; H, 5.24\%).
Monosilylation of (2-trimethylsilyl methoxymethoxybenzene)chromium tricarbonyl 208

![Chemical structure of 208 and 209]

To a THF solution (10 cm³) of 208 (0.089 g, 0.26 mmol) at -78°C was added 1.0 equivalents of n-BuLi (1.3M, 0.20 cm³, 0.26 mmol) and the reaction mixture stirred for 3 hours. Silylation was then carried out under the standard conditions for the silylation of (arene)chromium tricarbonyl complexes. Column chromatography [silica; petrol/diethyl ether, 10:1] afforded the disilylated product 209 as a yellow solid (0.08 g, 73%), which was recrystallised from petrol/diethyl ether, m.p. 103-104°C; ν max (KBry cm⁻¹ 1960, 1883 (C=O), 1251, 1057 (Ar-O-C); δH (300 MHz; CDCl₃) 5.64 (2H, d, J 6.2, ArCr(CO)₃), 4.95 (2H, s, OCH₂O), 4.80 (1H, t, 6.2, ArCr(CO)₃), 3.54 (3H, s, OCH₃), 0.39 (9H, s, TMS); δC (125.77 MHz, CDCl₃) 233.9 (Cr(CO)₃), 149.8 (ArCr(CO)₃:Cipso), 101.8, 101.0, (ArCr(CO)₃:C), 92.2 (ArCr(CO)₃: ipso), 87.7 (OCH₂), 57.3 (OCH₃), 0.2 (TMS); m/z (El) 418 (M⁺, 8%), 334 (M⁺-3(CO), 100); (Found C, 48.58; H, 6.36. C₁₇H₂₆O₅CrSi₂ requires C, 48.78; H, 6.26%).

Disilylation of (methoxymethoxy benzene)chromium tricarbonyl 207

To a THF solution (8 cm³) of 207 (0.23 g, 0.84 mmol) at -78°C was added 3.0 equivalents of n-BuLi (1.3 M, 1.9 cm³, 2.52 mmol) and the reaction mixture stirred for 3 hours. Silylation was then carried out under the standard conditions for the silylation of (arene)chromium tricarbonyl complexes. Column chromatography [silica; petrol/diethyl ether, 10:1] afforded the disilylated product 209 as a yellow solid (0.20 g, 55%), which was recrystallised from petrol/diethyl ether, m.p. 103-104°C.
Dideuteriation of (methoxymethoxy benzene)chromium tricarbonyl 207 with 3.0 equiv. of n-BuLi

To a THF solution (10 cm$^3$) of 207 (0.11 g, 0.40 mmol) was added 3 equivalents of n-BuLi (1.3M, 0.93 cm$^3$, 1.20 mmol) and the reaction was allowed to stir at -78°C for 3 hrs. Deuteriation was then carried out under the standard conditions for the deuteriation of (arene)chromium tricarbonyl complexes, to afford 210 (0.11 g, 99%); m.p. 77-78°C. The $^1$H nmr spectrum of the crude reaction product was similar to 207 except for a decrease in the resonance peak at 5.52 ppm, due to deuterium incorporation at the 2,6-position. Investigation of the mass spectrum confirmed the formation of the dideuteriated compound 210 by a molecular ion peak m/z (El) 276. δ$_H$ (300 MHz; CDCl$_3$), 5.32 (2H, d, J 6.2, ArCr(CO)$_3$), 5.06 (2H, s, OCH$_2$O), 4.91 (1H, t, J 6.2, ArCr(CO)$_3$), 3.49 (3H, s, OCH$_3$); m/z (El) 276 (M$^+$, 34%), 192 (M$^+$-3(CO), 58), 147 (M$^+$-Cr(CO)$_3$).

Dideuteriation of (methoxymethoxy benzene)chromium tricarbonyl 207 with 5.0 equivalents of t-BuLi

The same procedure was repeated, as described above. 207 (0.11 g, 0.39 mmol) was deprotonated with 5 equivalents of t-BuLi (1.7 M, 1.3 cm$^3$, 1.93 mmol) to afford 210 (0.11 g, 98%) upon deuterium quench with CD$_3$OD. The $^1$H nmr and mass spectra were identical to that shown above, except that product contained 96% deuterium incorporation at the 2,6-position.
Preparation of (anisole)chromium tricarbonyl $^{2} 212$

$$\begin{align*} \text{OMe} & \quad \text{Cr(CO)$_{6}$, Bu$_{2}$O/THF} & \quad \text{OMe} \\ \text{211} & \quad \text{35}\% & \quad \text{212} \end{align*}$$

To a solution of $211$ (2.0 g, 18.49 mmol) in Bu$_{2}$O:THF (10:1, 110 cm$^{3}$) was added chromium hexacarbonyl (5.70 g, 25.87 mmol) and the reaction mixture heated at reflux, under nitrogen, for 48 hr. The reaction was then cooled and filtered, under nitrogen, through a short column of alumina (grade v) and washed with petrol to remove all the Bu$_{2}$O and subsequently eluted with dichloromethane. The yellow solution was removed in vacuo to afford $212$ as a yellow solid (1.58 g, 35%) which was recrystallised from petrol/diethyl ether; m.p. 84-86°C; $\delta_{H}$ (300 MHz; CDCl$_{3}$) 5.56 (2H, m, ArCr(CO)$_{3}$), 5.14 (1H, d, $J$ 7.0, ArCr(CO)$_{3}$), 4.88 (1H, m, ArCr(CO)$_{3}$), 3.71 (3H, s, OCH$_{3}$).

Dideuteriation of (anisole)chromium tricarbonyl $212$ with 3 equiv. of n-BuLi

To a THF solution (10 cm$^{3}$) of $212$ (0.11g, 0.46 mmol) was added 3 equivalents of n-BuLi (1.3 M, 1.1 cm$^{3}$, 1.38 mmol) and the reaction was allowed to stir at -78°C for 3 hrs. Deuteriation was carried out under the standard conditions for the deuteriation of (arene)chromium tricarbonyl complexes to afford $213$ (0.11g, 95%). The $^{1}H$ nmr spectrum of the crude reaction product was similar to $212$, except for a decrease in the resonance peak at 5.11 ppm, due to deuterium incorporation at the 2, 6-position which was calculated as being 91%. Collapse of the multiplets at 5.58 ppm to a doublet, also helped confirm the structure of $213$; $\delta_{H}$ (300 MHz; CDCl$_{3}$) 5.58 (2H, d, $J$ 6.2, ArCr(CO)$_{3}$), 3.71 (3H, s, OCH$_{3}$).
Dimetallation of (anisole)chromium tricarbonyl 212 with 5.0 equiv. of t-BuLi

\[
\begin{align*}
\text{OMe} & \quad \text{ii) CD}_3\text{OD} \\
\text{D} & \quad 94%
\end{align*}
\]

The procedure was repeated as described above, 212 (0.1 g, 0.39 mmol) was deprotonated with 5.0 equivalents of t-BuLi (1.7 M, 1.1 cm\(^3\), 1.95 mmol) to afford 213 (0.09 g, 94%), upon deuterium quench with CD\(_3\)OD. The \(^1\)H nmr and mass spectra were identical to that shown for 213 above, except that product contained 97% deuterium incorporation at the 2,6-position.

Deuteriation of (anisole)chromium tricarbonyl 212 with 5 equiv. of LDA

\[
\begin{align*}
\text{OMe} & \quad \text{ii) CD}_3\text{OD} \\
\text{D} & \quad 99%
\end{align*}
\]

To a THF solution of LDA (5 equiv.) at -78°C was added 212 (0.08 g, 0.33 mmol) and the reaction was allowed to stir at -78°C for 3 hrs. Deuteriation was carried out under the standard conditions for the deuteriation of (arene)chromium tricarbonyl complexes to afford 214 (0.08 g, 99%) which contained 95% deuterium incorporation at the 2-position. The \(^1\)H nmr spectrum was similar to 212 except for a decrease in the resonance peak at 5.14 ppm so as to integrate for only one hydrogen atom, which is indicative of deuterium incorporation at the 2-position. Investigation of the mass spectrum confirmed the formation of the monodeuteriated compound 214 by a molecular ion peak m/z (EI) 245; \(\delta\)\(_H\) (300 MHz; CDCl\(_3\)) 5.56 (2H, m, ArCr(CO)\(_3\)), 5.14 (1H, d, \(J\) 7.0, ArCr(CO)\(_3\)), 4.89 (1H, d, \(J\) 6.1, ArCr(CO)\(_3\)), 3.71 (3H, s, OCH\(_3\)); m/z (EI) 245 (M\(^+\), 48%), 161 (M\(^+\)-3(CO)).

Preparation of (4-methylanisole)chromium tricarbonyl 216

\[
\begin{align*}
\text{OMe} & \quad \text{i) Cr(CO)}_6, \text{Bu}_2\text{O/THF} \\
\text{OMe} & \quad 60%
\end{align*}
\]
To a solution of 215 (11.5 cm$^3$, 98.0 mmol) in Bu$_2$O:THF (10:1, 110 cm$^3$) was added chromium hexacarbonyl (4 g, 18.2 mmol) and the reaction mixture heated to reflux, under nitrogen, for 48 hr. The reaction was then cooled and filtered under nitrogen, through a short column of alumina (grade v) and washed with petrol to remove all the Bu$_2$O and subsequently eluted with dichloromethane. The yellow solution was removed in vacuo to afford 216 as a yellow solid (2.8 g, 60%), which was recrystallised from n-pentane/diethyl ether; m.p. 46-48°C; $v_{\text{max}}$ (KBr/cm$^{-1}$) 1953, 1860 (C=O), 1241, 1020 (C-O-C); $\delta_H$ (300 MHz; CDCl$_3$) 5.41 (2H, d, J 6.9, ArCr(CO)$_3$), 5.13 (2H, d, J 6.9, ArCr(CO)$_3$), 3.67 (3H, s, OCH$_3$), 2.08 (3H, s, CH$_3$); $\delta_C$ (125.77 MHz, CDCl$_3$) 234.0 (Cr(CO)$_3$), 141.5, 101.4 (ArCr(CO)$_3$:C$_{ipso}$), 95.4, 78.9 (ArCr(CO)$_3$:C), 55.2 (OCH$_3$), 19.3 (CH$_3$); m/z (El) 258 (M+, 7%), 174 (M+-3(CO), 25), 52 (Cr, 100); (Found C, 51.18; H, 3.63. C$_{11}$H$_{10}$O$_4$Cr requires C, 51.17; H, 3.90%).

Dideuteriation of (4-methylanisole)chromium tricarbonyl 216

![Dideuteriation Scheme]

To a THF solution (5 cm$^3$) of 216 (0.05 g, 0.21 mmol) was added 5 equivalents of n-BuLi (1.3 M, 0.78 cm$^3$, 1.03 mmol) and the reaction was allowed to stir at -78°C for 3 hrs. Deuteriation was carried out under the standard conditions for the deuteriation of (arene)chromium tricarbonyl complexes to afford 219 (0.05 g, 95%), which contained 76% 2,6-dideuterium incorporation. Analysis of the $^1$H nmr spectrum showed it to be similar to 216 except for a decrease in the resonance peak at 5.13 ppm, due to deuterium incorporation at the 2,6-position, and collapse of the doublet at 5.41 ppm, to a broad singlet, this confirmed the structure of 219; $\delta_H$ (300 MHz; CDCl$_3$) 5.41 (2H, br s, ArCr(CO)$_3$), 3.67 (3H, s, OCH$_3$), 2.08 (3H, s, CH$_3$).

Silylation of (4-methylanisole)chromium tricarbonyl 216

![Silylation Scheme]
To a THF solution (10 cm$^3$) of 216 (0.24 g, 0.95 mmol) at -78°C was added 5.0 equivalents of n-BuLi (1.7M, 2.8 cm$^3$, 4.73 mmol) and the reaction mixture stirred for 3 hours. Silylation was then carried out under the standard conditions for the silylation of (arene)chromium tricarbonyl complexes. Column chromatography [silica; petrol/diethyl ether, 10:1] afforded the disilylated product 217 as a yellow solid (0.19 g, 49%) and a small amount of the monosilylated compound 218 (0.03 g, 10%).

217 was recrystallised from n-pentane/diethyl ether, m.p. 174-176°C; $\nu_{\text{max}}$ (KBr)/cm$^{-1}$ 1968, 1898 (C=O), 1250, 1011 (Ar-O-C); $\delta_H$ (300 MHz; CDCl$_3$) 5.55 (2H, s, ArCr(CO)$_3$), 3.69 (3H, s, OCH$_3$), 2.01 (3H, s, CH$_3$), 0.39 (18H, s, 2(TMS)); $\delta_C$ (125.77 MHz, CDCl$_3$) 234.2 (Cr(CO)$_3$), 152.1 (ArCr(CO)$_3$:Cipso), 103.0 (ArCr(CO)$_3$:C), 102.6, 91.7 (ArCr(CO)$_3$:Cipso), 63.2 (OCH$_3$), 19.7 (CH$_3$), 0.4 (TMS); m/z (CI) 403 (MH$^+$, 100%), 267 (MH$^+$-Cr(CO)$_3$, 5); (Found C, 50.91; H, 6.79. C$_{17}$H$_{26}$O$_4$CrSi$_2$ requires C, 50.72; H, 6.51%).

218 was recrystallised from n-pentane/diethyl ether, m.p. 112-113°C; $\nu_{\text{max}}$ (KBr)/cm$^{-1}$ 1962, 1887 (C=O), 1250, 1024 (Ar-O-C); $\delta_H$ (300 MHz; CDCl$_3$) 5.59 (1H, dd, J 1.8, 7.2 ArCr(CO)$_3$), 5.49 (1H, d, J 1.8, ArCr(CO)$_3$), 4.95 (1H, d, J 7.2, ArCr(CO)$_3$) 3.70 (3H, s, OCH$_3$), 2.04 (3H, s, CH$_3$), 0.32 (9H, s, TMS); $\delta_C$ (125.77 MHz, CDCl$_3$) 234.0 (Cr(CO)$_3$), 146.3 (ArCr(CO)$_3$:Cipso), 102.8, (ArCr(CO)$_3$:C) 100.4 (ArCr(CO)$_3$:Cipso), 96.8 (ArCr(CO)$_3$:C), 88.8 (ArCr(CO)$_3$:Cipso), 73.1 (ArCr(CO)$_3$:C), 55.4 (OCH$_3$), 19.9 (CH$_3$), -0.6 (TMS); m/z (El) 330 (M$^+$, 20%), 246 (M$^+$-3(CO), 100); (Found C, 51.10; H, 5.23. C$_{14}$H$_{18}$O$_4$CrSi requires C, 50.90; H, 5.49%).

**Preparation of (3-methylanisole)chromium tricarbonyl 220**

![](image)

To a solution of 219 (11.5 cm$^3$, 98.0 mmol) in Bu$_2$O:THF (10:1, 110 cm$^3$) was added chromium hexacarbonyl (4 g, 18.2 mmol) and the reaction mixture heated at reflux, under nitrogen, for 48 hr. The reaction was then cooled and filtered, under nitrogen, through a short column of alumina (grade v). The column was eluted with petrol to remove all the Bu$_2$O and subsequently with dichloromethane. The yellow solution was removed in vacuo to afford 220 as a yellow solid (2.50 g, 54%), which was recrystallised from petrol/diethyl ether, m.p. 77-78°C; $\nu_{\text{max}}$ (KBr)/cm$^{-1}$ 1945, 1847 (C=O), 1269, 1039 (C-O-C); $\delta_H$ (300 MHz; C$_6$D$_6$) 5.55 (1H, t, J 6.6, Ar(Cr(CO)$_3$), 5.04 (1H, d, J 0.9, Ar(Cr(CO)$_3$), 5.00 (1H, dd, J 1.5, 6.7, Ar(Cr(CO)$_3$), 4.75 (1H, d, J 6.2, ArCr(CO)$_3$), 3.72 (3H, s, OCH$_3$), 2.26 (3H, s, CH$_3$); $\delta_C$ (125.77 MHz, CDCl$_3$) 233.5 (Cr(CO)$_3$), 143.70, 110.7 (ArCr(CO)$_3$:Cipso), 94.9, 86.7, 80.3, 75.8 (ArCr(CO)$_3$:C), 55.5 (OCH$_3$), 20.9 (CH$_3$);
Deuteriation of (3-methylanisole)chromium tricarbonyl 220 with 4.4 equiv. of n-BuLi

To a THF solution of 220 (0.11 g, 0.43 mmol) at -78°C, was added 4.4 equiv. of n-BuLi (1.5 M, 1.3 cm³, 1.89 mmol) and the reaction was allowed to stir at -78°C for 3 hrs. Deuteriation was carried out under the standard conditions for the deuteriation of (arene)chromium tricarbonyl complexes to afford a mixture of inseparable products 221 and 222. The \(^1\)H nmr spectrum of the crude reaction products was similar to 220, except for a 43% decrease in the resonance peak at 4.41 ppm, due to deuterium incorporation at the 2-position, and a 89% decrease in the resonance peak at 4.20 ppm, due to deuterium incorporation at the 6-position, and collapse of the triplet resonance peak at 4.69 ppm to a doublet. Investigation of the mass spectrum showed a 1:1 ratio of the molecular ion peaks (M⁺) 260 and 259, which confirmed the formation of a mixture of the dideuteriated compound and monodeuteriated compound. Therefore from the \(^1\)H nmr spectrum it was calculated that the deuteriated reaction product mixture contained 48% of the dideuteriated species 221 and 52% of the monodeuteriated species 222. \(\delta_H\) (300 MHz; C\(_6\)D\(_6\)) 4.69 (1H, d, \(J\) 6.0, ArCr(CO)\(_3\)), 3.86 (1H, d, \(J\) 6.0, ArCr(CO)\(_3\)), 2.94 (3H, s, OCH\(_3\)), 1.62 (3H, s, CH\(_3\)); \(\delta_{H}\) nmr (76.75 MHz; C\(_6\)H\(_6\) spiked with C\(_6\)D\(_6\)) 4.39 (br s), 4.19 (br s); m/z (EI) 260 (M⁺, 8%), 259 (M⁺, 9%), 176 (M⁺-3(CO), 30), 175 (M⁺-3(CO), 42), 52 (Cr, 100%).

Deuteriation of (3-methylanisole)chromium tricarbonyl 220 with 4.0 equiv. of t-BuLi

Compound 220 (0.05g, 0.21 mmol) was deprotonated with 4.0 t-BuLi (1.7M, 0.49 cm³, 0.84 mmol) and deuteriation was carried out under the standard conditions for the deuteriation of (arene)Cr(CO)\(_3\), to afford a mixture of inseparable products 221 and 222.

m/z (EI) 258 (M⁺, 6%), 122 (M⁺-Cr(CO)\(_3\), 6), 52 (Cr, 100); (Found C, 51.38; H, 3.98. C\(_{11}\)H\(_{10}\)O\(_4\)Cr requires C, 51.17; H, 3.90%).
The $^1$H nmr spectrum of the crude reaction products was similar to 220, except for a 31% decrease in the resonance peak at 4.41 ppm, due to deuterium incorporation at the 2-position, and a 93% decrease in the resonance peak at 4.20 ppm, due to deuterium incorporation at the 6-position, and collapse of the triplet resonance peak at 4.69 ppm to a doublet. Investigation of the mass spectrum showed a 1:2 ratio of the molecular ion peaks (M+) 260 and 259, which confirmed the formation of a mixture of dideuteriated compound and monodeuteriated compound. Therefore from the $^1$H nmr spectrum it was calculated that the deuterium reaction products contained 33% of the dideuteriated species 221 and 67% of the monodeuteriated species 222. $\delta_H$ (300 MHz; C$_6$D$_6$) 4.69 (1H, d, $J$ 6.0, ArCr(CO)$_3$), 3.86 (1H, d, $J$ 6.0, ArCr(CO)$_3$), 2.94 (3H, s, OCH$_3$), 1.62 (3H, s, CH$_3$); $^2$H nmr (76.75 MHz; C$_6$H$_6$ spiked with C$_6$D$_6$) 4.39 (br s), 4.19 (br s); m/z (El) 260 (M+, 10%), 259 (M+, 23%), 176 (M+-3(CO), 43), 175 (M+-3(CO), 74), 52 (Cr, 100%).

Monosilylation of (3-methylanisole)chromium tricarbonyl 220 with 1.2 equiv. of n-BuLi

To a THF solution (2 cm$^3$) of 220 (0.24 g, 0.95 mmol) at -78°C was added 1.2 equivalents of n-BuLi (1.6 M, 0.7 cm$^3$, 1.13 mmol) and the reaction mixture stirred for 3 hours. Silylation was then carried out under the standard conditions for the silylation of (arene)chromium tricarbonyl complexes. Column chromatography [silica; petrol/diethyl ether, 10:1] afforded the monosilylated product 223 as a yellow solid (0.23 g, 73%), which was recrystallised from petrol/diethyl ether, m.p. 126-127°C; $\nu_{\text{max}}$ (KBr)/cm$^{-1}$ 1943, 1867 (C=O), 1250, 1031 (C-O-C); $\delta_H$ (300 MHz; CDCl$_3$) 5.54 (1H, d, $J$ 6.2, ArCr(CO)$_3$), 4.91 (1H, s, ArCr(CO)$_3$), 4.70 (1H, d, $J$, 5.4, ArCr(CO)$_3$), 3.74 (3H, s, OCH$_3$), 2.29 (3H, s, CH$_3$), 0.29 (9H, s, TMS); $\delta_C$ (125.77 MHz, CDCl$_3$) 233.9 (Cr(CO)$_3$), 147.6, 111.0, 109.9 (ArCr(CO)$_3$:Cipso), 101.4, 86.7, 76.0 (ArCr(CO)$_3$), 55.2 (OCH$_3$), 21.1 (CH$_3$), -0.6 (TMS); m/z (CI) 331 (MH+, 100%), 195 (MH+-Cr(CO)$_3$, 12); (Found C, 50.60; H, 5.30. C$_{14}$H$_{18}$O$_4$CrSi requires C, 50.90; H, 5.49%).
Monosilylation of (3-methylanisole)chromium tricarbonyl 220 with 1.1 equiv. of t-BuLi

![Diagram of monosilylation reaction]

To a THF solution (4 cm³) of 220 (0.21 g, 0.81 mmol) at -78°C was added 1.1 equivalents of t-BuLi (1.7 M, 0.52 cm³, 0.88 mmol) and the reaction mixture stirred for 3 hours. Silylation was then carried out under the standard conditions for the silylation of (arene)chromium tricarbonyl complexes. Column chromatography [silica; petrol/diethyl ether, 10:1] afforded the monosilylated product 223 as a yellow solid (0.16 g, 60%).

Reaction of (3-methylanisole)chromium tricarbonyl 220 with 5.0 equiv. of n-BuLi

![Diagram of reaction with n-BuLi]

To a THF solution (5 cm³) of 220 (0.31 g, 0.95 mmol) at -78°C was added 5 equivalents of n-BuLi (1.5 M, 4.0 cm³, 5.95 mmol) and the reaction mixture stirred for 3 hours. Silylation was then carried out under the standard conditions for the silylation of (arene)chromium tricarbonyl complexes. Column chromatography [silica; petrol/diethyl ether, 10:1] afforded the monosilylated product 223 as a yellow solid (0.22 g, 55%) and some disilylated product 224 (0.005 g, 1%); δH (300 MHz; CDCl₃) 5.64 (1H, d, J 6.3, ArCr(CO)₃), 4.68 (1H, d, J 6.3, ArCr(CO)₃), 3.64 (3H, s, OCH₃), 2.34 (3H, s, CH₃), 0.47, 0.35 (9H, s, TMS); m/z (CI) 403 (MH+, 100%), 267 (MH⁺-Cr(CO)₃, 4); (Found C, 50.58; H, 6.90. C₁₇H₂₆O₄CrSi₂ requires C, 50.72; H, 6.51%).
Silylation of (3-methylanisole)chromium tricarbonyl 220 with 4.0 equiv. t-BuLi

To a THF solution (5 cm³) of 220 (0.22 g, 0.85 mmol) at -78°C was added 4.0 equivalents of t-BuLi (1.7 M, 2.0 cm³, 3.41 mmol) and the reaction mixture stirred for 3 hours. Silylation was then carried out under the standard conditions for the silylation of (arene)chromium tricarbonyl complexes. Column chromatography [silica; petrol/diethyl ether, 10:1] afforded the monosilylated product 223 (0.07 g, 21%), the disilylated product 225 (0.25 g, 72%) and the trisilylated compound 226 (0.01 g, 2%).

225 was isolated as a yellow solid and recrystallised from petrol/diethyl ether, m.p. 108-110°C; ν max (KBr)/cm⁻¹ 1958, 1878 (C≡O), 1251, 1025 (C-O-C); δ H (300 MHz; CDCl₃) 5.53 (1H, d, J 6.2, ArCr(CO)₃), 4.79 (1H, s, ArCr(CO)₃), 4.56 (1H, d, J 5.8, ArCr(CO)₃), 3.72 (3H, s, OCH₃), 1.87, 1.95 (2H, AB system, J AB 13.5, CH₂TMS), 0.3, 0.1 (9H, s, TMS); δ C (125.77 MHz, CDCl₃) 234.3 (Cr(C=O)₃), 147.9, 116.1 (ArCr(CO)₃C ipso), 101.5, 85.7, 75.0 (ArCr(CO)₃C), 55.2 (OCH₃), 26.9 (CH₂TMS), -0.5, -1.8 (TMS); m/z (EI) 402 (M⁺, 12%), 318 (M⁺-3(CO), 100); Found C, 50.87; H, 6.54. C₁₇H₂₆O₄CrSi₂ requires C, 50.72; H, 6.51%.

226 was isolated as a yellow solid and its structure tentatively assigned from the ¹H nmr spectrum; δ H (300 MHz; CDCl₃) 5.65 (1H, d, J 6.4, ArCr(CO)₃), 4.54 (1H, d, J 6.4, ArCr(CO)₃) 3.63 (3H, s, OCH₃), 2.22, 2.01 (2H, AB system, J AB 13.5, CH₂ TMS), 0.48, 0.35, 0.07 (9H, s, TMS).

Deuteriation of (2-trimethylsilyl 5-methylanisole)chromium tricarbonyl 223 with 1.1 equiv. of n-BuLi

To a THF solution of 223 (0.05 g, 0.15 mmol) at -78°C, was added 1.1 equivalents of n-BuLi (1.6 M, 0.1 cm³, 0.17 mmol) and the reaction was allowed to stir at -78°C for 3 hrs. Deuteriation was carried out under the standard conditions for the deuteriation of
(arene)chromium tricarbonyl complexes to afford an inseparable mixture of 230 and 231 and some starting material 223. The $^1$H nmr spectrum of the crude reaction mixture was similar to 223, except for a 50% decrease in the resonance peak at 4.92 ppm, due to deuterium incorporation at the 6-position, and a 19% decrease in the resonance peak at 2.18 ppm, due to deuterium incorporation at the benzylic position. $^2$H nmr spectrum analysis also showed two peaks at 4.95 and 2.30 ppm. Investigation of the mass spectrum, after correcting for the naturally occurring $^{29}$Si and $^{30}$Si isotopes, showed only a mass peak 331 (M$^+$), which confirms the formation of a mixture of the two monodeuteriated compounds 230 and 231. $^\delta$H (300 MHz; CDCl$_3$) 5.54 (1H, d, J 6.2, ArCr(CO)$_3$), 4.70 (1H, d, J, 6.2, ArCr(CO)$_3$), 3.74 (3H, s, OCH$_3$), 2.18 (2H, m, CH$_2$D), 0.29 (9H, s, TMS); $^2$H nmr (76.75 MHz; CHCl$_3$ spiked with CDCl$_3$) 4.95 (br s), 2.30 (br s); m/z (EI) 331(M$^+$, 11%) 247 (M$^+$-3(CO), 100%), 52(Cr, 51%).

Reaction of (2-trimethylsilyl 5-methylanisoIe)chromium tricarbonyl 223 with 1.1 equiv. of $t$-BuLi

To a THF solution of 223 (0.05 g, 0.15 mmol) at -78°C, was added 1.1 equivalents of $t$-BuLi (0.1 cm$^3$, 0.17 mmol) and the reaction was allowed to stir at -78°C for 3 hrs. Deuteriation was carried out under the standard conditions for the deuteriation of (arene)chromium tricarbonyl complexes to afford 230. The $^1$H nmr spectrum of the crude product mixture was similar to 223, except for the resonance peak at 2.27 ppm which now only integrates for 2 hydrogen atoms, due to deuterium incorporation at the benzylic position. $^2$H nmr spectrum analysis showed a broad singlet 2.31 ppm. Investigation of the mass spectrum, after correcting for the naturally occurring $^{29}$Si and $^{30}$Si isotopes, showed only a mass peak 331 (M$^+$), which confirms the formation monodeuteriated compound 230; $^\delta$H (300 MHz; CDCl$_3$) 5.54 (1H, d, J 6.4, ArCr(CO)$_3$), 4.92 (1H, S, ArCr(CO)$_3$), 4.70 (1H, d, J, 6.4, ArCr(CO)$_3$), 3.74 (3H, s, OCH$_3$), 2.27 (2H, m, CH$_2$D), 0.29 (9H, s, TMS); $^2$H nmr (76.75 MHz; CHCl$_3$ spiked with CDCl$_3$) 2.31 (br s); m/z (EI) 331(M$^+$, 9%) 247 (M$^+$-3(CO), 100%), 52(Cr, 46%).
Silylation of (2-trimethylsilyl 5-methylanisole)chromium tricarbonyl 223

![Diagram of silylation reaction]

To a THF solution (5 cm³) of 223 (0.14 g, 0.42 mmol) at -78°C was added 1.1 equivalents of t-BuLi (1.7 M, 0.27 cm³, 0.47 mmol) and the reaction mixture stirred for 3 hours. Silylation was then carried out under the standard conditions for the silylation of (arene)chromium tricarbonyl complexes. Column chromatography [silica; petrol/diethyl ether, 10:1] afforded the disilylated product 225 (0.16 g, 95%) as a yellow solid.

Preparation of (1,4-dimethoxybenzene)chromium tricarbonyl 233

![Diagram of preparation reaction]

To a solution of 232 (4.0 g, 28.95 mmol) in Bu₂O:THF (10:1, 110 cm³) was added chromium hexacarbonyl (8.3 g, 37.73 mmol) and the reaction mixture heated to reflux, under nitrogen, for 48 hr. The reaction was then cooled and filtered, under nitrogen, through a short column of alumina (grade v). The column was eluted with petrol to remove all the Bu₂O and subsequently with dichloromethane. The yellow solution was removed in vacuo to afford 233 as a yellow solid (3.73 g, 47%) which was then recrystallised from petrol/diethyl ether; m.p. 96-99°C; \( \nu_{\text{max}} \text{(KBr/cm}^{-1}) 1942, 1860 \text{(C=O), 1243, 1028 (C-O-C); } \delta_{\text{H}} \text{(300 MHz; CDCl}_3) 5.26 \text{(4H, s, ArCr(CO}_3)_3, 3.63 \text{(6H, s, 2(OCH}_3)); } \delta_{\text{C}} \text{(125.77 MHz, CDCl}_3) 234.4 \text{(Cr(CO}_3)_3, 136.8 \text{(ArCr(CO}_3)_3:Cipso), 79.6 \text{(ArCr(CO}_3)_3), 55.8 \text{(OCH}_3); m/z (CI) 275 \text{(MH}^+, 100%), 138 \text{(M-Cr(CO}_3)_3, 25); (Found C, 48.25; H, 3.38. C_{11}H_{10}O_5Cr requires C, 48.19; H, 3.68%).}
Dideuteriation of (1,4-dimethoxybenzene)chromium tricarbonyl 233

\[
\text{MeO-} \overset{\text{Cr}}{\text{C}} \overset{\text{OMe}}{\text{OMe}} \xrightarrow{i) 2.2 \text{ equiv. n-BuLi}} \xrightarrow{\text{ii) CD}_3\text{OD}} \text{MeO-} \overset{\text{Cr}}{\text{C}} \overset{\text{OMe}}{\text{OMe}}
\]

92% dideuterium incorporation

To a THF solution of 233 (0.22 g, 0.80 mmol) at -78°C, was added 2.2 equivalents of n-BuLi (1.3 M, 1.35 cm³, 1.75 mmol) and the reaction was allowed to stir at -78°C for 3 hrs. Deuteriation was carried out under the standard conditions for the deuteriation of (arene)chromium tricarbonyl complexes to afford 234 (0.18 g, 83%), as a yellow solid (m.p. 95-97°C). Since the compound is symmetrical, it is not possible to assign the exact position of the deuterium atoms in the molecule. The $^1\text{H}$ nmr spectrum was similar to 233, except for the resonance peak at 5.26 ppm, which only integrated for 2 hydrogen atoms. A molecular ion peak of 277 (MH$^+$) in the mass spectrum, also confirmed the formation of the deuteriated species; $\delta_H$ (300 MHz; CDCl$_3$) 5.26 (2H, s, ArCr(CO)$_3$), 3.63 (6H, s, 2(OCH$_3$)); m/z (Cl) 277 (MH$^+$, 100%).

Disilylation of (1,4-dimethoxybenzene)chromium tricarbonyl 233 with 2.2 equiv. of n-BuLi

\[
\text{OMe} \overset{\text{C}}{\text{MeO}} \overset{\text{TMS}}{\text{MeO}} \overset{\text{i)2.2 equiv. of n-BuLi}} \overset{\text{ii) TMSCI}}{\text{TMS TMS}} \text{MeO} \overset{\text{C}}{\text{MeO}} \overset{\text{TMS}}{\text{TMS}}
\]

1:1 ratio

To a THF solution (20 cm³) of 233 (0.21 g, 0.75 mmol) at -78°C was added 2 equivalents of n-BuLi (1.3 M, 1.26 cm³, 1.65 mmol) and the reaction mixture stirred for 3 hours. Silylation was then carried out under the standard conditions for the silylation of (arene)chromium tricarbonyl complexes. Column chromatography [silica; petrol/diethyl ether, 10:1] afforded the disilylated products 235 (0.09 g, 28%) and 236 (0.08 g, 25%) as yellow solids, in a ratio of 1:1.

235 was recrystallised from petrol/diethyl ether, m.p. 106-107°C; $\nu_{\text{max}}$ (KBr)/cm$^{-1}$ 1940, 1856 (C=O), 1254, 1036 (C-O-C); $\delta_H$ (300 MHz; CDCl$_3$) 5.06 (2H, s, ArCr(CO)$_3$), 3.63 (6H, s, 2(OCH$_3$)), 0.35 (18H, s, 2(TMS)); $\delta_C$ (125.77 MHz, CDCl$_3$) 234.6 (Cr(CO)$_3$), 140.8, 91.1 (ArCr(CO)$_3$:C$_{ipso}$), 81.1 (ArCr(CO)$_3$:C), 56.2 (OCH$_3$), -0.8 (TMS); m/z (El)
Chapter 4

Experimental: Chapter 3

418 (M+, 8%), 334 (M+3(CO), 100); (Found C, 48.77; H, 6.05. C₁₇H₂₆O₅CrSi₂ requires C, 48.78; H, 6.26%).

236 was recrystallised from petrol/diethyl ether, m.p. 107-109°C; ν_max (KBr)/cm⁻¹ 1942, 1865 (C=O), 1253, 1041 (C-O-C); δ_H (300 MHz; CDCl₃) 5.47 (2H, s, ArCr(CO)₃), 3.67 (3H, s, OCH₃), 3.59 (3H, s, OCH₃), 0.40 (18H, s, 2(TMS)); δ_C (125.77 MHz, CDCl₃) 234.6 (Cr(CO)₃), 149.3, 135.6, 91.4 (ArCr(CO)₃:C_ipso), 88.9 (ArCr(CO)₃:C), 63.4 (OCH₃), 55.7 (OCH₃), 0.3 (TMS); m/z (El) 418 (M+, 10%), 334 (M+-3(CO), 100); (Found C, 48.92; H, 6.47. C₁₇H₂₆O₅CrSi₂ requires C, 48.78; H, 6.26%).

Disilylation of (1,4-dimethoxybenzene)chromium tricarbonyl 233 with 3.0 equiv. of t-BuLi

To a THF solution (20 cm³) of 233 (0.21 g, 0.78 mmol) at -78°C was added 3 equivalents of t-BuLi (1.37 cm³, 2.33 mmol) and the reaction mixture stirred for 3 hours. Silylation was then carried out under the standard conditions for the silylation of (arene)chromium tricarbonyl complexes. Column chromatography [silica; petrol/diethyl ether, 10:1] afforded the disilylated products 235 and 236 as yellow solids.

Monosilylation of (1,4-dimethoxybenzene)chromium tricarbonyl 233

To a THF solution (20 cm³) of 233 (0.35 g, 1.28 mmol) at -78°C, was added 1 equivalent of n-BuLi (1.3 M, 0.98 cm³, 1.28 mmol) and the reaction mixture stirred for 3 hours. Silylation was then carried out under the standard conditions for the silylation of (arene)chromium tricarbonyl complexes. Column chromatography [silica; petrol/diethyl ether, 10:1] afforded the monosilylated product 237 (0.26 g, 59%) which was then recrystallised from petrol/diethyl ether, m.p. 119-120°C; ν_max (KBr)/cm⁻¹ 1947, 1855...
Silylation of (2-trimethylsilyl 4-methoxyanisole)chromium tricarbonyl 237

![Reaction Scheme](image)

To a THF solution (20 cm³) of 237 (0.10 g, 0.30 mmol) at -78°C was added the required alkyl lithium base (1 or 1.1 equiv.) and the reaction mixture stirred for 3 hours. Silylation was then carried out under the standard conditions for the silylation of (arene)chromium tricarbonyl complexes. ¹H nmr spectroscopic analysis of the crude reaction products showed the presence of both disilylated products 235 and 236, the ratios of which are shown in **Table 8**.

**Table 8**

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<th>Ratio</th>
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<td>2</td>
</tr>
<tr>
<td>2</td>
<td>t-BuLi (1.0)</td>
<td>2</td>
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</tbody>
</table>

Preparation of (1,3-dimethoxybenzene)chromium tricarbonyl 239

![Reaction Scheme](image)

To a solution of 238 (15 cm³, 11.45 mmol) in Bu₂O:THF (10:1, 110 cm³) was added chromium hexacarbonyl (4.0 g, 18.18 mmol) and the reaction mixture heated to reflux, under nitrogen, for 48 hr. The reaction was then cooled and filtered, under nitrogen, through a short column of alumina (grade v). The column was eluted with petrol to remove all the Bu₂O and subsequently eluted with dichloromethane. The yellow
solution was removed in vacuo to afford 239 as a yellow solid (1.5 g, 48%), which was then recrystallised from petrol/diethyl ether; m.p. 121-123°C; $\nu_{\text{max}}$ (KBr)/cm$^{-1}$ 1972, 1849 (C=O), 1274, 1034 (C-O-C); $\delta_{H}$ (300 MHz; CDCl$_3$) 5.57 (1H, t, J 6.7, ArCr(CO)$_3$), 5.18 (1H, m, ArCr(CO)$_3$), 4.82 (2H, dd, J 1.7, 6.7, ArCr(CO)$_3$), 3.74 (6H, s, 2(OCH$_3$)); $\delta_{C}$ (125.77 MHz, CDCl$_3$) 233.5 (Cr(CO)$_3$), 143.9 (ArCr(CO)$_3$:C$_{ipso}$), 93.1, 72.9, 69.3 (ArCr(CO)$_3$:C), 55.7 (OCH$_3$); m/z (EI) 274 (M$^+$, 28%), 190 (M$^+$-3(CO), 100) (Found C, 47.87; H, 3.40. C$_{11}$H$_{10}$O$_5$Cr requires C, 48.19; H, 3.68%).

**Monodeuteriation of (1,3-dimethoxybenzene)chromium tricarbonyl 239**

![Chemical structure of 239 and 240](image)

To a THF solution of 239 (0.06 g, 0.22 mmol) at -78°C, was added 1.1 equivalents of n-BuLi (1.6 M, 0.15 cm$^3$, 0.24 mmol) and the reaction was allowed to stir at -78°C for 3 hrs. Deuteriation was carried out under the standard conditions for the deuteriation of (arene)chromium tricarbonyl complexes to afford 240. The $^1$H nmr spectrum was similar to 239, except that the resonance peak at 5.18 ppm has decreased by 94% and the resonance peak at 4.82 ppm has changed from a doublet of doublets to a doublet, due to deuterium incorporation at the 2-position. A molecular ion peak of 275 (M$^+$) in the mass spectrum, also confirmed the formation of the monodeuteriated species 240; $\delta_{H}$ (300 MHz; CDCl$_3$) 5.57 (1H, t, J 6.7, ArCr(CO)$_3$), 4.82 (2H, d, J , 6.7, ArCr(CO)$_3$), 3.74 (6H, s, 2(OCH$_3$); m/z (EI) 275 (M$^+$, 39%), 191 (M$^+$-3(CO), 100).

**Dideuteriation of (1,3-dimethoxybenzene)chromium tricarbonyl 239 with 4.0 equiv. of n-BuLi**

![Chemical structure of 239, 240, and 241](image)

To a THF solution of 239 (0.07 g, 0.26 mmol) at -78°C, was added 4.0 equivalents of n-BuLi (1.6 M, 0.64 cm$^3$, 1.02 mmol) and the reaction was allowed to stir at -78°C for 3
hrs. Deuteriation was carried out under the standard conditions for the deuteriation of (arene)chromium tricarbonyl complexes to afford a mixture of monodeuteriated 240 and dideuteriated compounds 241. The $^1$H nmr spectrum of the crude reaction mixture was similar to 239, except that the resonance peak at 5.18 ppm had decreased in area by 93% and the resonance peak at 4.82 ppm decreased by 16%, due to deuterium incorporation at the 2,6-position. Investigation of the mass spectrum showed the presence of the molecular ion peaks ($M^+$) 275 and 276, which confirmed the formation of a mixture of the monodeuteriated and dideuteriated compounds. From the $^1$H nmr spectrum it was calculated that the deuteriated reaction products consisted of 83% of the monodeuteriated product 240 and 17% of the dideuteriated product 241: $\delta_H$ (300 MHz; CDCl$_3$) 5.57 (1H, m, ArCr(CO)$_3$), 3.74 (6H, s, 2(OCH$_3$)); $^2$H nmr (76.75 MHz; CHCl$_3$ spiked with CDCl$_3$) 5.21 (br s), 4.87 (br s); m/z (EI) 276 (M$^+$, 6%), 275 (M$^+$, 12), 192 (M$^+$-3(CO), 25), 191 (M$^+$-3(CO), 50), 52 (Cr, 100).

Dideuteriation of (1,3-dimethoxybenzene)chromium tricarbonyl 239 with 4.0 equiv. of tBuLi

![Diagram of reaction]

100% dideuteriated

The standard procedure for the deuteriation of (arene)Cr(CO)$_3$ was used. 239 (0.09 g, 0.32 mmol) was deprotonated with 4.0 equivalents of t-BuLi (1.7 M, 0.75 cm$^3$, 1.27 mmol) and quenched with CD$_3$OD to afford the dideuteriated product 241. The $^1$H nmr spectrum of the product was similar to 239, except that the resonance peak at 4.82 and 5.18 ppm have disappeared and the resonance peak at 4.82 ppm integrated for only one hydrogen atom, due to complete deuterium incorporation at the 2,6-positions 241; $\delta_H$ (300 MHz; CDCl$_3$) 5.57 (1H, m, ArCr(CO)$_3$), 4.82 (1H, d, $J$ 6.7, Ar(Cr(CO)$_3$), 3.74 (6H, s, 2(OCH$_3$)); $^2$H nmr (76.75 MHz; CHCl$_3$ spiked with CDCl$_3$) 5.21 (br s), 4.87 (br s); m/z (EI) 276 (M$^+$, 17%), 192 (M$^+$-3(CO), 82), 52 (Cr, 100).
Disilylation of (1,3-dimethoxybenzene)chromium tricarbonyl 239

![Chemical Structure](image)

To a THF solution (4 cm$^3$) of 239 (0.20 g, 0.73 mmol) at -78°C, was added 4 equivalents of $t$-BuLi (1.7 M, 1.7 cm$^3$, 2.92 mmol) and the reaction mixture stirred for 3 hours. Silylation was then carried out under the standard conditions for the silylation of (arene)chromium tricarbonyl complexes. Column chromatography [silica; petrol/diethyl ether, 10:1] afforded the monosilylated product 242 (0.23 g, 75%) which was then recrystallised from petrol/diethyl ether, m.p. 134-136°C; $\nu_{\text{max}}$ (KBr)/cm$^{-1}$ 1942, 1865 (C=O), 1251, 1067 (C-O-C); $\delta_H$ (300 MHz; CDCl$_3$) 5.67 (1H, d, $J = 6.9$, ArCr(CO)$_3$), 4.75 (1H, d, $J = 6.9$, ArCr(CO)$_3$), 3.72 (3H, s, OCH$_3$), 3.67 (3H, s, OCH$_3$), 0.42 (9H, s, TMS), 0.33 (9H, s, TMS); $\delta_C$ (125.77 MHz, CDCl$_3$) 234.1 (Cr(CO)$_3$), 153.7, 149.3 (ArCr(CO)$_3$:C$_{ipso}$), 98.9 (ArCr(CO)$_3$:C), 87.9, 84.0 (ArCr(CO)$_3$:C$_{ipso}$), 72.1(ArCr(CO)$_3$:C), 64.2 (OCH$_3$), 55.5 (OCH$_3$), 1.8, 0.3 (TMS); m/z (EI) 418 (M+, 9%), 334 (M$^+$-3(CO), 100); (Found C, 48.53; H, 6.22. C$_{17}$H$_{26}$O$_5$CrSi$_2$ requires C, 48.78 H, 6.26%).
References

