

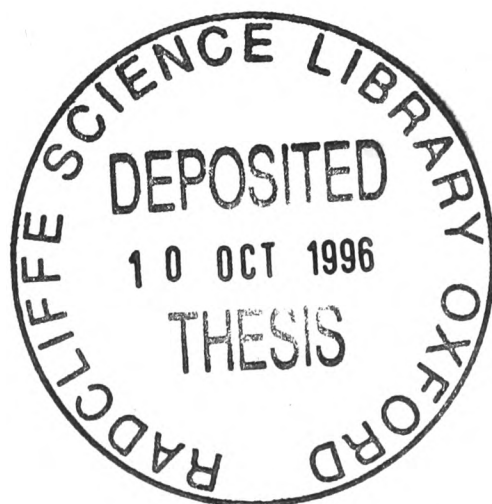
**SYNTHETIC APPLICATIONS OF ARENE CHROMIUM
TRICARBONYL COMPLEXES**

A thesis submitted in
partial fulfilment of the requirements
for the degree of Doctor of Philosophy
at the University of Oxford

by

Peter L. Dolan

St. Peter's College
Oxford



Trinity 1996

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

Acknowledgements

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.

A great deal of gratitude must go to the staff of the Dyson Perrins Laboratory, especially Elizabeth Mc Guinness, Tina Jackson, Dr Robin Aplin, Robin Procter and Val Lamburn, for their speedy technical services.

I have also been fortunate to share my three years in Lab 33 with some great characters. I would especially like to mention Dr David Fenwick, Dr Gilles Doisneau, Dr Francisco Valdés "Paco", and my-proof readers Darren Dixon, Dr Anthony Burke, David Hepworth, and Dr Steven Bull, who apart from giving great technical advice, could always be coaxed over to Halifax House!

Outside of the lab, I also made some great friends at St Peter's, especially all I met whilst rowing and playing rugby. The antics around college always kept things balanced with the lab, and made it worthwhile to still be a student.

My two years working at Bristol-Myers Squibb has also had a profound influence on my career, thus far, and I would like to thank Dr Graham Poindexter, Dr George Zavoico, Holly D'Amato, David Bucci and Dr Peter St Clair for all their help and friendship throughout my stay there.

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

D. Phil.

St. Peter's College

Trinity 1996

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 alkylolithium bases and the degree of dianion formation is confirmed by electrophilic quench of the dianionic intermediates with CD₃OD and TMSCl.

ABBREVIATIONS

General

Me	methyl
Ar	aryl
Et	ethyl
Pr ⁱ	isopropyl
Bu	butyl
Bu ^t	t-butyl
Ph	phenyl
Bn	benzyl
TMS	trimethylsilyl
X	leaving group
Nu	nucleophile
E	electrophile
m.p.	melting point
TLC	thin layer chromatography
MNDO	modified neglect of diatomic overlap
mol	Moles(s)
L	ligand
equiv.	equivalent(s)

Reagents

LDA	lithium diisopropylamine
THF	tetrahydrofuran
TFA	trifluoroacetic acid
TMEDA	<i>N,N,N',N'</i> -tetramethylethylene diamine
Dioxane	1,4-dioxane
<i>n</i> -BuLi	<i>n</i> -butyllithium
<i>t</i> -BuLi	<i>t</i> -butyllithium
MeLi	methyllithium
MeMgBr	methylmagnesium bromide
DMF	dimethylformamide
DMG	directing metallation group
HMDS	hexamethyldisilazane
LHMDS	lithium hexamethyldisilazide
KHMDS	potassium hexamethyldisilazide

DABCO

1,4-diazabicyclo[2.2.2]octane

Spectroscopy

nmr	nuclear magnetic resonance spectroscopy
UV	ultraviolet
IR	infrared
nOe	nuclear Overhauser effect
J	nmr coupling constant
m/z	mass to charge ratio
CI	chemical ionisation
EI	electron impact
M^+	molecular ion
MH^+	protonated molecular ion
$\nu_{\max}$	infrared absorption peak
δ	chemical shift in parts per million downfield from tetramethylsilane
s	singlet
d	doublet
dd	double of doublets
t	triplet
q	quartet
m	multiplet
de	diastereomeric excess
ee	enantiomeric excess

CONTENTS

Abstract

Acknowledgements

Abbreviations

Contents

Chapter 1

1 Introduction to Arene Chromium Tricarbonyl Chemistry

1.0	Synthesis of Arene Chromium Tricarbonyl Complexes	1
2.0	Arene Chromium Tricarbonyl Complexes in Organic Synthesis	2
2.1	Increased Stabilisation of Benzylic Carbocations	3
2.2	Steric Effect of the Chromium Tricarbonyl Unit	4
2.3	Chirality upon Complexation of an Arene to a Chromium Tricarbonyl Unit	4
2.4	Enhanced Acidity of Benzylic Protons	5
2.5	Enhanced Acidity of Arene Protons	6
2.6	Nucleophilic Aromatic Substitution	7
3.0	Nucleophilic Aromatic Substitution with Amines	12
3.1	Kinetic Studies	13
4.0	Nucleophilic Aromatic Substitution of Arene(Cr(CO) ₃) Complexes in Synthesis	15
5.0	References	18

Chapter 2

2 Asymmetric Synthesis of *N*-Phenyl Amino Acids

1.0	Introduction	20
2.0	Asymmetric Synthesis of <i>N</i> -Phenyl α - and β - Amino Acids	21
2.1	<i>N</i> -Arylation of α -Amino Acid Derivatives	21
2.2	Displacement of α -Substituted Esters	21
3.0	Aims	23
4.0	Asymmetric Synthesis of <i>N</i> -Phenyl α -Amino Alcohols	24

4.1	Asymmetric Synthesis of (S)-[η^6 N-Phenylphenylalinalol]Cr(CO) ₃	24
4.2	Asymmetric Synthesis of (S)-[η^6 N-Phenylprolinol]Cr(CO) ₃	25
4.3	N-Phenyl Amino Alcohols <i>Via</i> the Smiles Rearrangement	26
5.0	Asymmetric Synthesis of N-Phenyl α -Amino Esters	28
5.1	Asymmetric Synthesis of (S)-[N-Phenylvaline <i>t</i> -butyl ester]Cr(CO) ₃	28
5.2	Asymmetric Synthesis of (S)-N-Phenylvaline	33
5.3	Asymmetric Synthesis of (S)-[N-Phenylproline <i>t</i> -butyl ester]Cr(CO) ₃	34
5.4	Asymmetric Synthesis of (S)-N-Phenylproline <i>t</i> -butyl ester	35
5.5	Asymmetric Synthesis of (S)-[η^6 -N-Phenylphenylalanine <i>t</i> -butyl ester]Cr(CO) ₃	35
5.6	Asymmetric Synthesis of (S)-N-Phenylphenylalanine <i>t</i> -butyl ester	36
5.7	Asymmetric Symmetric of (S)-[N-Phenylalanine methyl ester]Cr(CO) ₃	37
5.8	Attempted Synthesis of Ridomil®	38
6.0	Asymmetric Synthesis of β Amino Acids	39
6.1	Introduction	39
6.2	Asymmetric Synthesis of (S)- β -Amino butyric ester	40
6.3	Asymmetric Synthesis of (3S)-[N-(<i>t</i> -Butyl 3-butanoate)aniline]Cr(CO) ₃	42
6.4	Asymmetric Synthesis of (3S)-N-(<i>t</i> -Butyl 3-butanoate)aniline	43
7.0	Asymmetric Synthesis of (S)-4-Methyl Azetidin-2-one	44
8.0	Asymmetric Synthesis of (-)-SCH 48461	46
8.1	Synthetic Strategy of (+)-(3S, 4R)-SCH 48461	47
8.2	Asymmetric Synthesis of (4R)-4-(4-Methoxyphenyl)-2-azetidinone	48
8.3	N-Phenylation of (4R)-4-(4-Methoxyphenyl)-2-azetidinone	51
8.4	Attempted Synthesis of (3R)-N-(Methyl 3-propanoate-3-((4-methoxybenzene))-4-methoxyaniline	52
8.5	Asymmetric synthesis of (3R)-[η^6 -N-(<i>t</i> -Butyl 3-propanoate-3-((4-methoxybenzene))-4-methoxyaniline]Cr(CO) ₃	55
8.6	Synthesis of (3R)-N-(<i>t</i> -Butyl 3-propanoate-3-	

(4-methoxybenzene))-4-methoxyaniline	56
8.7 Asymmetric Synthesis of (4 <i>R</i>)-1,4-bis(4-Methoxyphenyl)-2-azetidinone	56
8.8 Attempted Alkylation of (4 <i>R</i>)-1,4-bis(4-Methoxyphenyl)-2-azetidinone	57
9.0 Conclusion	59
10 References	60

Chapter 3

3 Introduction to Directed Metallation Chemistry

1.0 Regioselective Deprotonation in Electron Rich Aromatic Systems	62
1.1 General Characteristics of DoM Chemistry	63
1.2 Mechanism	63
1.2.1 Coordination Mechanism	63
1.2.2 Inductive Mechanism	66
1.3 DMG	67
1.4 Bases	68
1.5 Steric Effects	70
2.0 Regioselective Deprotonation in Chromium Tricarbonyl Chemistry	71
3.0 Introduction to Dimetallation Chemistry	76
3.1 Dianions in Electron Rich Aromatic Systems	76
3.2 Dianions in Chromium Tricarbonyl Complexes	80
3.2.1 Aims	83
3.2.2 Metallation studies of (Methoxy methyl phenol)Cr(CO) ₃	83
3.3.3 Metallation Studies of (Anisole)Cr(CO) ₃	86
3.3.4 Metallation Studies of (4-Methylanisole)Cr(CO) ₃	89
3.3.5 Metallation Studies of (3-Methylanisole)Cr(CO) ₃	90
3.3.6 Metallation Studies of (1,4-Dimethoxybenzene)Cr(CO) ₃	99
3.3.7 Metallation Studies of (1,3-Dimethoxybenzene)Cr(CO) ₃	102
4.0 Conclusion	105

5.0	References	107
Chapter 4		
	General Experimental	110
	Experimental: Chapter 2	112
	References	141
	Experimental: Chapter 3	142
	References	162

Chapter 1

1 Introduction to Arene Chromium Tricarbonyl Chemistry

Arene chromium tricarbonyl complexes ($\eta^6(\text{arene})\text{Cr}(\text{CO})_3$)* 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).

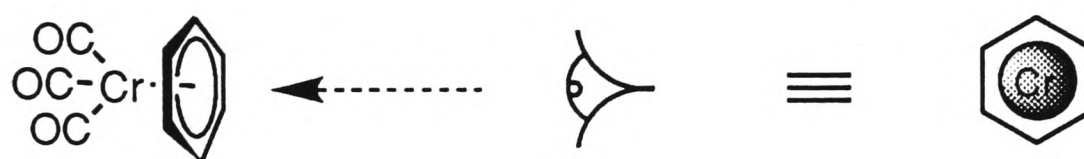


Figure 1

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

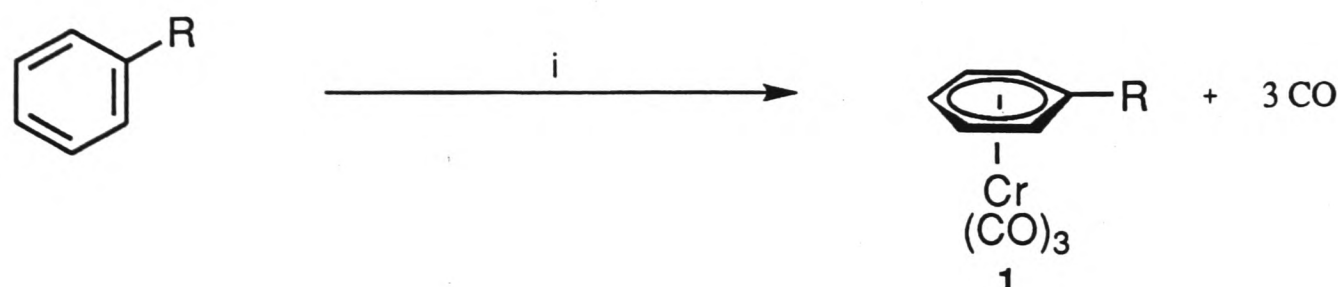
The characteristic spectroscopic properties of these complexed arenes include two strong carbonyl stretching absorption bands between 2000-1800 cm^{-1} in the IR spectrum and an upfield shift of the arene ring protons to 6.0-5.0 ppm in the ^1H nmr spectrum.

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

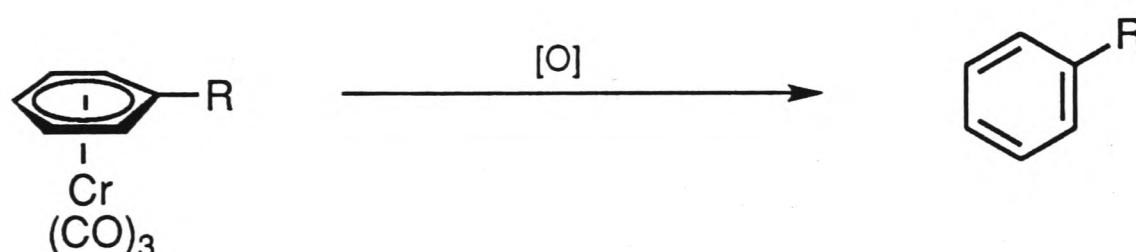
* η^N : N represents the number of carbon atoms of the arene ligand bonded to the metal; henceforth, the prefix η^6 is omitted for clarity, except when it is necessary to identify between complexed and uncomplexed arenes in a molecule

containing ligands which are more labile than CO, e.g. $\text{Cr}(\text{CO})_3\text{L}_3$ ($\text{L}=\text{NH}_3$,³ CH_3CN ,⁴ or pyridine⁵).



Scheme 1: Reagents : i) $\text{Cr}(\text{CO})_6$, $\text{Bu}_2\text{O}/\text{THF}$, 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),⁶ or by leaving an ether solution of the complex in sunlight and air (whereby peroxides are generated *in situ.*),⁷ 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.



Scheme 2

2.0 Arene Chromium Tricarbonyl Complexes in Organic Synthesis

The ease with 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.

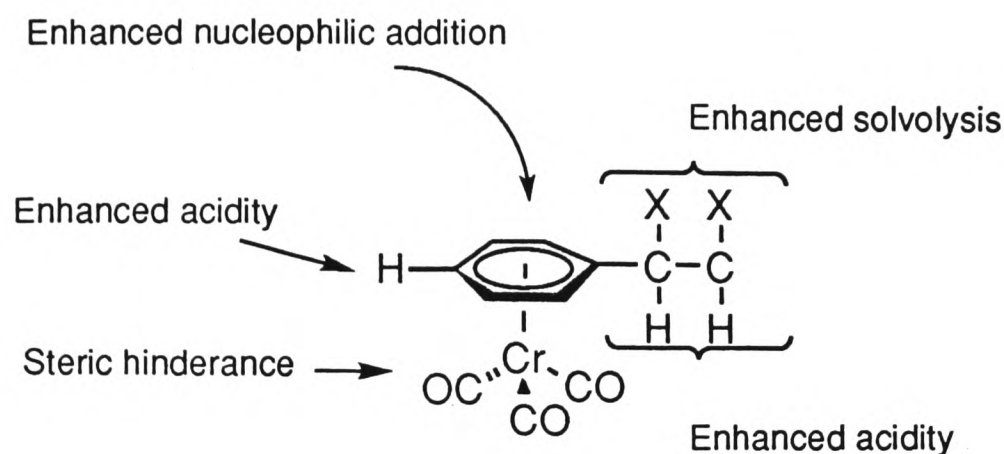
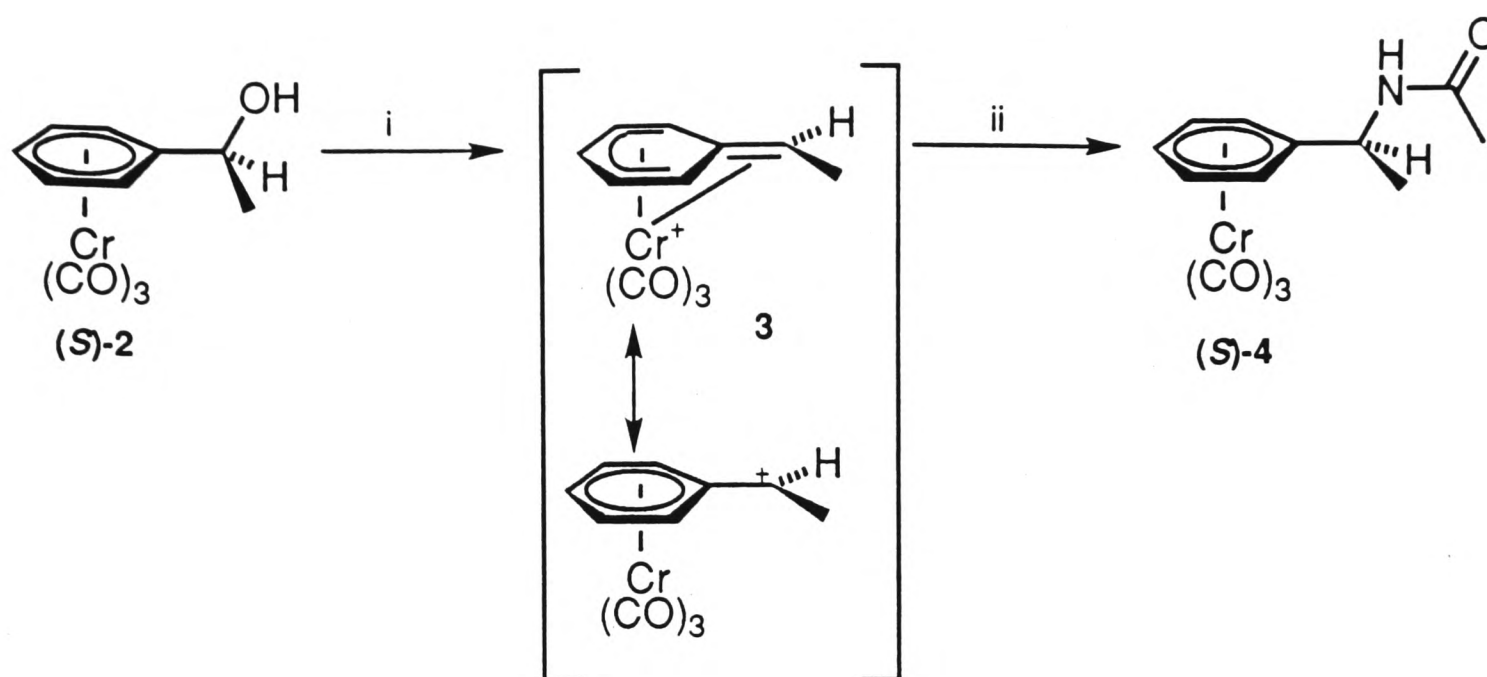


Figure 2

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.⁹ The most stable resonance structure of the intermediate contains exocyclic double bond character, which causes restricted rotation about the $\text{C}_\alpha\text{-C}_{\text{ipso}}$ bond.

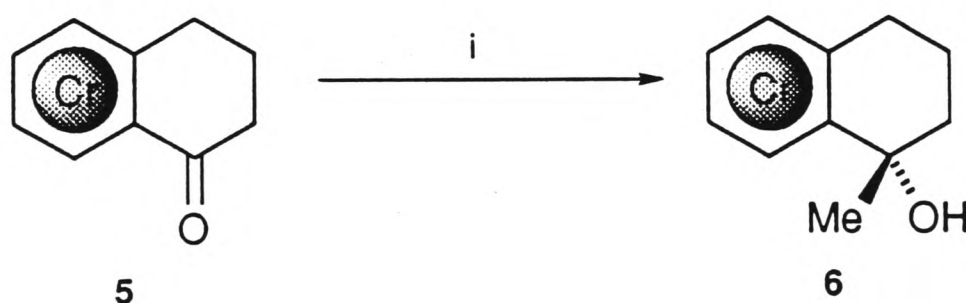
An illustrated example of benzylic carbocation stabilisation by the chromium tricarbonyl moiety can be seen in the synthesis of (*S*)-(-)-(*N*-acyl- α -methylbenzylamine) Cr(CO)_3 **4**, carried out by Jaouen and Top¹⁰ (Scheme 3). On reaction of (*S*)-(+)-(1-phenethyl alcohol) Cr(CO)_3 **2** with acid 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.



Scheme 3: Reagents : i) H_2SO_4 , CH_3CN ; ii) H_2O

2.2 Steric Effect of the Chromium Tricarbonyl Unit

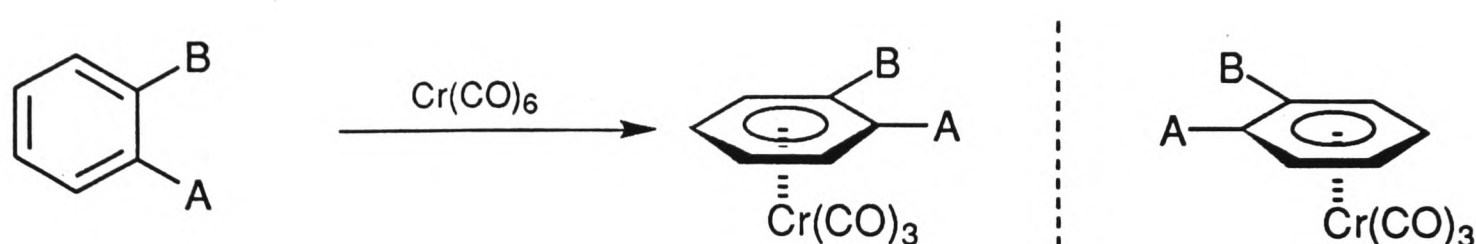
The complexation of the bulky chromium tricarbonyl unit to one face of the arene ring, effectively shields this face of the molecule from attack by reagents. An illustrated example of this is seen in the nucleophilic attack of methyl magnesium bromide on the carbonyl group of (1-tetralone) $\text{Cr}(\text{CO})_3$ **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) $\text{Cr}(\text{CO})_3$ **6**.¹¹



Scheme 4: Reagents : i) MeMgBr

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).



Scheme 5

Several of these type of complexes can be resolved by classical methods; for example by enzymatic resolution,¹² crystallisation of diastereomeric ammonium salts formed with homochiral amines or homochiral acids,¹³ and chemical resolution (i.e the separation of diastereomers formed by the reaction of the racemate with an enantiomerically pure reagent).¹⁴

When a substituted arene ring containing a stereogenic centre 'X' is complexed with a chromium tricarbonyl unit, the *ortho* protons H_S and H_R 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.¹⁵

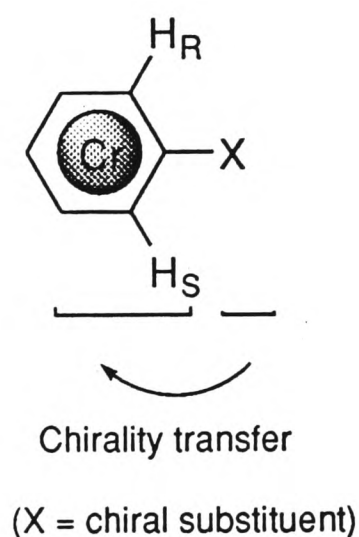
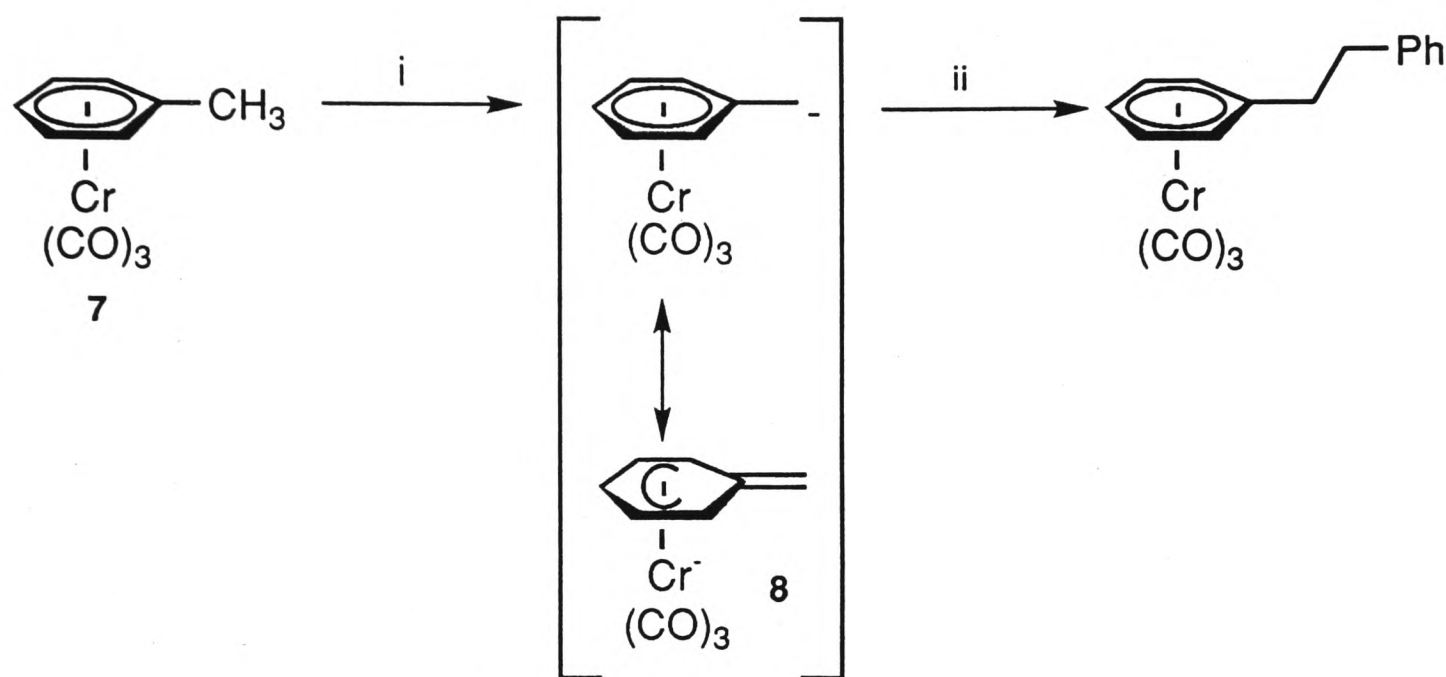


Figure 3

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. ^1H Nmr spectroscopy has shown that the anion intermediate has a high degree of exocyclic

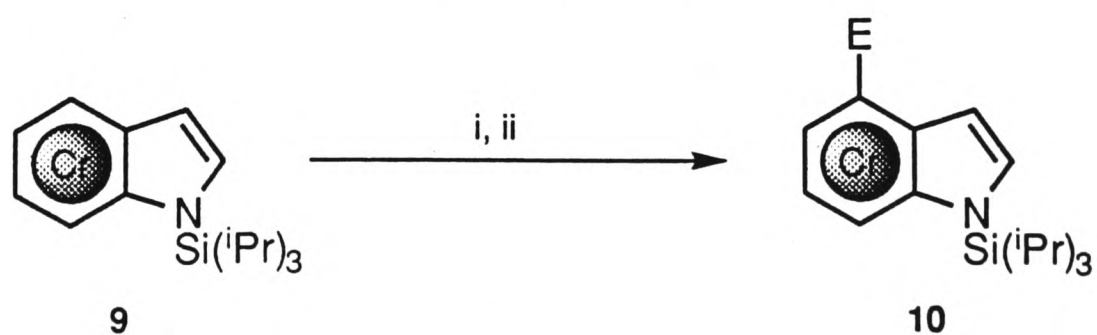
double bond character **8**.¹⁶ The benzylic anion is thermodynamically more stable than that of the arene anion and therefore by varying the base used it is possible to selectively remove either an arene or benzylic proton. An illustrative example shows the benzylic deprotonation of (toluene)Cr(CO)₃ **7** with *t*-butoxide (Scheme 6).¹⁷



Scheme 6: Reagents : i) *t*BuOK; ii) PhCH₂Br

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.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,¹⁹ whereby a series of 4-substituted indoles **10** were synthesised by the regioselective C-4 deprotonation of the 1-triisopropylsilylindole complex **9** with *n*-BuLi at low temperatures (Scheme 7).

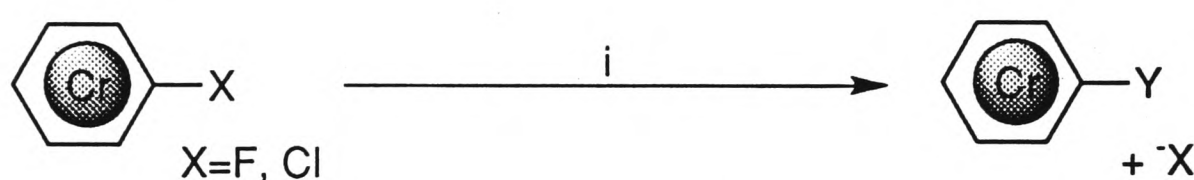


Scheme 7: Reagents : i) *n*-BuLi, TMEDA; ii) E⁺

2.6 Nucleophilic Aromatic Substitution

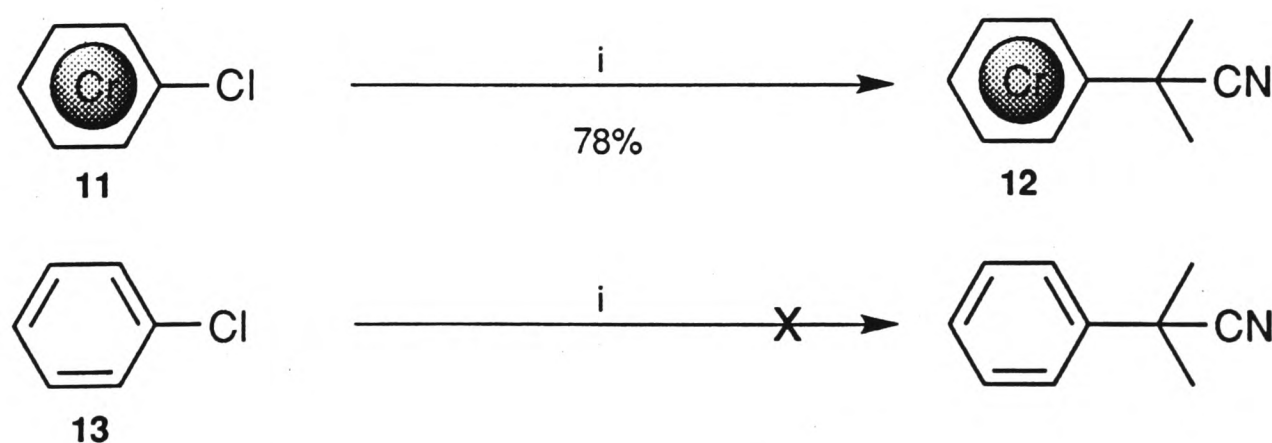
The strong electron withdrawing ability of a $\text{Cr}(\text{CO})_3$ moiety on a complexed arene unit as well as its reversibility of attachment, makes it a powerful tool in synthetic organic chemistry.^{8,34} The reversal of polarity in the complexed ring by the $\text{Cr}(\text{CO})_3$ unit makes it susceptible to nucleophilic substitution to an extent similar to nitro substituents on a haloarene ring.^{20,21}

Following the initial discovery by Nichols and Whiting²² in 1959 of the nucleophilic substitution of (chlorobenzene) $\text{Cr}(\text{CO})_3$ with sodium methoxide, numerous other nucleophiles have been examined, for example alkoxides,²³ sulfides,²⁴ carbanions^{25, 26, 27} and amines (Scheme 8).^{21, 28, 29}



Scheme 8: Reagents : i) ^-Y , $Y=\text{OR}$, SR , NHR , R

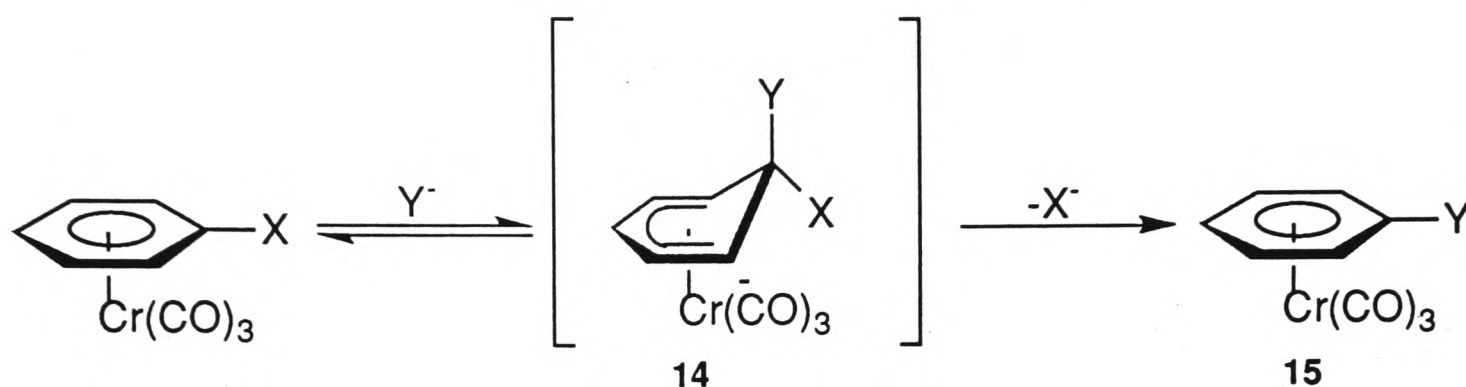
The enhanced ability of appropriately substituted arene chromium tricarbonyl compounds towards nucleophilic substitution, is seen in the conversion of (chlorobenzene) $\text{Cr}(\text{CO})_3$ **11** to **12**, in comparison to the lack of reactivity between **13** and the anion under similar conditions (Scheme 9).²⁶



Scheme 9: Reagents : i) $^-C(\text{CH}_3)_2\text{CN}$, THF, 20h, rt

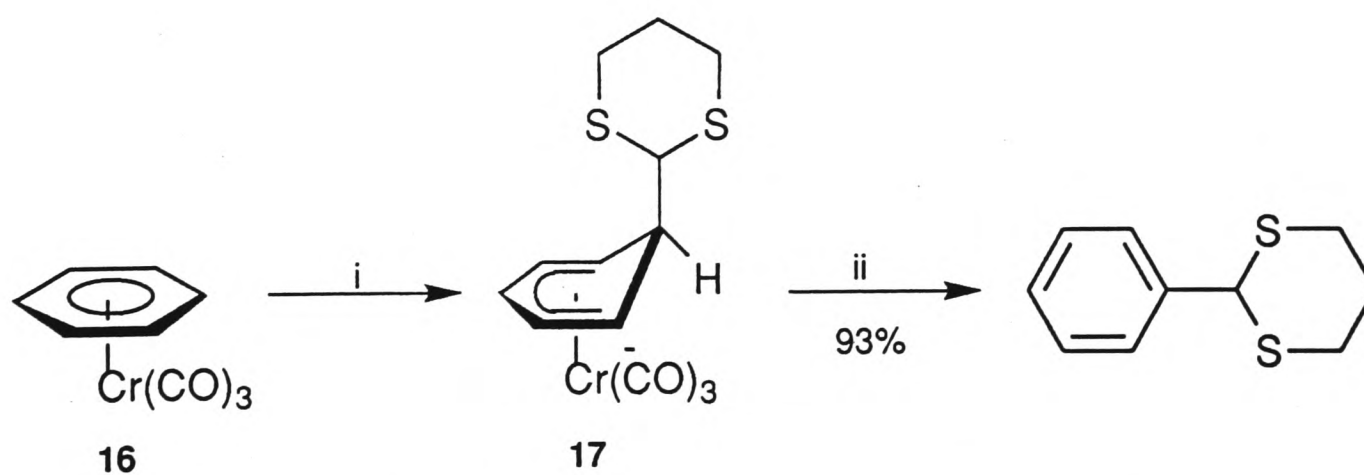
A plausible mechanism for the reaction is seen in (Scheme 10). The *exo* attack of the nucleophile on the arene ring to form a π -(cyclohexadienyl) chromium tricarbonyl anion

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.³⁰ However, the mechanism for the complexed arene case is more complicated, with nucleophilic addition as well as nucleophilic substitution occurring.²⁷



Scheme 10

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) $\text{Cr}(\text{CO})_3$ in THF at 0°C (**Scheme 11**).⁶ The X-ray structure shows the carbon at the site of addition to be 38.6° out of the pentadienyl plane.

Scheme 11: Reagents : i) 2-lithio-1,3-dithiane, -78°C to 0°C ; ii) I_2

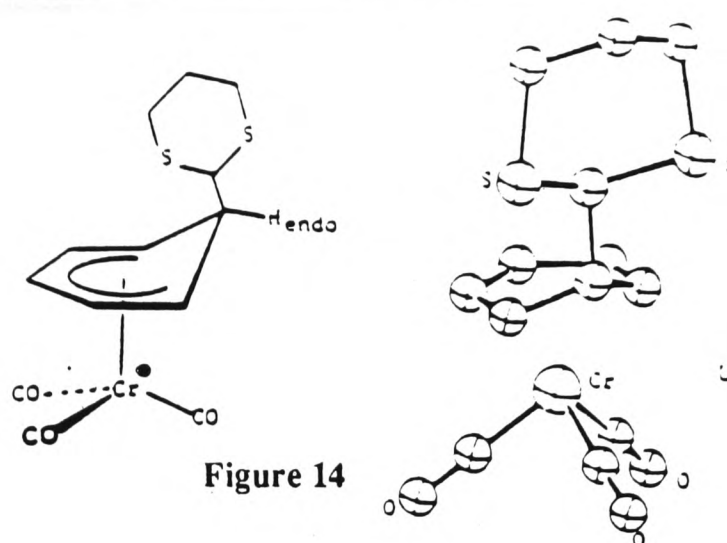
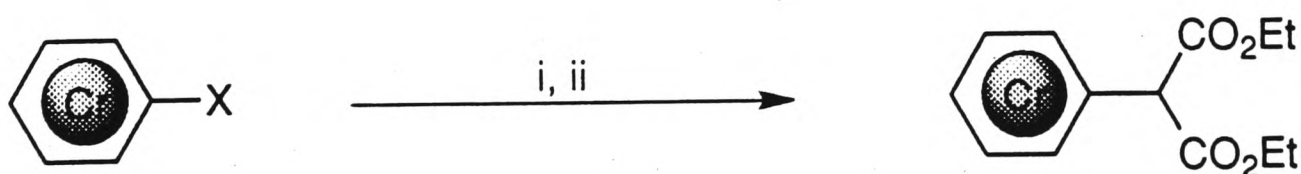


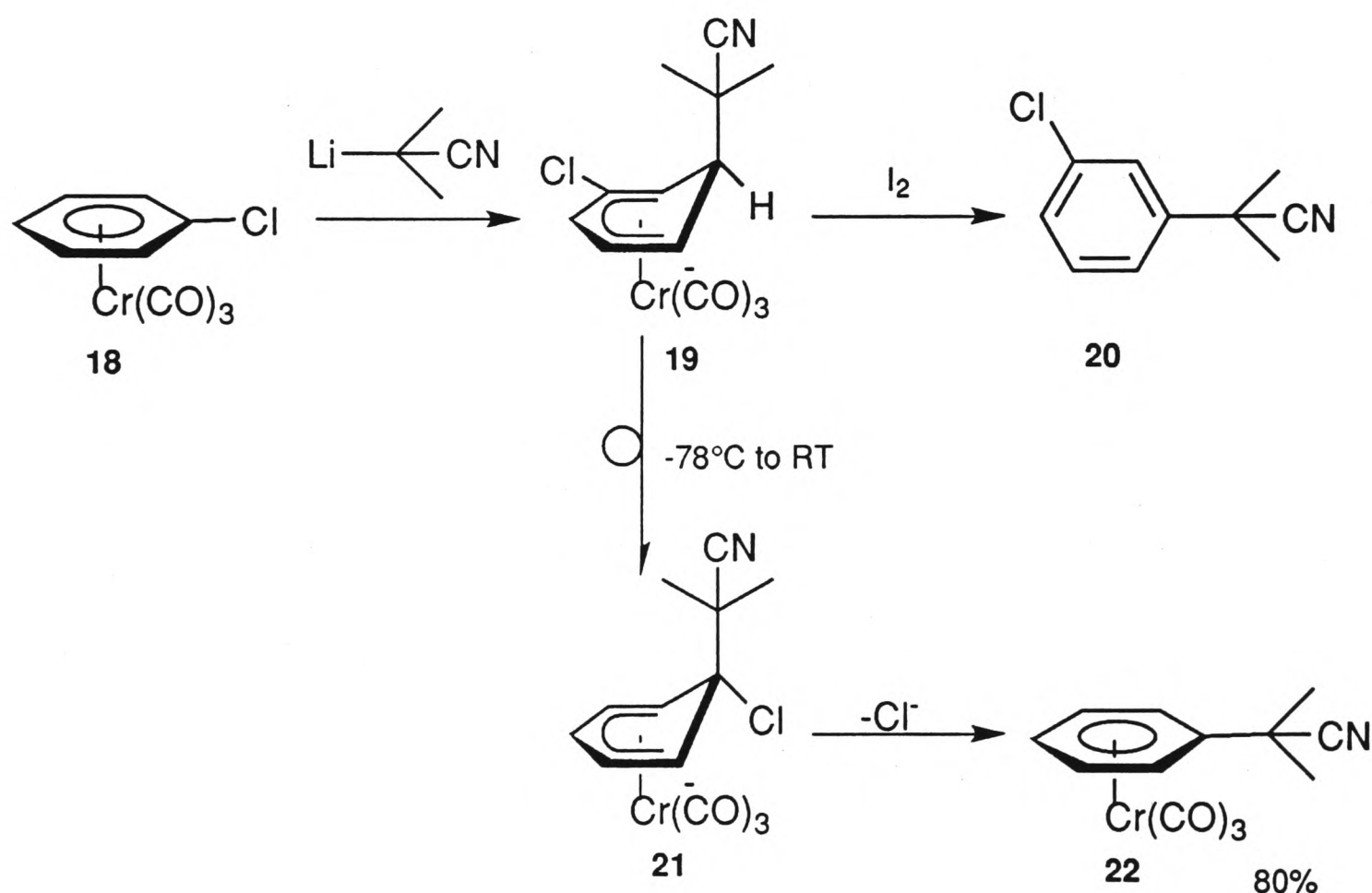
Figure 14

The reactivity of the haloarene chromium tricarbonyl complexes towards nucleophilic substitution is of the order $F \gg Cl \approx Br \approx I$ and kinetic measurements³¹ 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.²¹ The order of reactivity of haloarene complexes can be seen in the reaction of sodium diethylmalonate with various (haloarene)Cr(CO)₃ complexes (**Scheme 12**) under similar conditions.

Scheme 12: Reagents : i) NaCH(CO₂Et)₂, 50°C, 24h

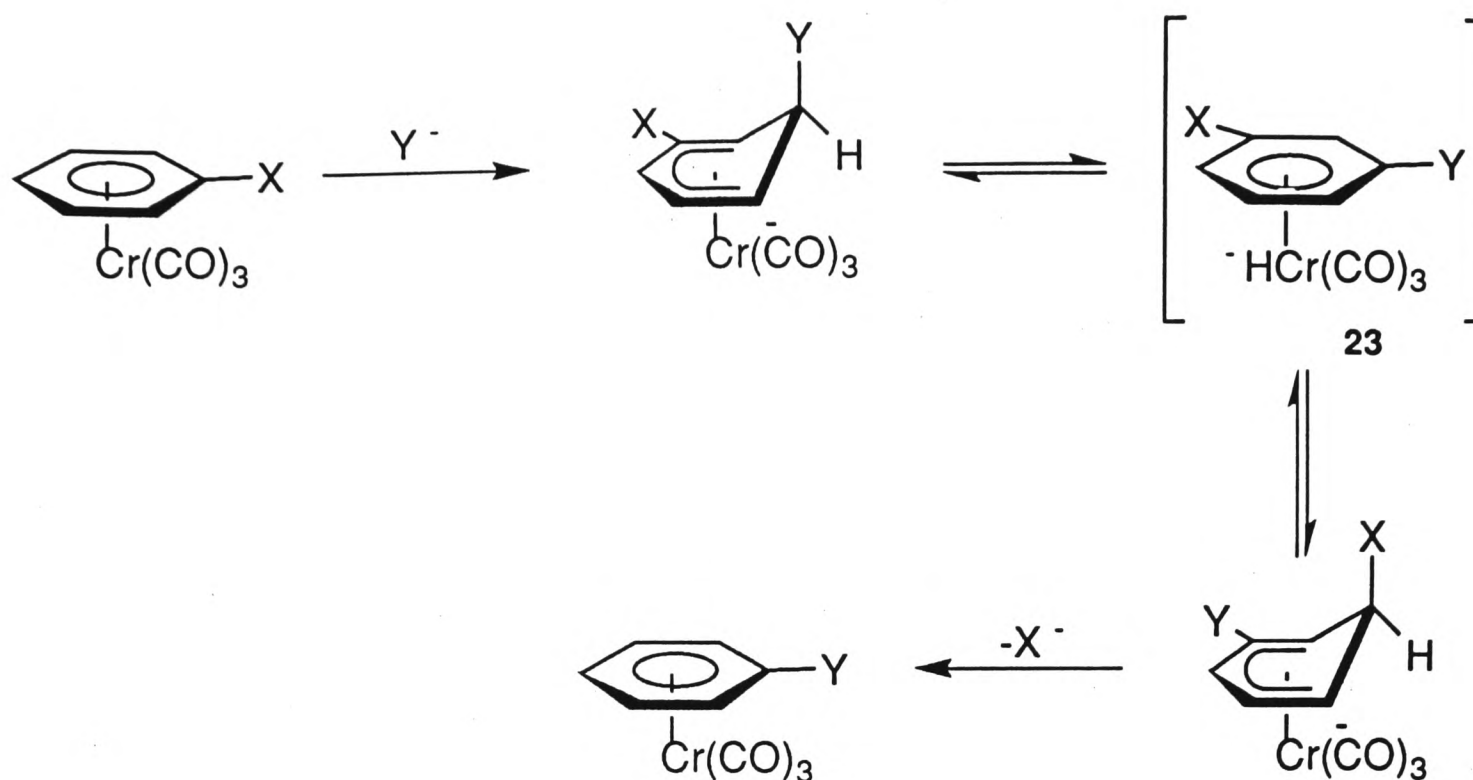
X	Product %
Cl	5
I	0
F	63

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**.

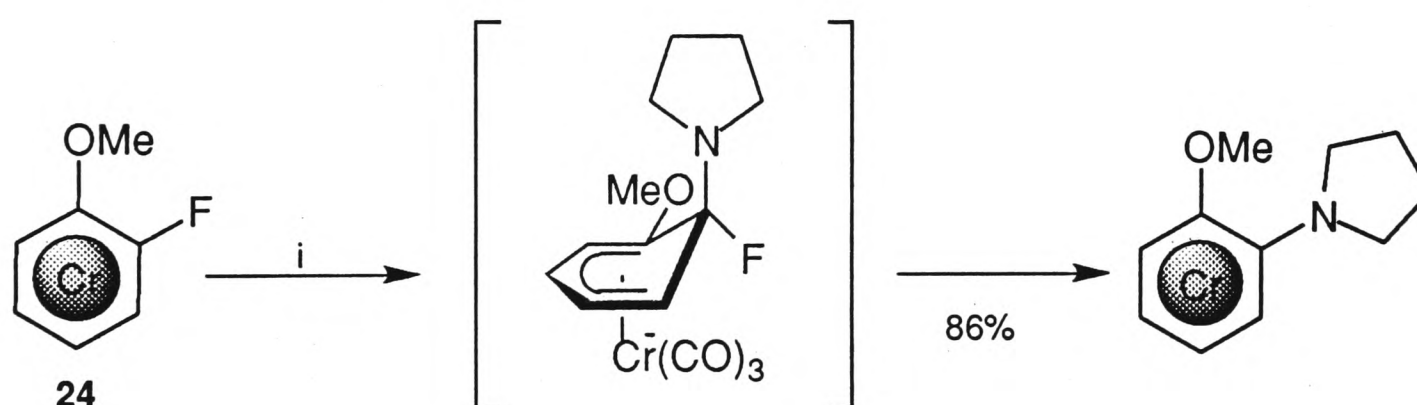


Scheme 13: Reagents : i) $^-\text{C}(\text{CH}_3)_2\text{CN}$

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

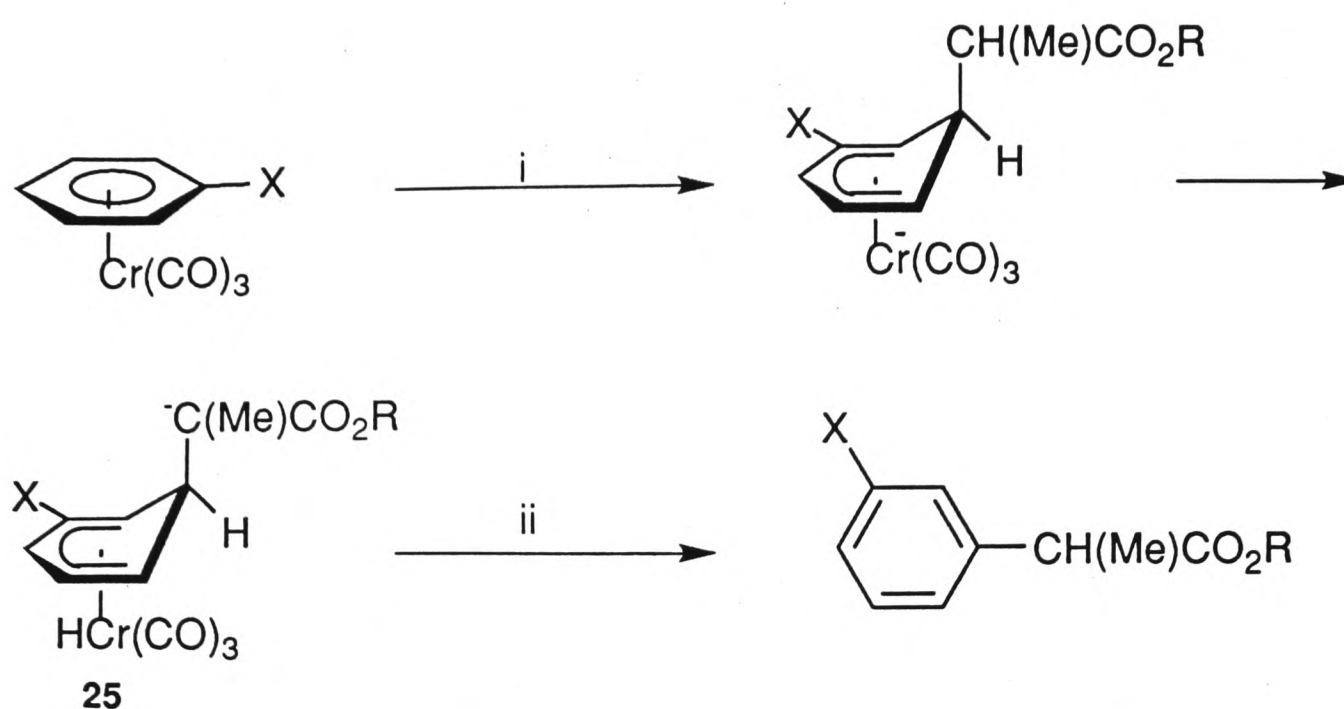


Less reactive nucleophiles however, only undergo direct *ipso* substitution, for example, the reaction of (2-fluoroanisole) $\text{Cr}(\text{CO})_3$ **24** with pyrrolidine (Scheme 15).³⁵



Scheme 15: Reagents : i) pyrrolidine, CH_3CN , rt

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}

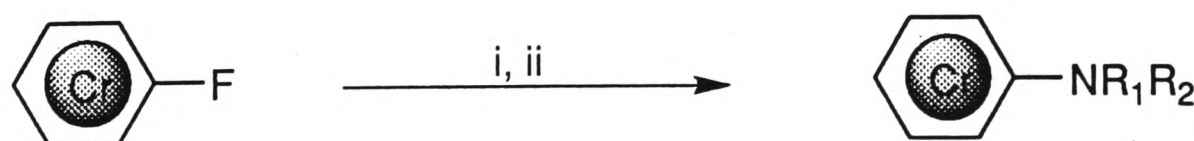


Scheme 16: Reagents : i) $^-CH(Me)CO_2R$, THF, -78 to $0^\circ C$; ii) oxidative step

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

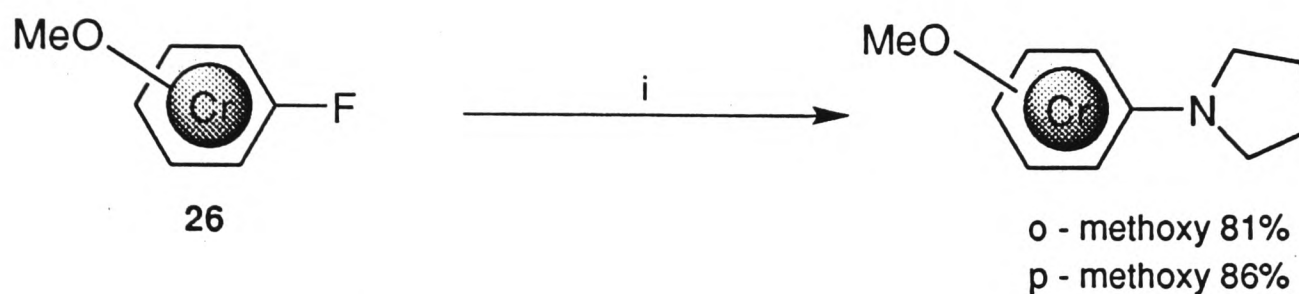
Even though there is a great demand for *N*-phenylated nitrogen containing functional groups for commercial as well as medicinal use, very little reference has been made to the reaction of π -haloarene complexes with amine nucleophiles.^{21, 28, 35} It was first discovered by Whiting²⁹ in 1967 in the reaction of a range of amine nucleophiles with (fluorobenzene) $Cr(CO)_3$ in polar aprotic solvents (**Scheme 17**).



Scheme 17: Reagents : i) NHR_1R_2 , rt

NHR_1R_2	Yield %
$MeNH_2$	84%
Me_2NH	84%
$PhNH_2$	87%
$t-BuNH_2$	88%

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**).³⁵

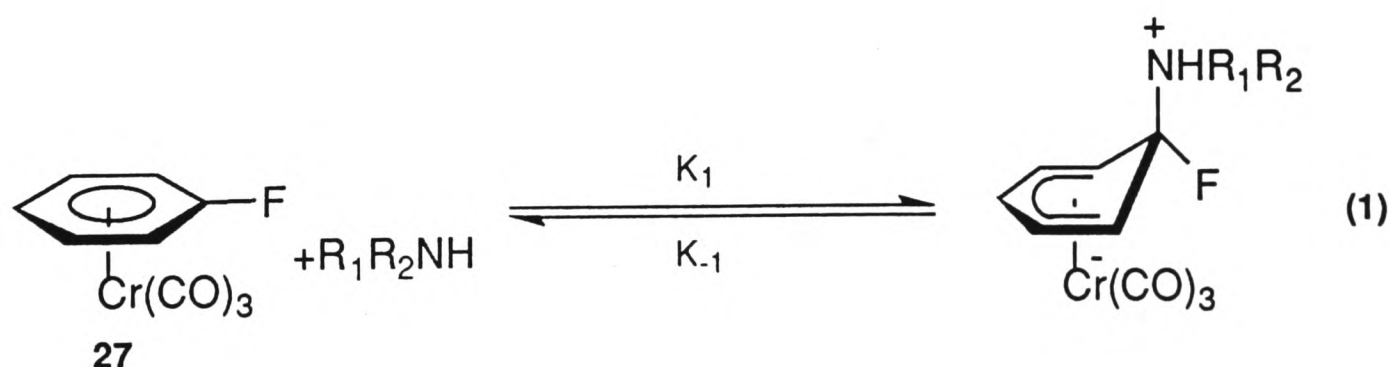


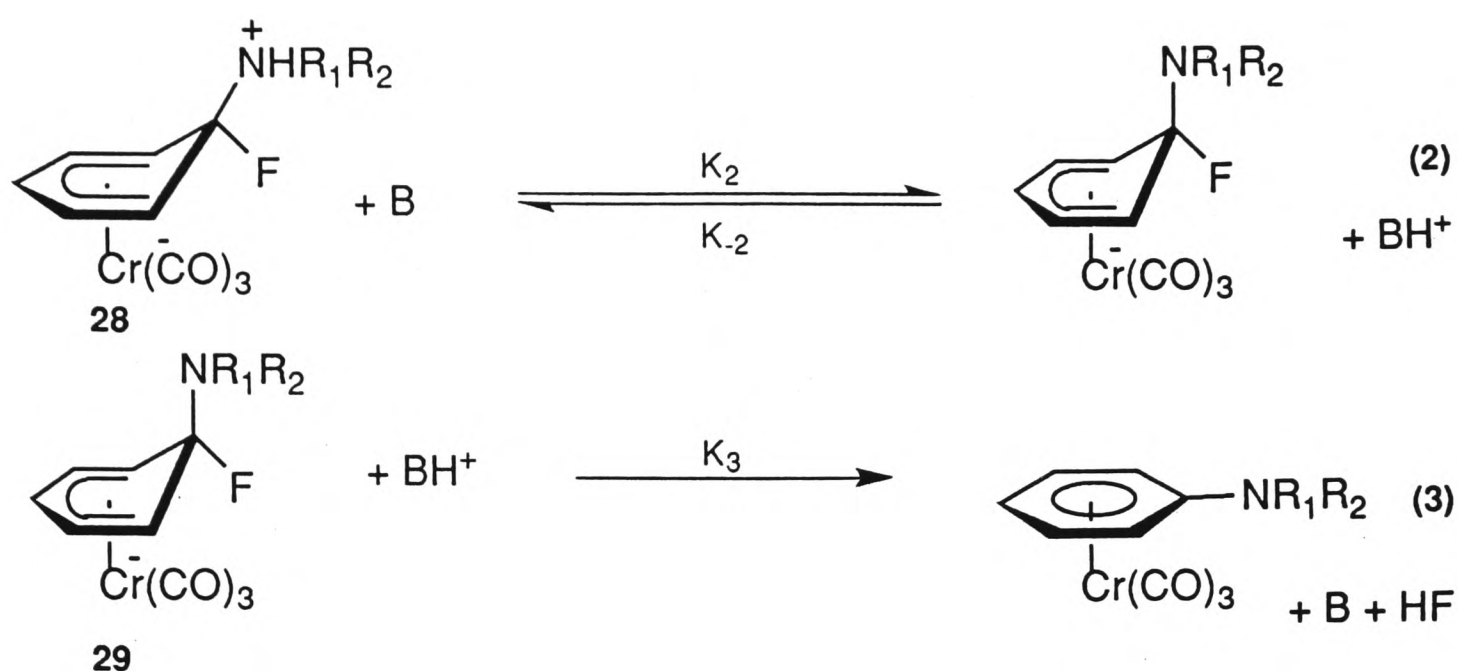
Scheme 18: Reagents : i) pyrrolidine, CH₃CN, rt

3.1 Kinetic Studies

Kinetic studies on the nucleophilic aromatic substitution of (haloarene)Cr(CO)₃ with amine nucleophiles has been studied by Bunnet²¹ and Olienik²⁸. 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.^{30, 37}

In the reaction of (fluorobenzene)Cr(CO)₃ **27** 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.





Scheme 19

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 Et₃N, observed by Bunnet²¹ may be due to the steric hindrance of the quaternary ammonium salt on its approach to the *endo* side of the arene ring (**Figure 5**).

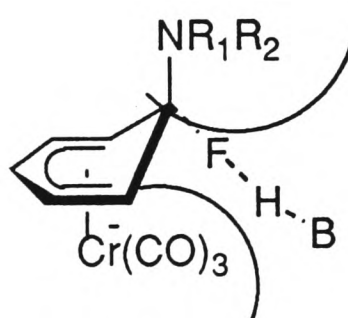


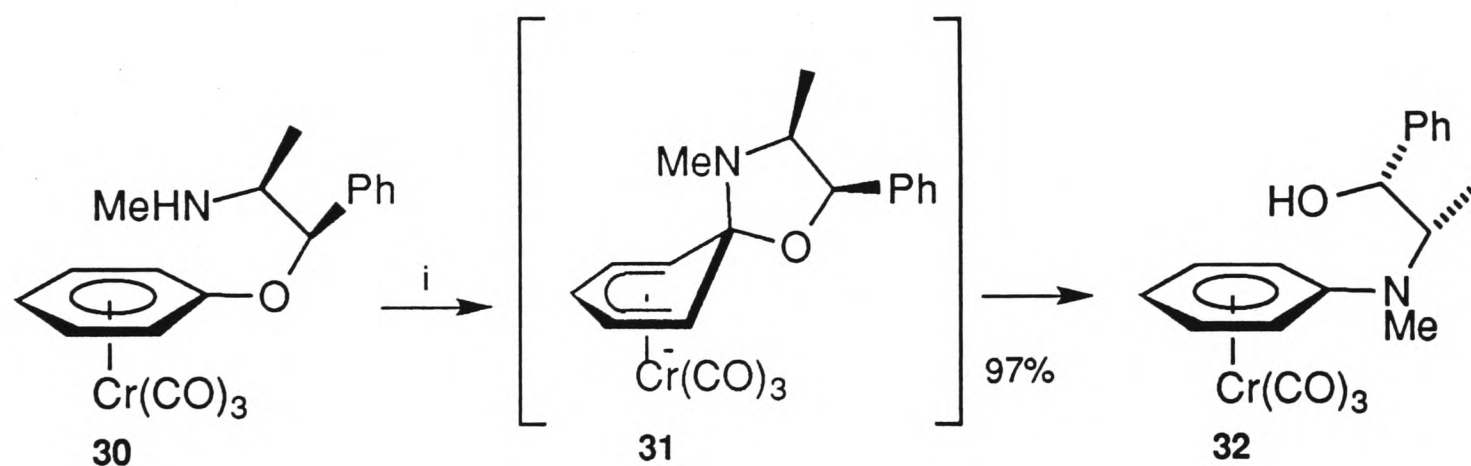
Figure 5

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 $\text{Cr}(\text{CO})_3$ 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 $n\text{-BuLi}$ at -78°C caused it to undergo intramolecular *exo* attack at the *ipso* carbon to form the η^5 -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.

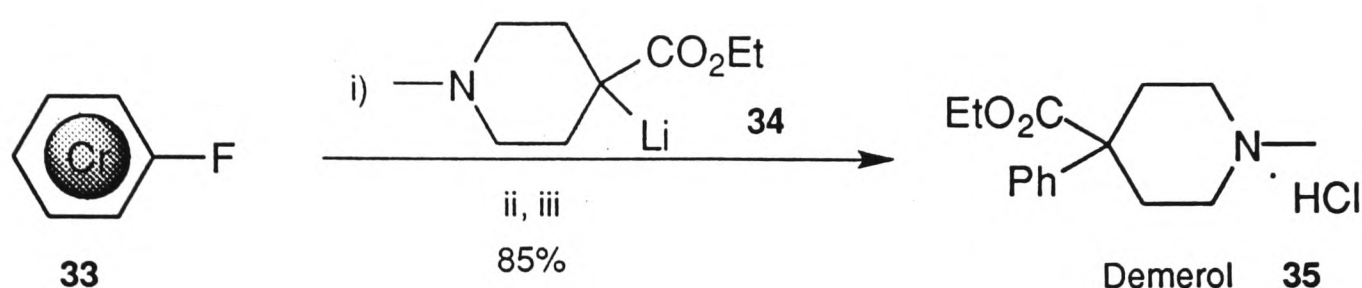


Scheme 20: Reagents : i) $n\text{-BuLi}$, THF, -78°C

4.0 Nucleophilic Aromatic Substitution of Arene($\text{Cr}(\text{CO})_3$) Complexes in Synthesis

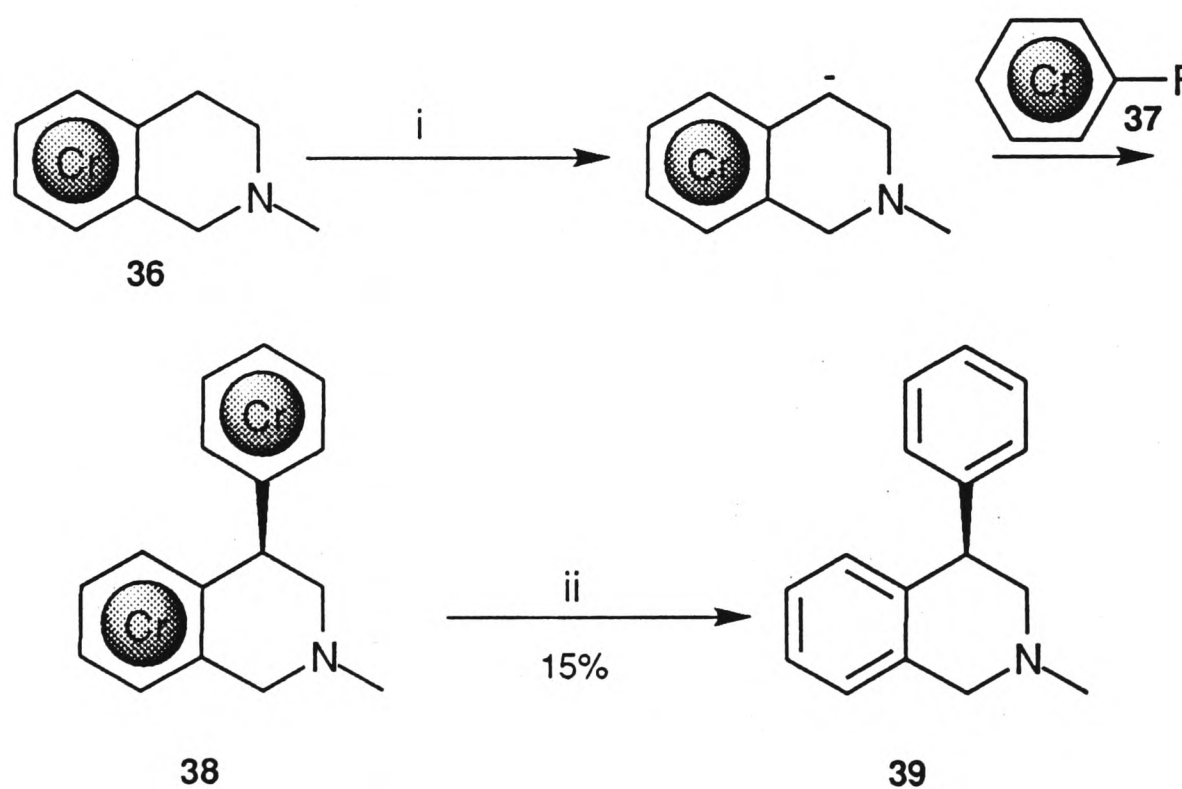
The ability of (arene) $\text{Cr}(\text{CO})_3$ complexes to act as a phenyl cation synthon has allowed for the synthesis of a wide variety of phenylated compounds. With metallation of a substrate and quenching with an electrophile such as (fluorobenzene) $\text{Cr}(\text{CO})_3$, phenyl substituents can be incorporated into a wide range of compounds.

A good illustration of this is in the synthesis of Demerol **35** (Scheme 21).²⁵ The reaction of (fluorobenzene) $\text{Cr}(\text{CO})_3$ **33** with **34** at room temperature, gave the desired phenylated product **35** in 85% yield.



Scheme 21: Reagents : i) **34**; ii) I_2 ; iii) HCl , Et_2O

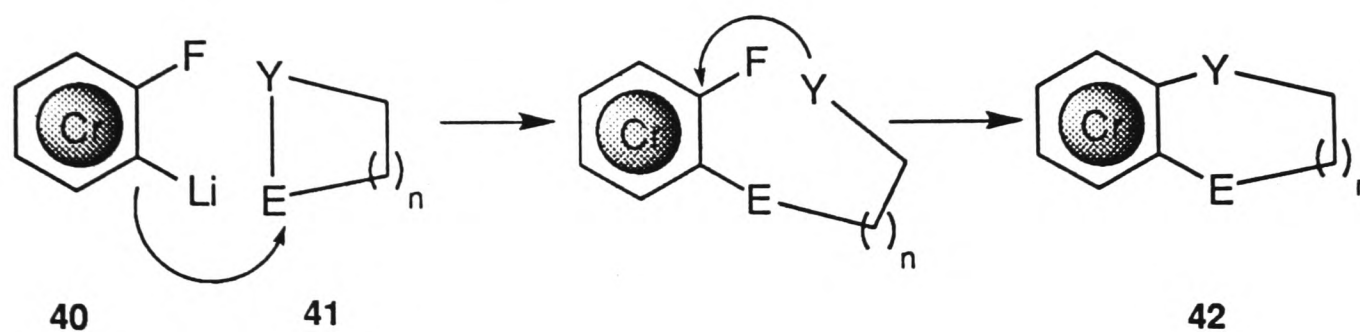
Also research by Blagg³⁹ has shown the ease of incorporation of a phenyl group both regioselectively and stereoselectively (Scheme 22). Deprotonation of the Tetrahydroisoquinone complex **36** with $n\text{-BuLi}$ and addition of a THF solution of (fluorobenzene) $\text{Cr}(\text{CO})_3$ **37** at -40°C generated the 4-*exo*-complex **38**. Decomplexation gave the 4-phenyl Tetrahydroisoquinoline derivative **39**, which is a known dopamine agonist, in 15% yield.⁴⁰



Scheme 22: Reagents : i) $n\text{-BuLi}$, **37**; ii) oxidative reaction

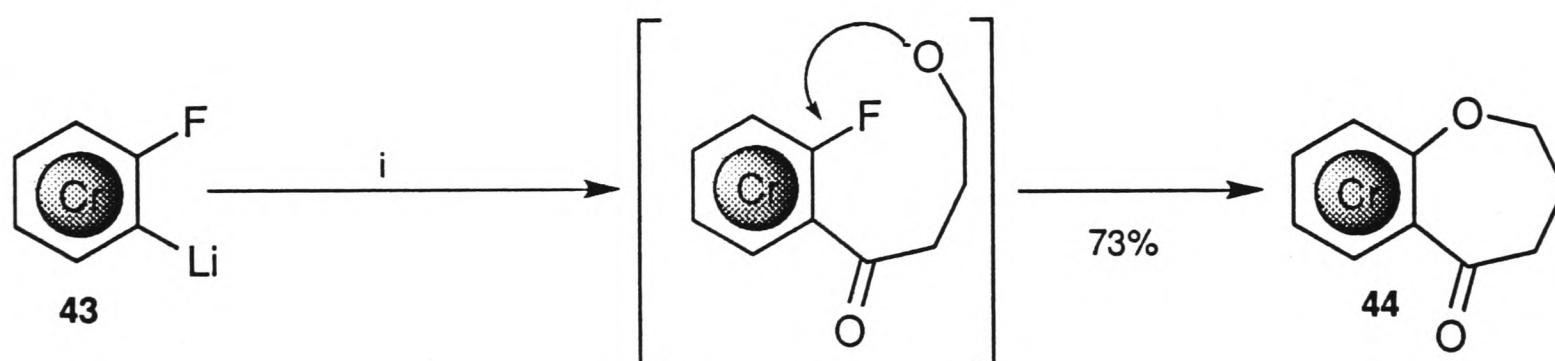
Widdowson has reacted *ortho* lithiated (fluorobenzene) $\text{Cr}(\text{CO})_3$ **40** (which in effect is a 1,2-dipolar synthon) with a wide variety difunctional electrophiles, to give benzo-fused compounds.⁴¹

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

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 : i) γ -butyrolactone, THF, -78°C to rt

5.0 References

1. M. F. Bailey and L. F. Dahl, *Inorg. Chem.*, 1965, **4**, 1314; O. L. Carter, A. T. McPhail and G. A. Sim, *J. Chem. Soc. (A)*, 1966, 822.
2. C. A. L. Mahaffy and P. L. Pauson, *Inorg. Synth.*, 1979, **19**, 154; S. Top and G. Jaouen, *J. Organomet. Chem.*, 1979, **182**, 381.
3. D. Seyferth, J. S. Merola and C. S. Eschbach, *J. Am. Chem. Soc.*, 1978, **100**, 4124.
4. W. S. Trahanovsky, *J. Am. Chem. Soc.*, 1969, **91**, 5870.
5. D. E. F. Gracey, W. R. Jackson, W. B. Jennings and T. R. B. Mitchell, *J. Chem. Soc. (B)*, 1969, 1204.
6. For example, M. F. Semmelhack, H. T. Hall Jr., R. Farina, M. Yoshifuji, G. Clark, T. Bargar, K. Hirotsu, and J. Clardy, *J. Am. Chem. Soc.*, 1979, **101**, 3535.
7. For example, M. Uemura, N. Nishikawa, Y. Hayashi, *Tetrahedron Lett.*, 1980, **21**, 2069.
8. J. P. Coleman and L. S. Hegedus, "Principles and Applications of Organotransition Metal Chemistry", University Science Books, Mill Valley California, 1980, Chapter 14; M. F. Semmelhack, "Comprehensive Organic Synthesis", eds. B. M. Trost, I. Fleming, Pergamon Press, vol. 4, Chapter 2.4; G. Jaouen, "Transition Metal Organometallics: Arene Complexes in Organic Synthesis", ed. H. Halper, Academic Press, New York, 1978, vol. 2, p 65.
9. G. O Lah, S. H. Yu, *J. Org. Chem.*, 1976, **41**, 1694.
10. S. Top and G. Jaouen, *J. Org. Chem.*, 1981, **46**, 78.
11. G. Jaouen and A. Meyer, *J. Am. Chem. Soc.*, 1975, **97**, 4667; A. Meyer and G. Jaouen, *J. Chem. Soc. Chem. Commun.*, 1964, 787.
12. S. Top, G. Jaouen, J. Gillois, C. Baldoli, S. Maiorana, *J. Chem. Soc., Chem. Commun.*, 1988, 1284; K. Nakamura, K. Ishihara, A. Ohno, M. Uemura, H. Nishimura and Y. Hayashi, *Tetrahedron Lett.*, 1990, **31**, 3603.
13. A. Mandelbaum, Z. Neuwirth and N. Cais, *Inorg. Chem.*, 1963, **2**, 902.
14. S. G. Davies and C. L. Goodfellow, *J. Chem. Soc. Perk. Trans. 1*, 1989, 193; A. Solladie-Cavallo, G. Solladie, E. Tsamo, *Inorg. Synth.*, 1985, **23**, 85.
15. J. Blagg, S. G. Davies, C. Goodfellow and K. Sutton, *J. Chem. Soc. Perkin Trans. 1*, 1987, 1805; J. A. Heppert, J. Aube, M. E. Thomas-Miller, M. L. Milligan and F. Takusagawa, *Organometallics*, 1990, **9**, 727; S. G. Davies and T. Loveridge, *J. Chem. Soc., Chem. Commun.*, 1995, 817.
16. A. Ceccon, A. Gambaro and A. Venzo, *J. Organomet. Chem.*, 1984, **275**, 209.
17. G. Simonneaux and G. Jaouen, *Tetrahedron*, 1979, **35**, 2249.
18. M. F. Semmelhack, J. Bisaha, M. Czarny, *J. Am. Soc.*, 1979, **101**, 768.
19. D. A. Widdowson, *Phil. Trans. R. Soc. Lond. A.*, 1988, **326**, 595.

20. D. A. Brown, J. R. Raju, *J. Chem Soc (A)* 1966, 40.
21. J. F. Bunnet, H. Hermann, *J. Org. Chem.* 1971, **36**, 4081.
22. B. Nichols, M. C. Whiting, *J. Chem Soc* , 1959, 551.
23. M. Fukui, Y. Endo, T. Oishi, *Chem. Pharm. Bull.*, 1980, **28**, 3639; C. Baldoli, P. Del Buttero, S. Maiorana, A. Papagni, *J. Chem. Soc. Chem. Commun.* 1985, 1181.
24. A. Alemagna, P. Cremonesi, P. Del Buttero, E. Licandro, S. Maiorana, *J. Org. Chem.*, 1983, **48**, 3114; A. Alemagna, P. Del Buttero, C. Gorini, D. Landini, E. Licandro, S. Maiorana, *J. Org. Chem.*, 1983, **48**, 605.
25. M. F. Semmelhack, G. R. Clark, J. L. Garcia, J. J. Harrison, Y. Thebtaranonth, W. Wulff, A. Yamashita, *Tetrahedron*, 1981, **37**, 3957.
26. M. F. Semmelhack, H. T. Hall, *J. Am. Chem. Soc.*, 1974, **96**, 7091.
27. M. F. Semmelhack, H. T. Hall, *J. Am. Chem. Soc.*, 1974, **96**, 7092.
28. I. I. Oleinik, P. P. Kun, V. V. Litvak, V. D. Shteingarts, *J. Org. Chem. of the U.S.S.R.*, 1988, **87**, 2277.
29. M. Whiting U. S. Patent 3,317,522, 1967; *Chem. Abstr.*, 1967, **67**, 64543.
30. J. F. Bunnet, *Quart. Rev. Chem., Soc.*, 1959, **12**, 1.
31. A. C. Knipe, S. J. McGuinness, W. E. Watts, *J. Chem. Soc., Chem. Commun.*, 1979, 842.
32. M. F. Semmelhack, H. T. Hall, M. Yoshifuji and G. Clark, *J. Am. Chem. Soc.*, 1975, **97**, 1247.
33. M. F. Semmelhack, H. T. Hall, M. Yoshifuji, *J. Am. Chem. Soc.*, 1976, **98**, 6387.
34. S. G. Davies, *Organotransition Metal Chemistry: Applications to Organic Synthesis*, 1982, Pergamon Press, Oxford.
35. J. P. Gilday, D. A. Widdowson, *Tetrahedron Lett.*, 1986, **27**, 5525.
36. H. M. Walborsky, *J. Am. Chem. Soc.*, 1971, **93**, 1971.
37. J. F. Bunnet, J. J. Randall, *J. Am. Chem. Soc.*, 1958, **80**, 6020.
38. S. G. Davies, W. E. Hume, *Tetrahedron Lett.*, 1995, **36** 2673.
39. J. Blagg, S. G. Davies, B. E. Mobbs, *J. Chem. Soc. Chem. Comm.*, 1985, 618.
40. K. Freter, E. Dubois, A. Thomas, *J. Heterocyclic Chem.* 1970, 159.
41. M. Ghavshou, D. A. Widdowson, *J. Chem. Soc. Perkin Trans. 1*, 1983, 3065.

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.¹ For example ($\pm$) **45**, which is a *N*-phenylvaline derivative, is a known insecticides against *Musca domestica* (Figure 6).²

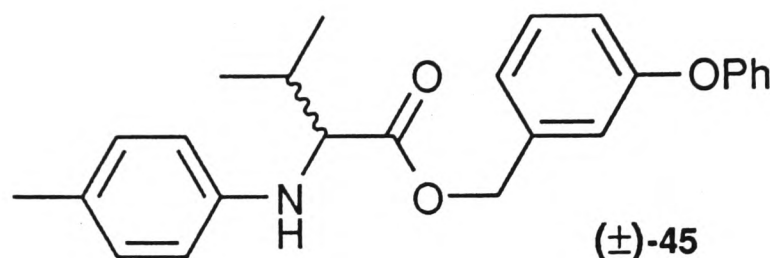
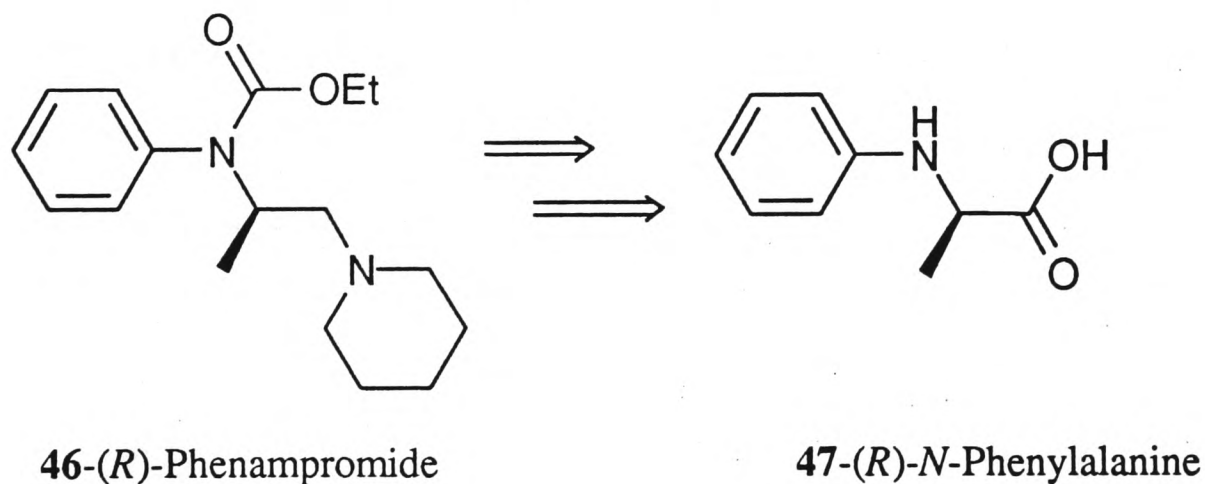


Figure 6

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

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

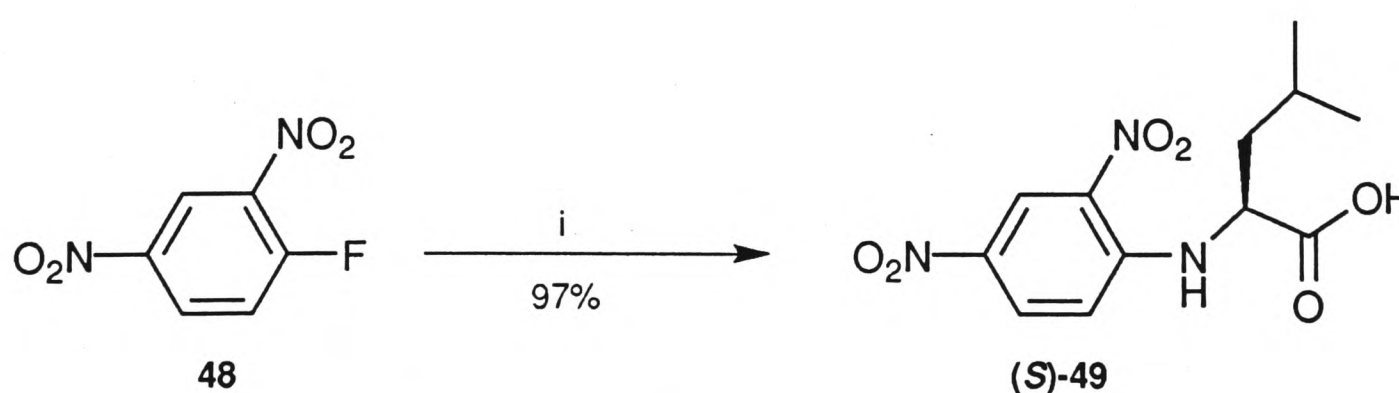
2.0 Asymmetric Synthesis of *N*-Phenyl α - and β - Amino Acids

There has been few reports in the literature of the asymmetric synthesis of *N*-phenyl- α -amino acids^{7, 8, 9} 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 S_NAr displacement of an activated aromatic compound^{7, 11} 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 (*S*)-2,4-dinitrophenyl leucine **49** from 2,4 dinitrofluorobenzene **48** and (*S*)-leucine.⁷ However, this method limits the range of substituents which can be placed on the *N*-aryl group.

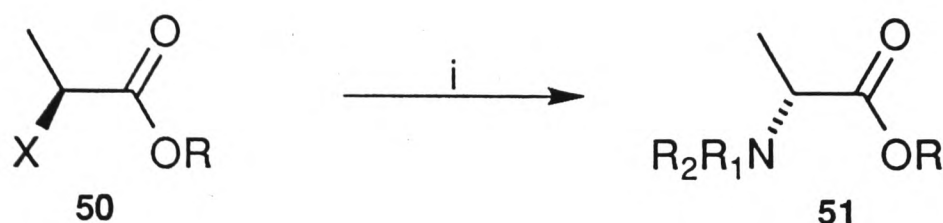


Scheme 26: Reagents : i) (*S*)-leucine, NaCO₃, H₂O, 40°C, 0.5h

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 α -carbon, with Walden inversion to give the chiral α -amino esters **51**.

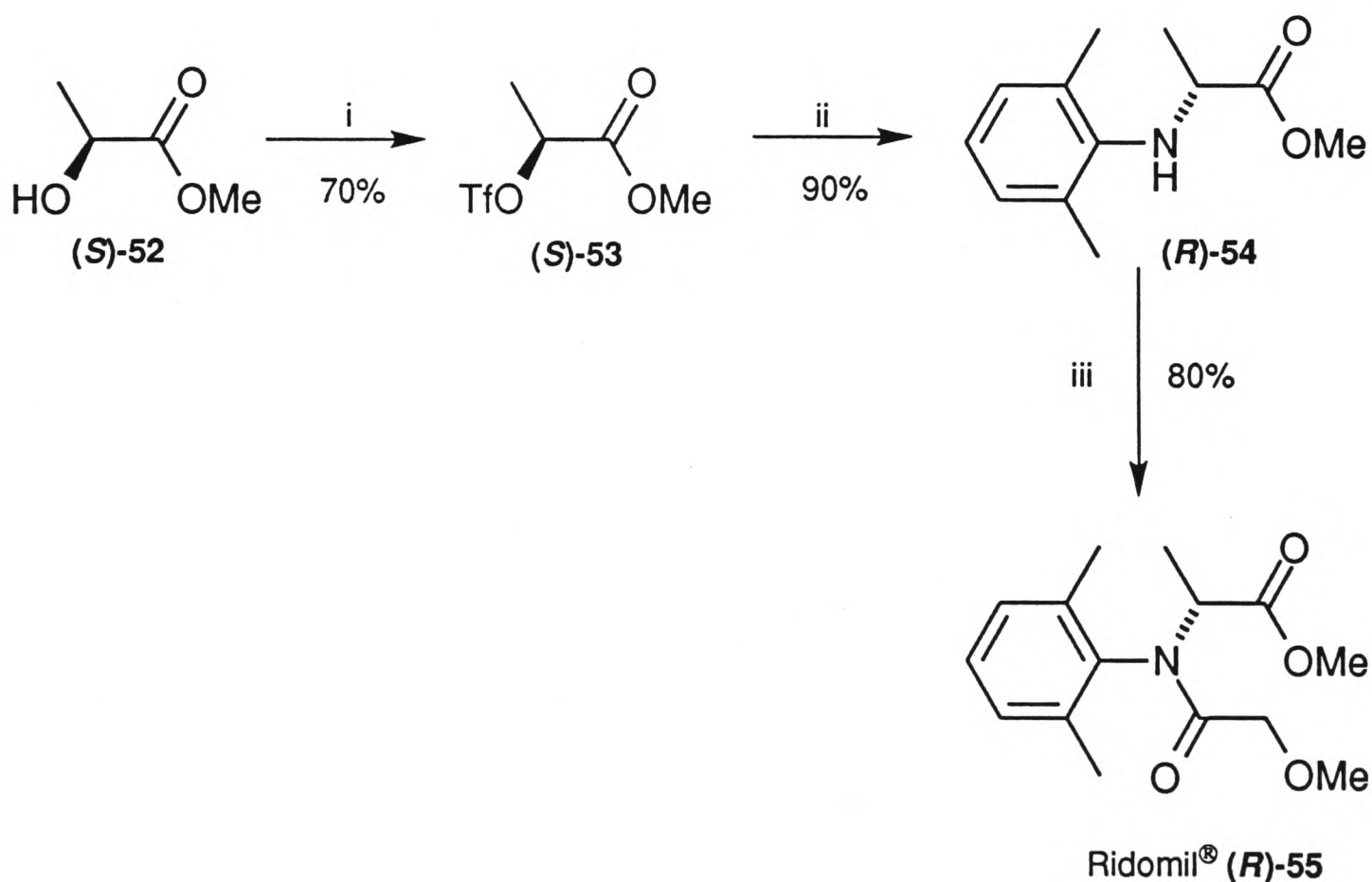


Scheme 27: Reagents : i) NHR_1R_2 , rt, CH_2Cl_2

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

triflate $\gg$ bromide $>$ mesylate $\geq$ tosylate $>$ 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).⁸ However this method is limited to the availability of homochiral α -substituted esters **50**.



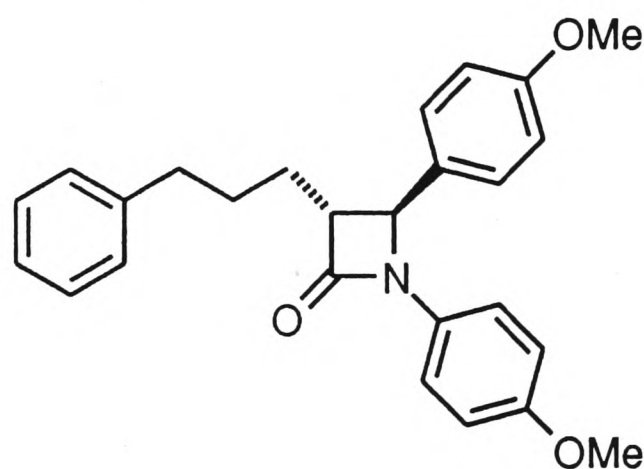
Scheme 28: Reagents : i) Tf_2O Pyridine; ii) 2,6-dimethylaniline, rt, 17h, CH_2Cl_2 ;

iii) $MeOCH_2COCl$, $NaHCO_3$

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.^{13, 14} For example (-) SCH 48461 (**Figure 7**), which is a known cholesterol reuptake inhibitor developed by Schering Plough.¹⁴

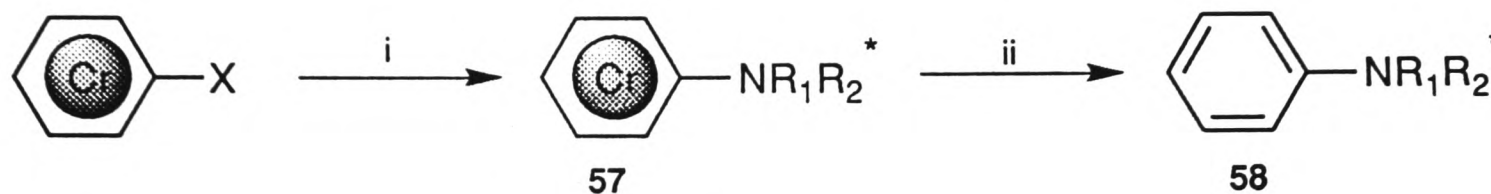


(-) SCH 48461

Figure 7

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).



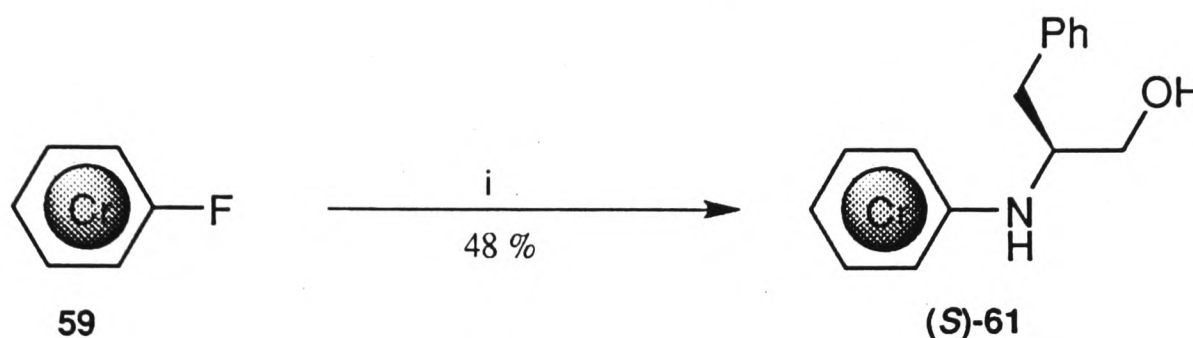
Scheme 29: Reagents : i) **56**; ii) $h\nu$, Et₂O

This chapter describes the *N*-phenylation of naturally occurring α -amino alcohols, and α and β -amino esters and the use of *N*-phenyl β -amino esters in the synthesis of homochiral β -lactams.

4.0 Asymmetric Synthesis of *N*-Phenyl α -Amino Alcohols

4.1 Asymmetric Synthesis of (*S*)-[η^6N -Phenylphenylalinalin] Cr(CO)₃

The reaction of (*S*)-phenylalaninol **60** with (fluorobenzene)CrCO₃ **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.¹⁵ The (fluorobenzene)Cr(CO)₃ **59** was obtained in 50% yield by complexation of the arene with chromium hexacarbonyl, under standard conditions.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)

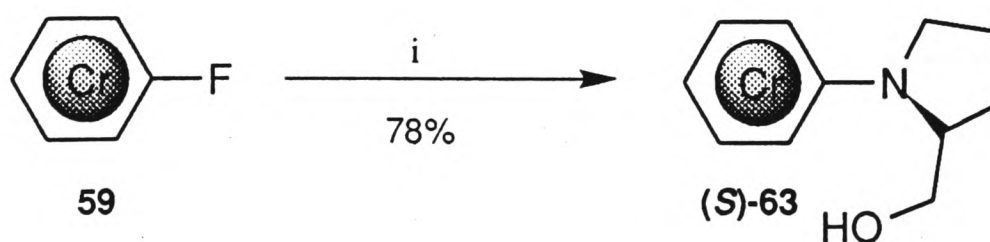


Scheme 30: Reagents : i) (S)-60, rt, DMF

The ^1H 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 fluorine 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 $\text{Cr}(\text{CO})_3$ 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)-[η^6N -Phenylprolinol] $\text{Cr}(\text{CO})_3$

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).

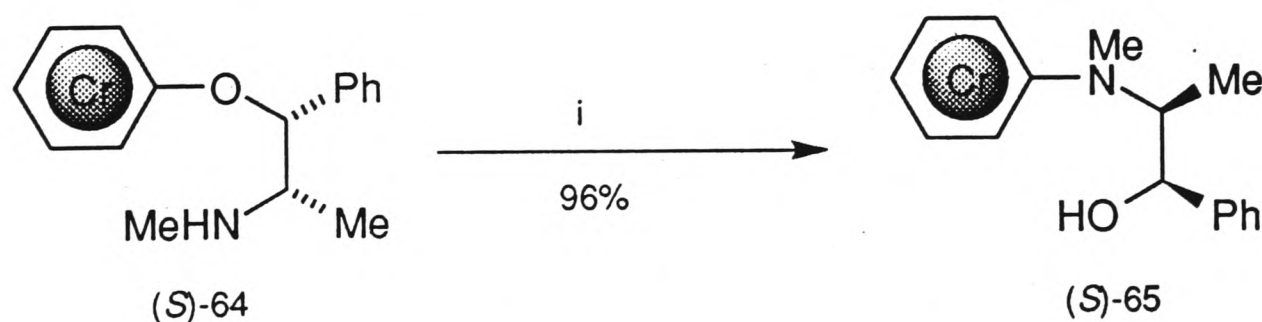


Scheme 31: Reagents : i) (S)-62, rt, DMF

Analysis of the ^1H 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 ^1H 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 $\text{Cr}(\text{CO})_3$ 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

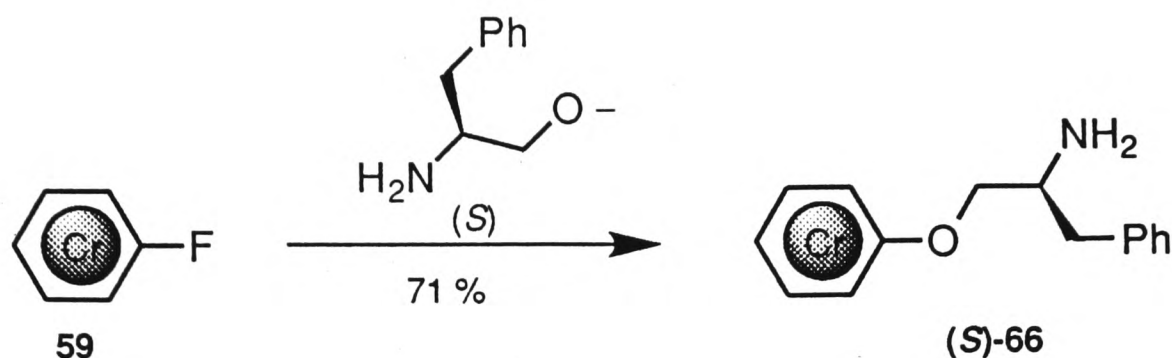
It has been recently been discovered by Hume¹⁷ that the ephedrine derivative **64** undergoes a Smiles rearrangement on reaction with *n*-BuLi at -78°C to afford the *N*-phenyl derivative **65** in excellent yield 96%, (Scheme 32). It was hoped that this methodology could be developed as a general approach to the synthesis of *N*-phenyl amino alcohols.



Scheme 32: Reagents : i) *n*-BuLi, THF, -78°C

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

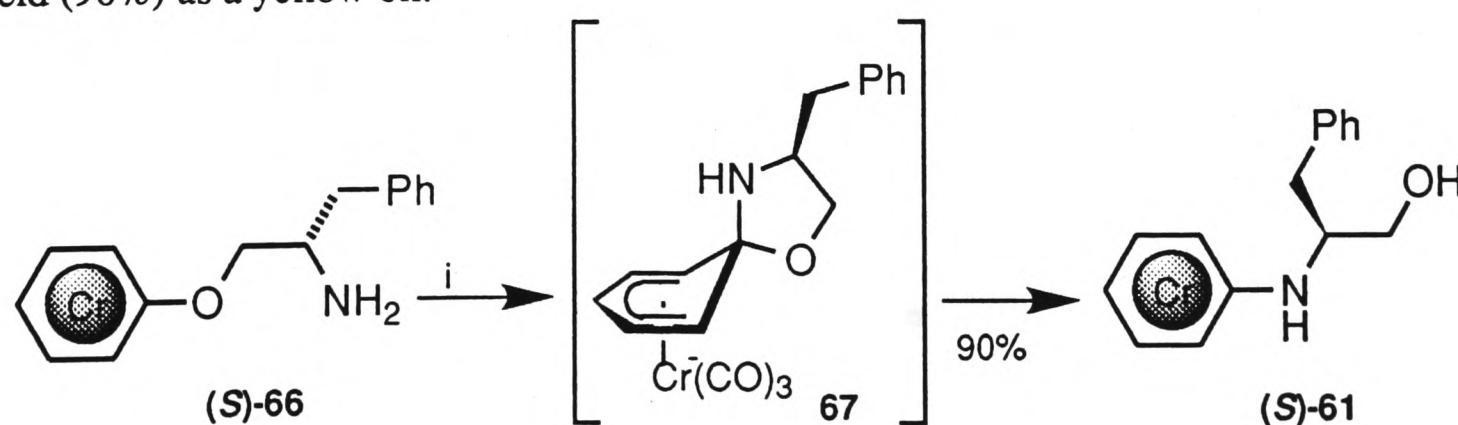
occurred (**Scheme 33**). Work-up and column chromatography afforded the *o*-phenyl ether species (**66**) in good yield (71%) as a yellow solid (m.p. 82-83°C).



Scheme 33: Reagents : i) (S)-**60**, THF, 0°C

Analysis of the ^1H 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 *ipso* attack at the *exo* face of the carbon bearing the fluorine atom, to give a 5-membered intermediate **67**, which *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

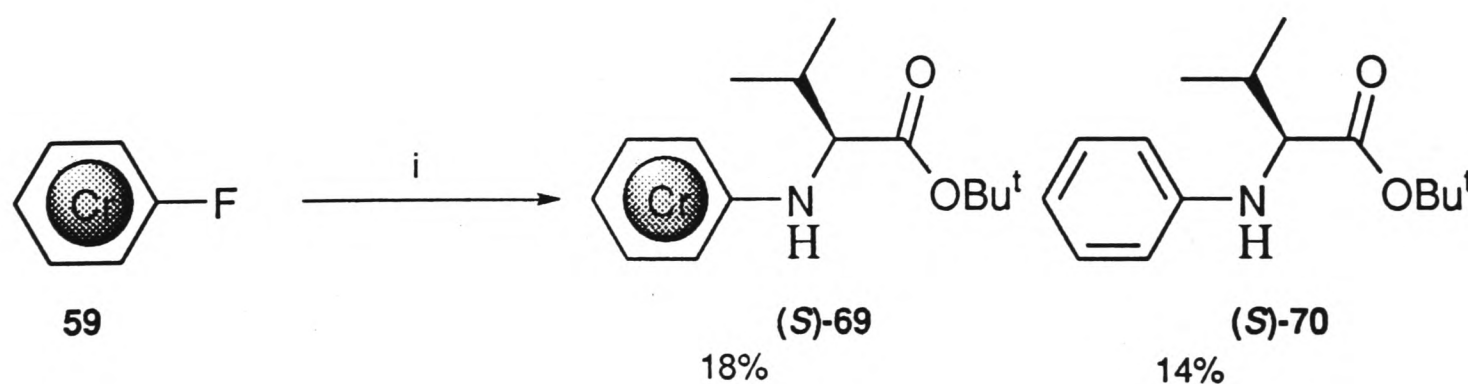
The ^1H nmr spectrum of this Smiles rearranged product (*S*)-**61** was identical to the ^1H nmr spectrum of the *N*-phenyl compound (*S*)-**61** derived from the direct *N*-phenylation of **59** with (*S*)-phenyl alaninol **60** in DMF, described previously.

5.0 Asymmetric Synthesis of *N*-Phenyl α -Amino Esters

The synthesis of *N*-phenyl α -amino esters was first attempted using the same conditions as for the synthesis of the *N*-phenyl α -amino alcohols.

5.1 Asymmetric Synthesis of (*S*)-[*N*-Phenylvaline *t*-butyl ester] $\text{Cr}(\text{CO})_3$

The reaction of (fluorobenzene) $\text{Cr}(\text{CO})_3$ **59** with (*S*)-valine *t*-butyl ester (*S*)-**68** was first examined. Compound (*S*)-**68** was obtained in high yield (74%) from (*S*)-valine, according to the literature procedure.¹⁹ 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

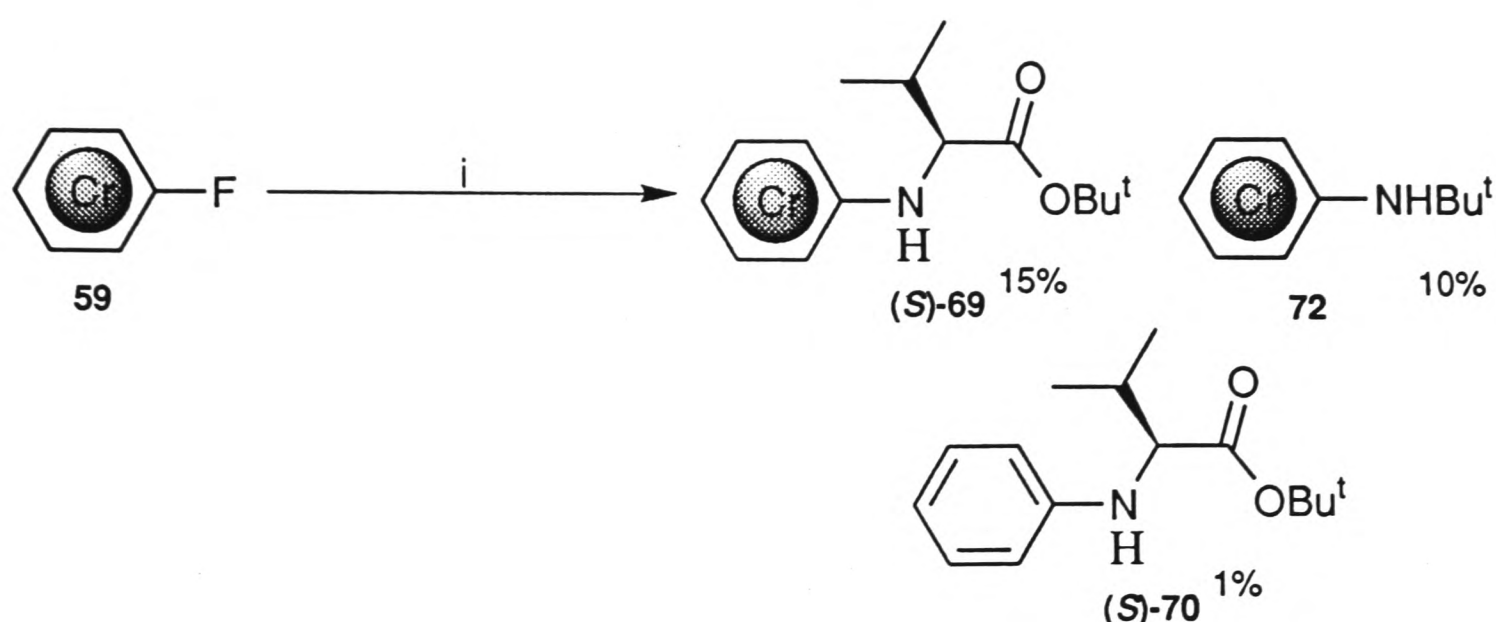
Analysis of the ^1H nmr spectrum of (*S*)-**69** showed a downfield shift of 0.42 ppm for the proton at the stereogenic centre, relative to the starting material, as well as a NH

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 ^1H , ^{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**.

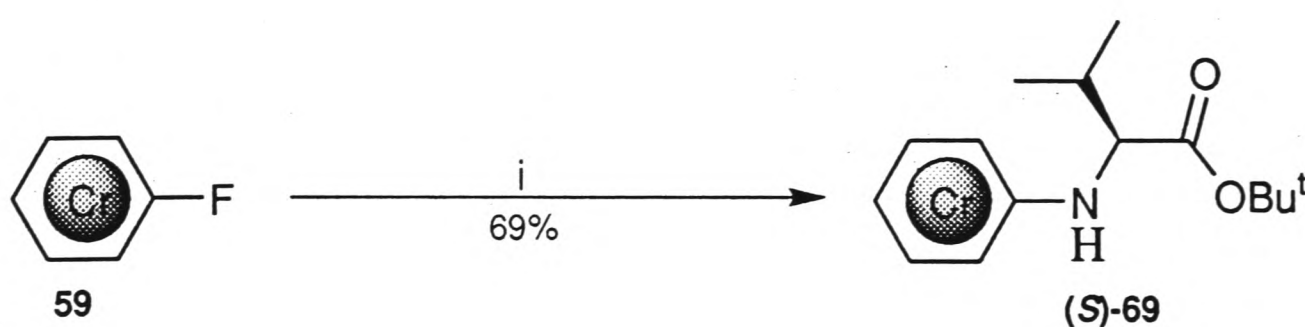
However this reaction was very sluggish, requiring stirring for 37 days, before affording the product (*S*)-**69** in poor yield. Bunnett *et al*¹⁸ observed that nucleophilic substitution of (fluorobenzene) $\text{Cr}(\text{CO})_3$ with amines was base catalysed either by the reacting amine or by an 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 undergone nucleophilic substitution with **59** at a similar rate, to afford **72** (10%), which was fully characterised.



Scheme 36: Reagents : i) (S)-valine *t*-butyl ester, *t*-butyl amine, DMF, rt

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).



Scheme 37: Reagents : i) (S)-**68**, quinuclidine, DMF, rt

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).

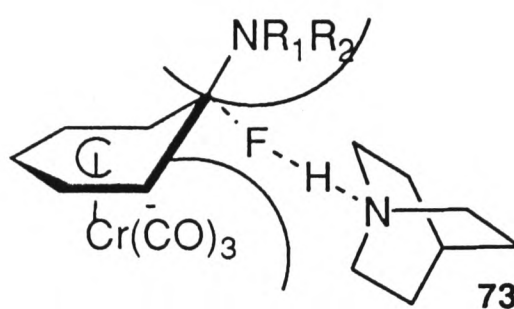
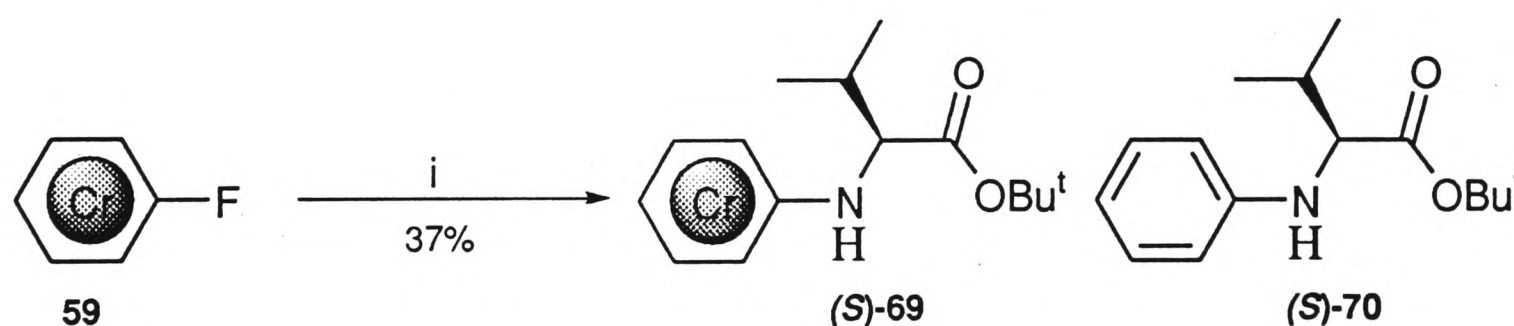


Figure 8

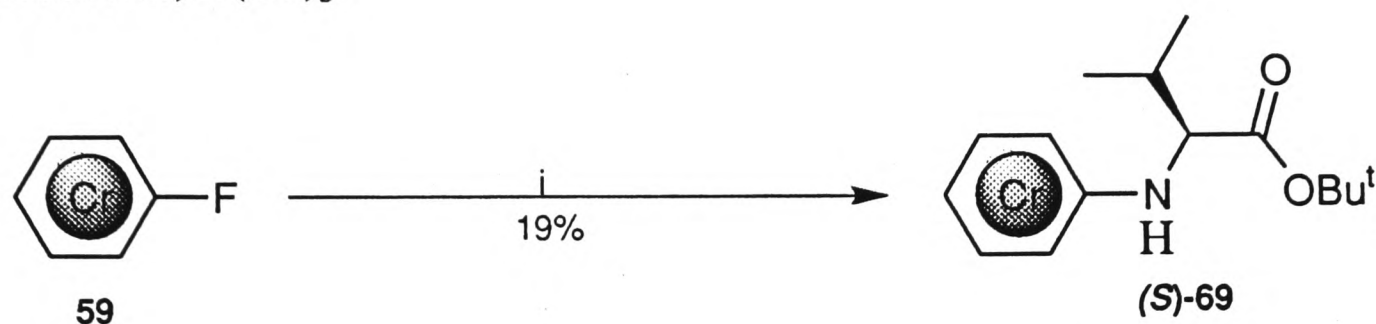
Since the α -amino alcohols reacted without an external amine to give *n*-phenylated amino alcohols in high yields and at a faster rate than their ester derivatives, it was thought that the alcohol functionality maybe assisting in the electrophilic expulsion of the fluoride ion. With this in mind, 3-quinuclidinol 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).

Scheme 38: Reagents : i) (*S*)-**68**, 3-quinuclidinol, DMF, rt

Attempts at increasing the rate of the reaction by heating were also investigated. An excess of (*S*)-**68** was stirred with **59** and quinuclidine **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.

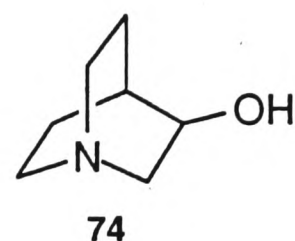
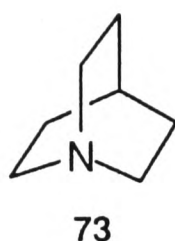
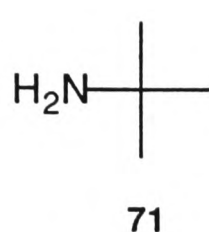


Scheme 39: Reagents : i) (*S*)-**68**, quinuclidine, DMF, 50°C

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)

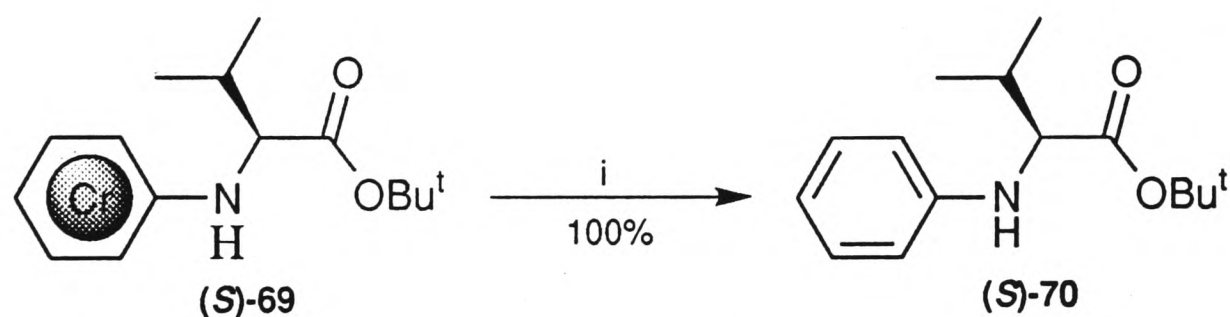
Table 1

Entry	Base	Days	Product (%)		Recovered Material (%)	
			complexed	decomplexed	(<i>s</i>)-valine	(fluorobenzene)
			69	70	<i>t</i> -butyl ester	Cr(CO) ₃
1	none	37 (rt)	18	14	74	24
2	<i>t</i> -butylamine (71)	11 (rt)	15	1	73	48
3	quinuclidine (73)	14 (rt)	69	0	74	28
4	3-quinuclidinol (74)	19 (rt)	37	17	72	45
5	quinuclidine (73)	2 (50°C)	19	0	87	24



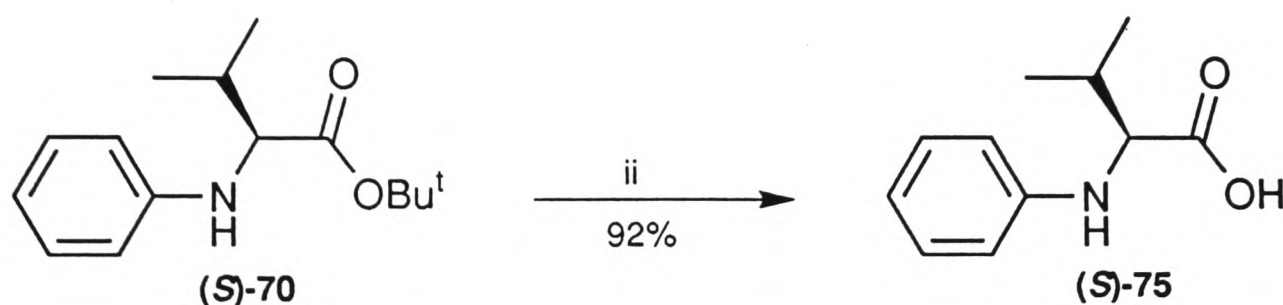
5.2 Asymmetric Synthesis of (S)-N-Phenylvaline

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 ^1H 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**.



Scheme 38: Reagents : i) $h\nu$, Et_2O

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 $\text{EtOH}/\text{H}_2\text{O}$ to afford a white crystalline solid, in excellent yield (92%) (m.p. 123-124°C).

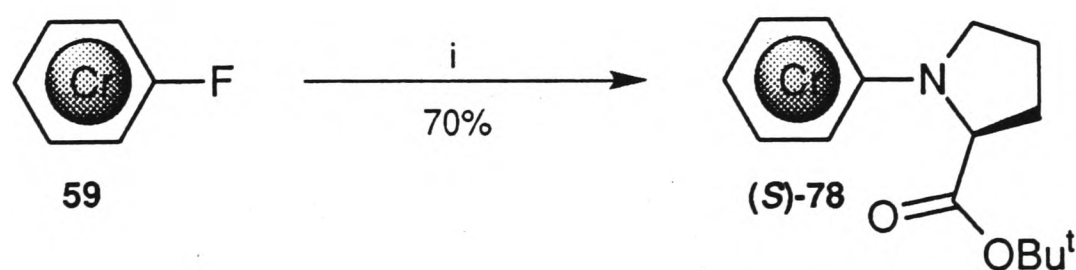


Scheme 40: Reagents : i) TFA

Analysis of the ^1H 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 $[\alpha]_{\text{D}}^{22}$ -86.77, (C 0.31, EtOH); lit¹¹ $[\alpha]_{\text{D}}^{25}$ -86.0, (C 1.2, EtOH)}.

5.3 Asymmetric Synthesis of (S)-[N-Phenylproline *t*-butyl ester] $\text{Cr}(\text{CO})_3$

(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.

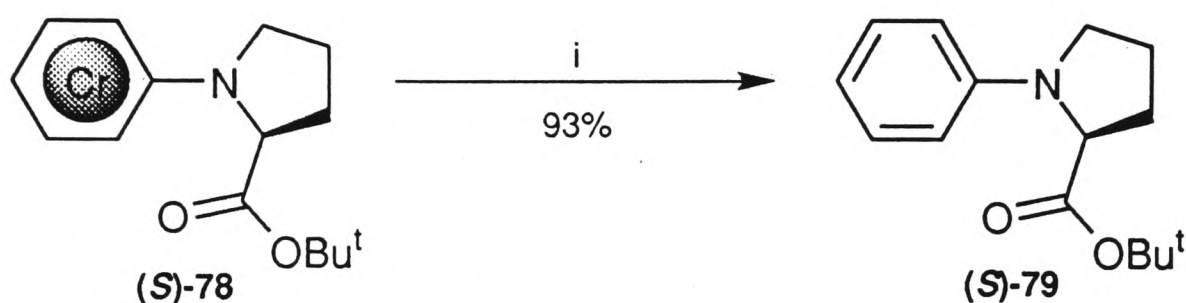
Scheme 41: Reagents : i) (S)-76 *t*-butyl ester, quinuclidine, rt, DMF

^1H 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.

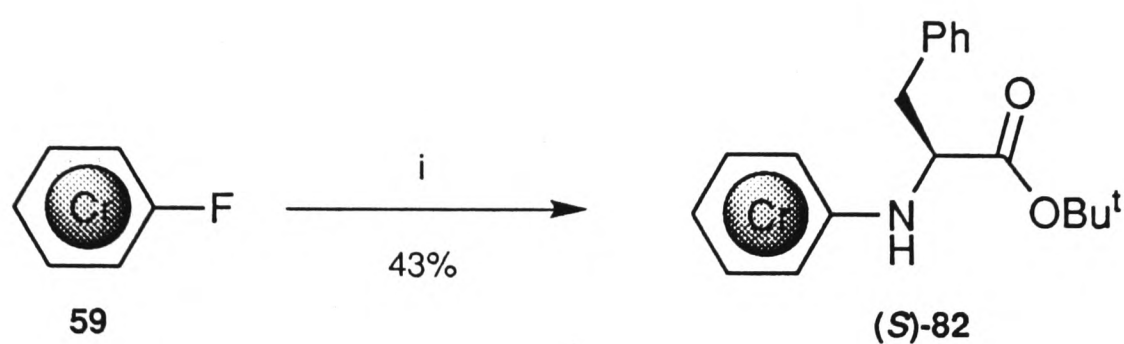


Scheme 42: Reagents : i) $h\nu$, Et_2O

1H , ^{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%).

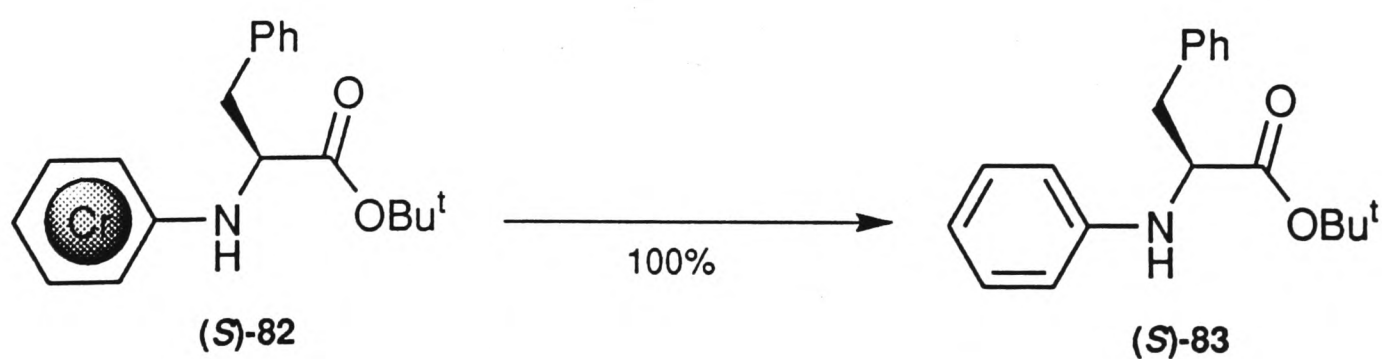


Scheme 43: Reagents : i) **(S)-81**, quinuclidine, rt, DMF

Investigation of the ^1H 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. $81\text{--}82^\circ\text{C}$.



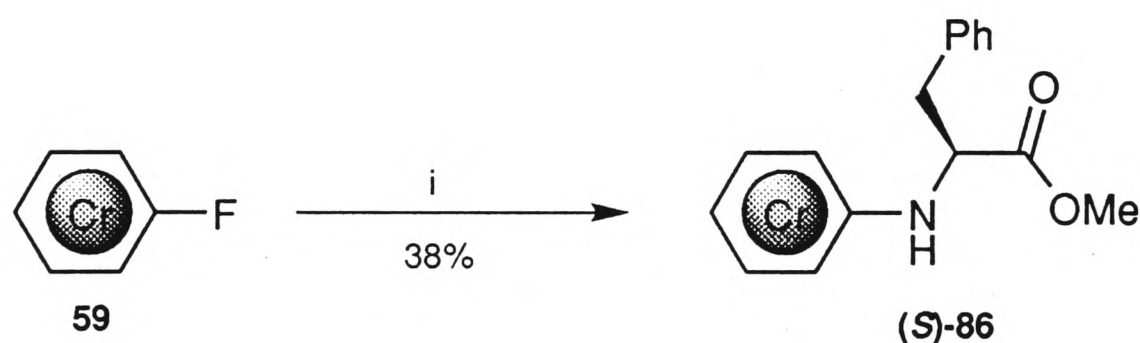
Scheme 44: Reagents : i) $h\nu$, Et_2O

^1H 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 Synthesis of (*S*)-[*N*-Phenylalanine methyl ester] $\text{Cr}(\text{CO})_3$

The (*S*)-phenylalanine methyl ester **85** was formed by stirring (*S*)-phenylalanine (**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 led to the isolation of **86** in 38% yield as a yellow solid (m.p. 88-90°C) and some starting material **59** (30%).

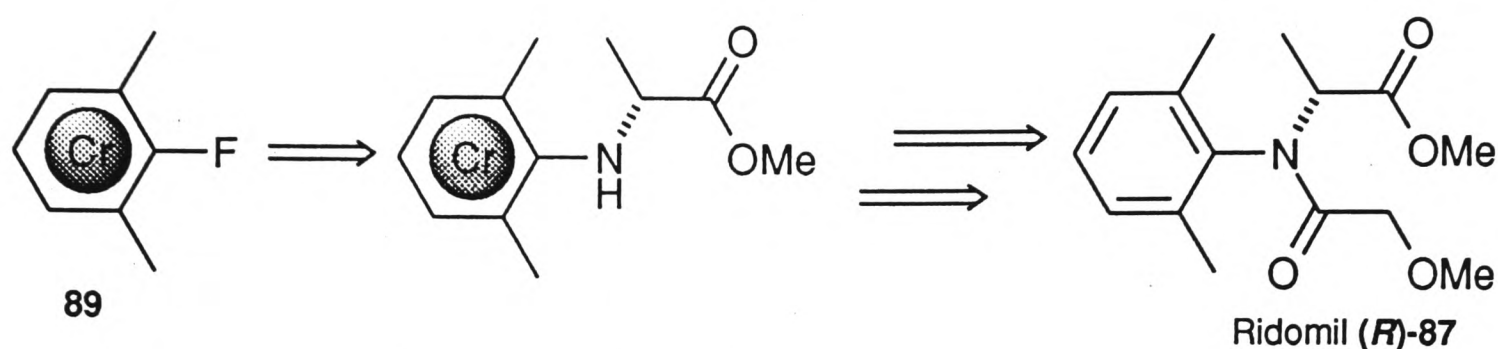


Scheme 45: Reagents : i) (*S*)-**85**, quinuclidine, rt, DMF

Examination of the ^1H 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®

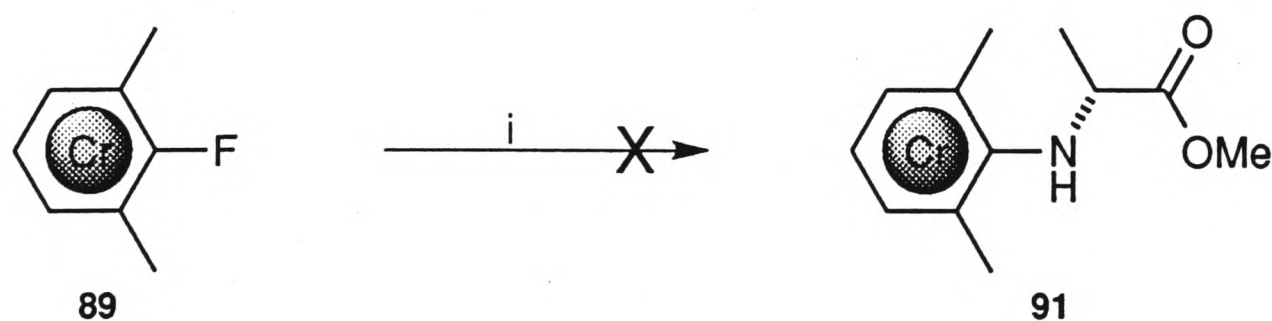
A new route to the synthesis of the herbicide Ridomil® **87** was next investigated. It was envisaged that **87** could be synthesised by reacting (2,6-dimethylfluorobenzene)Cr(CO)₃ **89** with (*R*)-alanine methyl ester **90** (Scheme 46).



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.

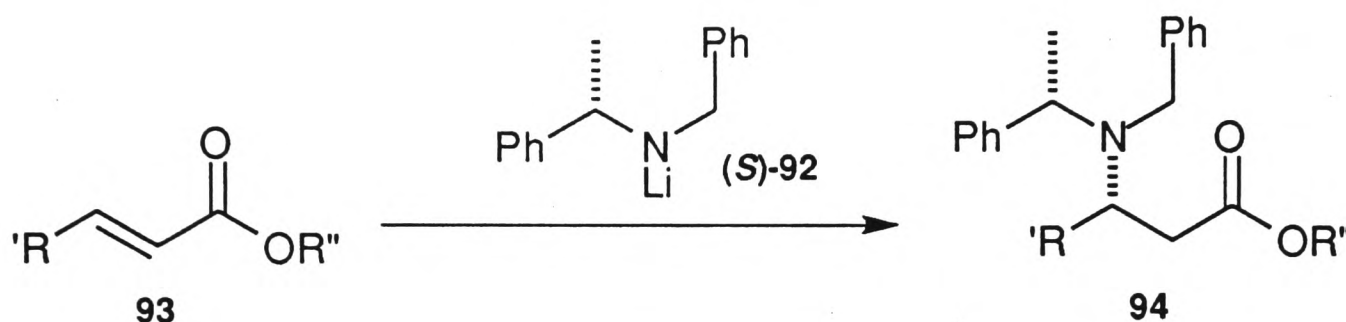


Scheme 47: Reagents : i) (*R*)-**90** quinuclidine, rt, DMF

6.0 Asymmetric Synthesis of β Amino Acids

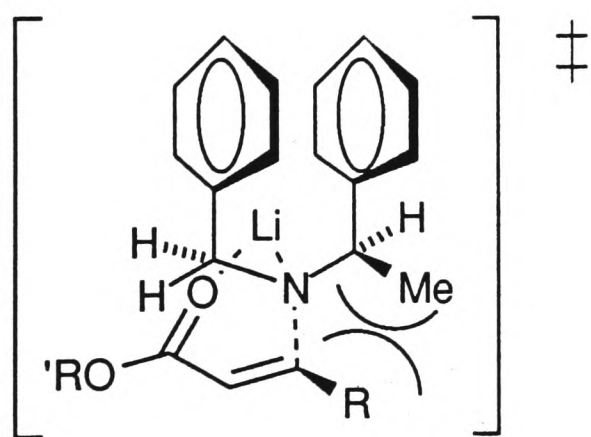
6.1 Introduction

Recently, a novel method of synthesising β -amino acids in their homochiral form was discovered in this laboratory.²⁰ This entails a stereoselective Michael addition of chiral lithium amides **92** to α,β -unsaturated esters **93** (Scheme 48), to afford the Michael addition product **94** in high yield and with high diastereoselectivity.



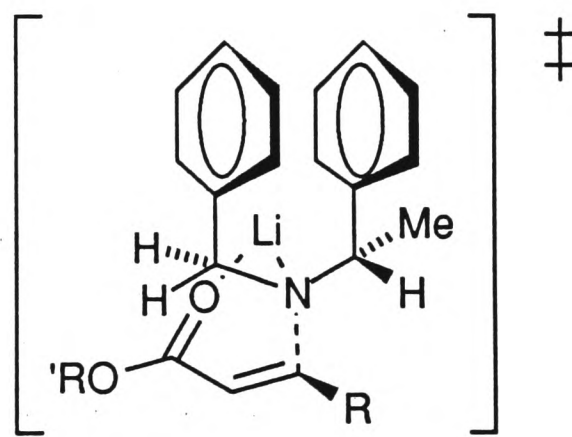
Scheme 48: Reagents : i) (S)-**92**, THF, -78°C

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



disfavoured

Fig 9a



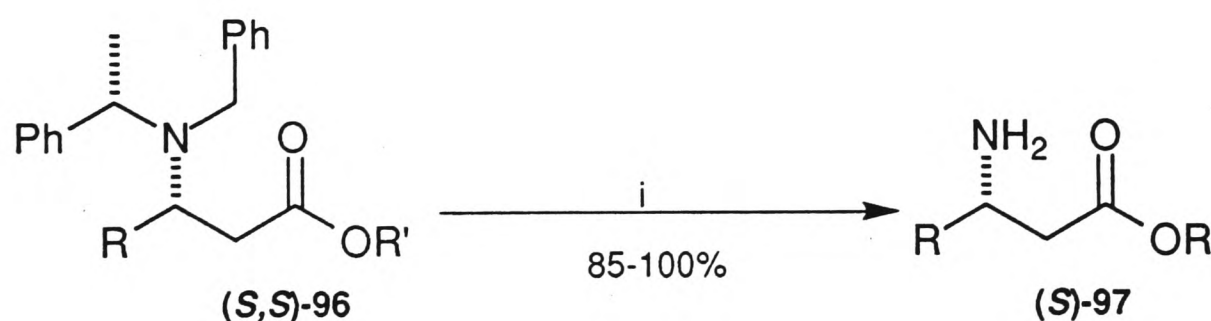
favoured

Fig 9b

The addition of the lithium amide **92** to the α,β -unsaturated ester **93** is anticipated to occur *via* a six membered chelated transition state, with the ester in a *s-cis* conformation,²¹ 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 α -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 α -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 α -methyl benzylamine. After formation of the Michael adduct **96** the benzyl groups can be removed by catalytic hydrogenolysis (**Scheme 49**), to form the β -amino ester **97**, without racemisation.



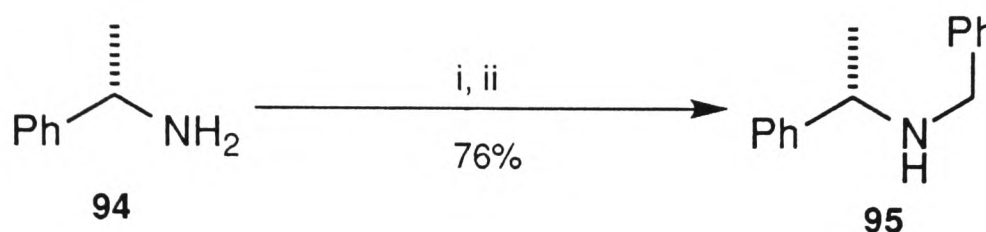
Scheme 49: Reagents : i) Pd(OH)₂/C/H₂ (5atm.)

Using this methodology and the (fluorobenzene)Cr(CO)₃ complex as a phenyl cation synthon, it was envisaged that *N*-phenyl β -amino esters could be synthesised stereoselectively and be used as chiral starting materials for the asymmetric synthesis of *N*-phenyl β -lactams.

6.2 Asymmetric Synthesis of (*S*)- β -Amino Butyric Ester **101**

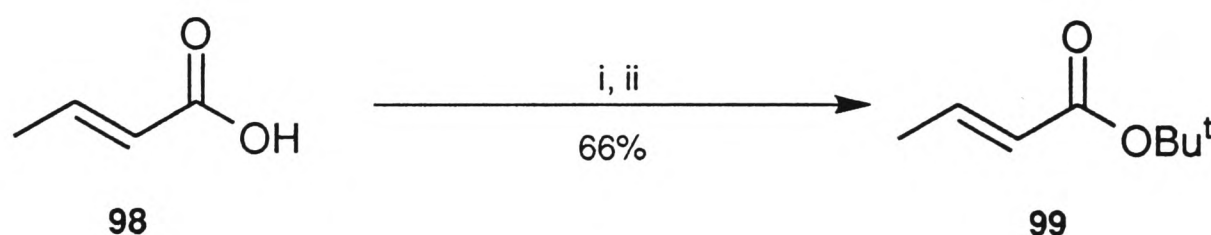
The chiral secondary amine **95** was prepared by condensation of (*S*)- α -methylbenzylamine (*S*)-**94** with benzaldehyde in ethanol, followed by reduction of the

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%) {[α]_D²⁵ -53.8 (*c* 3.2, EtOH); lit²² [α]_D²⁵ -53.6 (*c* 3.8, EtOH)}.



Scheme 50: Reagents : i) PhCHO, EtOH, reflux; ii) NaBH₄

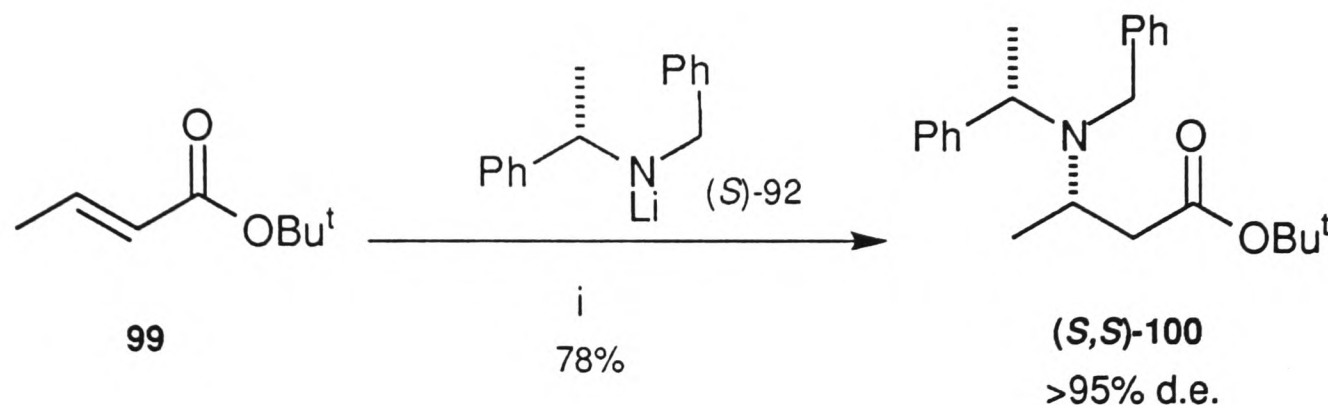
(*E*)-*t*-Butyl crotonate **99** was prepared by the esterification of crotonic acid **98** with isobutylene, under acidic conditions (**Scheme 51**). Flash chromatography afforded **99** as a colourless oil in 66% yield.



Scheme 51: Reagents : i) isobutylene, CH₂Cl₂, H₂SO₄, ii) NaHCO₃

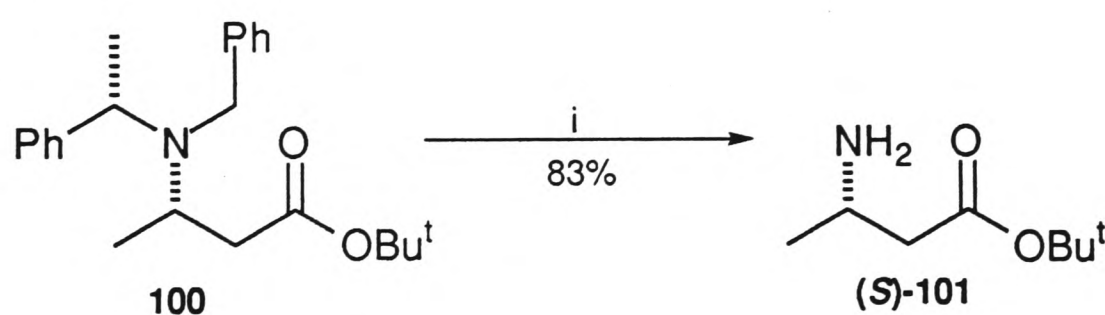
Addition of *n*-BuLi to the amine at -78°C afforded a pink solution of the lithium amide **92**. Subsequent addition of a THF solution of the *t*-butyl crotonate **99** to the lithium amide solution, afforded an orange solution, presumably of the *t*-butyl amino enolate. (**Scheme 52**). Upon quenching the reaction with saturated ammonium chloride and aqueous work-up, analysis of the crude ¹H 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 β-stereogenic centre (CHCH₂CO₂). Analysis of the crude ¹H nmr spectrum showed the reaction occurred with excellent diastereoselectivity

(*S,S*) (>95% d.e.). Column chromatography allowed isolation of **100** in high yield (78%) $\{[\alpha]_{\text{D}}^{25} +4.36$ (*c* 0.90, CHCl_3); lit²³ for (*R,R*)-**100** $[\alpha]_{\text{D}}^{25} -4.3$ (*c* 1.06, CH_2Cl_2) $\}$.



Scheme 52: Reagents : i) (*S*)-**92**, -78°C , THF

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 β-amino ester **101** was isolated in 83% yield $\{[\alpha]_{\text{D}}^{22} -35.03$ (*c* 1.73, CHCl_3) $\}$. ^1H 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 debenylation of this group took place.

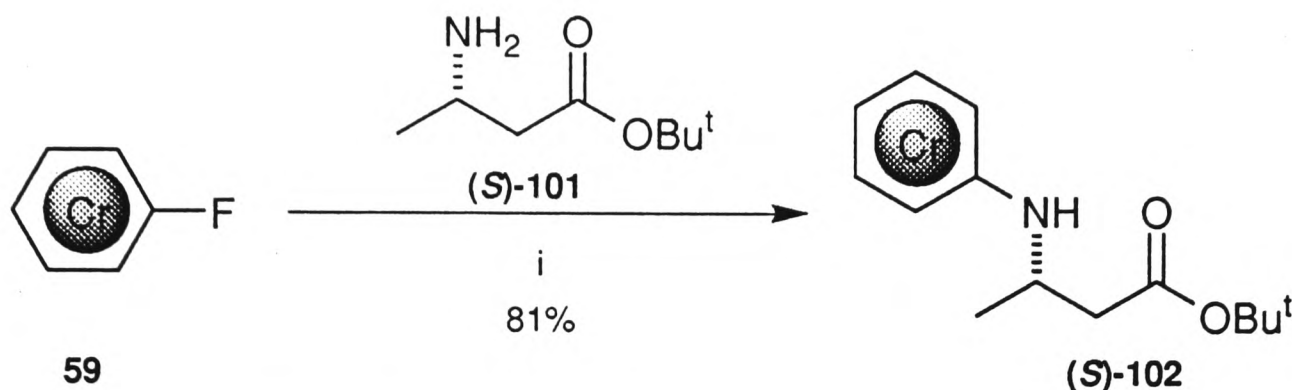


Scheme 53: Reagents : i) $\text{Pd}(\text{OH})_2/\text{C}$

6.3 Asymmetric Synthesis of (3*S*)-[*N*-(*t*-butyl 3-butanoate)aniline] $\text{Cr}(\text{CO})_3$ (*S*)-**102**

With the (*S*)-**101** in hand, *N*-phenylation was attempted. An excess of the β-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.

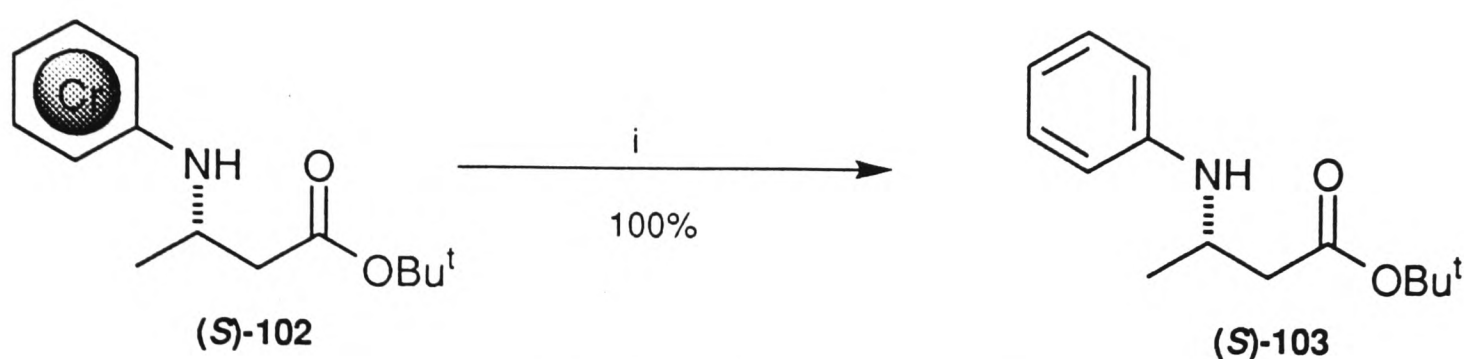


Scheme 54: Reagents : i) (S)-101, quinuclidine, DMF, rt

^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 $\text{Cr}(\text{CO})_3$ moiety. This together with a molecular ion of $m/z=372$ (MH^+) and microanalysis confirmed the proposed structure of this novel chromium tricarbonyl complex.

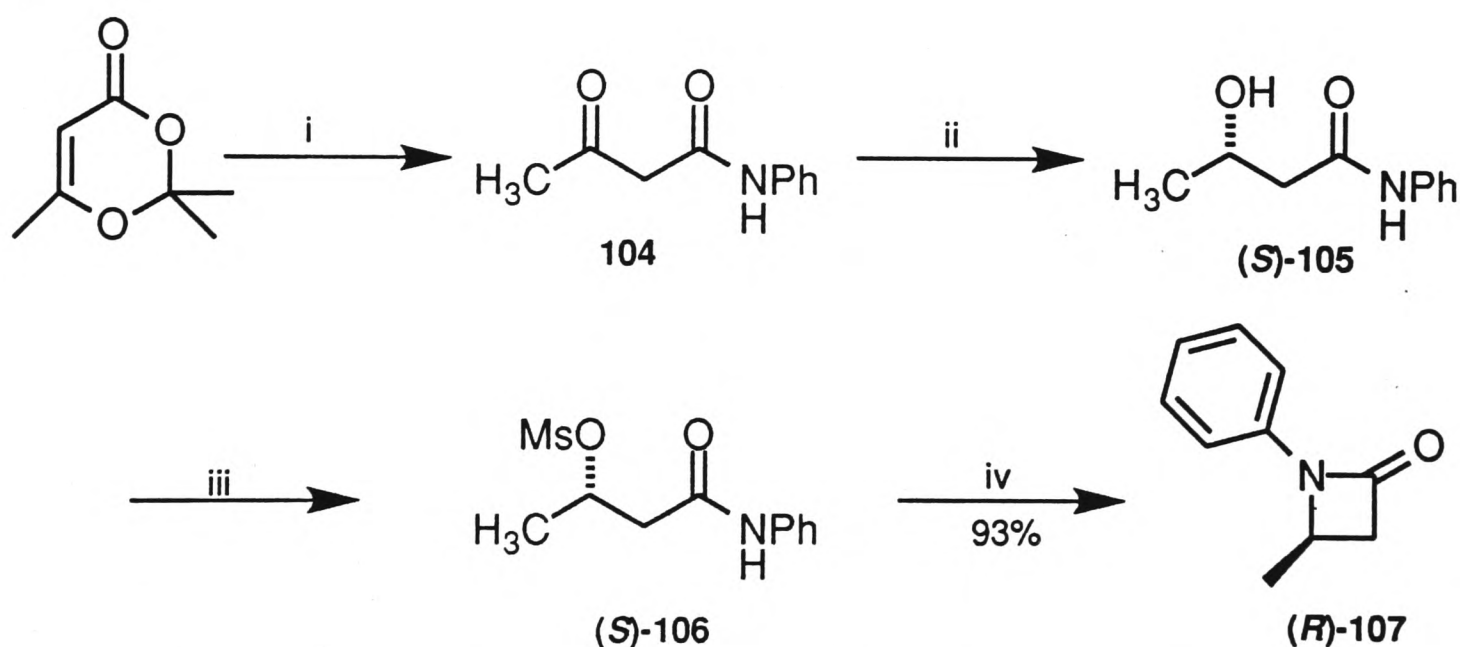
6.4 Asymmetric Synthesis of (3S)-N-(t-butyl 3-butanoate)aniline (S)-103

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 *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.

Scheme 55: Reagents : i) $h\nu$, Et_2O

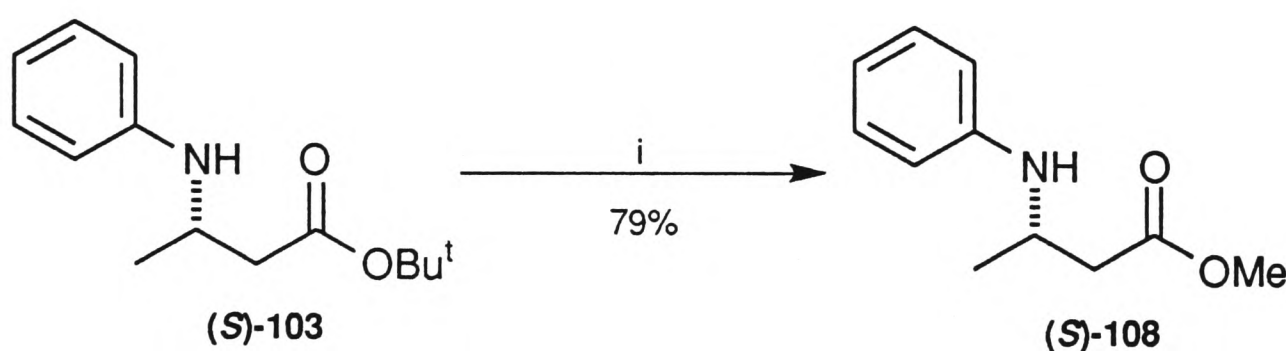
7.0 Asymmetric Synthesis of (*S*)-4-Methyl Azetidin-2-one (*S*)-107

Sakaki²⁴ 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 form the opposite enantiomer by bromination of the mesylate 106 only led to racemisation.

Scheme 56: Reagents : i) PhNH_2 , Xylene; ii) Baker's yeast; iii) MsCl , pyridine;iv) NaH , $\text{CH}_2\text{Cl}_2/\text{DMF}$

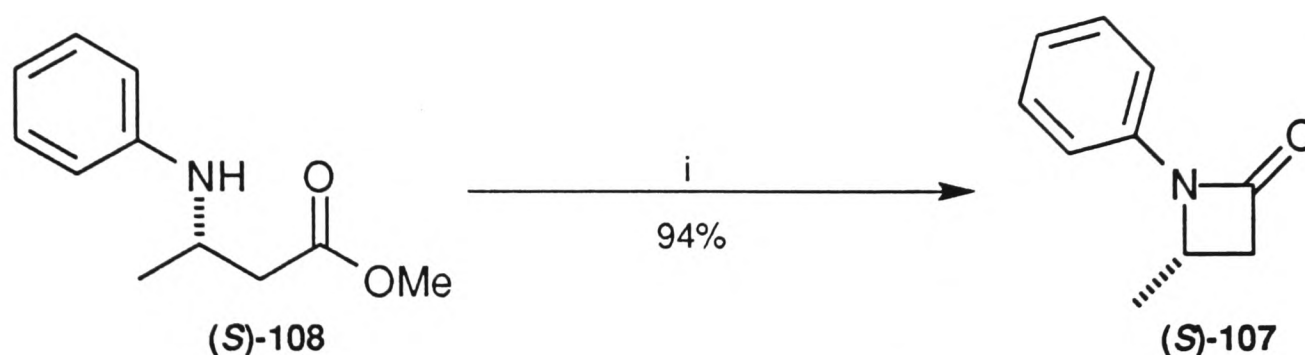
However using the aforementioned stereoselective synthesis of *N*-phenyl β -amino esters, it is envisaged that either enantiomer of 107 could be formed.

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 ^1H 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**) $[\alpha]_{\text{D}}^{22} +7.51$, (*c* 0.95, CHCl_3); lit¹⁰ (*R*)-**108** $[\alpha]_{\text{D}} -7.0$ (*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.



Scheme 57: Reagents : i) MeOH , H^+

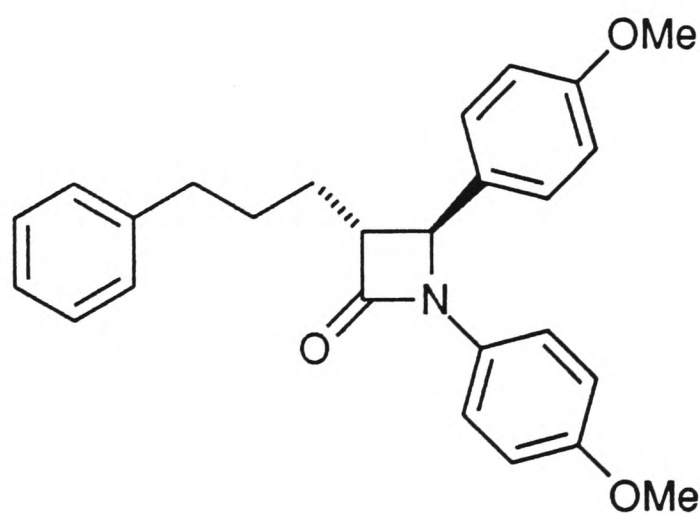
Next, cyclisation of (*S*)-**108** was induced by the Breckpot reaction with CH_3MgBr (**Scheme 58**), to afford the *N*-phenyl β -lactam (*R*)-**107** in 94% yield after work-up and column chromatography. The ^1H nmr spectrum and the specific rotation obtained were in excellent agreement with the literature data for (*R*)-**107** {(*S*)-**107** $[\alpha]_{\text{D}}^{22} +113.9$ (*c* 0.61, CHCl_3 , for lit²⁴ [(*R*)-**107** $[\alpha]_{\text{D}}^{25} -117$ (*c* 1.34, CHCl_3)}.



Scheme 58: Reagents : i) CH₃MgBr, THF, 0°C

8.0 Asymmetric Synthesis of (-)-SCH 48461

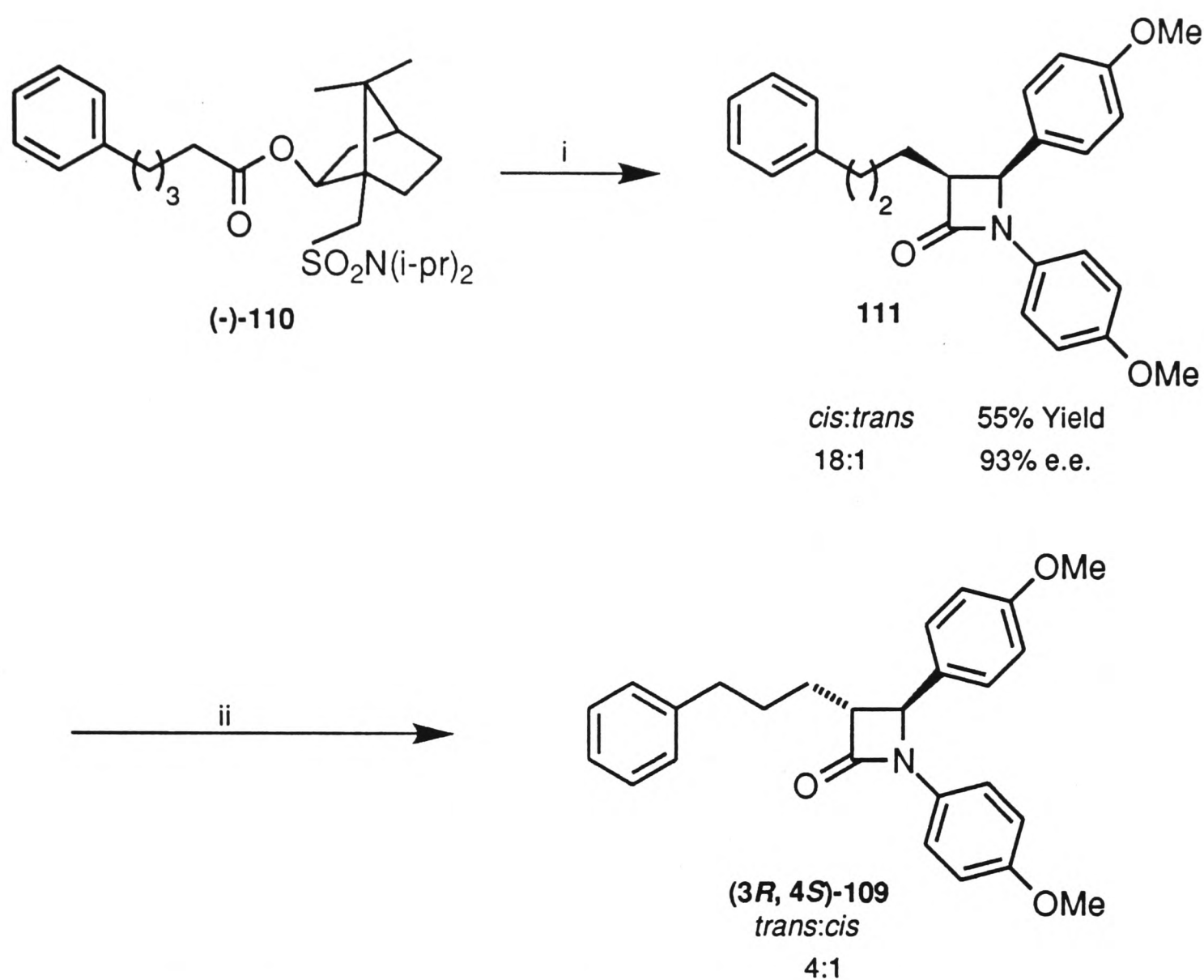
(-)-SCH 48461 **109** has recently been synthesised by Scherring Plough (**Figure 10**) and has been shown to be a potent inhibitor of acyl-CoA: cholesterol acyltransferase, an enzyme which is involved in the reabsorption of cholesterol in the large intestine.²⁵



(-) SCH 48461

Figure 10

The synthesis of this compound by Burnett *et al*²⁵ 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 (3*R*,4*S*) was isolated by chromatography and further purified by Chiralcel OD column, to give **109** in its homochiral form (3*R*,4*S*).¹⁴



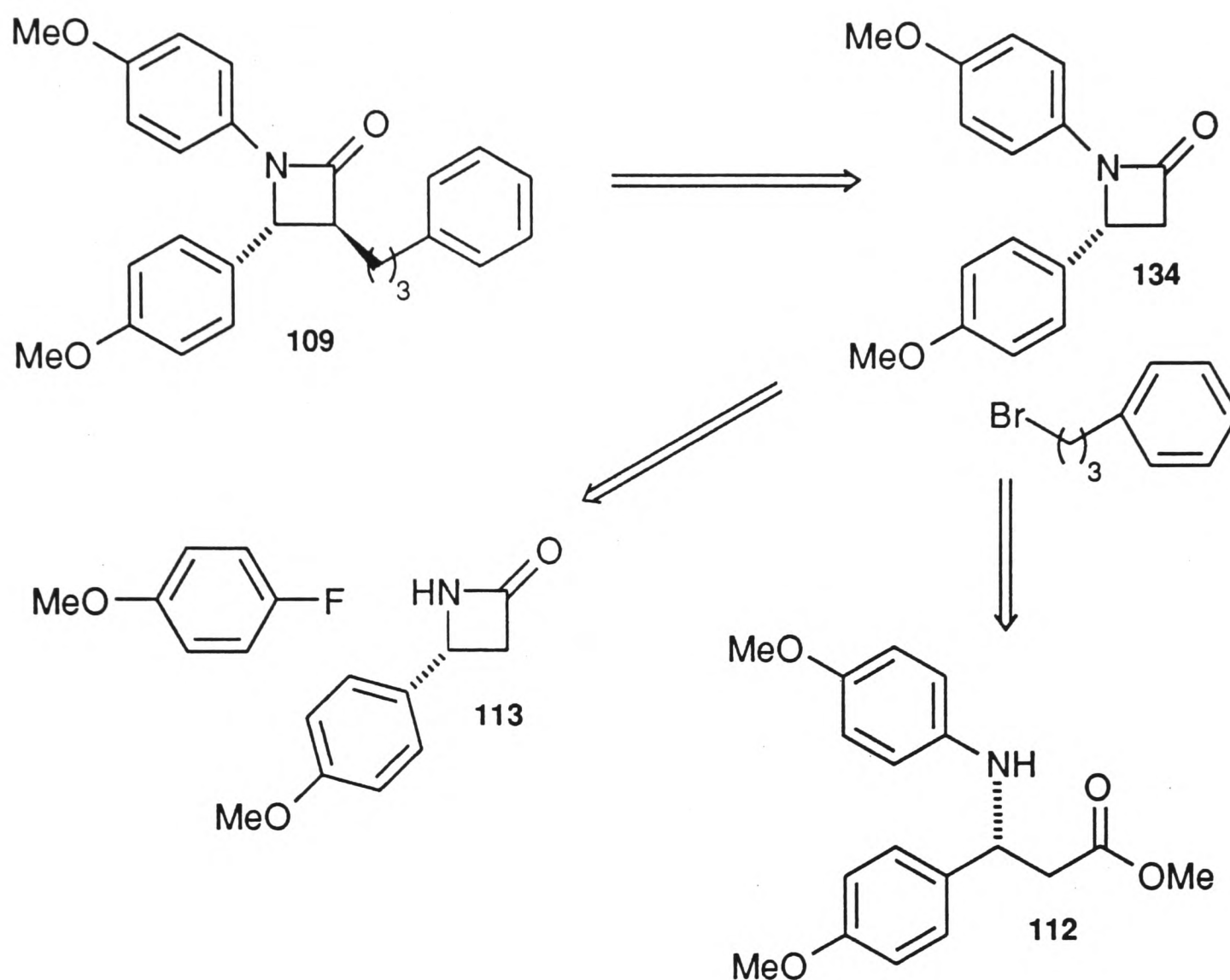
Scheme 59: Reagents : i) *N*-(4-methoxybenzylidene)anisidine, LDA, THF, -78°C;

ii) KO^tBu

In the next section, the asymmetric synthesis of the opposite enantiomer (3*S*,4*R*)-(+)-SCH 48461 is attempted using methodology previously described for the asymmetric synthesis of β-amino acids and *N*-phenylation using (4-fluoroanisole)Cr(CO)₃, with a view to its general use in forming either enantiomer.

8.1 Synthetic Strategy of (+)-(3*S*, 4*R*)-SCH 48461 109

A simple retrosynthetic analysis of **109** shows two alternative starting materials, either the (*R*)-*N*-phenyl β-amino ester **112** or the (*R*)-β-lactam **113** (Scheme 60).

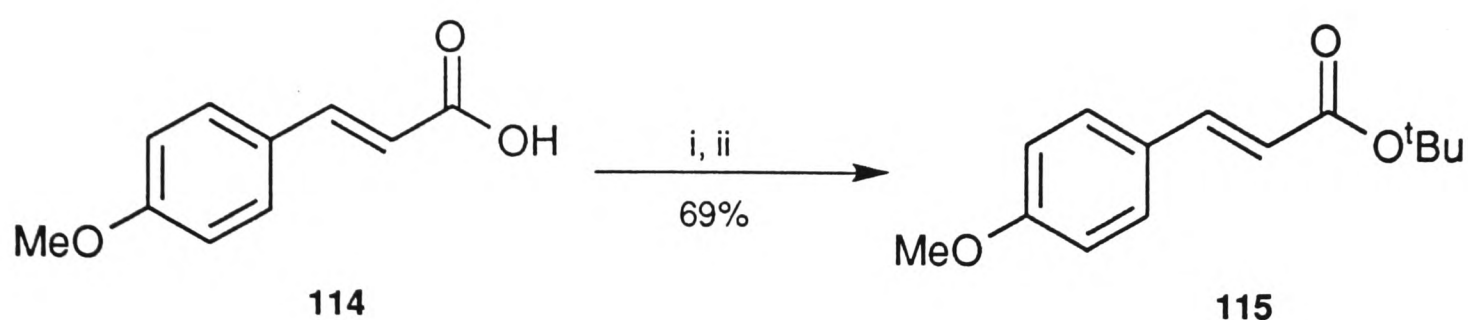


Scheme 60

The first approach in this section will involve the asymmetric synthesis of the β -lactam **113** with a view to using (4-fluoroanisole) $\text{Cr}(\text{CO})_3$ as an aryl cation synthon to arylate **113**.

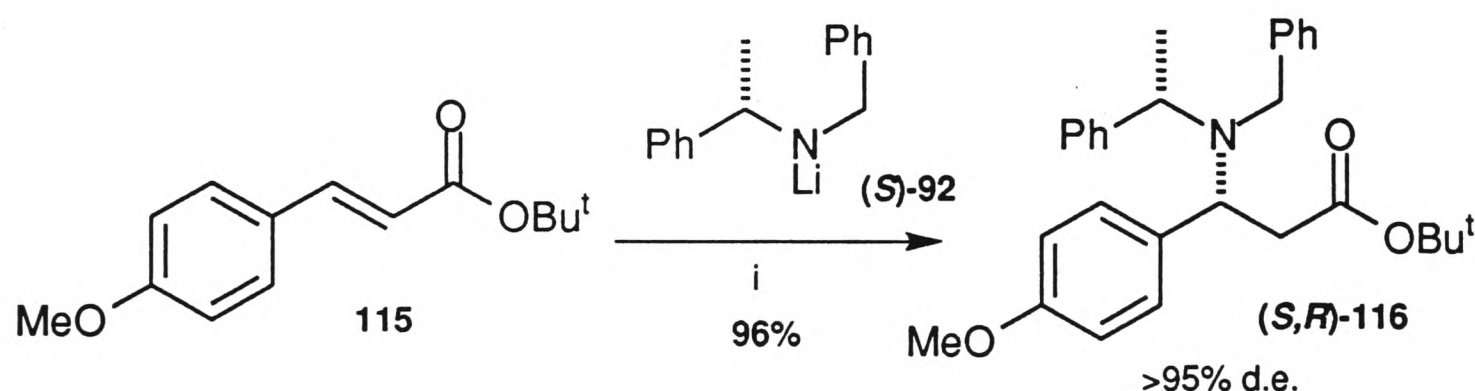
8.2 Asymmetric Synthesis of (4*R*)-4-(4-Methoxyphenyl)-2-azetidinone

The α,β -unsaturated ester **115** is readily synthesised from reacting 4-methoxy cinnamic acid **114** with isobutylene in acidic CH_2Cl_2 (69% yield, m.p. 44-45°C) (**Scheme 61**).



Scheme 61: Reagents : i) isobutylene, CH₂Cl₂, H₂SO₄; ii) NaHCO₃

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 ¹H nmr spectrum of the crude reaction product, showed the formation of the Michael adduct (*S,R*)-**116** in >95% d.e..

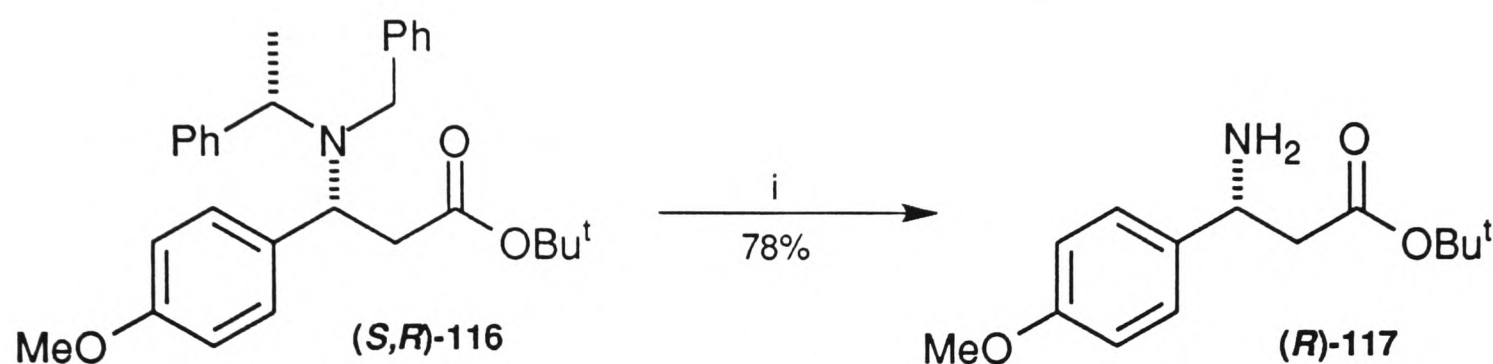


Scheme 62: Reagents : i) (*S*)-**92** , -78°C, THF

After purification by column chromatography the desired product (*S,R*)-**116** was isolated in 96% yield and fully characterised {[α]_D²² -2.69 (c 1.41, CHCl₃)}. ¹H 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 β-stereogenic centre (CHCH₂CO₂) and a multiplet at 3.99 ppm representing the proton at the β-stereogenic centre.

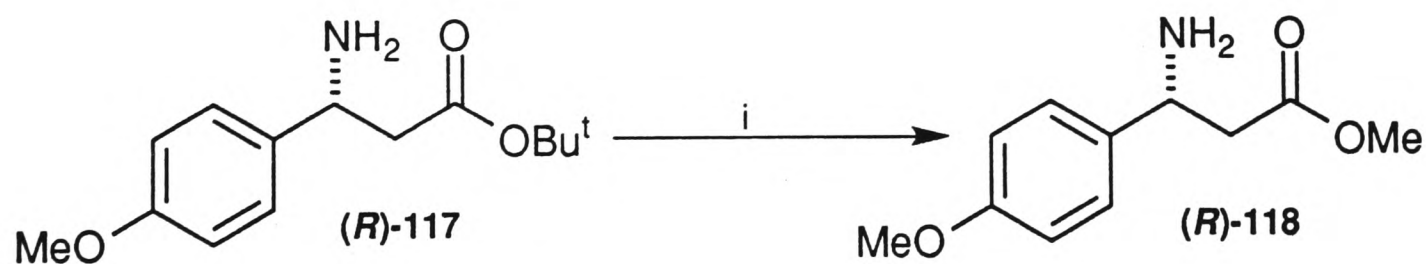
Catalytic hydrogenolysis of the Michael adduct (*S,R*)-**116** using Pearlman's catalyst under 5 atm of hydrogen at 50°C (**Scheme 63**), afforded after work-up, the (*R*)-β-amino ester (*R*)-**117** in 78% yield {[α]_D²² +10.41 (c 0.73, CHCl₃)}. The ¹H and ¹³C nmr spectra of (*R*)-**117** showed that the desired debenzylolation 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.



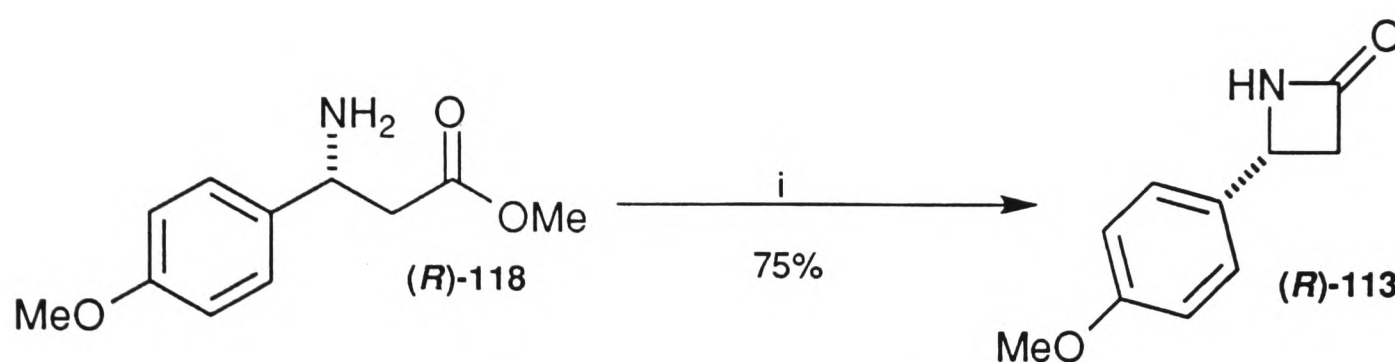
Scheme 63: Reagents : i) $\text{Pd}(\text{OH})_2/\text{C}$

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 ^1H 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 data²⁶ allowed the unambiguous assignment of the absolute configuration of **118** as (**R**) $\{[\alpha]_{\text{D}}^{22} -90.2$ (c 1.4, MeOH); lit²⁶ $[\alpha]_{\text{D}}^{25} -91.5$ (c 1.42, MeOH)}.



Scheme 64: Reagents : i) MeOH, H^+

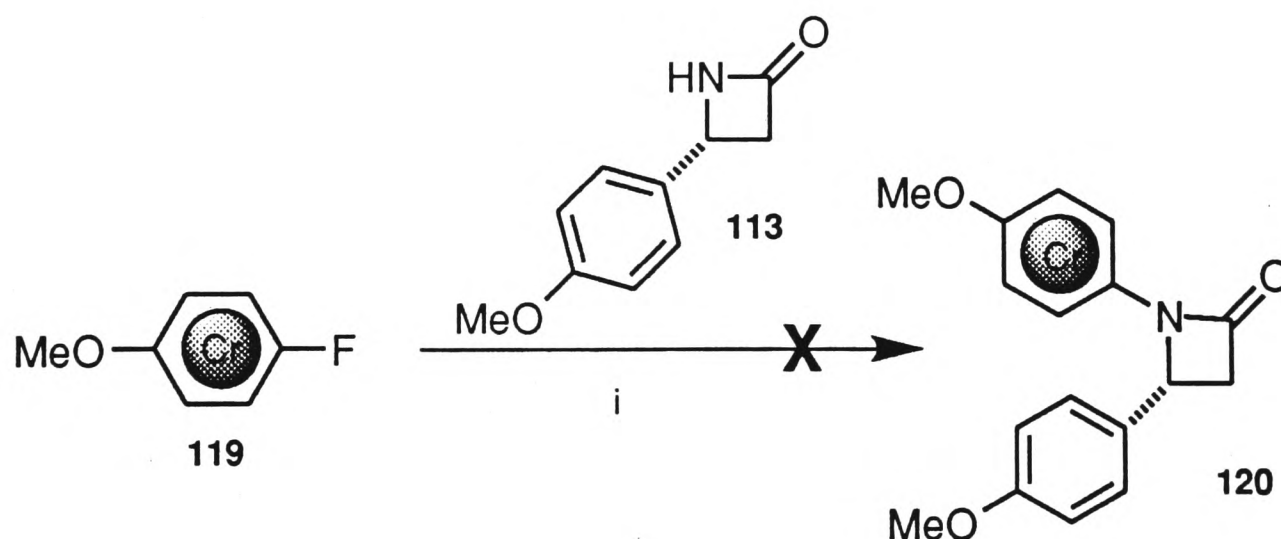
The β -amino ester (**R**)-(**118**) was then cyclised on reaction with $\text{Al}(\text{Me})_3$ at 0°C , to afford the β -lactam (**R**)-**113** in 75% yield $\{[\alpha]_{\text{D}}^{22} +131.3, (c$ 0.115, $\text{CHCl}_3)\}$ (Scheme 65).



Scheme 65: Reagents : i) $\text{Al}(\text{Me})_3$, toluene, 0°C

8.3 *N*-Phenylation of (4*R*)-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) $\text{Cr}(\text{CO})_3$ 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).

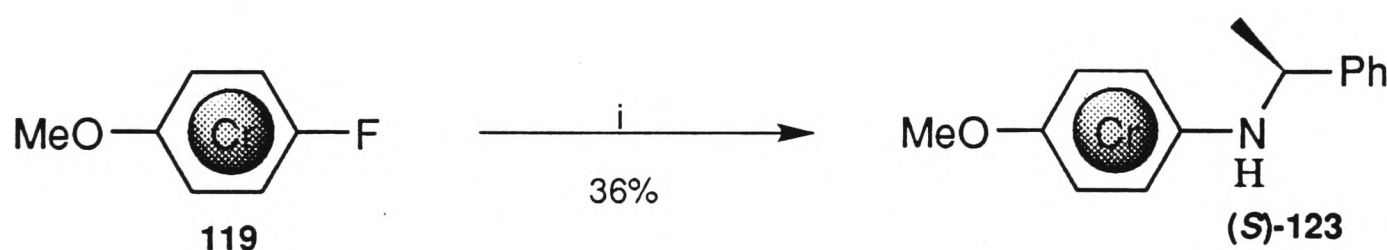


Scheme 60: Reagents : i) 113, KHMDS

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) $\text{Cr}(\text{CO})_3$.

8.4 Asymmetric Synthesis of (3*R*)-*N*-(methyl 3-propanoate-3-(4-methoxybenzene))-4-methoxyaniline (*R*)-112

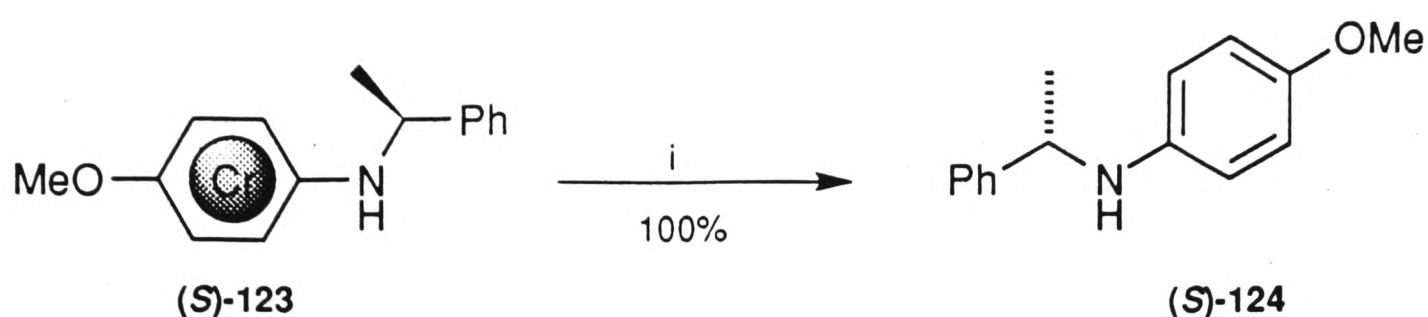
Consequently, attention was turned to the asymmetric synthesis of (*R*)-112 via a stereoselective Michael addition of the chiral lithium amide 125 with the *t*-butyl ester of 4-methoxycinnamate 121. The Michael acceptor 121 was readily made as described previously. The chiral amine 123 was synthesised by stirring (*S*)- α -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), $\{[\alpha]_{\text{D}}^{22} -275.21$ (*c* 0.48, CHCl₃) $\}$ and 26% starting material 119.



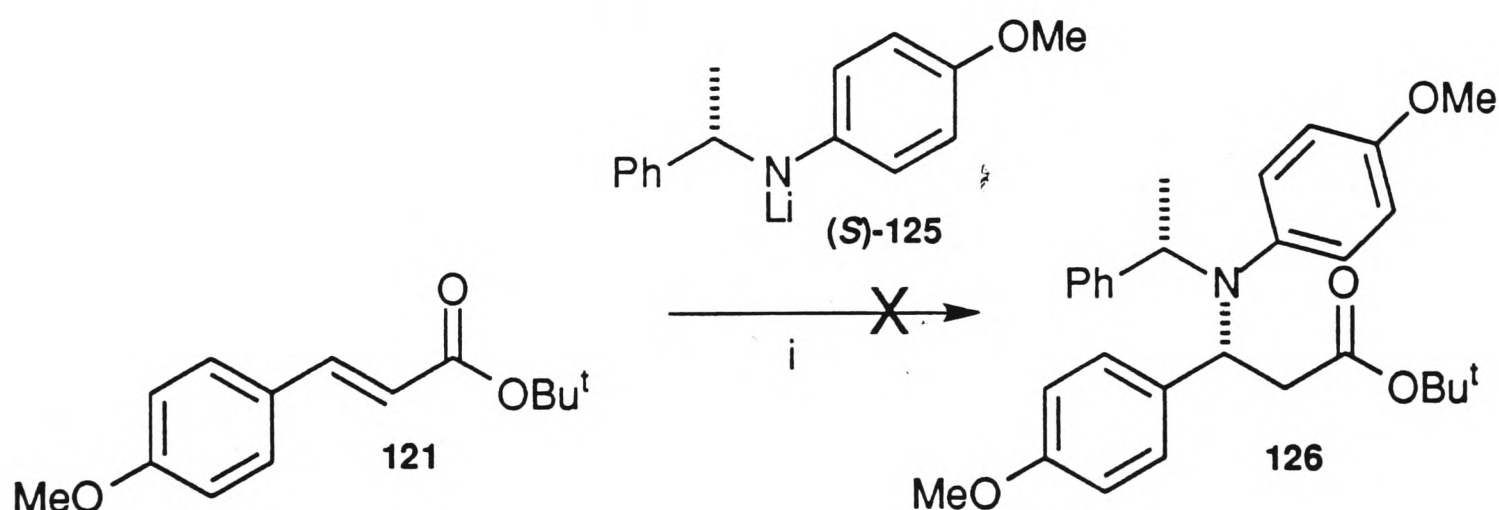
Scheme 67: Reagents : i) (*S*)-94, rt, DMF

¹H 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 $\{[\alpha]_{\text{D}}^{22} -8.83$ (*c* 1.67, CH₃OH) $\}$ (Scheme 68). Analysis of the ¹³C and infra-red spectra confirmed the removal of the chromium tricarbonyl unit and the ¹H nmr spectrum was identical in all respects to the known racemic compound.²⁷

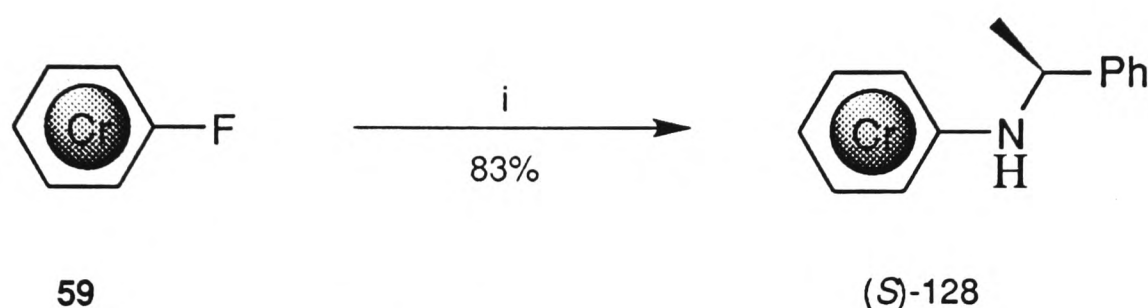
Scheme 68: Reagents : i) $h\nu$, Et_2O

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.

Scheme 69: Reagents : i) (S)-125, -78°C to 0°C , THF

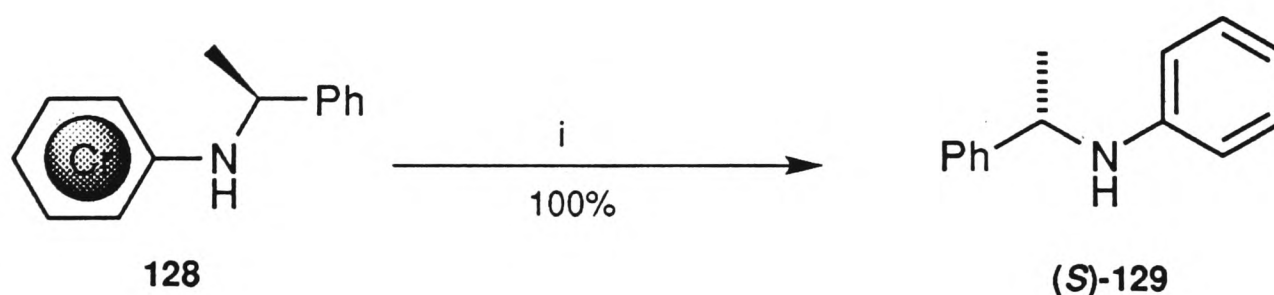
The softer nucleophile **127** (Scheme 72) was also investigated to see if addition could be induced. Compound **128** was made by stirring (fluorobenzene) $\text{Cr}(\text{CO})_3$ in (S)- α -methylbenzylamine **94** for three days at room temperature (Scheme 70) to yield (S)-(**128**) (83%) as a yellow 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 $\text{Cr}(\text{CO})_3$ 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**.



Scheme70: 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. $43\text{-}45^{\circ}\text{C}$. (Scheme 71).

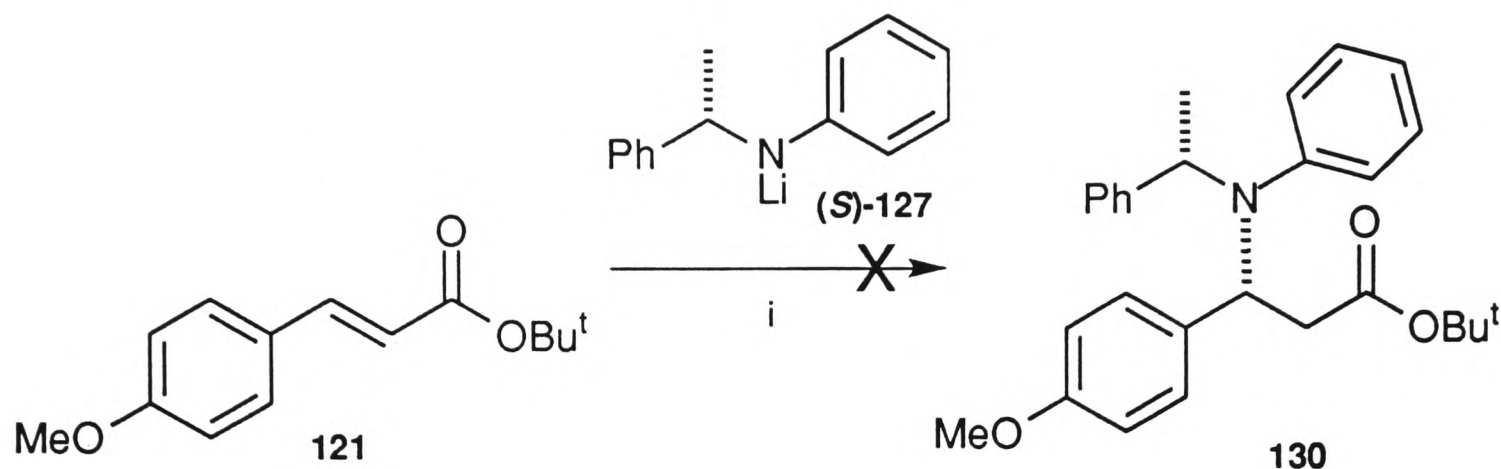


Scheme 71: Reagents : i) $h\nu$, Et_2O

Both ^1H and infra-red analysis confirmed the removal of the $\text{Cr}(\text{CO})_3$ 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**) $[\alpha]_{\text{D}}^{22} +20.9$ (c 1, MeOH); lit²⁸ (*R*)-(**129**) $[\alpha]_{\text{D}}^{22} -19.5$ (c 1, 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

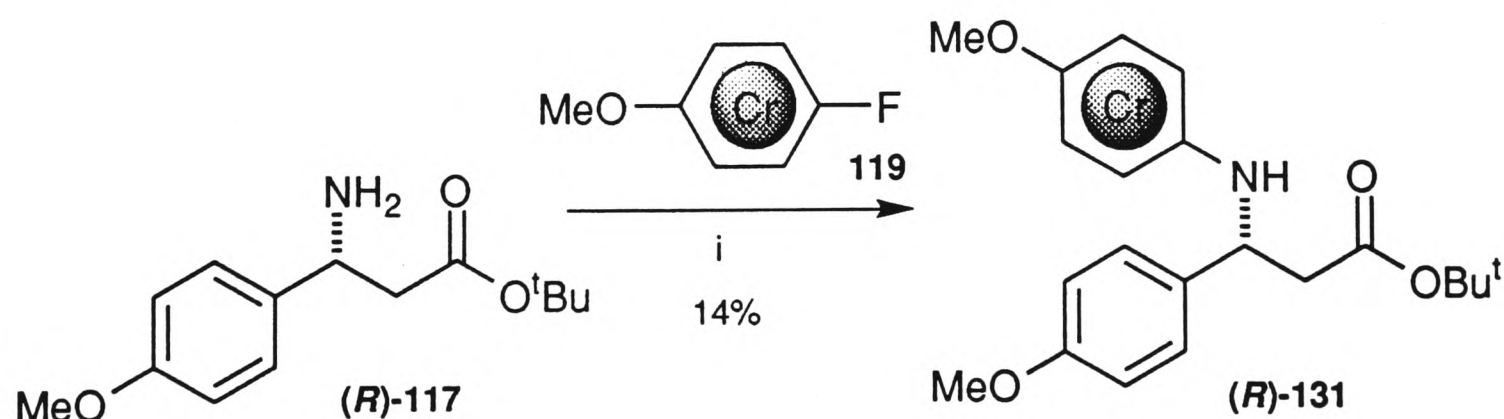
postulated that the addition reaction did occur but was followed by concurrent elimination of the amide, due to its good leaving group ability.



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

8.5 Asymmetric synthesis of (3*R*)-[η^6 -*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.



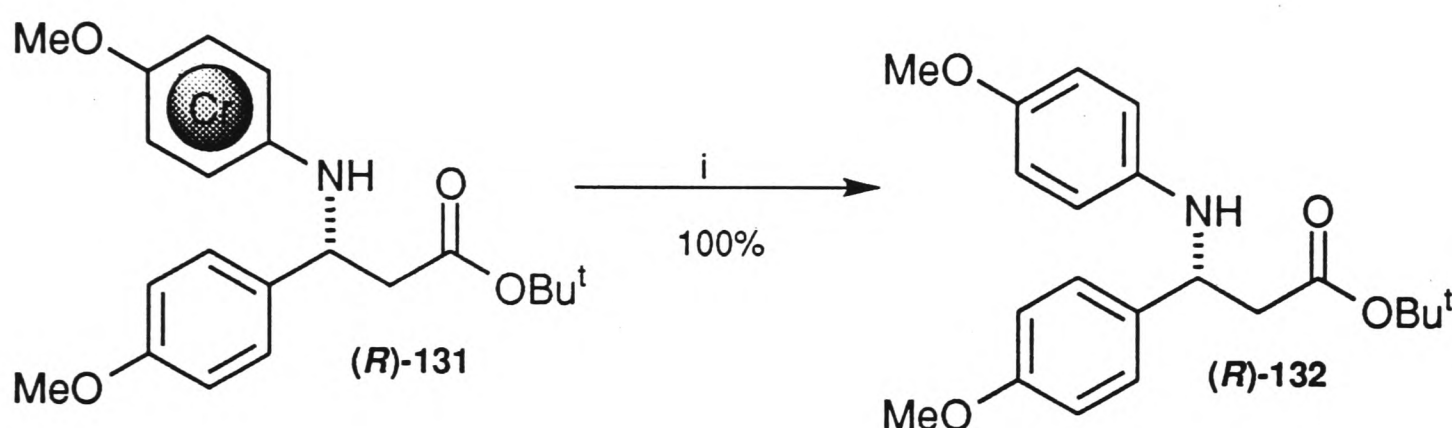
Scheme 73: Reagents : i) 119, quinuclidine, rt, DMF

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 (3*R*)-*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 $\{[\alpha]_{\text{D}}^{22} +16.25$ (c 0.72 in CHCl_3) as a white solid mp 95-96°C (Scheme 74).

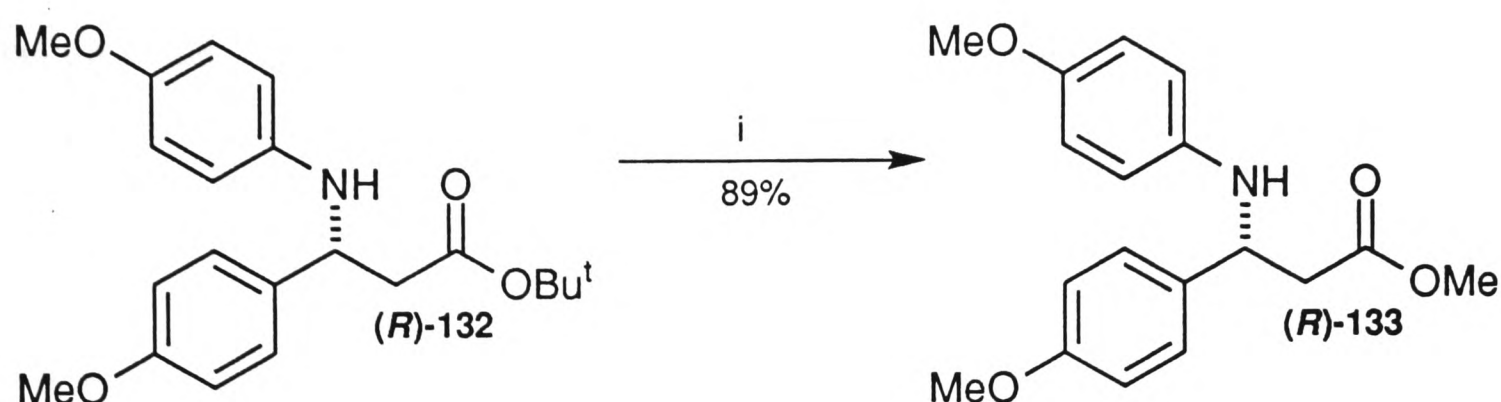


Scheme 74: Reagents : i) $h\nu$, Et_2O

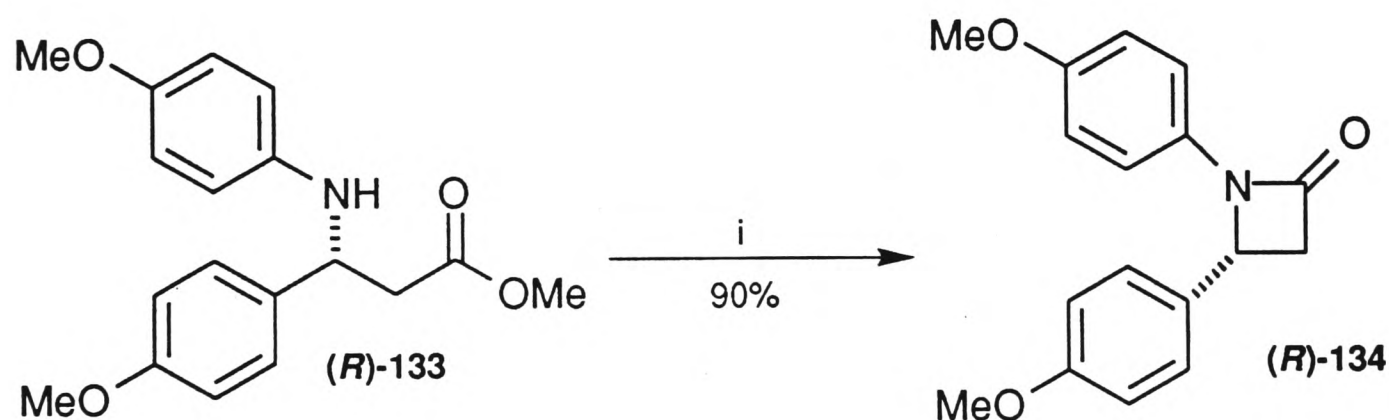
^1H and ^{13}C spectral analysis indicates a shift of 0.34 ppm of the proton at the stereogenic centre and the appearance of two doublet of doublets at 6.53 and 6.70 ppm are indicative of the 4-methoxyaniline ring system. Also a molecular ion peak of $m/z = 210$ (MH^+) helped confirm the structure.

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

Transesterification of **(R)-131** in acidic methanol overnight (Scheme 75) afforded the methyl ester **(R)-133** quantitatively $\{[\alpha]_{\text{D}}^{22} 11.78$ (c 0.28, CHCl_3).

Scheme 75: Reagents : i) MeOH, H⁺

This was confirmed by analysis of the ¹H nmr spectrum in which the *t*-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 CH₃MgBr in Et₂O at 0°C (Scheme 76) gave the β-lactam **(4R)-(134)** {[α]_D²² +98.46, (*c* 0.65, CHCl₃)} in 89% yield, upon work-up and column chromatography.

Scheme 76: Reagents : i) MeMgBr, 0°C, Et₂O

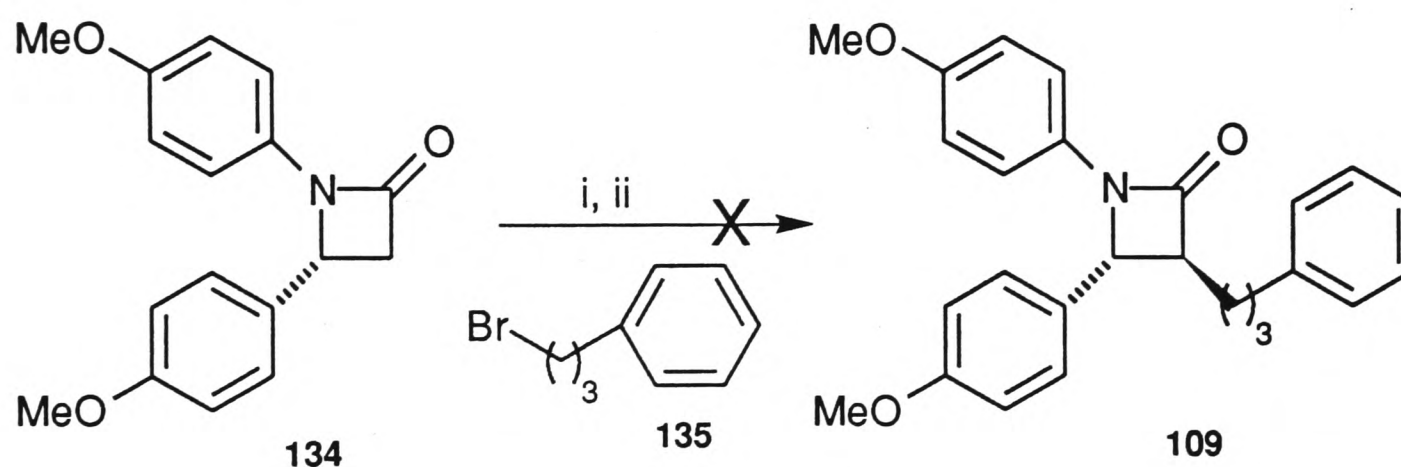
Analysis of the ¹H nmr spectrum, together with a molecular ion peak of *m/z*=284 (MH⁺), confirmed the formation of the **(4R)-β-lactam 134**.

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

To complete the total synthesis of (+)-SCH48461, alkylation of **(4R)-134** at the α-position with alkyl halide **135** had to be investigated. It was envisaged that alkylation at this α-position would occur with some degree of stereoselectivity, owing to the stereogenic

centre at the β -position disfavours 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.



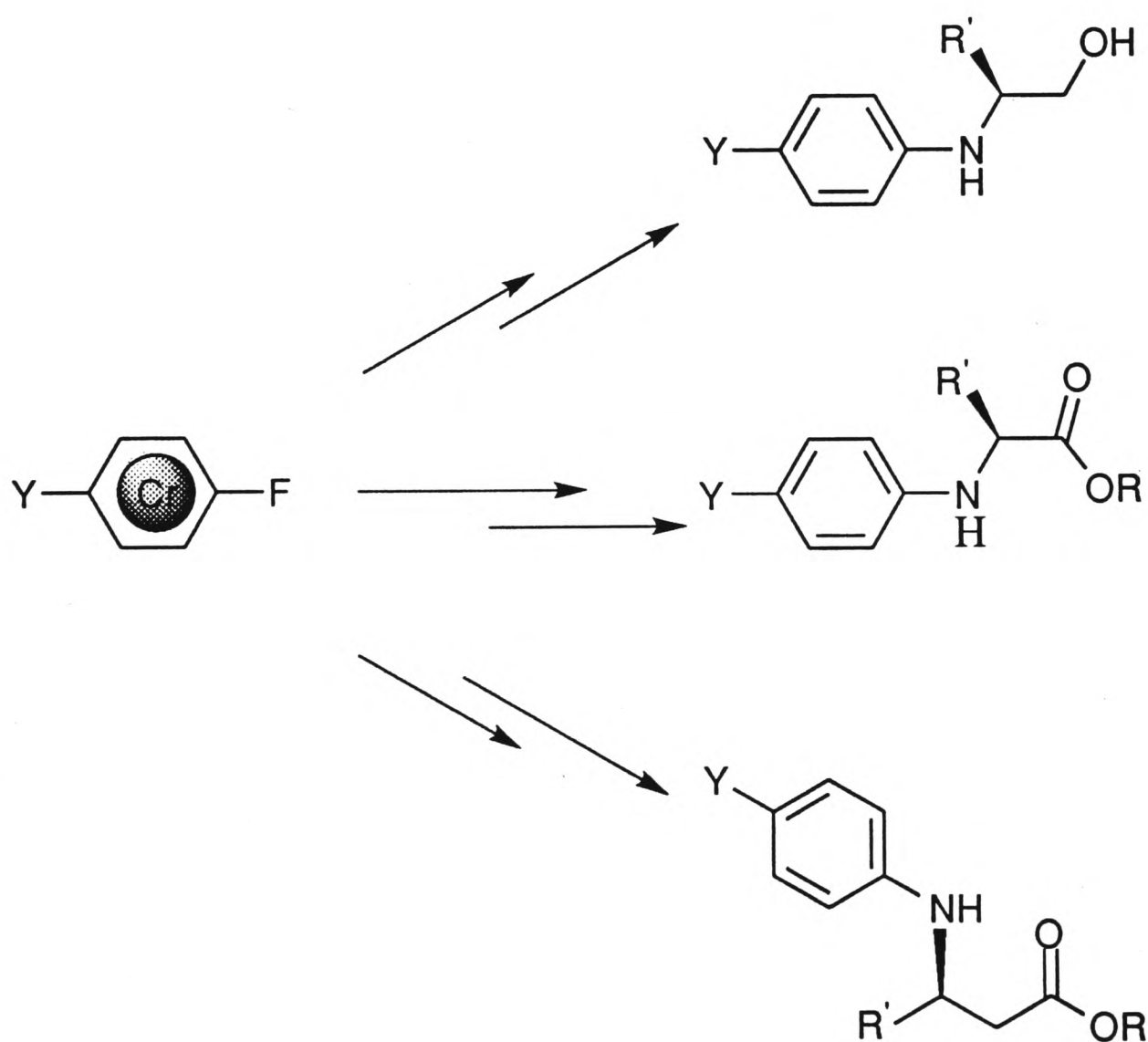
Scheme 77: Reagents : i) (Li or)KHMDS; ii) **135**

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.



Scheme 78

10.0 References

1. D. R. Curtis, J. C. Watkins, *Nature*, 1961, **19**, 1010; P. Rydberg, B. Luning, C. A. Watchmeister, M. Tornqvist, *Acta Chem. Scand.*, 1993, **47**, 813; A. Hubele, Ciba Geigy, Swiss 609,964, *Chem. Abstr.* 1979, **91**, 56594t; J. Abblard, G. Lacroix, Rhone Poulenc Agrochimie, Eur. Pat. Appl. 14,167; *Chem. Abstr.*, 1981, **94**, 776.
2. C. A. Henrick, B. A. Garcia, Zoecon Corp., U.S. 4,243,819; *Chem. Abstr.*, 1982, **96**, 751.
3. J. C. Watkins, *J. Med. Pharm. Chem.*, 1962, **5**, 1187.
4. P. S. Portuguese, *J. Med. Chem.*, 1965, **8**, 147.
5. D. F. Biggs, R. T. Coutts, M. L. Selley, G. A. Towill, *J. Pharm. Sci.*, 1972, **11**, 1739.
6. G. Guanti, E. Narisano, L. Banfi, *Tetrahedron Lett.* 1987, **28**, 4331; G. Guanti, E. Narisano, L. Banfi, *Tetrahedron Lett.* 1987, **28**, 4335; F. Dardoize, J. Moreau, M. Gaudemar, *Bull. Chim. Fr.*, 1973, **5**, 1668; C. Palomo, J. M. Aizpurua, R. Urchegui, M. Iturburu, A. O. Retana, C. Cuevas, *J. Org. Chem.*, 1991, **56**, 2244; S. Kano, S. Shibuya, T. Ebata, *J. Chem. Soc. Perkin Trans. 1*, 1982, 257.
7. J. Sanger, *J. Biochem.*, 1945, **39**, 507; A. Levy, *J. Am. Chem.*, 1955, **77**, 2899.
8. F. Effenberger, U. Burkard, J. Willfahrt, *Leibigs Ann. Chem.*, 1986, 314.
9. F. Effenberger, U. Burkard, J. Willfahrt, *Angew. Chem. Int. Ed. Engl.*, 1983, **22**, 65.
10. M. P. Paradisi, A. Romeo, *J. Chem. Soc. Perkin Trans. 1*, 1977, 596.
11. J. F. Klebe, H. Finkbeiner, *J. Am. Chem. Soc.* 1968, **90**, 7255.
12. K. Koh, *Tetrahedron Lett.* 1993, **34**, 4473.
13. M. Sato, *Chem Pharm Bull.*, 1990, **38**, 393.
14. D. Burnett., *Tetrahedron Lett.*, 1994, **35**, 7339.
15. A. Abiko, S. Masamune, *Tetrahedron Lett.* 1992, **33**, 5517.
16. C.A.L Mahaffy and P. L. Pauson, *Inorg. Synth.*, 1979, **19**, 154.
17. S. G. Davies, W. E. Hume, *Tetrahedron Lett.* 1995, **36**, 2673.
18. J. F. Bunnet, H. Hermann, *J. Org. Chem.* 1971, **36**, 4081.
19. R. Roeske, *J. Org. Chem.*, 1963, **28**, 1251.
20. S. G. Davies and O. Ichihara, *Tetrahedron Asymmetry*, 1991, **2**, 3483.
21. O. Ichihara, D. Phil. Thesis, Oxford 1994.
22. M. C. Cain, R. P. Cousins, G. Coumbarides, N. S. Simpkins, *Tetrahedron*, 1990, **46**, 523.

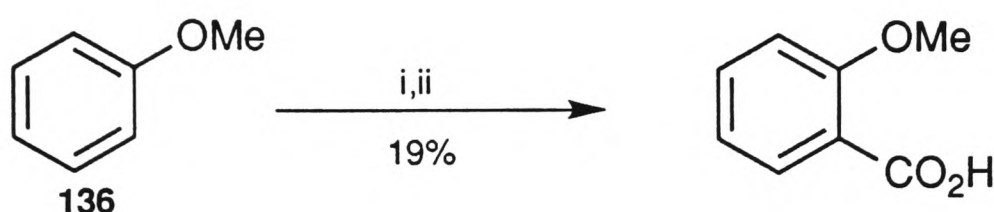
23. M. E. Bunnage, D. Phil. Thesis, Oxford, 1993.
24. J. Sakaki, S. Kobayashi, M. Sato, C. Kaneko, *Chem. Pharm. Bull.*, 1989, **37**, 2952.
25. D. A. Burnett, M. A. Caplen, H. R. Davis, R. E. Burrier, J. W. Clader, *J. Med. Chem.* 1994, **59**, 1733.
26. K. S. Chu, G. R. Negrete, J. P. Konopelski, *J. Org. Chem.*, 1991, **56**, 5201.
27. Nakagawa, T. Kawate, T. Kakikawa, H. Yamada, T. Matsui, T. Hino, *Tetrahedron*, 1993, **49**, 1739.
28. G. Wittig, U. Theile, *Ann. Chem.*, 1969, **1**, 726; G. Tsuchihashi, S. Iriuchijima, K. Maniwa, *Tetrahedron Lett.* 1973, **14**, 3389.
29. M. Browne, D. A. Burnett, M. A. Caplan, L. Chen, J. W. Clader, M. Domalski, S. Dugar, P. Pushpavanam, R. Sher, W. Vaccaro, M. Vizio, H. Zhao, *Tetrahedron Lett.*, 1995, **36**, 2555.

Chapter 3

3 Introduction to Directed Metallation Chemistry

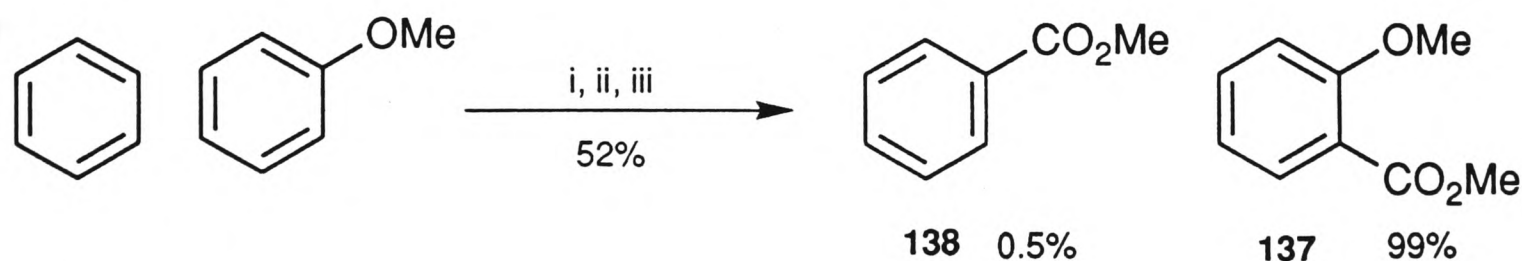
1.0 Regioselective Deprotonation in Electron Rich Aromatic Systems

Since the initial independent discovery by Gilman¹ and Wittig² of *ortho* deprotonation of anisole **136** (Scheme 79) and the commercial availability of alkyllithium in the 1970's, 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),³ 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 10² 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.⁴

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.

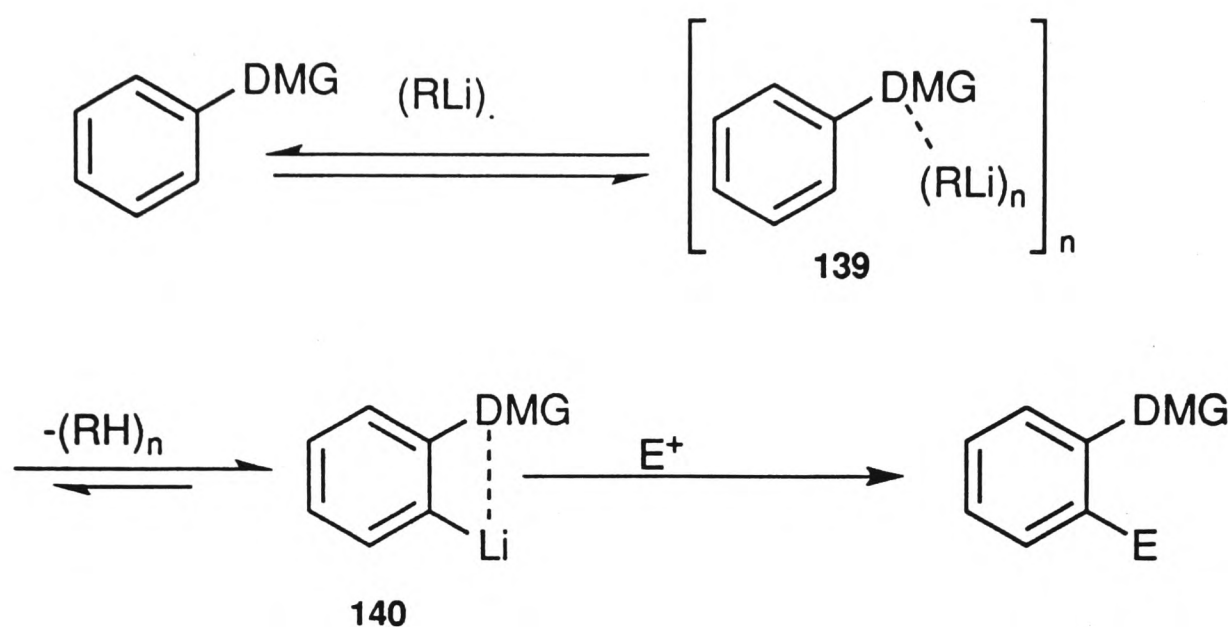
1.2.1. Coordination Mechanism

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 measured⁶ and the enthalpies of 2-lithiated aryl ethers are calculated as being ca.20 KJ/(mol RLi) lower than their 4-lithiated isomers.⁷



Scheme 81

It has been proposed⁸ that in the case of anisole, the availability of the pair of electrons on the methoxyl group is decreased due 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.

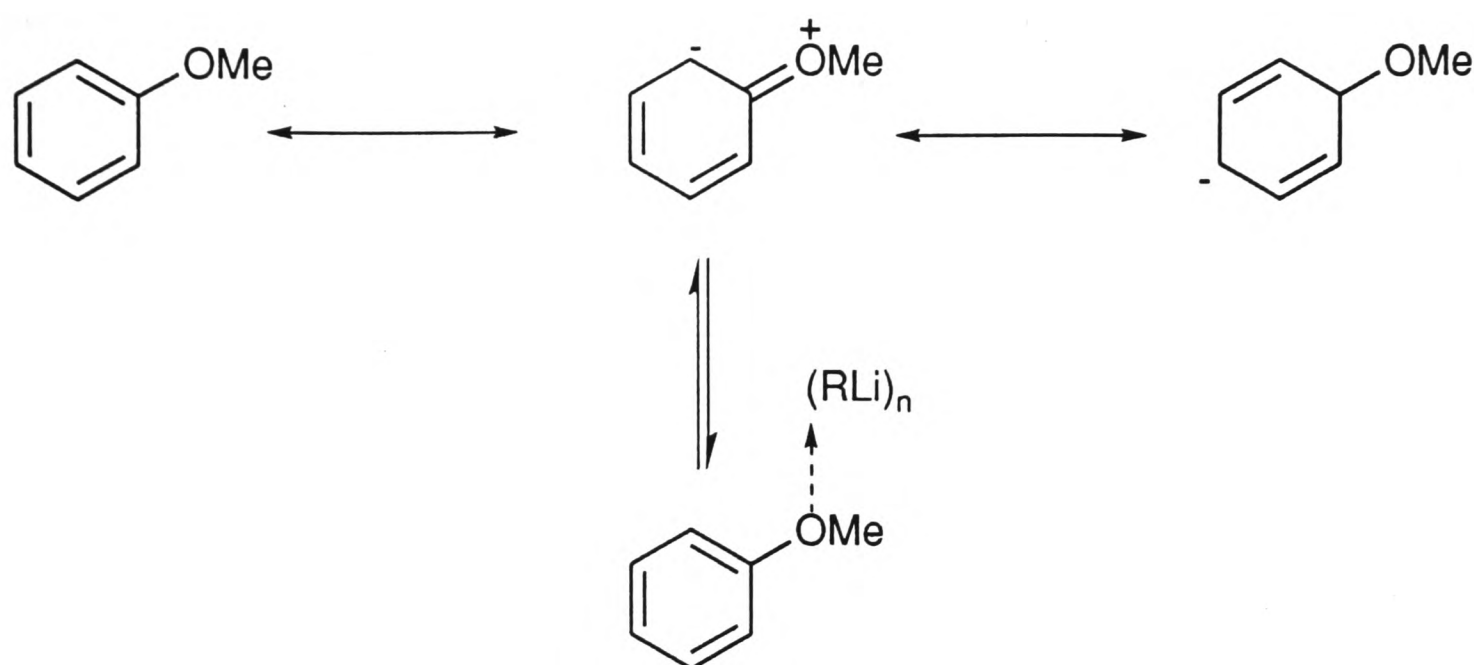


Figure 11

In order to discover the role that coordination plays in the deprotonation of anisole, Slocum *et al*⁹ performed metallation studies on an anisole derivative whose ability to chelate to the alkyllithium was reduced. *o*-*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.

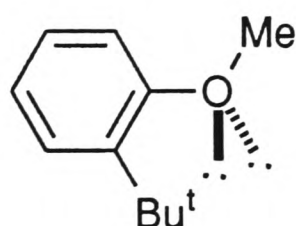
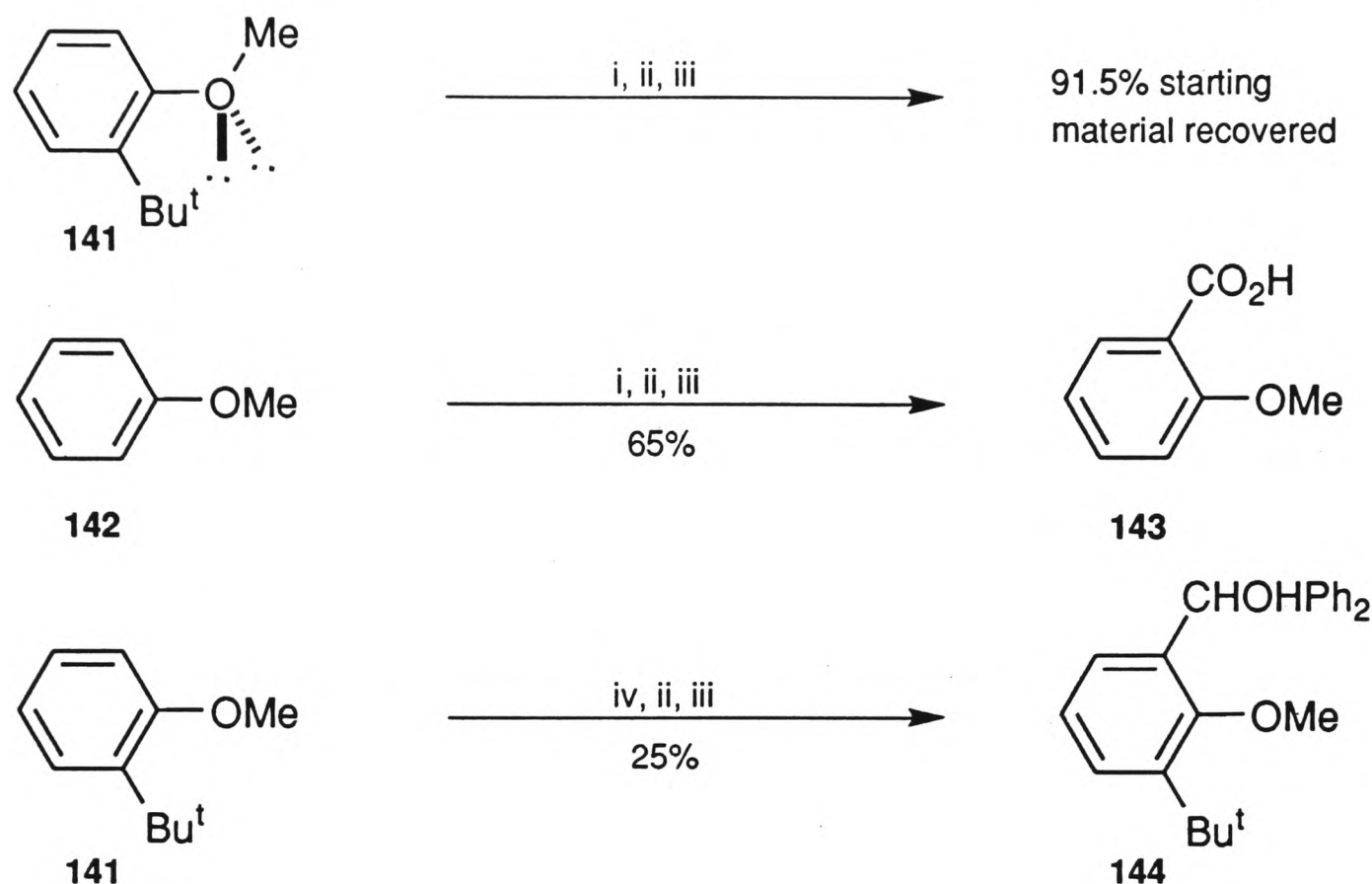


Figure 12

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 concluded from this that deprotonation didn't occur with *n*-BuLi due to the failure of the alkyllithium 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.

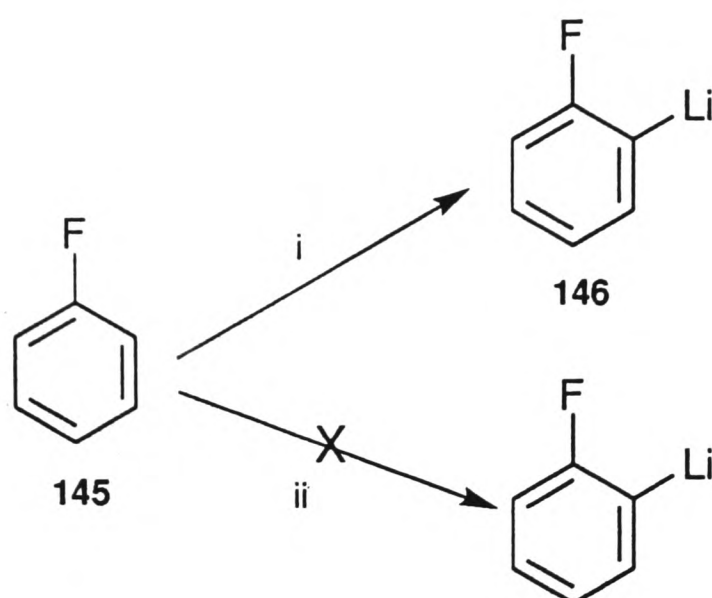


Scheme 82: Reagents : i) *n*-BuLi; ii) CO₂; iii) H⁺, H₂O; iv) *n*-BuLi/TMEDA

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.

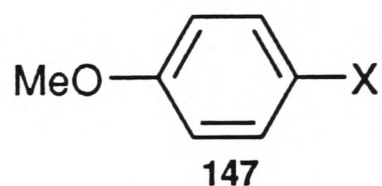
A prime example of deprotonation by an inductive mechanism can be seen in the work carried out by Bauer¹⁰ on the *ortho* deprotonation of fluorobenzene **145** (Scheme 83). When **145** is treated with 1 equiv. of *n*-BuLi in toluene-d₈, ⁶Li, ¹H Hoesy experiments and the ¹³C nmr spectrum show no co-ordination of the alkyllithium to fluorobenzene. On addition of 1 equiv. of TMEDA to the reaction, ¹H and ¹³C nmr spectra still showed no co-ordination of the alkyllithium to the fluorine atom, however deprotonation occurs slowly to form the *O*-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-*d*₈; ii) *n*-BuLi, toluene-*d*₈

1.3 DMG

The ability of substituents on aromatic ring systems to act as directed metallation groups have been thoroughly investigated.⁴ 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 Slocum¹¹ have determined the relative strength of a range of DMGs by intramolecular competition reactions using 4-methoxyphenyl derivatives **147** (Figure 13). The order of the directing ability was determined as:



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

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,¹² 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,¹³ however on addition of THF, this is converted into an equilibrating mixture of solvated tetramer **148** and dimer forms **149** (Figure 14)¹⁴. The proportion of the dimer structure is said to increase with a decrease in temperature and is readily distinguished below -60°C by ⁶Li, ¹H nmr studies.^{14,15}

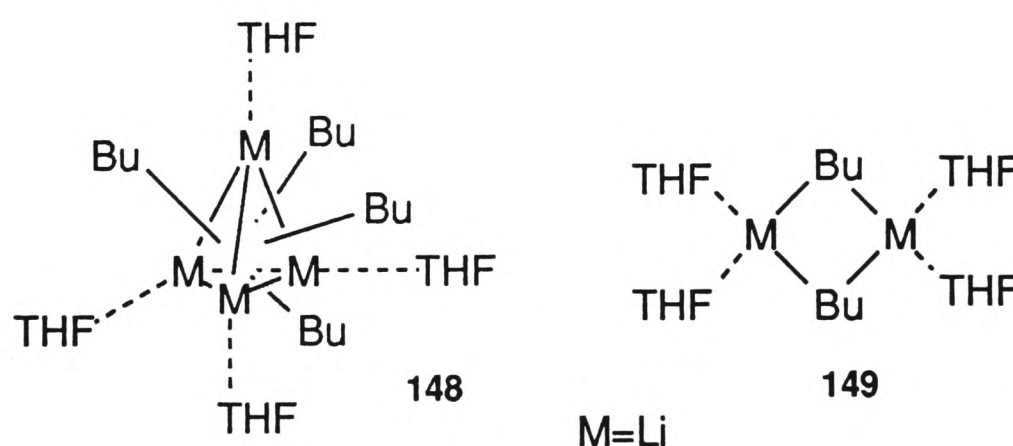
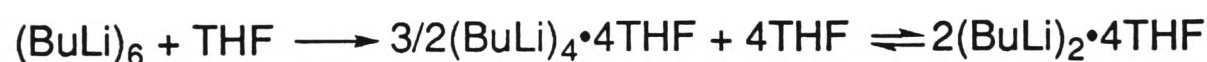
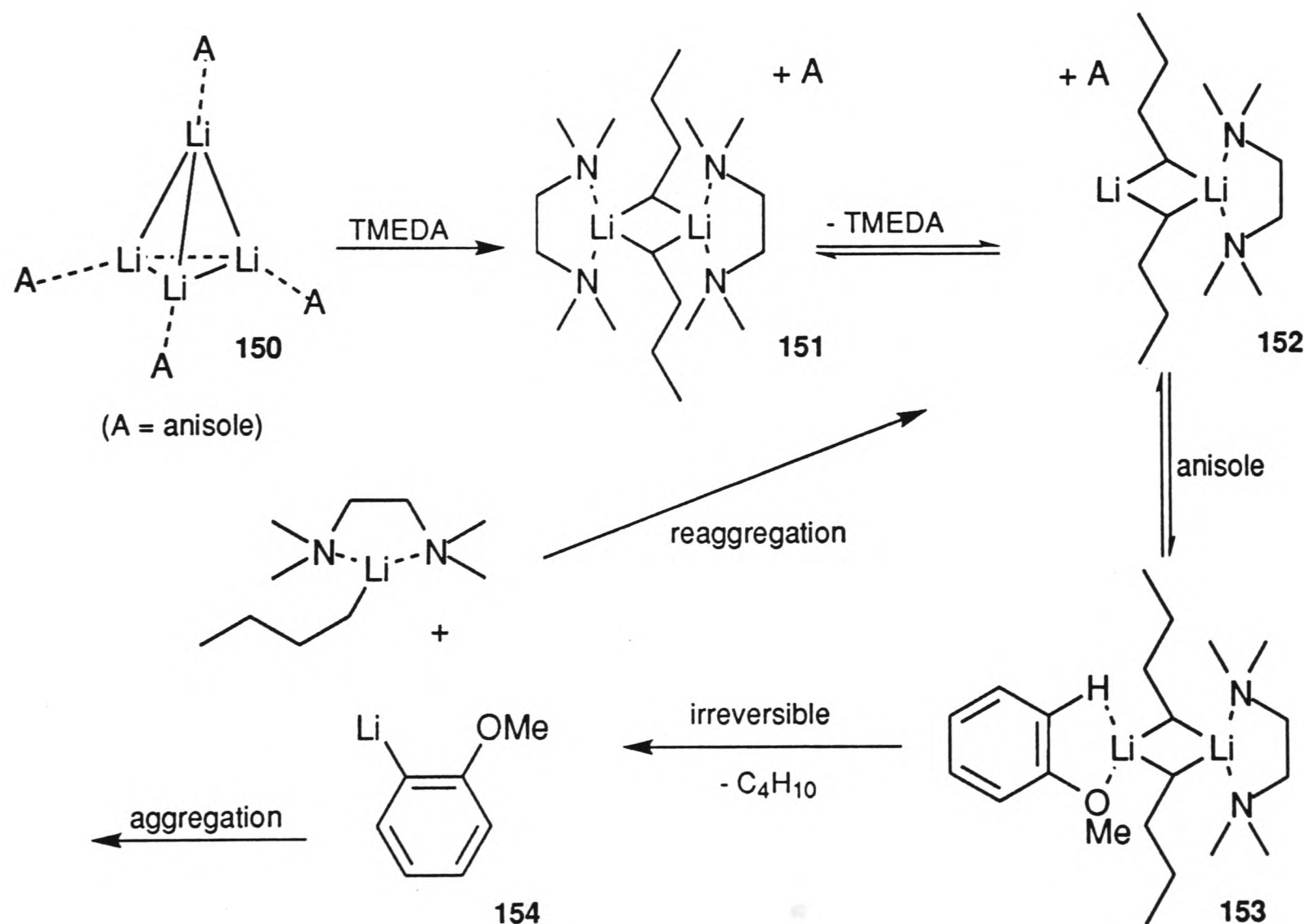


Figure 14

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 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*¹⁰ using nmr and MNDO calculations. Analysis of the ⁶Li, ¹H 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**. ¹³C, 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 ¹H nmr shows anisole as being uncomplexed. ⁶Li, ¹H Hoesy now shows only aggregation between TMEDA and butyllithium and rapid deprotonation occurs.



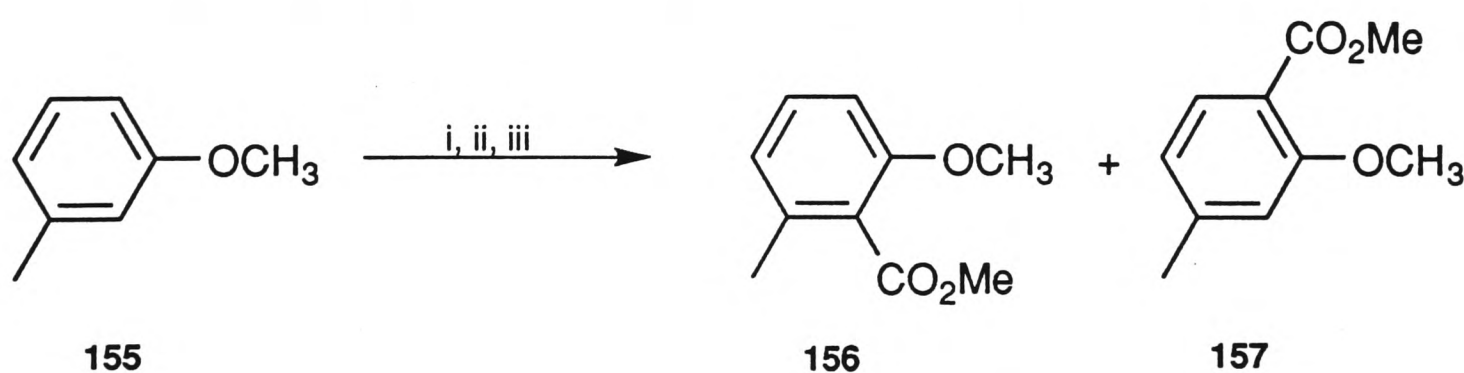
Scheme 84

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).¹⁰ 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

Table 1

entry	RLi	Solvent	oligomer	(156) %	(157) %
1	<i>n</i> -BuLi	cyclohexane	hexamer	09	91
2	<i>n</i> -BuLi	Et ₂ O	dimer/ tetramer	39	61
3	<i>t</i> -BuLi	cyclohexane	tetramer	30	70
4	<i>n</i> BuLi/TMEDA	Et ₂ O	monomeric	47	53

Shirley suggested that since the alkyllithiums 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 alkyllithium 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**).

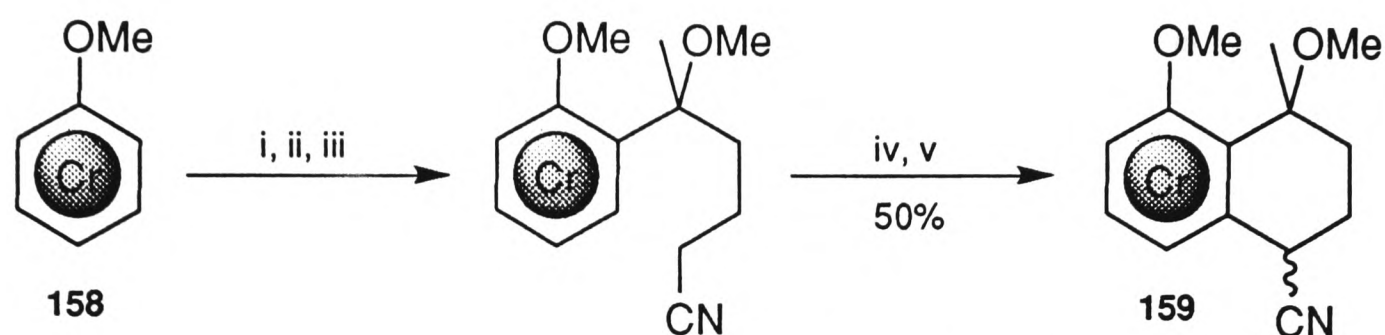
In comparing the deprotonation rates of *n*-BuLi and *t*-BuLi at the more hindered C-2 site, it is noted that *t*-BuLi deprotonates to a greater extent, **156** (30%) (**Table 1, Entry 3**) than that of *n*-BuLi **156** (9%) (**Table 1, Entry 1**). This is in contrast to what you would expect as *t*-BuLi 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 monomer²³ 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

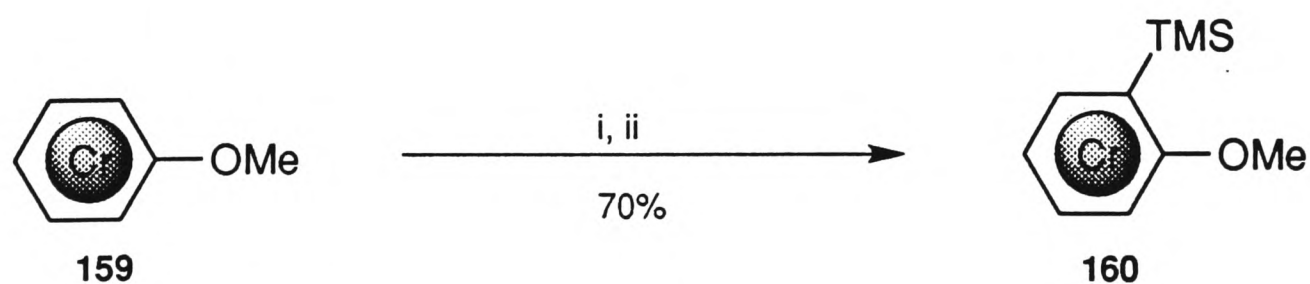
Over the past three decades there has been considerable interest in the novel properties imparted on arene systems complexed to the electron withdrawing chromium tricarbonyl unit. This moiety activates the ring system towards nucleophilic addition and metallation by alkyllithiums.²⁴ It is the ease at 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

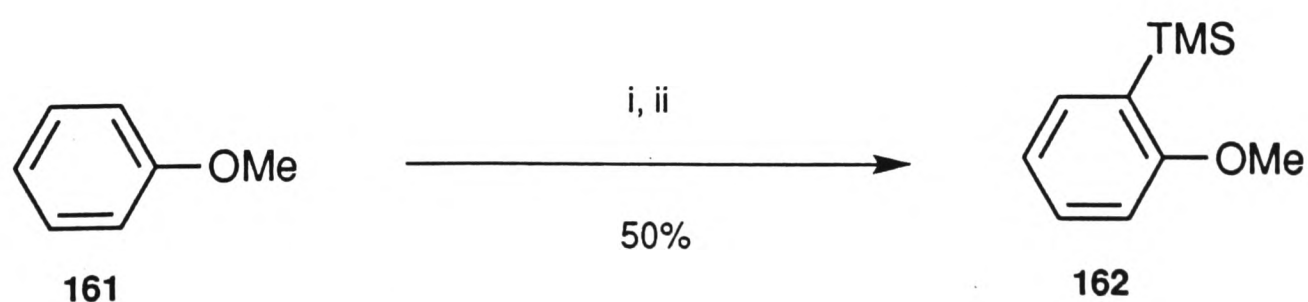


Scheme 86: Reagents : i) *n*-BuLi; ii) CH₃CO(CH₂)₃CN; iii) CH₃I, iv) LiNR₂; v) I₂

Considerable interest has been shown in the ease with which the system undergoes both ring²⁷ 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°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 formed⁸ (Scheme 88).

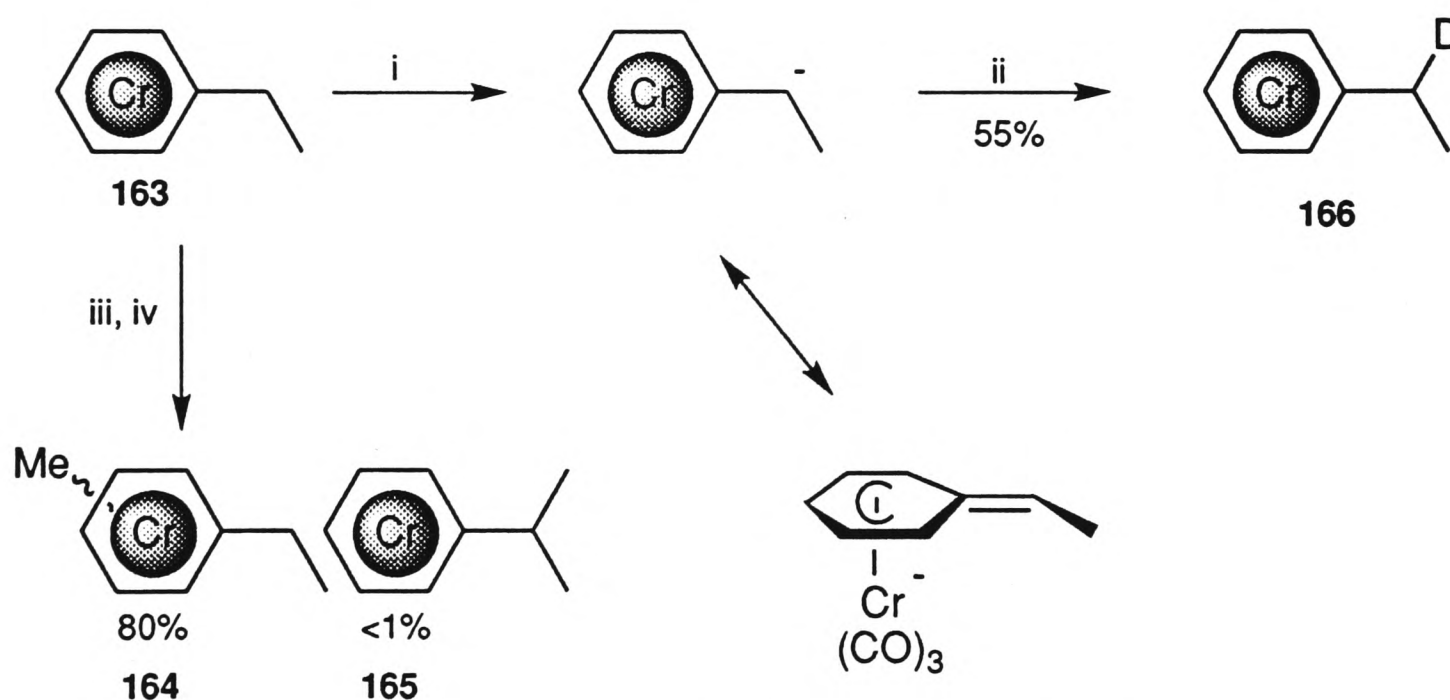


Scheme 87: Reagents : i) *n*-BuLi, Et₂O, 0.5h, -35°C; ii) TMSCl



Scheme 88: Reagents : i) *n*-BuLi, Et₂O, 24h, 25°C; ii) TMSCl

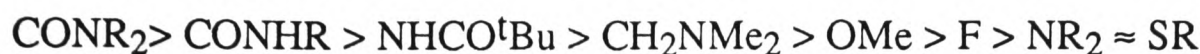
In the free arene, the benzylic protons are kinetically 150 times more acidic than the arene protons,³ thus making the metallation of ring protons on alkyl substituted arenes inefficient. However, co-ordination of the $\text{Cr}(\text{CO})_3$ unit to an alkyl substituted arene causes the arene protons to become more kinetically acidic²⁹ while the benzylic protons are thermodynamically more acidic due to resonance stabilisation of the benzylic anion.³⁰ For example, treatment of (ethylbenzene) $\text{Cr}(\text{CO})_3$ **163** with 8 equiv. of $n\text{-BuLi}$ at -20°C gives predominantly arene metallation **164** (80%) and a small amount of benzylic metallation **165** (<1%)²⁹ whereas the use of $t\text{-BuOK}$ in DMSO at room temperature gives rise to exclusive benzylic deprotonation to afford **166** (55%) upon electrophilic quench with $(\text{CD}_3)_2\text{CO}$ (Scheme 89).³¹ Thus enabling the selective deprotonation of protons on alkyl substituted arenes by altering the conditions and bases used.



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

iii) 8 equiv $n\text{-BuLi}$, THF, -20°C ; iv) MeI

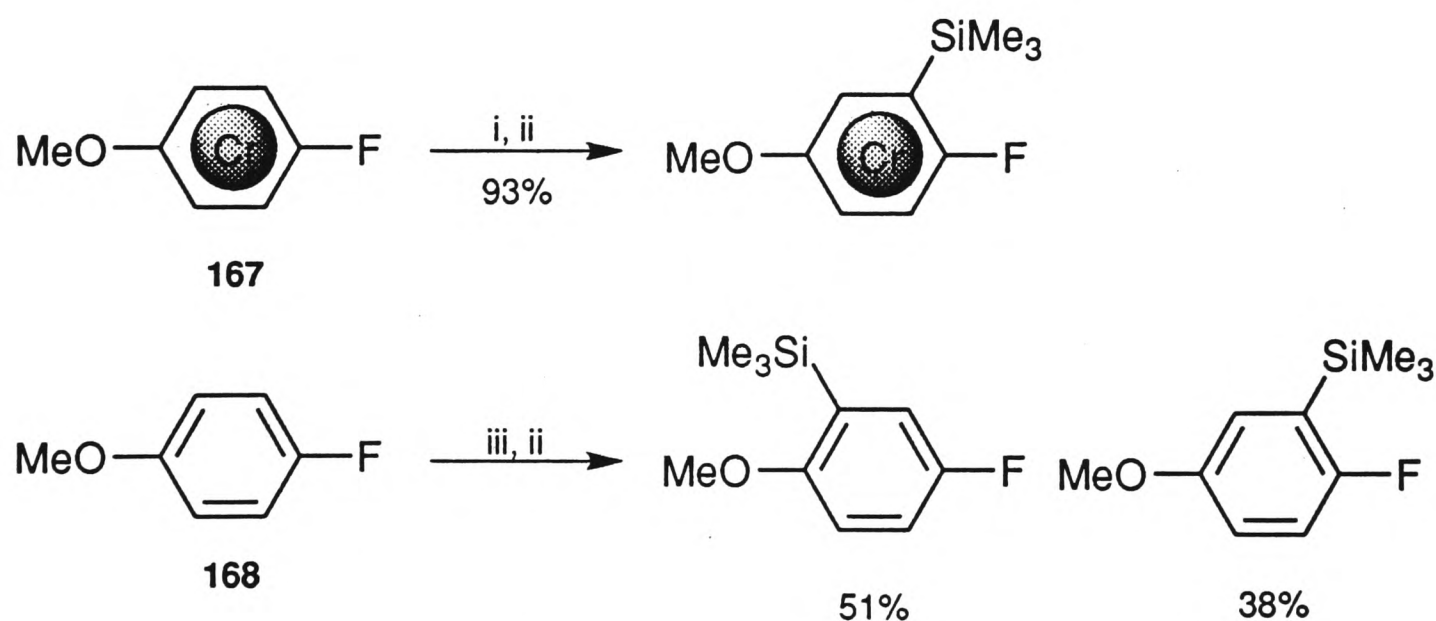
Widdowson has investigated the *ortho* directing ability of a number of heteroatoms on substituted arene complexes. However, the sequence of their *ortho* directing abilities has been shown to be different from those on the free parent molecule.^{32,33,34,35} The general order^{4,16,36} of *ortho* directing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

Uncomplexed

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

Complexed

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 **167**. It was revealed that in the deprotonation of **167** with *n*-BuLi, deprotonation occurred exclusively *ortho* to the fluorine atom, not *ortho* to the methoxyl group as observed in the free arene **168** (Scheme 90).



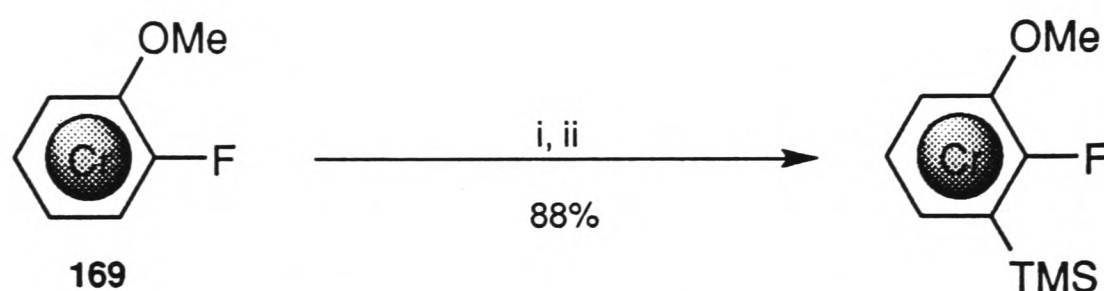
Scheme 90: Reagents : i) 1 eq. *n*-BuLi, THF, -78°C, 0.75 h; ii) TMSCl

iii) *s*-BuLi, THF, -78°C, 1.5h;

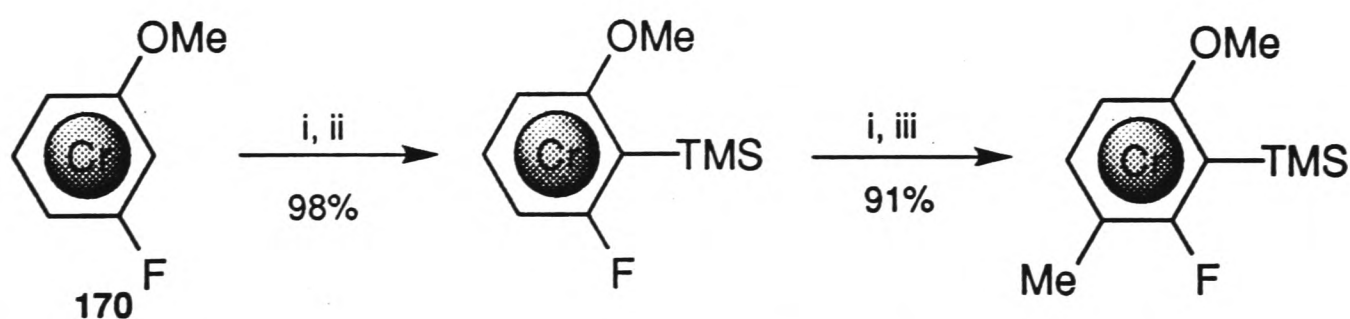
From X-ray analysis of (4-fluoroanisole)Cr(CO)₃ **167**, it is observed that the aryl-oxygen bond becomes shorter, upon complexation, and double bond characteristics develop, due to the mesomeric donation of the lone pair of electrons on oxygen into the arene ring.³³ A slight positive charge develops 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".³⁵ 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.^{33,37}

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).³³



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



Scheme 92: Reagents : i) *n*-BuLi, THF, -78°C; ii) TMSCl; iii) MeI

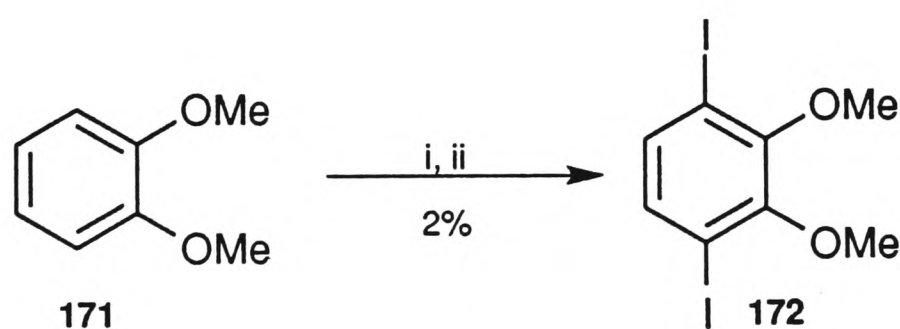
3.0 Introduction to Dimetallation Chemistry

3.1 Dianions in Electron Rich Aromatic Systems

Since the late 1920's the generation of monometallated aromatics has been thoroughly investigated.³⁸ However the generation of dilithiated species constituted until recently, a relatively unknown and underdeveloped methodology in the core area of metallation chemistry^{39, 40} except through their generation via halogen-metal and metal-metal exchange.⁴²

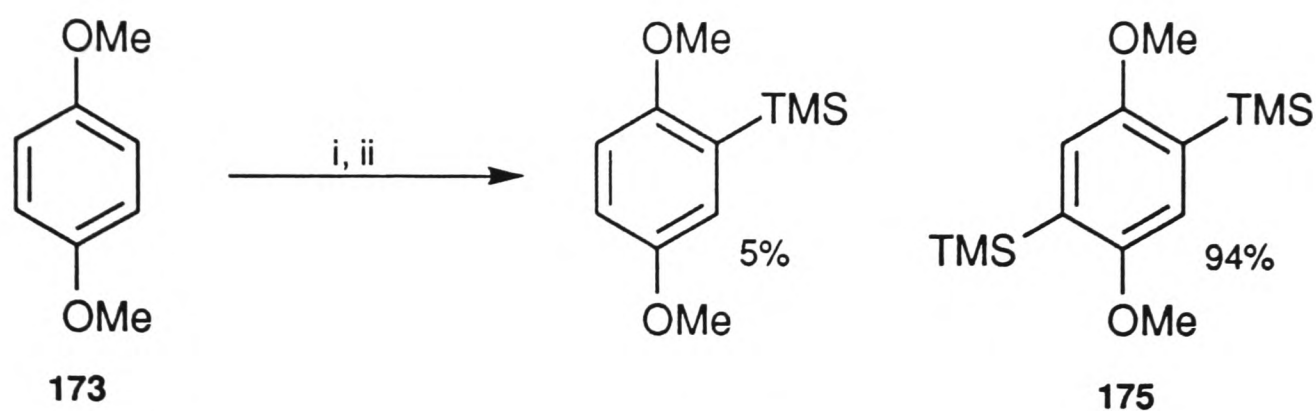
One of the first discoveries of dilithiation of aromatic systems was reported by Bryce-Smith.⁴³ On refluxing phenyllithium with 0.5 equiv. *n*-BuLi for 20h in benzene, it was observed that the aryl lithiated product was formed (5%) consisting of a ration of 2:1 *meta* and *para* dianions.

The dilithiation of aromatic ethers was first discovered by Pring⁴⁴ 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).

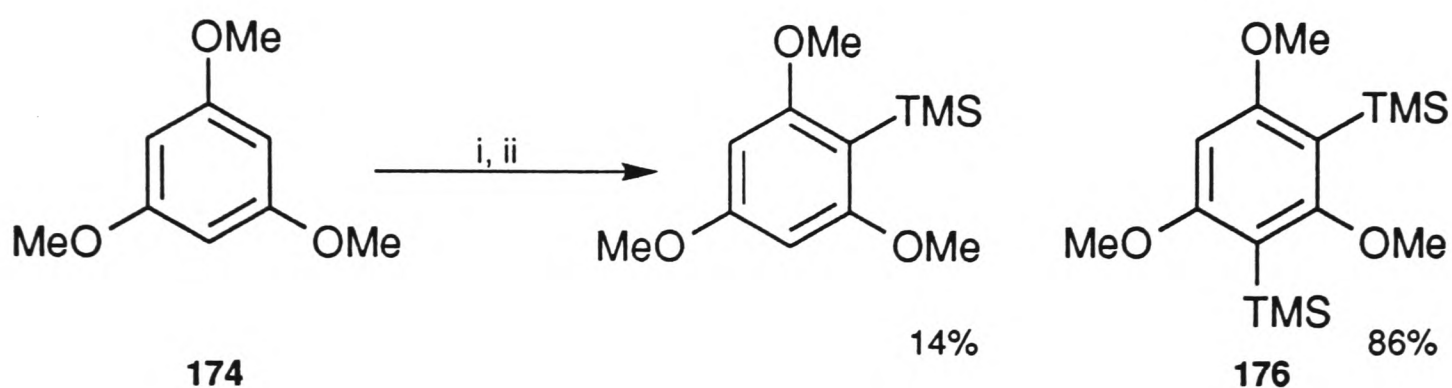


Scheme 93: Reagents : i) 2.5 eq. *n*-BuLi/TMEDA, rt, 20h; ii) I₂

Further research was carried out by Crowther and Cabiddu,³⁹ who noted that a series of aryl ethers gave dianions after stirring in excess alkylolithium 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.

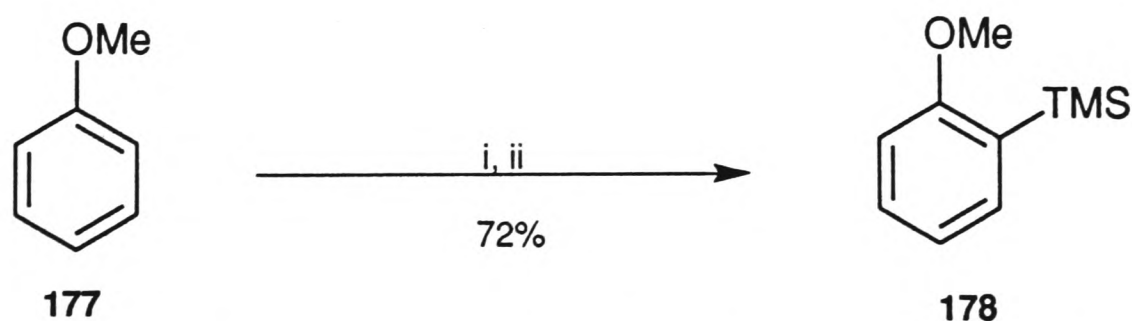


Scheme 94: Reagents : i) 3 eq. *n*-BuLi/TMEDA, hexane, rt, 91h; ii) TMSCl



Scheme 95: Reagents : i) 3 eq. *n*-BuLi/TMEDA, Et₂O, rt, 11h; ii) TMSCl

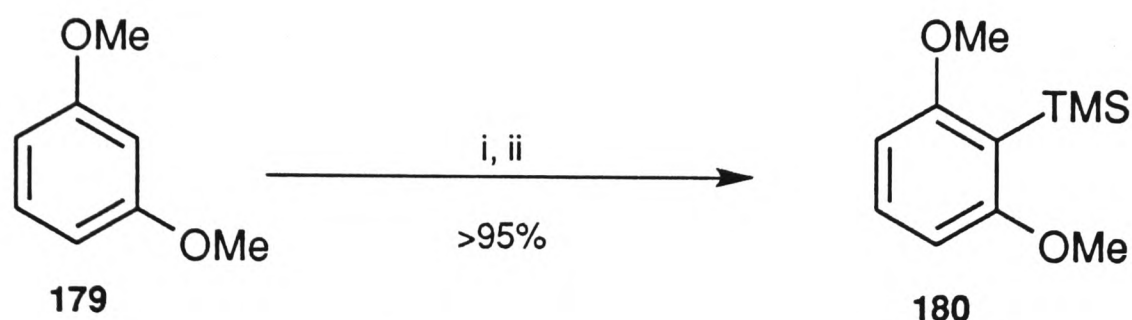
The high yielding dilithiation of **173** and **174** can be looked upon as being due to a kinetic phenomena, where the alkyllithium is able to coordinate freely with each of the methoxyl groups and so generate the dilithiated species. However no dilithiation was observed in the reaction of anisole **177** (Scheme 96) or 1,3-dimethoxybenzene **179** (Scheme 97), which only afforded the monosilylated products **178** and **180** upon reaction with TMSCl.



Scheme 96: Reagents : i) 3.1 eq. *n*-BuLi/TMEDA, rt, 12h; ii) TMSCl

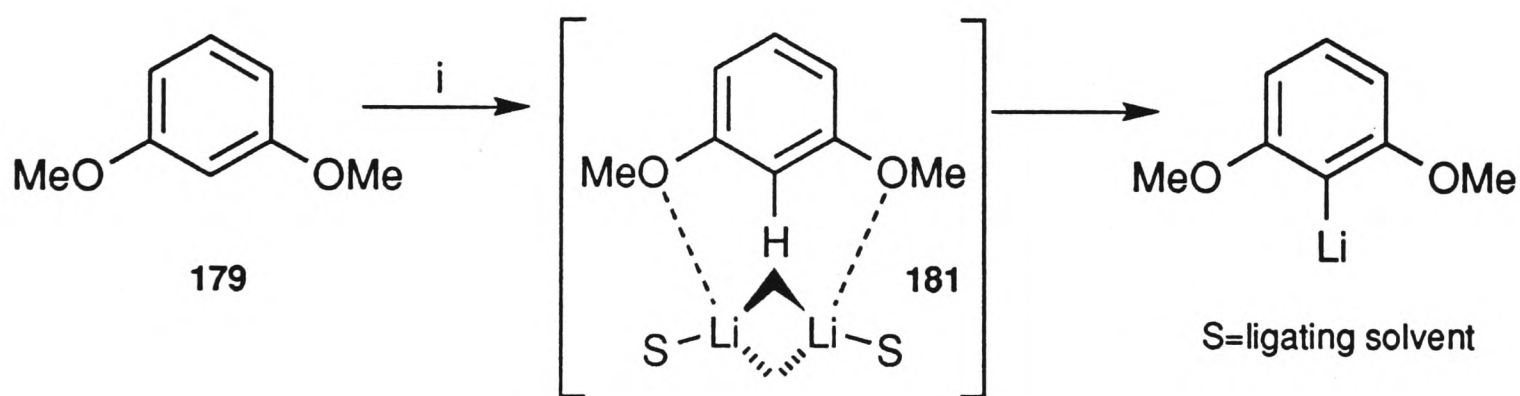
The exclusive monometallation of anisole **177** maybe due to deactivation of the other *ortho* position by the generation of the first metallated species which diminishes the effectiveness of the methoxyl group to chelate to the second alkyllithium for the formation

of a dilithiated species. In the case of the 1,3-dimethoxy species **179**, metallation only occurs at C-2, the most acidic site.



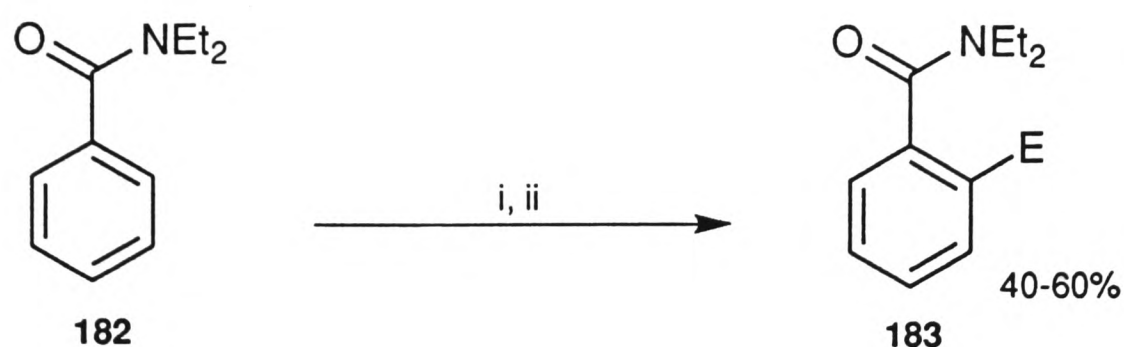
Scheme 97: Reagents : i) 2.1 eq. *n*-BuLi/TMEDA, rt, 11h; ii) TMSCl

Semi-empirical MNDO calculations⁴⁵ for the regioselective deprotonation of **179** by CH₃Li indicates that deprotonation occurs by a tweezer mechanism, whereby both methoxyl groups chelate to the alkyllithium 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 alkyllithium to coordinate to the methoxyl groups as they are already involved in chelation at the first lithiated site.



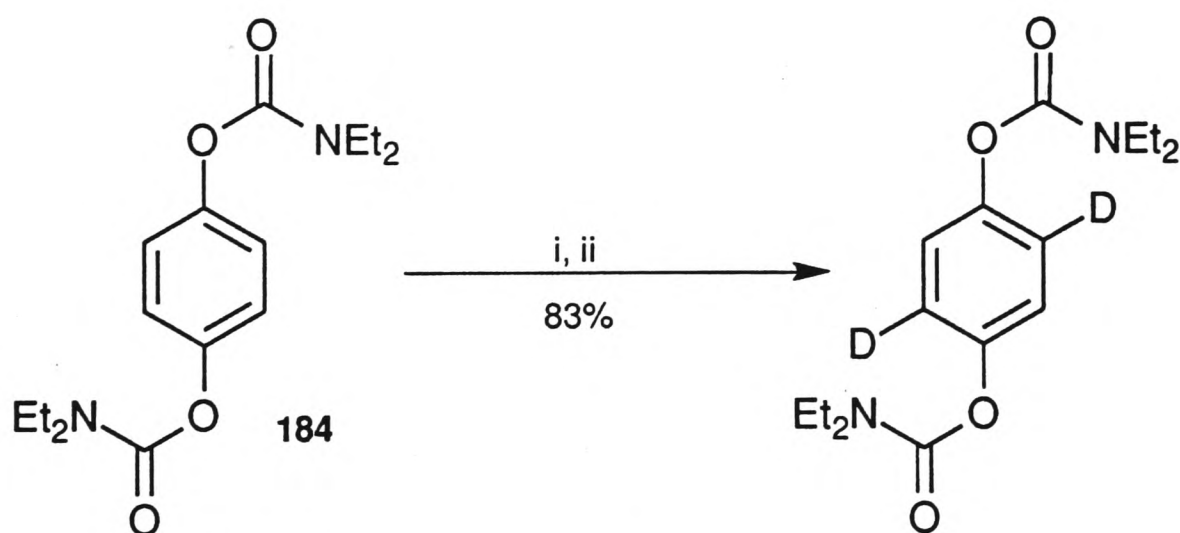
Scheme 98: Reagents : i) CH₃Li

Snieckus⁴¹ 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.



Scheme 99: Reagents : i) 3 eq. *s*-BuLi/TMEDA -78°C; ii) E⁺

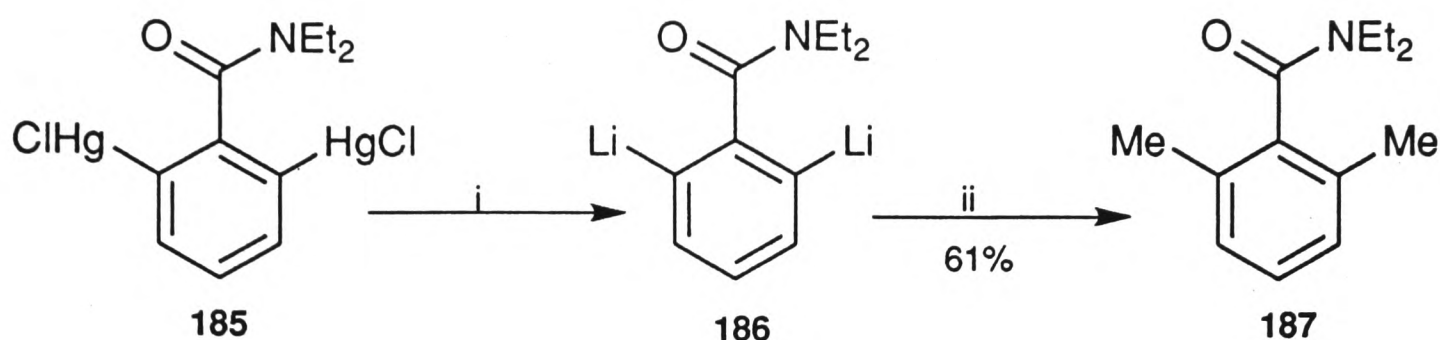
However, it was only Snieckus's investigation of the dimetallation of *O,O'*-aryl dicarbamates **184** that generated dilithiated products in substantial yield,⁴¹ from direct deprotonation with *s*-BuLi (**Scheme 100**). The reason for this was that the first alkyllithium deprotonated *ortho* to the carbamate and deactivated it from further deprotonation thus forcing the second site to occur *ortho* to the other carbamate.



Scheme 100: Reagents : i) 2.2 equiv *s*-BuLi/TMEDA, -78°C; ii) CD₃OD

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.⁴² Eaton⁴⁶ 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**)

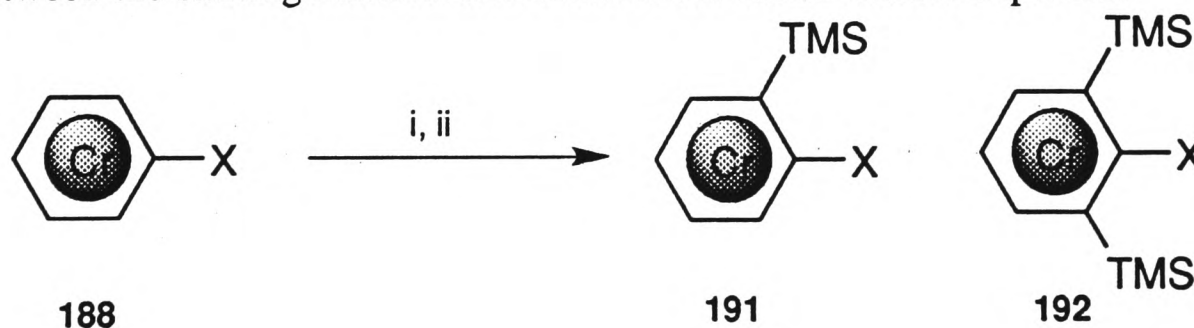


Scheme 101: Reagents : i) 4.4 eq, *n*-BuLi, THF, -60°C; ii) MeI

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.

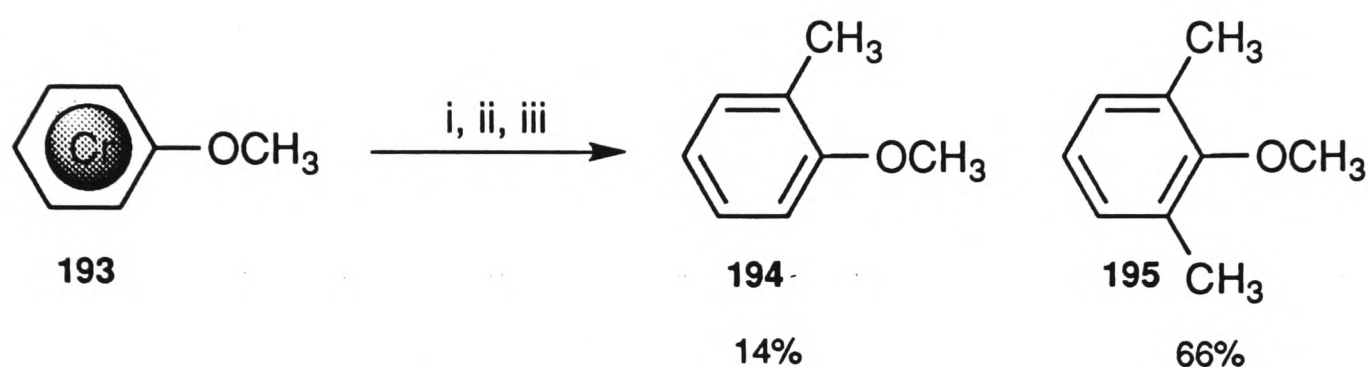


Scheme 102: Reagents : i) BuLi, -35°C, 0.5h; ii) TMSCl

Table 2

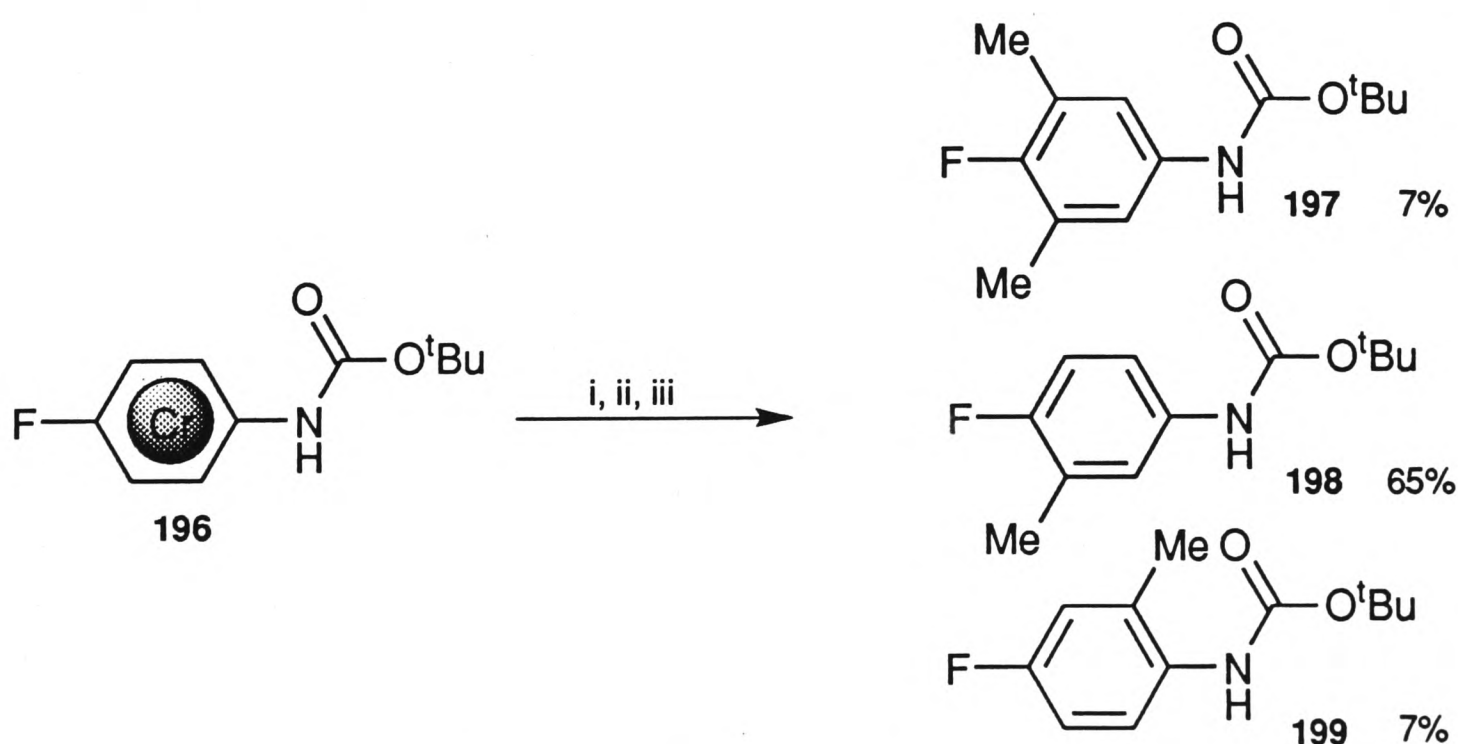
	X	191 (%)	192 (%)
188	OCH ₃	70	10-20
189	F	46	10-20
190	Cl	49	10-20

Card and Trahanovsky²⁹ also observed the formation of the 2,6-disubstituted species **195** in the metallation of (anisole)Cr(CO)₃ **193** with 4 equivalents of *t*-BuLi at -40°C, which afforded the monomethylated species **194** (14%) and the 2,6-dimethylated species **195** (66%) being formed on treatment with MeI (Scheme 104).



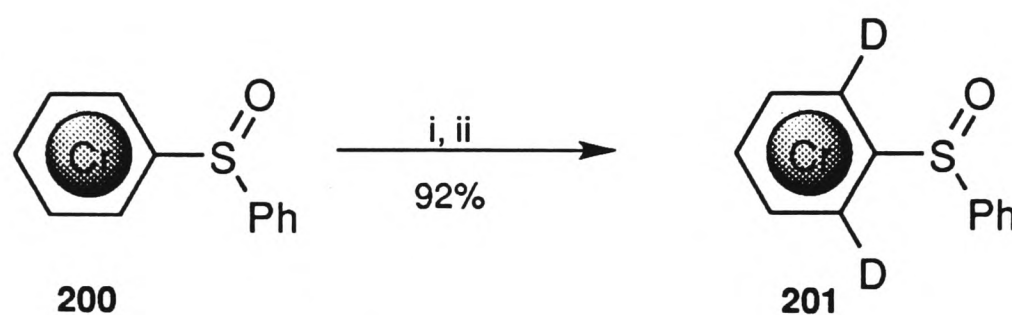
Scheme 103: Reagents : i) 4.0 equiv *n*-BuLi, -40°C; ii) CH₃I; iii) hν

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



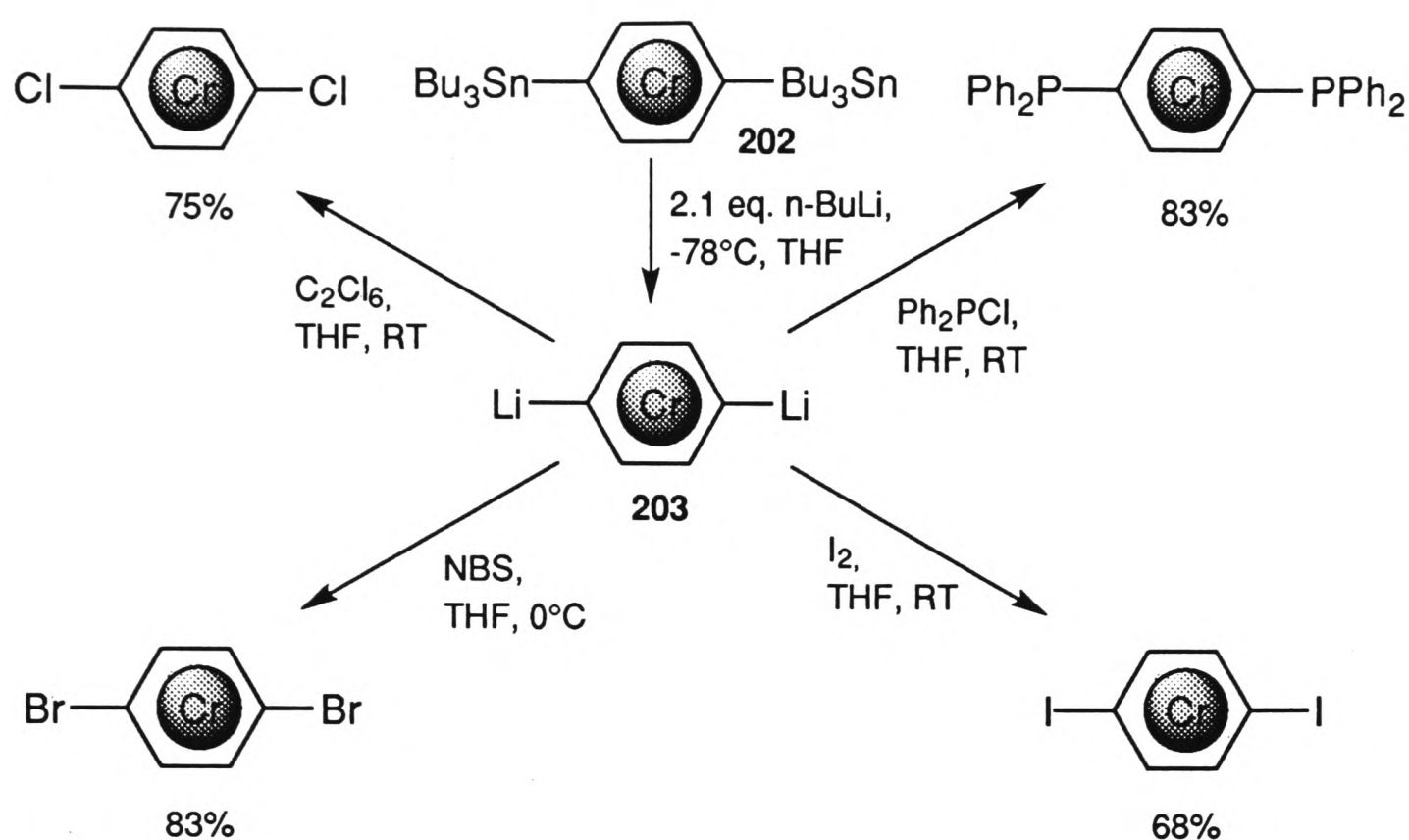
Scheme 104: Reagents : i) 2.2 equiv *n*-BuLi; ii) CH₃I; iii) hν

However, recent research in our group has unequivocally established the formation of dianions on diphenylsulfoxide chromium tricarbonyl complexes under mild conditions (**Scheme 105**).⁴⁷ On reacting the (*S*)-(diphenylsulfoxide)Cr(CO)₃ **200** with two equivalents of LDA, followed by electrophilic quench with CD₃OD, the dimetallated species **201** was obtained in 92% yield. This confirms that dianions had been formed here, since the instantaneous electrophilic quench with CD₃OD of the excess alkyllithium and aryl anion eliminates the possibility of rapid proton transfer or further deprotonation occurring after addition of the electrophile.



Scheme 105: Reagents : i) LDA, -78°C, THF; ii) CD₃OD

Transmetallation has also been used recently in the formation of dianions of arene chromium tricarbonyls.⁴⁹ 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**).



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

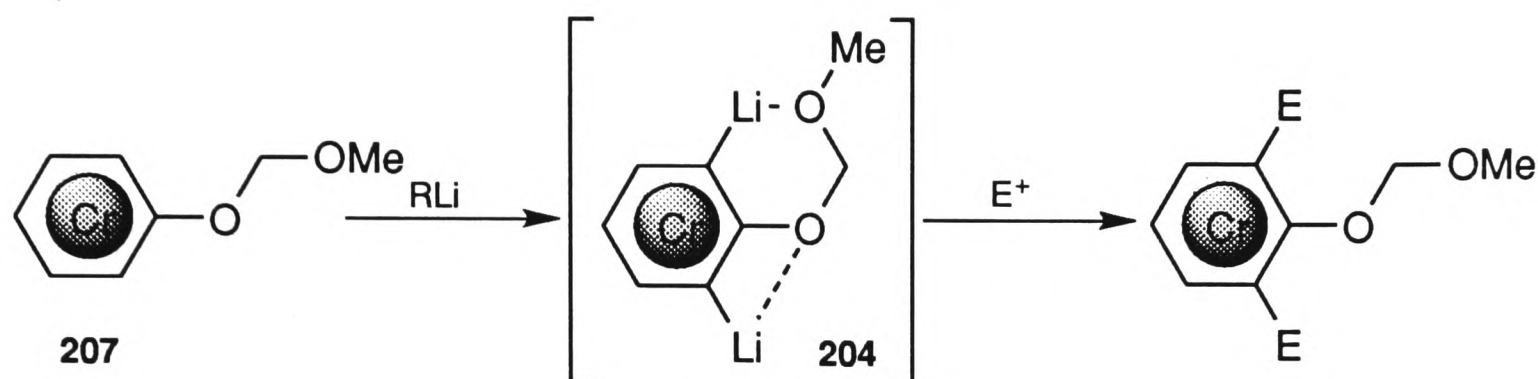
It was envisaged that the electron withdrawing ability of the chromium tricarbonyl moiety, together with the inductive and chelation effects of a DoM group, would enhance dianion formation by increasing the acidity of the arene protons.

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 regioisomers of *meta* and *para* substituted anisole were also investigated.

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

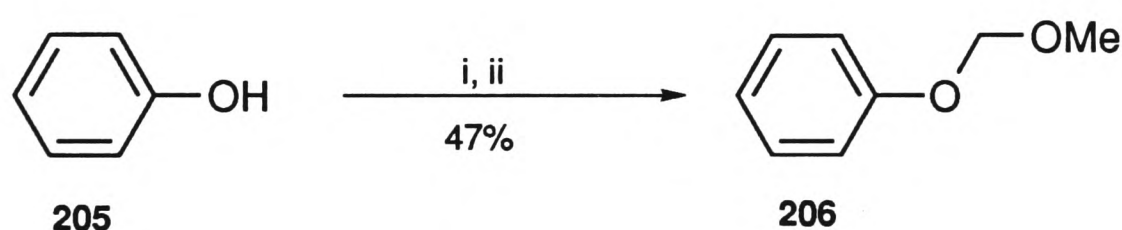
Dianion studies were first investigated using the MOM protected chromium tricarbonyl complex **207** shown in Scheme 107. It was thought that the strong *ortho* directing ability of the MOM group, as well as the availability of two heteroatoms which

could chelate to the metallation sites **204**, would assist in the generation of the dianion at the 2,6-positions (**Scheme 107**).



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**).



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

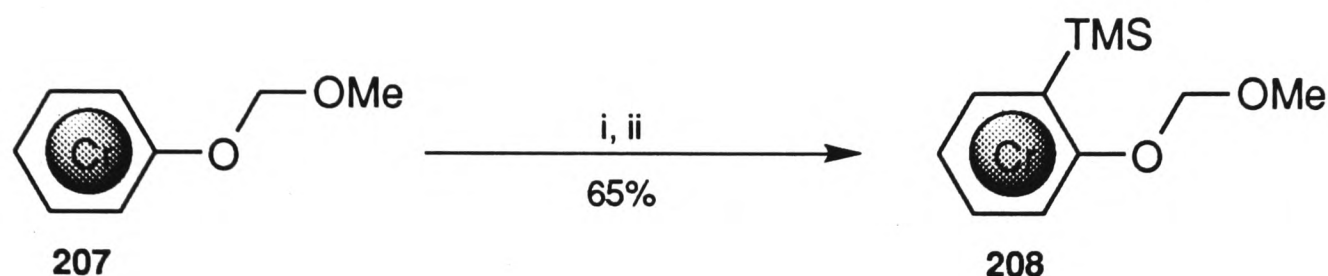
With the protected phenol in hand **206**, this was then heated with chromium hexacarbonyl in a solution of dibutyl ether-THF at reflux for 2 days, in the absence of light. Purification by column chromatography brought about the isolation of **207** as a yellow crystalline solid (m.p. 77-79°C) in 35%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



Scheme 109: Reagents : i) Cr(CO)₆, dibutyl ether-THF

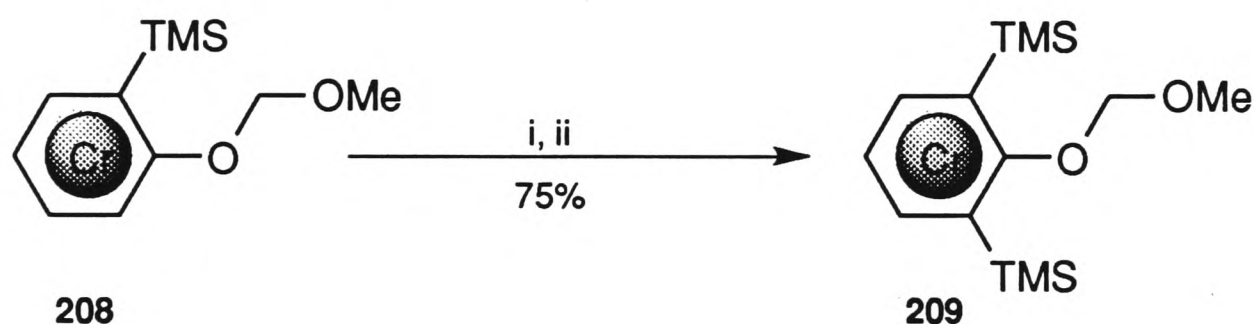
Examination of a stepwise deprotonation was undertaken first to generate the 2,6-disilylated product **209**. The monosilylated compound **208** was readily formed by

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).



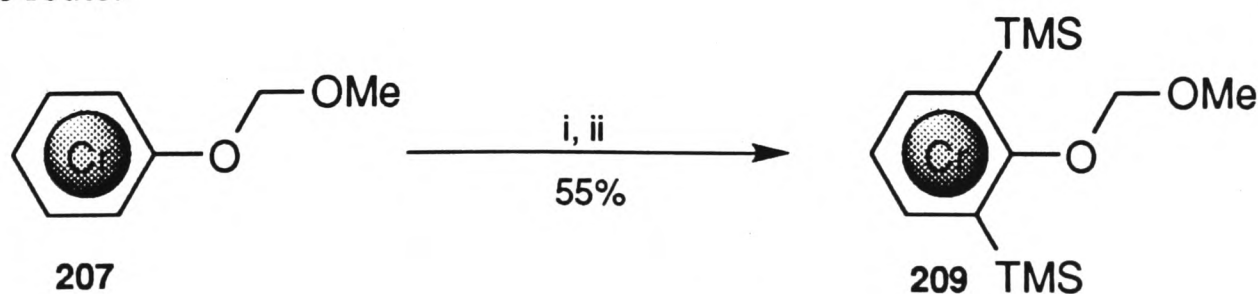
Scheme 110: Reagents : i) 1.0 equiv., *n*-BuLi; ii) TMSCl

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).



Scheme 111: Reagents : i) 1.0 equiv., *n*-BuLi; ii) TMSCl

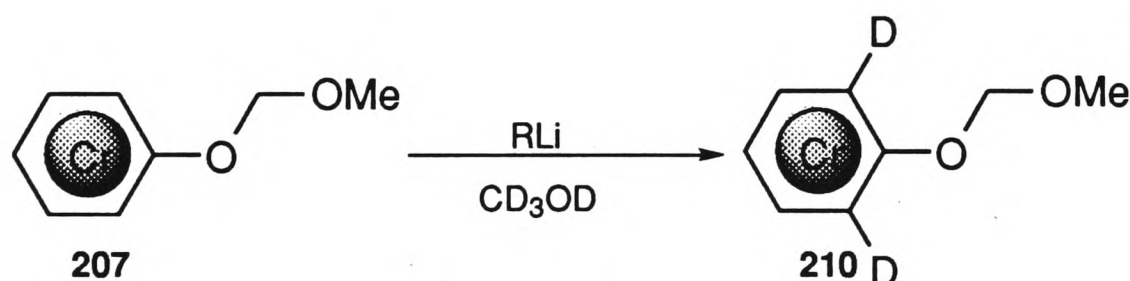
Subsequently, the possible formation of **209** by generation of the 2,6-dianion with excess alkyl lithium and electrophilic quench with TMSCl was examined. On reacting **207** with 3.0 equivalents of *n*-BuLi at -42°C for 3 hours and subsequent quenching with TMSCl, the 2,6-disilylated compound **209** 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.



Scheme 112: Reagents : i) 3.0 equiv. *n*-BuLi; TMSCl

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 metallation during silylation. To prove unequivocally the formation of the 2,6-dianion, the metallation reaction was repeated under similar conditions as before, but was quenched with CD₃OD, which instantaneously quenches both the aryl anions and excess alkyllithiums 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 CD₃OD gave **210** in 99% yield (Scheme 113). The ¹H 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

Table 3

Entry	RLi (equiv.)	2,6-deuterium incorp. (210)	yield
1	<i>n</i> -BuLi (3.0)	97%	99%
2	<i>t</i> -BuLi (5.0)	96%	98%

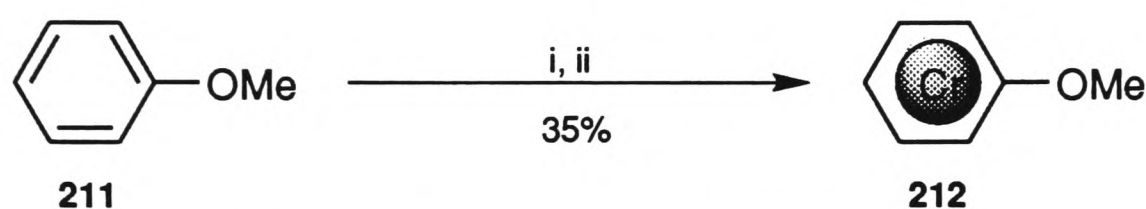
3.3.3 Metallation Studies of (Anisole)Cr(CO)₃ (**212**)

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 alkyllithium followed by electrophilic quench

with either TMSCl or MeI, the possibility of a stepwise deprotonation during the electrophilic quench was not eliminated.

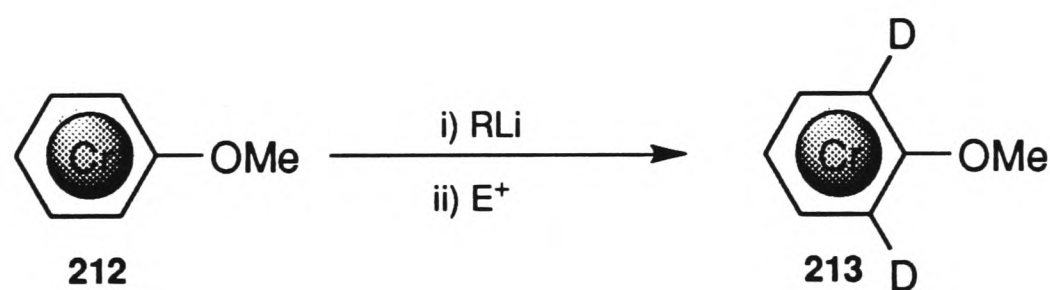
Accordingly, the metallation studies analogous to those described above were performed on (anisole)Cr(CO)₃, to unequivocally prove the generation of dianions on (anisole)Cr(CO)₃.

(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

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

Table 4

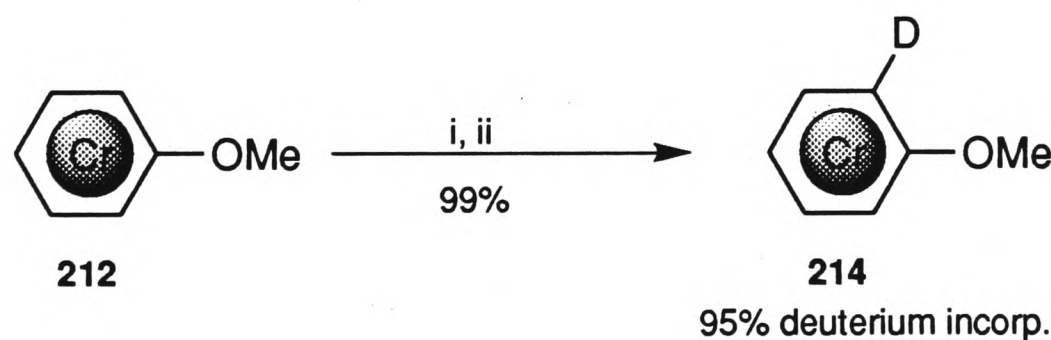
Entry	RLi (equiv.)	E ⁺	2,6-deuterium incorp.	213 yield
1	<i>n</i> -BuLi (3.0)	CD ₃ OD	95%	95%
2	<i>t</i> -BuLi (5.0)	CD ₃ OD	97%	94%

Analysis of the crude ^1H 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_3OD (Scheme 115), **213** was isolated in 94% yield (Table 4, entry 2) and upon examination of the crude ^1H 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) $\text{Cr}(\text{CO})_3$ 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_3OD , afforded **214** in 99% yield after work-up (Scheme 116).



Scheme 116: Reagents : i) 5.0 equiv. LDA; ii) CD_3OD

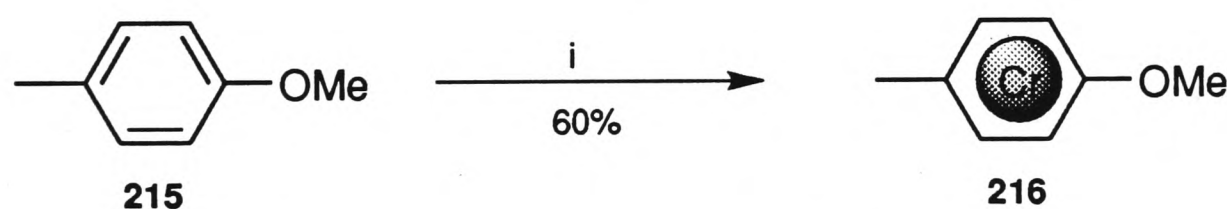
On examination of the crude ^1H nmr spectrum, 95% deuterium incorporation was observed at the C-2 position, indicative of the generation of only the mono-anion with LDA also a mass peak of $m/z=245$ (M^+), helped confirm the above structure. In

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 alkyllithium 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**)

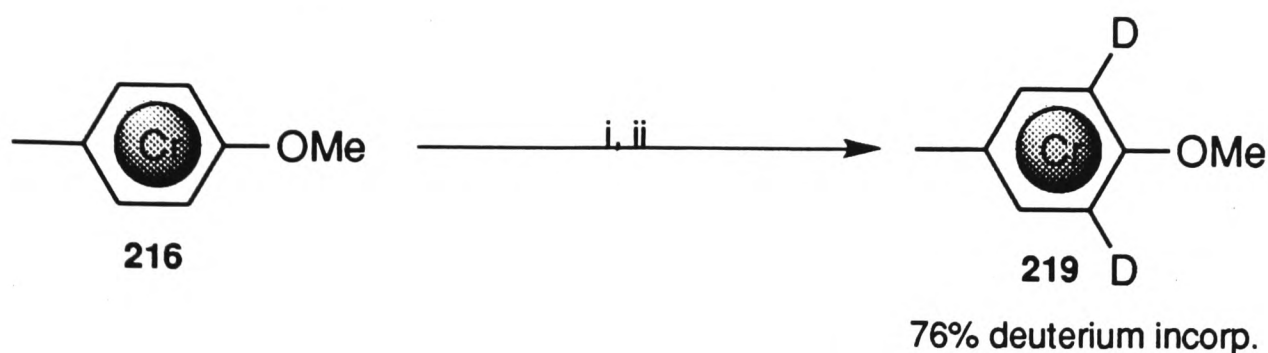
The formation of dianions with disubstituted compounds was next investigated. (4-methylanisole)Cr(CO)₃ **216** was formed by refluxing 4-methylanisole **215** with chromium hexacarbonyl in a dibutyl ether-THF solution for 2 days in the dark. After column chromatography **216** was isolated as a yellow crystalline solid (m.p. 46-48°C) in 60% yield (**Scheme 117**).



Scheme 117: Reagents : i) Cr(CO)₆, dibutyl ether-THF

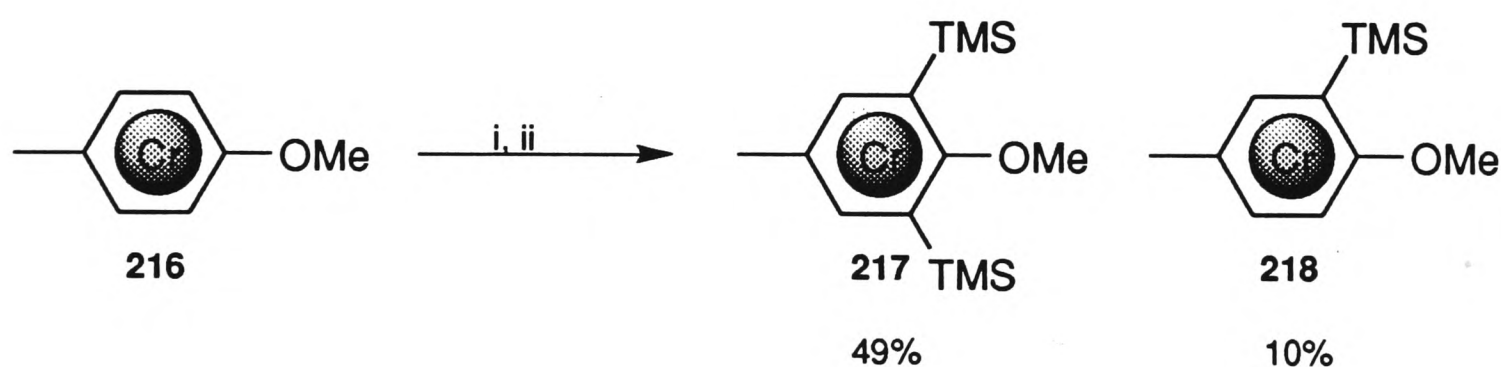
¹H nmr analysis showed two doublets at 5.13 and 5.14 ppm indicative of the four arene protons. These protons were assigned with the aid of nOe studies.

Compound **216** was treated with 5.0 equivalents of *n*-BuLi at -78°C for 4 hours, followed by electrophilic quench with CD₃OD (**Scheme 118**). Upon work-up, the ¹H nmr spectrum of **219** was observed to be identical to **216** except for a decrease in the resonance peak at 5.13 ppm, which indicated 76% deuterium incorporation at the 2,6-positions **219**. No deuterium incorporation was observed at any other position in the molecule, indicating regiospecific dianion formation at only the 2,6-positions.



Scheme 118: Reagents : i) 5.0 equiv. *n*-BuLi; CD₃OD

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%).

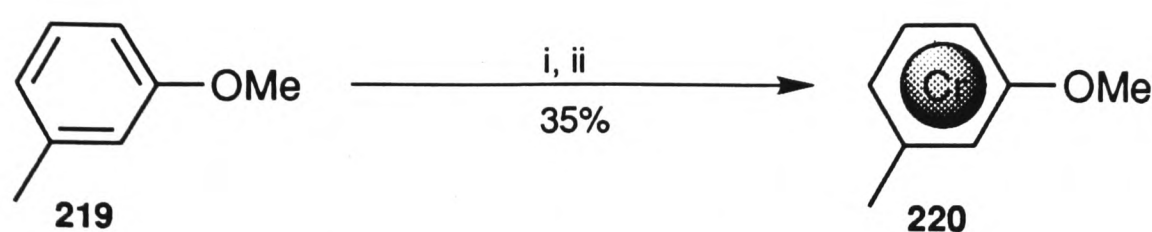


Scheme 119: Reagents : i) 5.0 equiv., *n*-BuLi; ii) TMSCl

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.

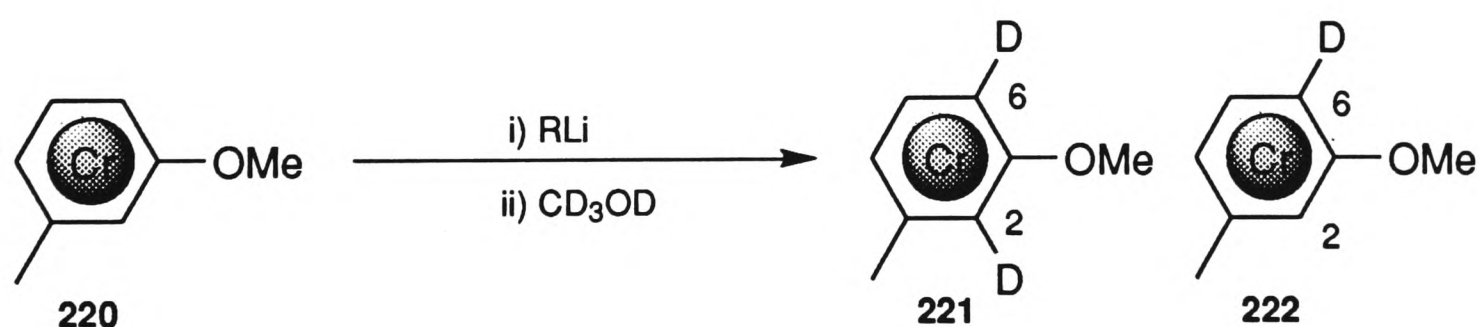
The compound (3-methylanisole)Cr(CO)₃ **220** was formed by heating 3-methylanisole **219** with chromium hexacarbonyl in a solution of dibutyl ether-THF at reflux, for 2 days under standard conditions (Scheme 120), to afford **220** as a yellow crystalline solid (m.p. $77-78^{\circ}\text{C}$) in 35%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



Scheme 120: Reagents : i) $\text{Cr}(\text{CO})_6$, dibutyl ether-THF

Generation of the dianion of **220** with excess alkyllithium 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°C and subsequent quenching with CD_3OD (**Scheme 121**), a mixture of deuteriated products were formed (**Table 5, entry 1**). ^1H 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 4.41ppm, 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 ^2H 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 (M^+) 260 and 259, which confirm the formation of a mixture of dideuteriated and monodeuteriated compounds. Therefore from the ^1H 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**.



Scheme 121

Table 5

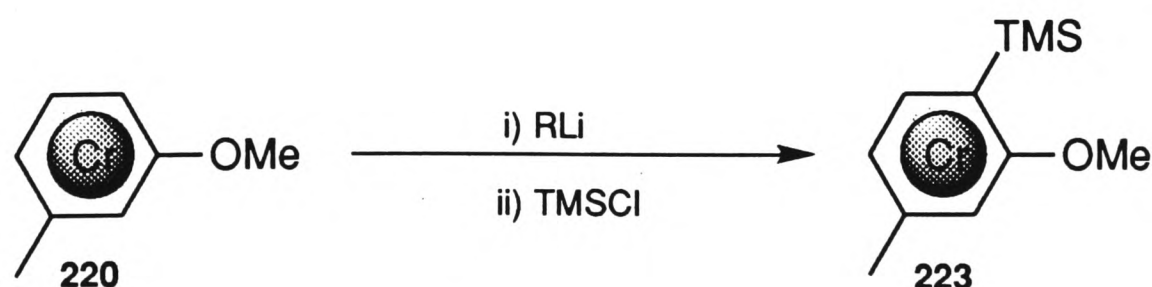
Entry	RLi (equiv.)	E^+	Yield (%)	
			221	222
1	<i>n</i> -BuLi (4.4)	CD_3OD	48	52
2	<i>t</i> -BuLi (4.0)	CD_3OD	33	67

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 CD₃OD a mixture of deuteriated products were obtained. The ¹H 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 ¹H 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).

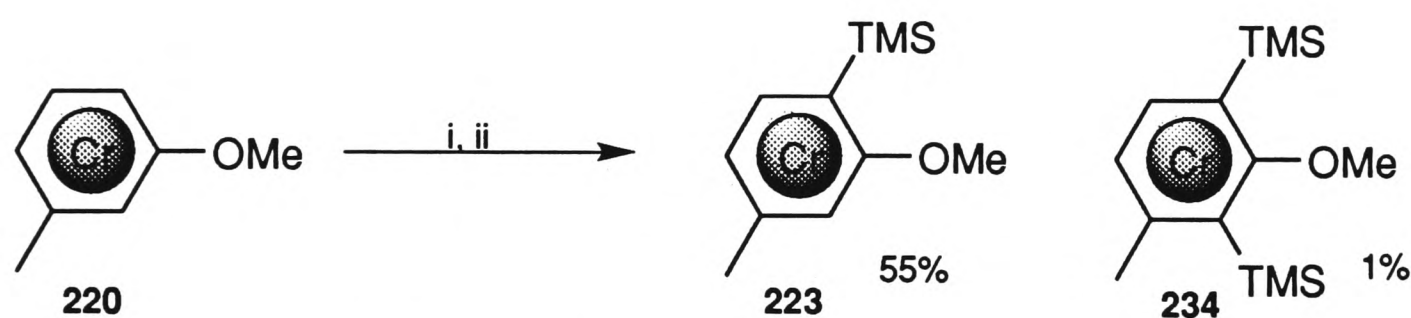


Scheme 122

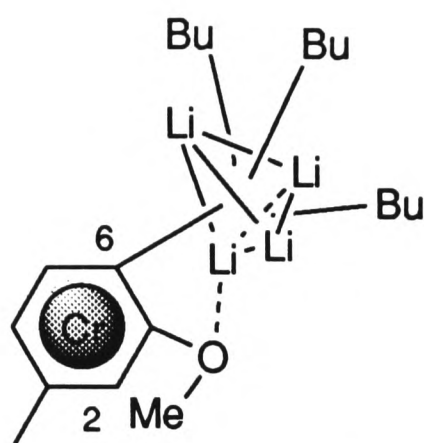
Table 6

Entry	RLi (equiv.)	223
1	<i>n</i> -BuLi (1.2)	73%
2	<i>t</i> -BuLi (1.1)	60%

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

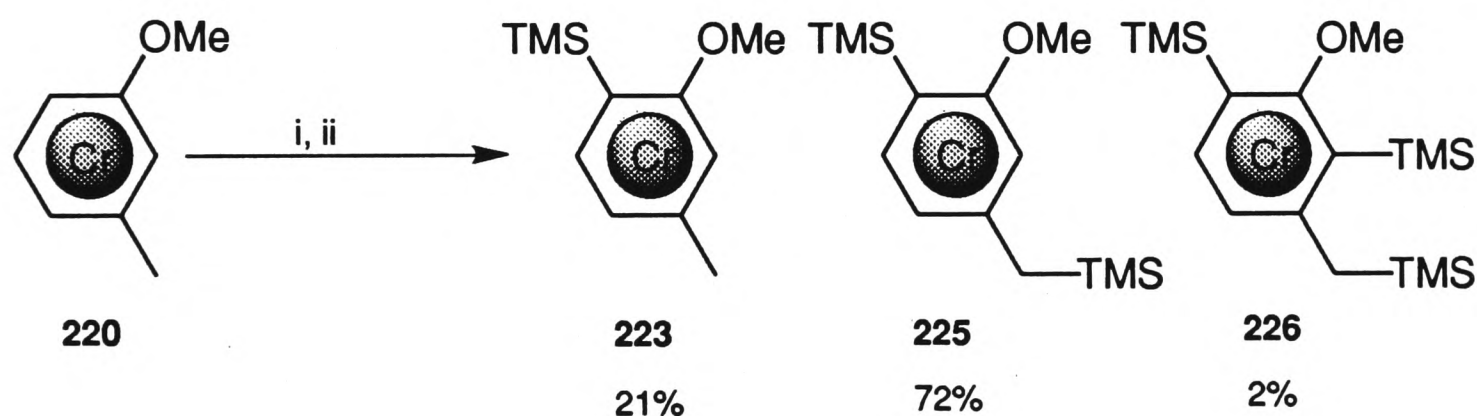
This was thought to be due to generation of the dianion at the 2,6-positions as proven previously (Table 4, Entry 1) but reaction of the anion at C-2 with the bulky TMSCl is very slow due to the steric hindrance at the C-2 site. It is postulated that upon chelation of *n*-BuLi to the lone pair of electrons 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).



(solvating molecules have been omitted for clarity)

Figure 15

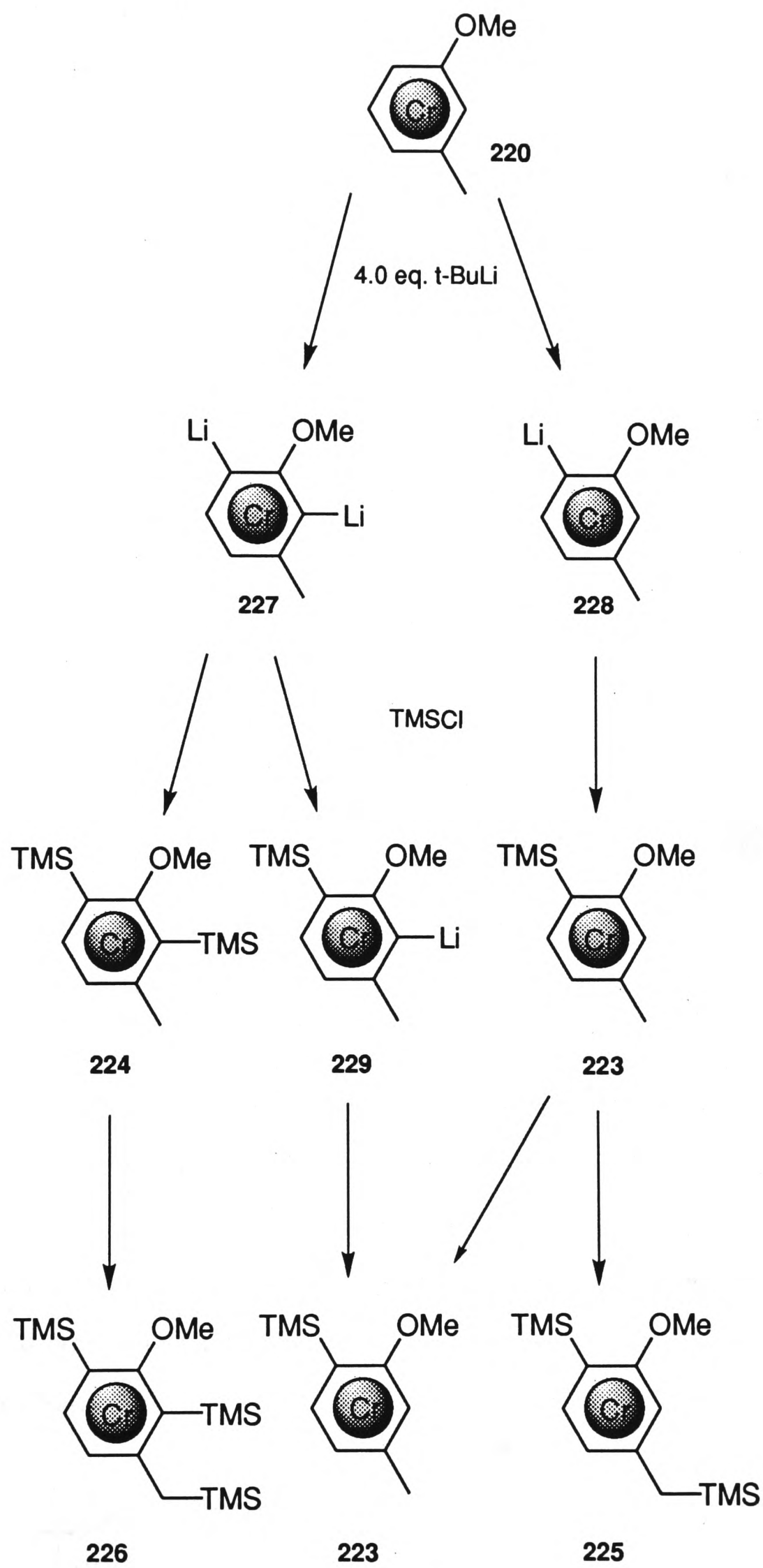
Interestingly, on repeating the reaction with excess *t*-BuLi at -78°C and quenching with TMSCl, three reaction products were obtained (Scheme 124). The monosilylated compound **223** (21%), the disilylated compound **225** (72%) and a small amount of the trisilylated compound (2%), assigned tentatively as **226**.



Scheme 124: Reagents : i) 4.0 equiv. *t*-BuLi, TMSCl

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 *t*-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.

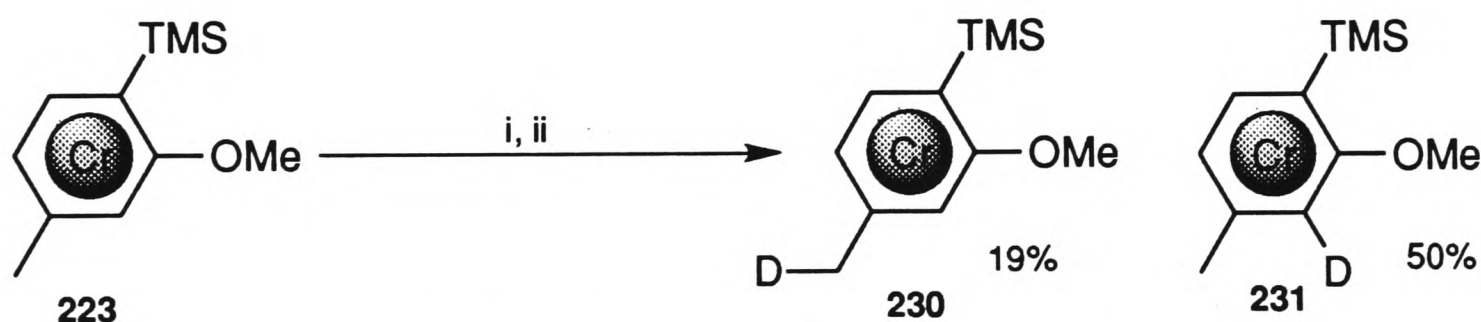
Also, a second deprotonation step occurs in the reaction mixture due to the excess *t*-BuLi still present. The 6-silylated compound **223** and the 2,6-disilylated compound **224** both undergo deprotonation again, and *in situ* quench with TMSCl, affords the **225** (72%) and **226** (2%). This observation is not seen in the previous reaction with *n*-BuLi (Scheme 123) as the excess *n*-BuLi reacts faster with excess TMSCl relative to *t*-BuLi⁵² 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 CD₃OD, to afford a mixture of deuteriated products (Scheme 126). Analysis of the crude ¹H 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 ²H 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 ²⁹Si and ³⁰Si 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.



Scheme 126: Reagents : i) 1.1 equiv. *n*-BuLi; ii) CD₃OD

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.⁵³ This enhanced acidity is thought to be due to back donation of the π -electrons from the arene ring into the 3d orbitals of the silicon atom (2p π -3d π bonding), stabilising the resultant benzylic anion (Figure 16).

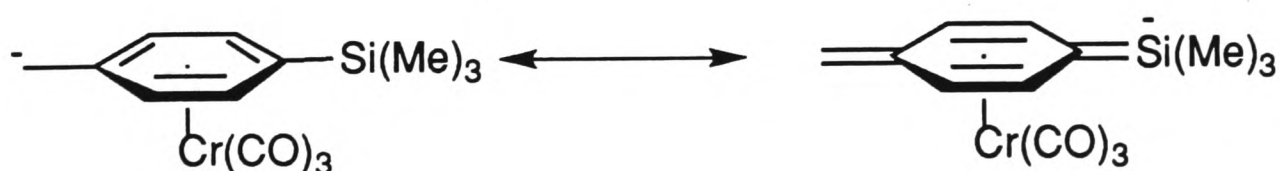
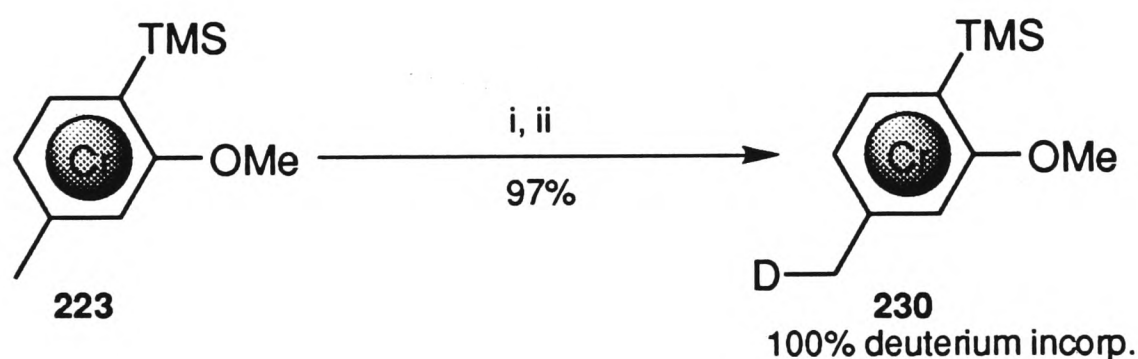


Figure 16

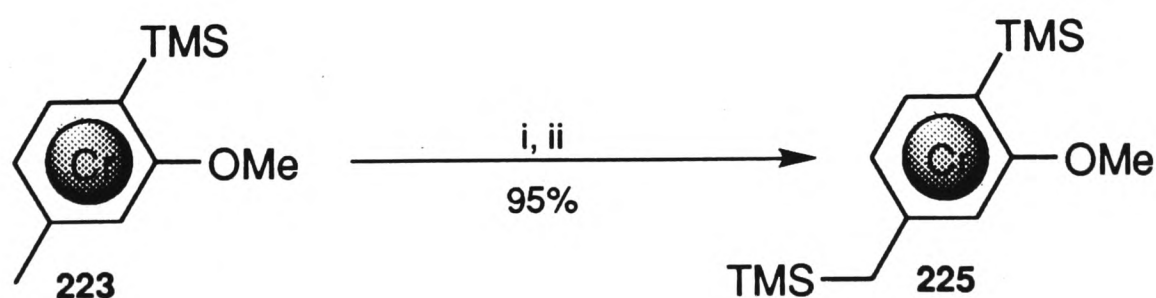
Since the proton at C-2 is quite hindered, deprotonation here is somewhat slow (as seen in (Scheme 121), and concurrent deprotonation at the next most acidic site, the benzylic group, occurs.

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 ^1H 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 ^2H 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 monodeuteriated 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_3OD

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)

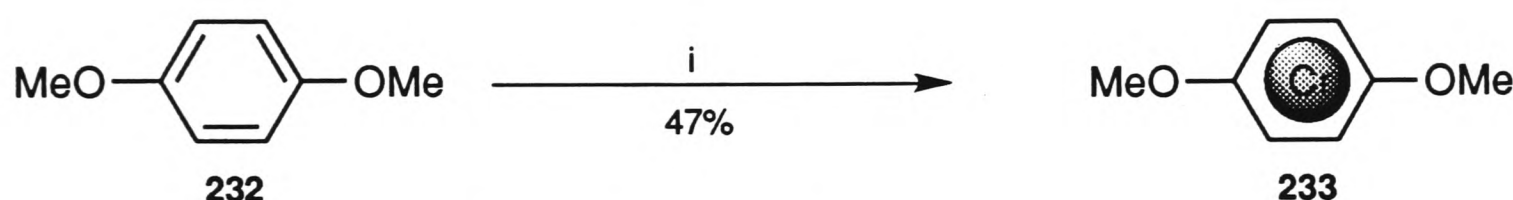


Scheme 128 Reagents : i) 1.1 equiv. *t*-BuLi; ii) TMSCl

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**)

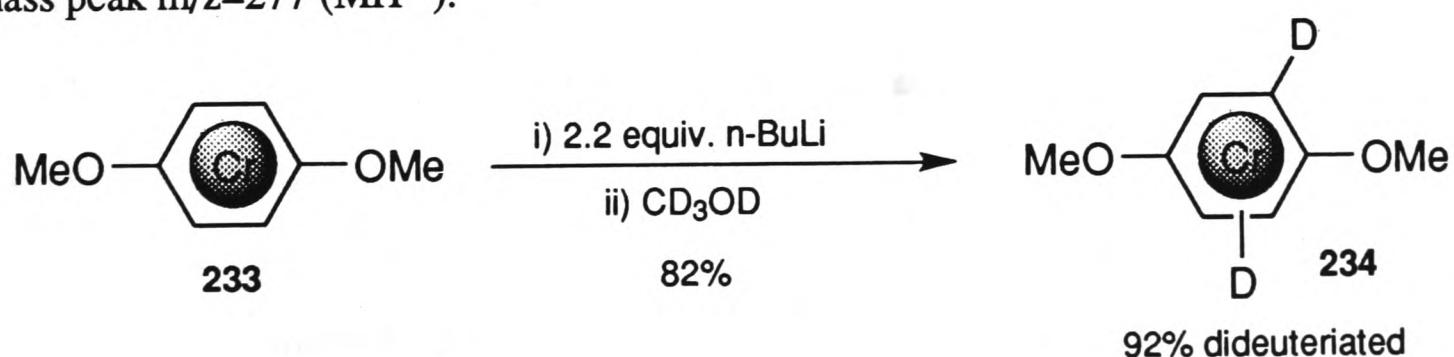
Similar metallation studies were next carried out on (1,4-dimethoxybenzene)Cr(CO)₃ **233**, which has two DoM groups *para* to one another. The compound **233** was readily made by heating 1,4-dimethoxybenzene **232** with chromium hexacarbonyl in a solution of dibutyl ether-THF at reflux for two days 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

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.

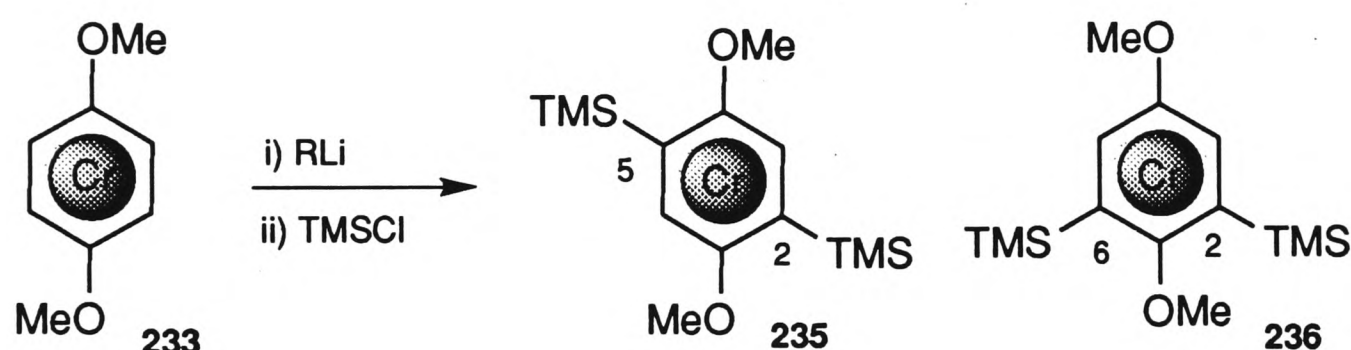
The compound **233** was deprotonated using 2.2 equivalents of *n*-BuLi and after 3 hours at -78°C was quenched with CD₃OD (**Scheme 130**). Work-up afforded the deuteriated species **234**, in 82% yield and analysis of the ¹H nmr spectrum of the crude reaction product showed it to be identical to **233**, 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

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 ^1H 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 ^1H 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

Table 7

Entry	RLi (equiv.)	235	236
		Ratio	
1	<i>n</i> -BuLi (2.0)	1	1
2	<i>t</i> -BuLi (3.0)	7	1

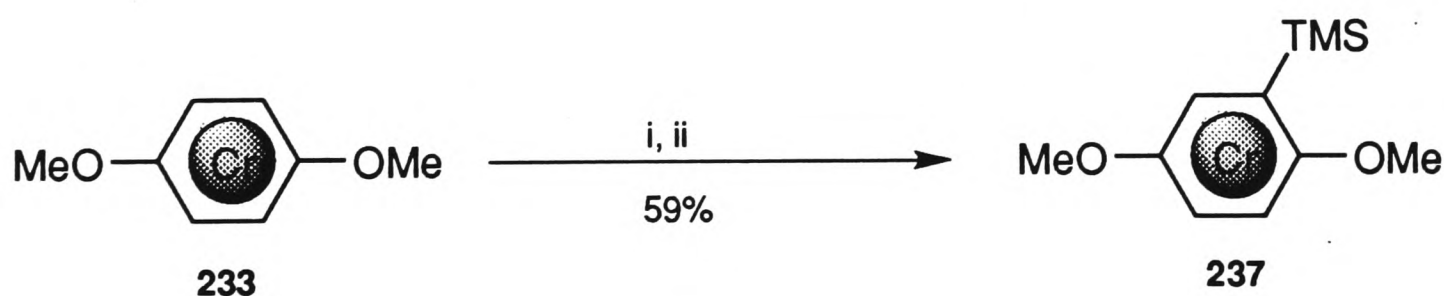
Repeating the metallation reaction of **233** with 3.0 equivalents of *t*-BuLi and quenching with TMSCl overnight, afforded upon work-up and column chromatography the 2,5-disilylated compound **235** (27%) and the 2,6-disilylated derivative **236** (4%) (Table 7, entry 2) in a ratio of 7:1.

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.

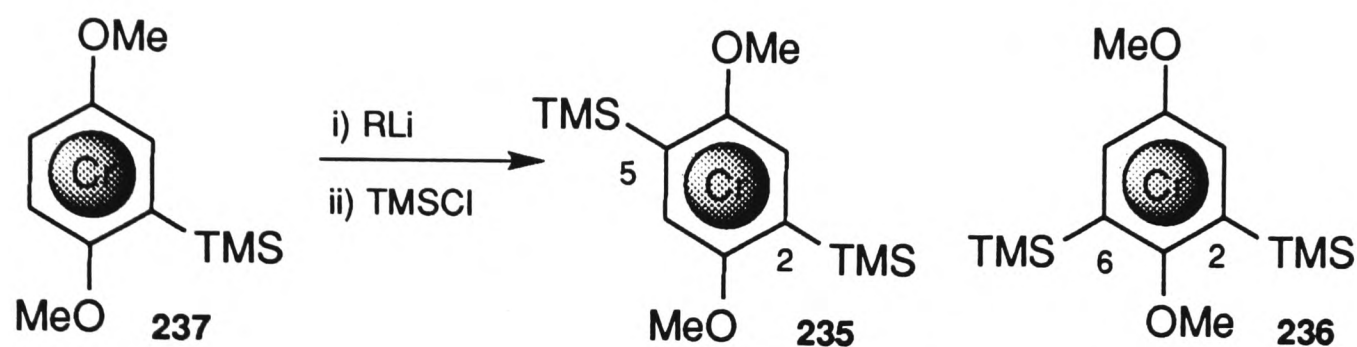
The compound **237** was afforded as a yellow crystalline solid (m.p. 119-120°C) in 59% yield by subjecting (1,4-dimethoxybenzene)Cr(CO)₃ **233** to deprotonation with 1 equivalent of *n*-BuLi and upon electrophilic quench with TMSCl (Scheme 132).



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 ¹H 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 ^1H nmr analysis (Table 8, Entry 2).



Scheme 133: Reagents : i) 1.0 equiv RLi; ii) TMSCl

Table 8

Entry	RLi (equiv.)	235	236
		Ratio	
1	<i>n</i> -BuLi (1.0)	2	1
2	<i>t</i> -BuLi (1.0)	2	1

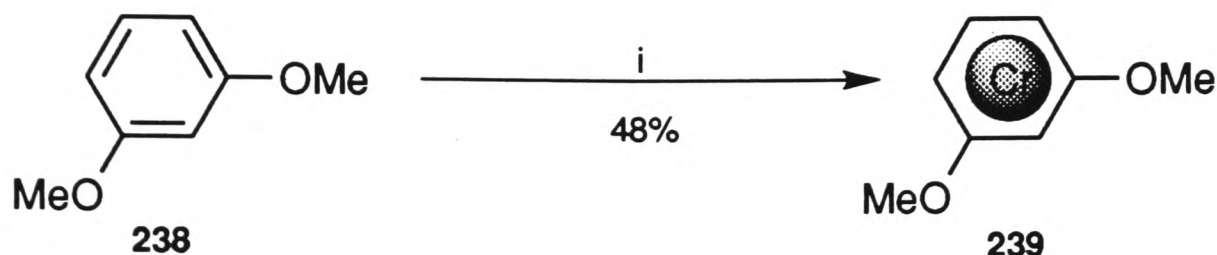
This ratio shows that the kinetic acidity of the proton at C-5 is greater than that at C-6. This is possibly due to the methoxyl group sitting distal to the bulky silyl group at C-2 causing increased steric hindrance at the C-6 site. Therefore, one would expect a faster rate of deprotonation at C-5 due 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.

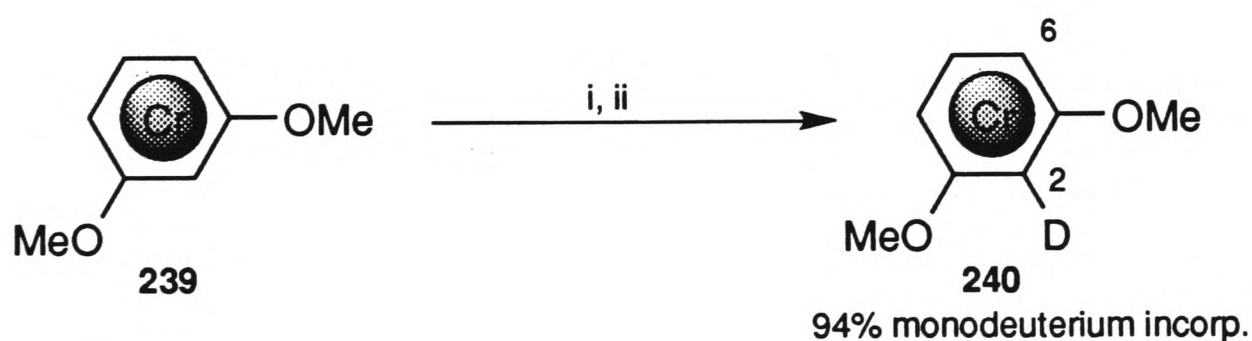
The compound **239** was formed by refluxing 1,3-dimethoxybenzene **238** with Cr(CO)₆ in a solution of dibutyl ether-THF for two days (Scheme 134), to afford upon

work-up and column chromatography, the desired product **239** was isolated as a yellow crystalline solid (m.p. 121-123°C) in 48% yield.



Scheme 134: Reagents : i) $\text{Cr}(\text{CO})_3$, dibutyl ether-THF

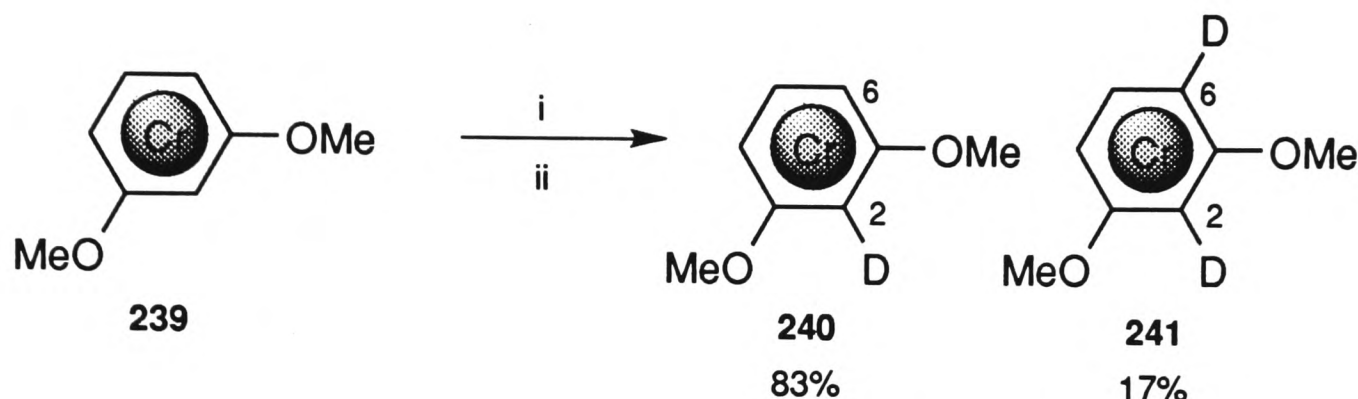
Formation of the mono-anion was first examined. On reacting **239** with 1.1 equivalents of *n*-BuLi at -78°C for 3 hours followed by electrophilic quench with CD_3OD , the deuteriated compound **240** was isolated quantitatively (Scheme 135). ^1H nmr spectroscopic analysis showed deuterium incorporation (94%) at the most acidic C-2 position. This was confirmed by a mass peak $m/z=275$ (M^+).



Scheme 135: Reagents : i) 1.1 equiv. *n*-BuLi; ii) CD_3OD

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_3OD , afforded a mixture of deuteriated products (Scheme 136). The ^1H 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 ^1H nmr spectrum it was calculated that the deuteriated reaction products consisted of 83% of **240** and 17% of **241**.



Scheme 136: Reagents : i) 4.0 equiv. $n\text{-BuLi}$; ii) CD_3OD

The low proportion of **241** in Scheme 136 is thought to be due to the slow deprotonation of at the 6-position with $n\text{-BuLi}$. 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 $t\text{-BuLi}$ at -78°C for three hours. Electrophilic quench with CD_3OD afforded the dideuteriated species **241** with 100% deuterium incorporation at both the C-2 and C-6 positions (Scheme 137).

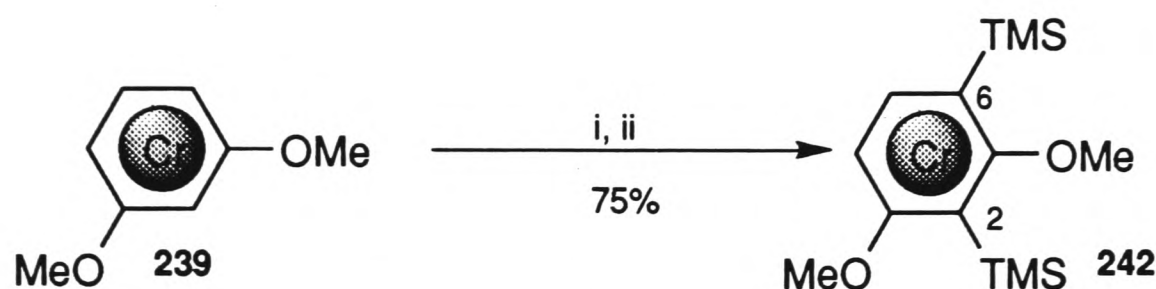


Scheme 137: Reagents : i) 4.0 equiv. $t\text{-BuLi}$; ii) CD_3OD

^1H 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 ^2H 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 **239** with TMSCl as the electrophile was studied (Scheme 138).



Scheme 138: Reagents : i) 4.0 equiv. *n*-BuLi; ii) TMSCl

The compound **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 **242** was isolated in 75% yield as a yellow crystalline solid (m.p. $134\text{--}136^{\circ}\text{C}$). It is interesting to compare this result with the poor yield in the disilylation of (3-methylanisole) $\text{Cr}(\text{CO})_3$ 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) $\text{Cr}(\text{CO})_3$ complexes with excess alkyllithium, it can be seen that dianion formation occurs readily at low temperature.

It was also observed from the dimetallation studies of (anisole) $\text{Cr}(\text{CO})_3$ **212**, (4-methylanisole) $\text{Cr}(\text{CO})_3$ **216** and (3-methylanisole) $\text{Cr}(\text{CO})_3$ **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

1. H. Gilman, Y.V. Young, *J. Am. Chem. Soc.*, 1934, **56**, 1415.
2. G. Wittig, G. Fuhrman, *Chem. Ber.*, 1940, **73**, 1197.
3. C. D. Broaddus, *J. Org. Chem.*, 1970, **35**, 10.
4. V. Sneikus, *Chem. Rev.*, 1990, **90**, 879; *FMC Lithium Link*, Spring 1992; *FMC Lithium Link*, FMC, Spring 1993.
5. J. D. Roberts, D. Y. Curtin, *J. Am. Chem. Soc.*, 1946, **68**, 1658.
6. R. R. Fraser, M. Bresse, T. S. Mansour, *J. Am. Chem. Soc.*, 1983, **105**, 7790.
7. G. W. Klump, M. J. Sinnige, *Tetrahedron Lett.*, 1986, **27**, 2247.
8. D. W. Slocum, R. Moon, J. Thompson, D. S. Coffey, J. D. Li, A. Seigel, R. Gayton-Garcia, *Tetrahedron Lett.*, 1994, **35**, 385.
9. D. W. Slocum, B. P. Koonsvitsky, *J. Org. Chem.*, 1973, **38**, 1675.
10. W. Bauer, P. R. Schleyer, *J. Am. Chem. Soc.*, 1989, **111**, 7189.
11. D. W. Slocum, C. A. Jennings, *J. Org. Chem.*, 1976, **41**, 3653.
12. W. Schlenk, E. Bergmann, *Ann*, 1928, **98**, 463.
13. H. L. Lewis, T. L. Brown, *J. Am. Chem. Soc.*, 1970, **92**, 4664.
14. J. F. Mc Garrity, C. A. Ogle, *J. Am. Chem. Soc.*, 1984, **107**, 1805.
15. D. Seebach, R. Hassig, J. Gabriel, *Helv. Chim. Acta*, 1983, **66**, 308.
16. B. J. Wakefield, "The Chemistry of Organolithium Compounds", Pergamon, 1974.
17. D. W. Slocum, G. Book, C. A. Jennings, *Tetrahedron Lett.*, 1970, **11**, 3443.
18. D. A. Shirley, T. E. Harmon, C. F. Cheng, *J. Organomet. Chem.*, 1974, **69**, 327.
19. T. L. Brown, *J. Am. Chem. Soc.*, 1970, **92**, 4664.
20. J. J. Eastham, *J. Am. Chem. Soc.*, 1964, **86**, 1076.
21. P. West, R. J. Waak, *J. Am. Chem. Soc.*, 1967, **89**, 4395.
22. P. West, *Inorg. Chem.* 1962, **1**, 654.
23. A. Langer, *Advances in Chemistry Series*, 1972, **130**, 2.
24. M. F. Semmelhack, "Comprehensive Organic Synthesis", eds. B. M. Trost, I. Fleming, Pergamon Press, vol. 4, Chapter 2.4, 361; S. G. Davies, "Organotransition Metal Chemistry: Applications to Organic Synthesis", Pergamon Press, Oxford, 1982.
25. M. Uemura, K. Take, Y. Hayashi, *J. Chem. Soc., Chem. Commun.*, 1983, 858; M. F. Semmelhack, A. Zask, *J. Am. Chem. Soc.*, 1983, **105**, 2034.

26. M. F. Semmelhack, *J. Am. Chem. Soc.*, 1979, **101**, 689.
27. J. Bisaha, M. Czarny, M. F. Semmelhack, *J. Am. Chem. Soc.*, 1979, **101**, 768.
28. R. A. Finnegan, J. W. Altschuld, *J. Organomet. Chem.*, 1967, **9**, 193.
29. R. J. Card, W. S. Trahanovsky, *J. Org. Chem.*, 1980, **45**, 2560.
30. W. S. Trahanovsky, R. J. Card, *J. Am. Chem. Soc.*, 1972, **94**, 2896.
31. J. Brocard, J. Lebibi, D. Couturier, *J. Chem. Soc., Chem. Commun.*, 1981, 1264.
32. J. P. Gilday, J. T. Negri, D. A. Widdowson, *Tetrahedron*, 1989, **45**, 4605.
33. J. P. Gilday, D. A. Widdowson, *J. Chem. Soc., Chem. Commun.*, 1986, 1235.
34. D. A. Widdowson, *Phil. Trans. R. Soc. Lond. A*, 1988, **326**, 595.
35. P. J. Dixon, J. P. Gilday, J. T. Negri, D. A. Widdowson, *Pure & Appl. Chem.*, 1990, **62**, 575.
36. H. Gilman, T. S. Soddy, *J. Org. Chem.* 1957, **22**, 1715.
37. N. F. Masters, D. A. Widdowson, *J. Chem. Soc., Chem. Commun.*, 1983, 955.
38. H. Gilman, J. W. Morton, *Org. React.*, 1954, **8**, 258; H. W. Geshwend, H. R. Rodriguez, *Org. React.*, 1979, **26**, 1; H. Gilman, R. L. Bebb, *J. Am. Chem. Soc.*, 1939, **61**, 109.
39. S. Cabiddu, L. Contini, C. Fattuoni, C. Floris, G. Gelli, *Tetrahedron*, 1991, **47**, 9279; G. P. Crowther, R. J. Sundberg, A. M. Sarpeshkar, *J. Org. Chem.*, 1984, **49**, 4657.
40. S. Cabiddu, C. Floris, S. Melis, *Tetrahedron Lett.*, 1986, **27**, 4625; S. Cabiddu, L. Contini, C. Fattuoni, C. Floris, G. Gelli, S. Melis, *Tetrahedron*, 1993, **49**, 4965; S. Cabiddu, C. Fattuoni, C. Floris, G. Gelli, S. Melis, F. Sotgiu, *Tetrahedron*, 1990, **46**, 861; I. Haiduc, H. Gilman, *J. Orgmetal. Chem.*, 1968, **12**, 394.
41. R. J. Mills, R. F. Horvath, M. P. Sibi, V. Sniekus, *Tetrahedron Lett.*, 1985, **26**, 1145.
42. H. Gilman, E. A. Zuech, *Chem. and Ind.*, 120, 1960; H. Gilman, D. S. Melstrom, *J. Am. Chem. Soc.* 1950, **72**, 2953; H. Hart, G. C. Nwokogu, *Tetrahedron Lett.*, 1983, **24**, 5721.
43. D. Bryce-Smith, E. E. Turner, *J. Chem. Soc.* 1953, 861.
44. B. Pring, *Acta. Chem Scand.*, 1973, **27**, 3878.
45. J. M. Saa, P. M. Deya, G. A. Suner, A. Frontera, *J. Am. Chem. Soc.*, 1992, **114**, 9093.
46. P. Eaton, R. M. Martin, *J. Org. Chem.*, 1988, **53**, 2728.
47. S.G. Davies, T. Loveridge, *J. Chem. Soc., Chem. Commun.*, 1995, 817.
48. B. Nichols, M. C. Whiting, *J. Chem. Soc.*, 1959, 551.

49. M. E. Wright, *Organometallics*, 1989, **8**, 407.
50. E. O. Fischer, K. Ofele, H. Essler, W. Frohlich, P. Mortensen, W. Semmlinger, *Chem. Ber.*, 1958, **91**, 2763; W. Strohmeier, P. Hartmann, *Z. Naturforsch*, B, 1963, **18**, 506; G. Klopman, F. Calderazzo, *Inorg. Chem.*, 1967, **6**, 977.
51. S. Harder, J. Boersma, L. Brandsma, G. P. Mier, J. Kanter, *J. Orgmetal. Chem.*, 1989, 364, 1.
52. A. E. Bey, D. R. Weyenberg, *J. Org. Chem.*, 1965, **30**, 2436.
53. S. G. Davies, In *Advances in Metal-Organic Chemistry*, L., Liebeskind, Ed., 1991, **2**, 1.
54. R. Adams, H. C. Yuan, *Chem. Rev.*, 1933, **12**, 261.

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 *in vacuo* before use. The diastereoselectivities cited were determined by peak integration of the crude reaction products' ¹H nmr spectrum. The percentage of deuterium incorporation was calculated by measurement of the respective peak heights in the ¹H 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 *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 hexamethyldisylilamide (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 GF₂₅₄ 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 ^{13}C ; 125.7 MHz; ^2H 76.75 MHz) or Varian Gemini 200 (^1H ; 200 MHz) instruments; ^{13}C 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 ^{13}C 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.

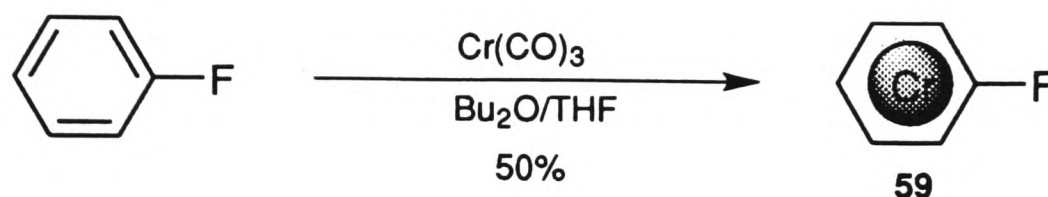
10. Elemental Analysis

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

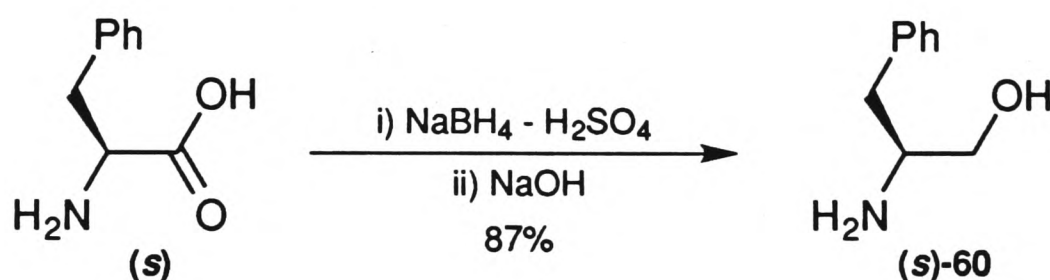
11. Yields

All quoted yields refer to isolated material unless otherwise indicated.

Experimental: Chapter 2

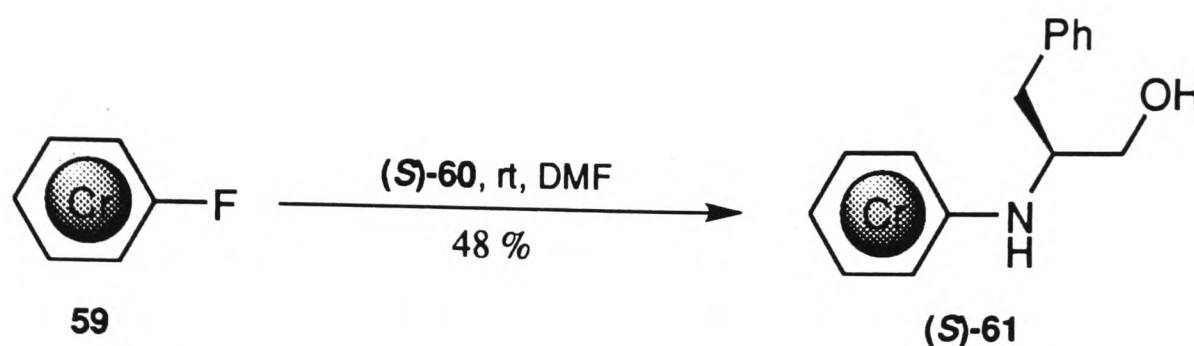
Preparation of [fluorobenzene] chromium tricarbonyl¹ **59**

To a solution of fluorobenzene (15 cm³, 15.98 mmol) in Bu₂O:THF (10:1, 110 cm³) 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 Bu₂O then subsequently eluted with dichloromethane and the yellow solution was removed *in vacuo* to afford **59** as a yellow solid (1.84 g, 50%); δ_{H} (200 MHz; CDCl₃) 5.51 (2H, dt, *J* 6.5, 3.1, ArCr(CO)₃), 5.33 (2H, m, ArCr(CO)₃), 4.86 (1H, dt, *J* 6.2, 2.9, ArCr(CO)₃).

Preparation of (*S*)-phenylalaninol² **60**

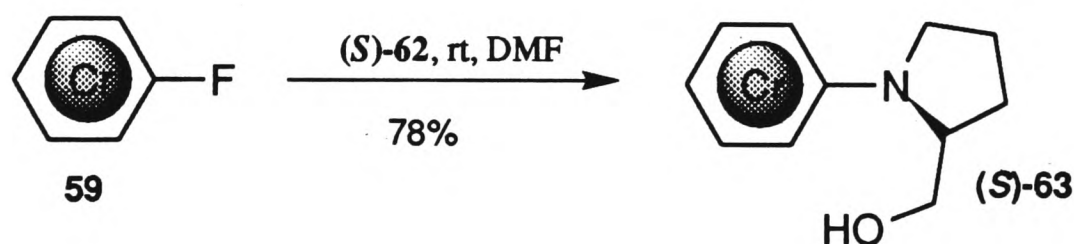
To a stirred suspension of sodium borohydride in 100 cm³ of THF was added (*S*)-(-) phenylalanine (4.0 g, 24.2 mmol). The flask was then cooled to 0°C and a concentrated solution of H₂SO₄ (15 cm³, 30.25 mmol) in THF (10 cm³) was added slowly, keeping the temperature below 20°C. The reaction mixture was then allowed to stir overnight at room temperature. MeOH (20 cm³) was added and the reaction mixture concentrated to 30 cm³. A solution of 5N Sodium hydroxide (100 cm³) 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® then subsequently washed with water. The filtrate and washings were then combined, diluted with water (100 cm³) and washed with CH₂Cl₂ (4 x 50 cm³) and then the solvent removed *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]; [α]_D²² -23.2 (*c* 1, 1N HCl)); {lit.³ [α]_D²² -22.8 (*c* 1.2, 1N HCl)}; δ_{H} (300 MHz; CDCl₃) 7.34-7.18 (5H, m, Ph), 3.63, 3.38 (2H, AB of ABX, *J*_{AB} 10.6, *J*_{AX} 7.2, *J*_{BX} 3.8, CH₂Ph), 3.12 (1H, m, CH₂CH), 2.70, 2.52 (2H, AB of ABX, *J*_{AB} 13.5, *J*_{AX} 8.6, *J*_{BX} 5.2, CH₂CH), 1.74 (3H, br s, NH₂, OH).

Preparation of (S)-[η^6 -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); ν_{max} (CHCl₃)/cm⁻¹ 3626 (O-H), 1959, 1878 (C≡O), 1548 (N-H), 1320 (C-N), 798 (N-H); δ_{H} (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), 3.53 (2H, m, CH₂OH), 2.99-2.83 (2H, AB of ABX system, *J*_{AB} 13.6, *J*_{AX} 5.7, *J*_{BX} 7.6, CH₂Ph), 1.88 (1H, br s, CH₂OH); δ_{C} (125 MHz; CDCl₃) 234.83 (Cr(CO)₃), 137.26 (Ph:C_{ipso}), 132.83 (ArCr(CO)₃:C_{ipso}), 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%).

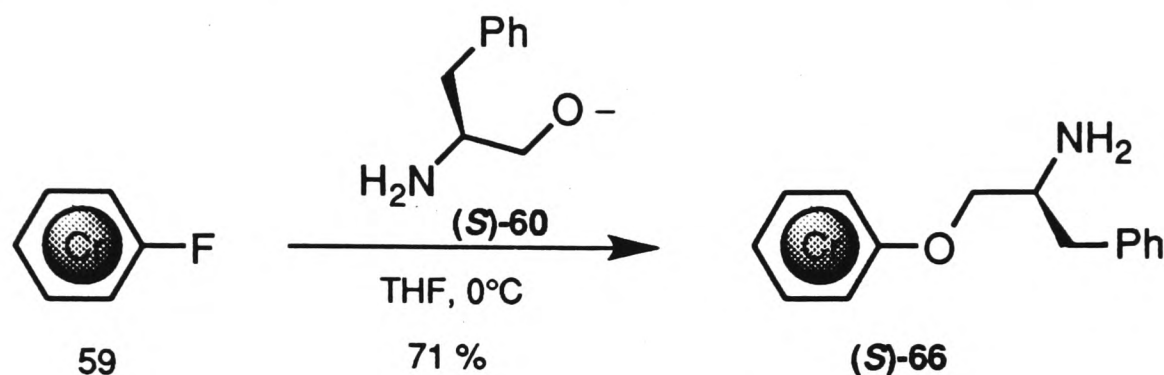
Preparation of (S)-[N-phenylprolinol] chromium tricarbonyl (S)-63



(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); ν_{max} (CHCl₃)/cm⁻¹ 3398 (O-H), 1936, 1849 (C≡O), 1364 (N-C); δ_{H} (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,

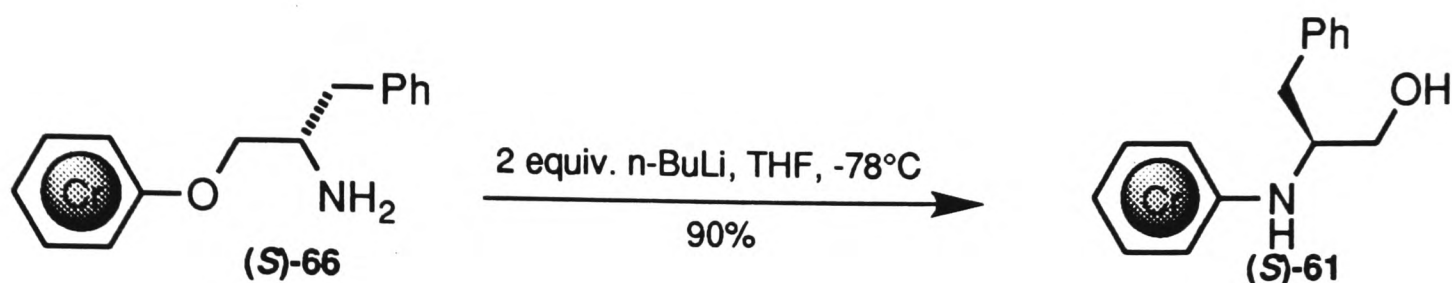
Ar(Cr(CO)₃), 3.79 (1H, m, NCH), 3.70-3.58 (2H, m, CH₂OH), 3.33, 3.10 (2H, m, NCH₂), 2.10-1.95 (4H, m, CH₂CH₂), 1.65 (1H, br s, OH); δ_C (125 MHz; CDCl₃) 234.74 (Cr(CO)₃), 133.47 (ArCr(CO)₃:C_{ipso}), 97.27, 97.11, 82.63, 76.33, 75.33 (ArCr(CO)₃:C), 63.88 (CH₂OH), 60.35 (NCH), 49.27 (CHCH₂), 28.37 (NCHCH₂), 23.51 (NH₂CH₂); m/z (EI) 313 (M, 23%), 177 (M-Cr(CO)₃), 12, 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)- η^6 -phenyl] chromium tricarbonyl (66)



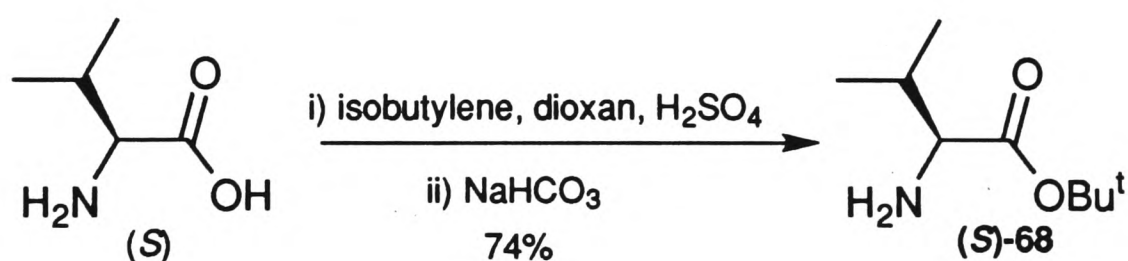
To a solution of NaH (1.5 g, 6.46 mmol) in THF, was added a THF solution of (S)-phenylalaninol (S)-60 at 0°C. The reaction was stirred for 0.5h, after which (fluorobenzene)Cr(CO)₃ was added and the reaction was warmed to room temperature overnight. The solvent was removed *in vacuo* to give a yellow 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; $[\alpha]_D^{22} +5.45$ (c 0.52, CHCl₃); $\nu_{\max}$ (KBr)/cm⁻¹ 1952, 1855 (C≡O), 1368 (C-N), 1251 (C-O-C), 1085 (C-N), 1058 (C-O-C); δ_H (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, *J*_{AB} 8.6, *J*_{AX} 6.6, *J*_{BX} 4.2, OCH₂), 3.47 (1H, m, PhCH₂CH), 2.91, 2.68 (2H, AB of ABX system, *J*_{AB} 13.5, *J*_{AX} 8.3, *J*_{BX} 5.5, CH₂Ph), 2.18 (2H, s, NH₂); δ_C (125 MHz; CDCl₃) 223.11 (Cr(CO)₃), 142.26 (Ph:C_{ipso}), 138.00 (ArCr(CO)₃:C_{ipso}), 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 (CI) 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)-[η^6 -N-phenyl(phenylalaninol)] chromium tricarbonyl (S)-61 via Smiles rearrangement

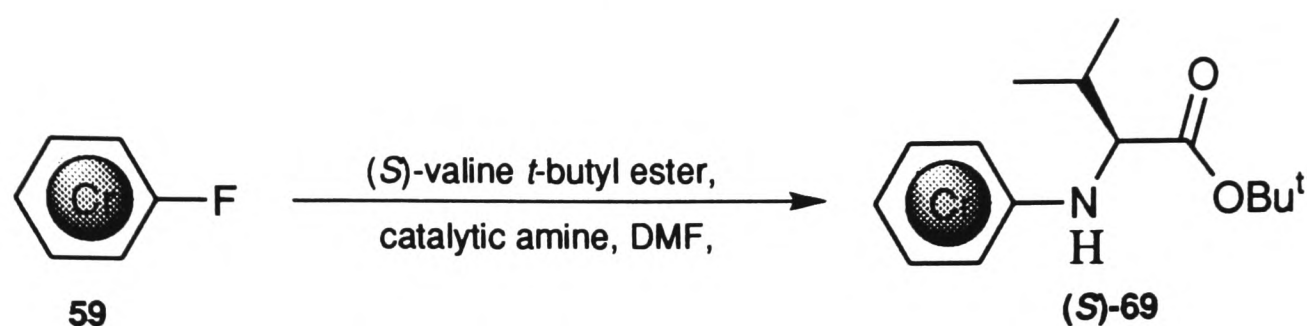


To a THF solution of (S)-66 at -78°C was added 2 equivalents of *n*-BuLi (0.3 ml, 34.79 mmol) and the reaction stirred for 2 h. The reaction was then quenched with MeOH and concentrated to give a crude yellow oil. The oil was taken up in CH_2Cl_2 and passed through a small column of deactivated alumina 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%); $[\alpha]_{\text{D}}^{22} +33.02$ (*c* 1.81, CHCl_3) δ_{H} (300 MHz; CDCl_3) 7.38-7.15 (5H, m, Ph), 5.55 (2H, m, $\text{ArCr}(\text{CO})_3$), 4.80 (2H, m, $\text{ArCr}(\text{CO})_3$), 4.70 (1H, m, $\text{ArCr}(\text{CO})_3$), 4.0 (1H, d, *J* 7.1, CHNH), 3.73 (1H, m, NHCH), 3.55 (2H, m, CH_2OH), 3.02-2.83 (2H, AB of ABX system, *J*_{AB} 13.6, *J*_{AX} 5.7, *J*_{BX} 7.6, CH_2Ph), 1.92 (1H, br s, CH_2OH)

Preparation of (S)-valine *t*-butyl ester⁴ (S)-68



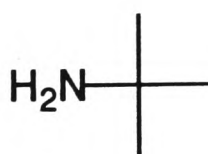
To a 500 cm³ round bottom flask containing a solution of (S)-valine (5.0 g, 42.7 mmol) in dioxane (80 cm³) and concentrated H_2SO_4 (8 cm³) at -78°C , was bubbled isobutylene gas (80 cm³). The reaction was then sealed with a rubber stopper and allowed to warm to room temperature overnight. The excess 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 MgSO_4 and concentrated *in vacuo* to give an oil. Purification of the oil by column chromatography on silica gel (50% petrol/ethyl acetate) afforded (S)-68 as a yellow oil (5.5 g, 74%); $[\alpha]_{\text{D}}^{22} +25.3$ (neat), {lit.⁵ $[\alpha]_{\text{D}}^{20} +25.6$ }; δ_{H} (300 MHz; CDCl_3) 3.18 (1H, d, *J* 5.0, CH_2CH), 1.99 (1H, dq, *J* 4.9, 6.8, $(\text{CH}_3)_2\text{CH}$), 1.65 (2H, s, NH_2), 1.47 (9H, s, $\text{C}(\text{CH}_3)_3$), 0.96 (3H, d, *J* 7.0, CHCH_3), 0.90 (3H, d, *J* 7.0, CHCH_3).

Preparation of (S)-[N-phenylvaline *t*-butyl ester] chromium tricarbonyl (S)-69

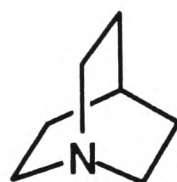
A variety of conditions and external amines have been investigated. The experimentals are discussed below and the results summarised in Table 1.

Table 1

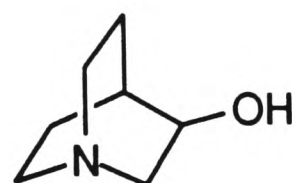
Base	Days	Product (%)		Recovered Material (%)	
		complexed 69	decomplexed 70	amine 68	(fluorobenzene) Cr(CO) ₃
none	37 (rt)	18	14	74	24
<i>t</i> -butylamine (71)	11 (rt)	15	1	73	48
quinuclidine (73)	14 (rt)	69	0	74	28
3-quinuclidinol (74)	19 (rt)	37	17	72	45
quinuclidine (73)	2 (50°C)	19	0	87	24



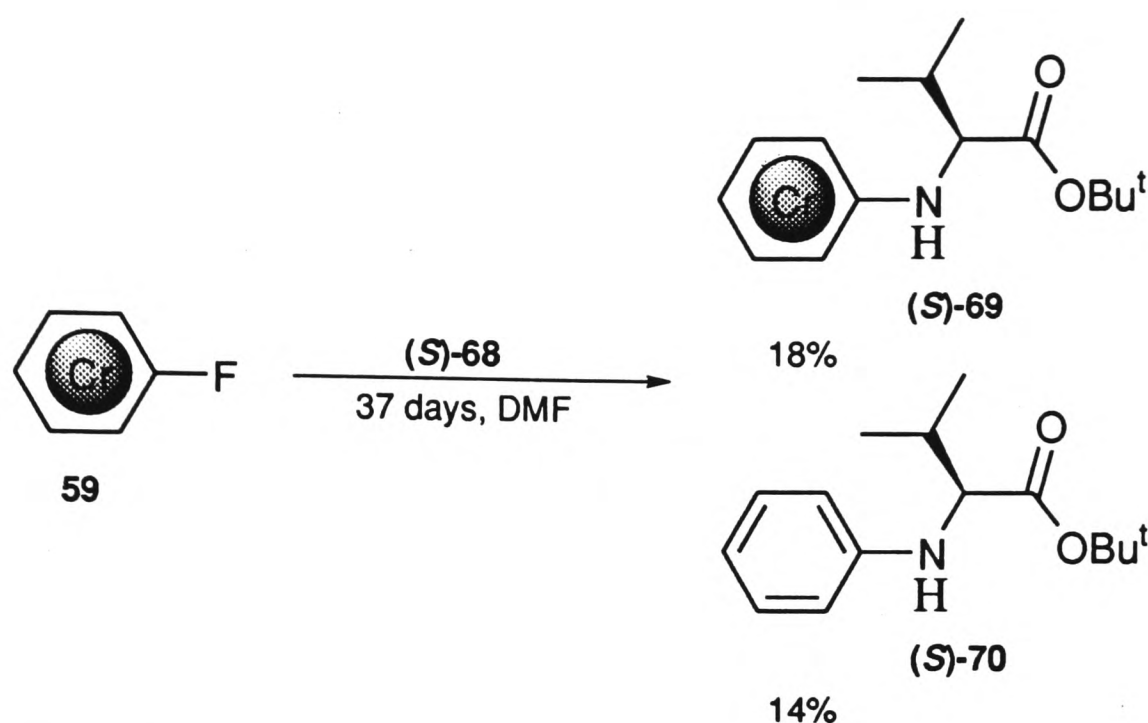
71



73



74

Preparation of (S)-[N-phenylvaline *t*-butyl ester] chromium tricarbonyl (S)-69

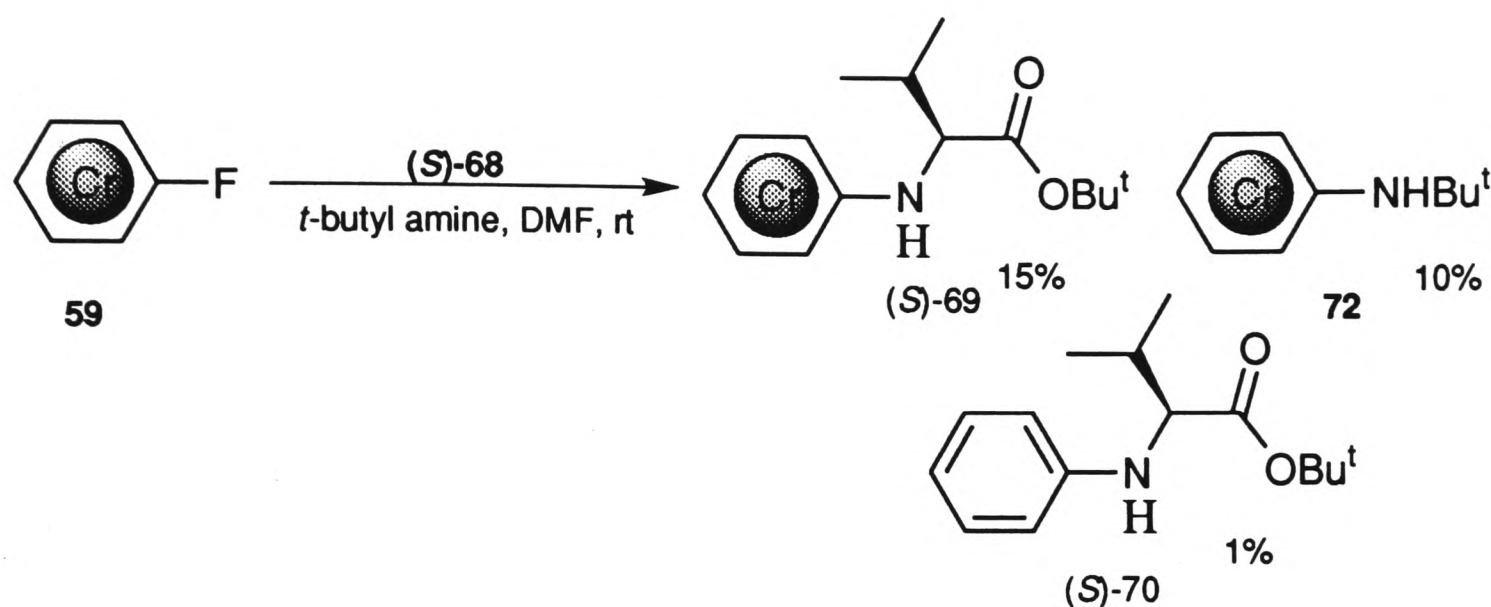
To a DMF (0.5 cm³) solution of **59** (0.22 g, 0.95 mmol) was added (S)-(+)-valine *t*-butyl ester **68** (0.76 g, 4.4 mmol) and the reaction was allowed to stir at room temperature for 37 days. Dichloromethane was then added to the reaction mixture and solution was passed through deactivated alumina. 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; $[\alpha]_{\text{D}}^{25} +7.12$ (c 0.18, CHCl₃); ν_{max} (KBr)/cm⁻¹ 2974 (N-H), 1947, 1860 (C≡O), 1714 (C=O), 1148 (CO₂); δ_{H} (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), 2.10 (1H, m, CH₃CH), 1.47 (9H, s, C(CH₃)₃), 0.99 (3H, d, *J* 2.0, CHCH₃), 0.97 (3H, d, *J* 2.0, CHCH₃); δ_{C} (125 MHz; CDCl₃) 234.19 (Cr(CO)₃), 170.4 (C=O), 132.48 (ArCr(CO)₃:C_{ipso}), 96.47, 96.25, 83.06 (ArCr(CO)₃:C), 82.81 (C(CH₃)₃), 76.34, 74.85 (ArCr(CO)₃:C), 61.35 (NHCH), 31.64 (CH₃CH), 28.01 (C(CH₃)₃), 18.73 (CHCH₃), 18.27 (CHCH₃); *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. $[\alpha]_{\text{D}}^{22} -54.4$ (c 0.68, CHCl₃); ν_{max} (KBr)/cm⁻¹ 3383 (N-H), 1710 (C=O), 1369 (N-C), 1247 (C-N); δ_{H} (500 MHz; CDCl₃) 7.17 (2H, m, Ph), 6.72 (1H, m, Ph), 6.66 (2H, m, Ph), 4.14 (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, CHCH₃), 1.03 (3H, d, *J* 4.4, CHCH₃); δ_{C} (125 MHz; CDCl₃) 172.75 (CO₂), 147.60 (Ph:C_{ipso}), 129.18, 117.91, 113.62 (Ph), 81.44 (C(CH₃)₃), 62.85 (NHCH), 31.47 (CH₃CH), 28.07 (C(CH₃)₃), 18.97 (CHCH₃), 18.65 (CHCH₃). *m/z* (EI) 249 (M, 36), 150

(M-C₅H₉O₂, 100); (Found C, 72.55; H, 9.48; N, 5.64. C₁₅H₂₃NO₂ requires C, 72.25; H, 9.30; N, 5.62%).

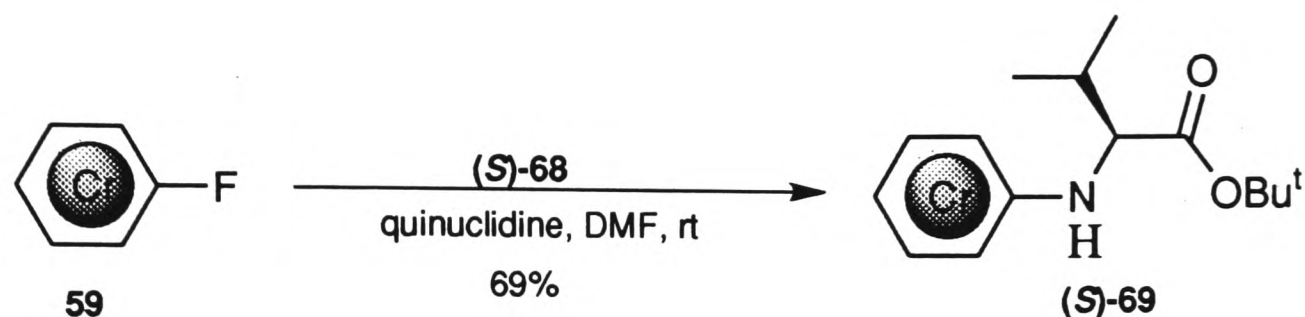
Preparation of (*S*)-[*N*-phenylvaline *t*-butyl ester] chromium tricarbonyl (*S*)-69 with *t*-butylamine as an amine catalyst



To a DMF (0.5 cm³) 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 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** (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%).

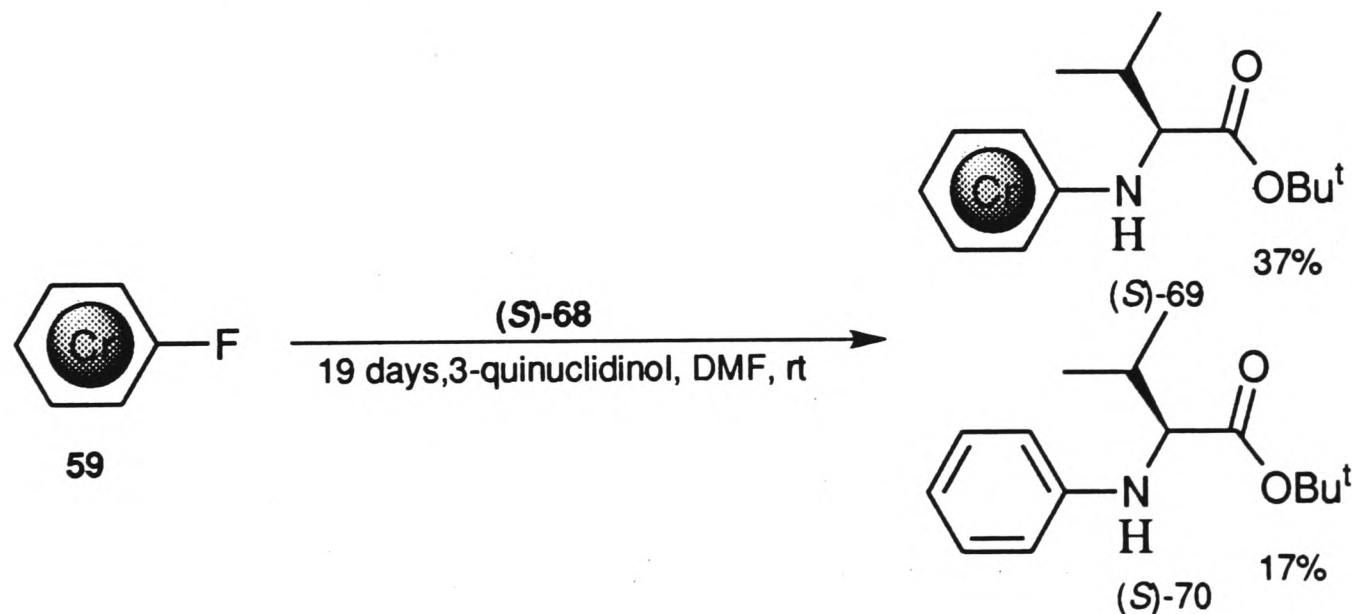
The compound **72** was recrystallised from petrol/diethyl ether to afford the product as a yellow crystalline solid; m.p. 128-130°C; ν_{max} (KBr)/cm⁻¹ 1937, 1844 (C≡O), 1504 (N-H), 1383 (C-H), 1372 (N-C), 1322 (C-N); δ_{H} (300 MHz; CDCl₃) 5.54 (2H, m, ArCr(CO)₃), 4.77 (3H, m, ArCr(CO)₃), 3.63 (1H, br s, NH), 1.37 (9H, s, C(CH₃)₃); δ_{C} (125 MHz; CDCl₃) 234.83 (Cr(CO)₃), 132.83 (ArCr(CO)₃:C_{ipso}), 96.56, 82.45, 76.28 (ArCr(CO)₃:C), 51.65 (C(CH₃)₃), 29.19 (C(CH₃)₃); m/z (EI) 285 (M, 23%), 229 (M-C₄H₉, 14), 149 (m-Cr(CO)₃, 6), 52 (Cr, 100); Found C, 54.68; H, 5.43; N, 4.93. C₁₃H₁₅NO₃Cr 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

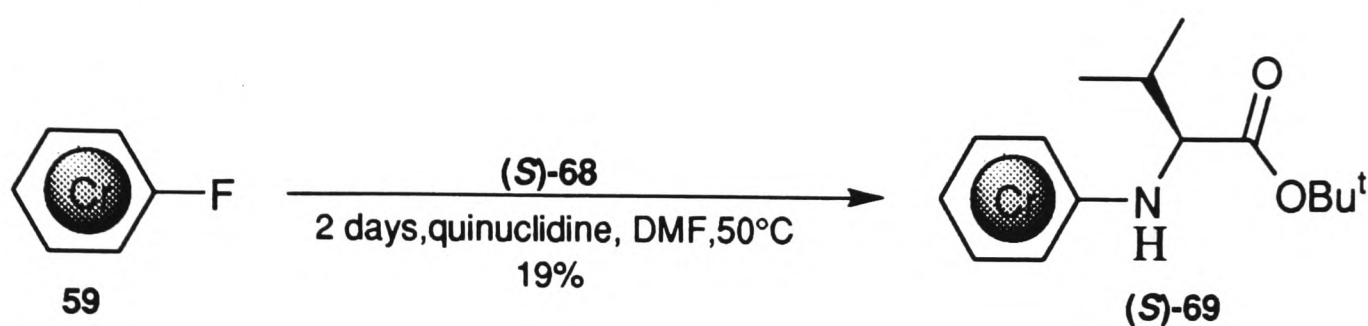


To a DMF (0.5 cm³) solution of **59** (2.0 g, 8.62 mmol) and quinuclidine **73** (0.958 g, 8.62 mmol) was added (S)-valine *t*-butyl ester **68** (7.5 g, 43.08 mmol) and the reaction was allowed to stir at room temperature for 14 days. Dichloromethane was then added to the reaction mixture which was then columned through deactivated alumina and concentrated to give a crude yellow oil. Purification by column chromatography yielded the product (S)-**69**. ¹H nmr spectroscopic analysis was identical with that obtained earlier for this compound.

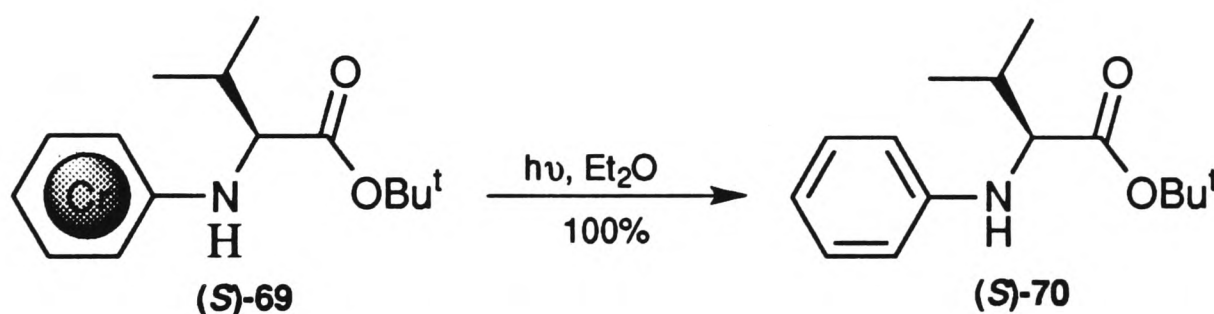
Preparation of (S)-[N-phenylvaline *t*-butyl ester] chromium tricarbonyl (S)-69 with 3-quinuclidinol as an amine catalyst



To a DMF (0.2 cm³) 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 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, 37%) and the decomplexed product (S)-**70** (0.02 g, 17%). ¹H nmr spectroscopic analysis was identical with that obtained earlier for this compound.

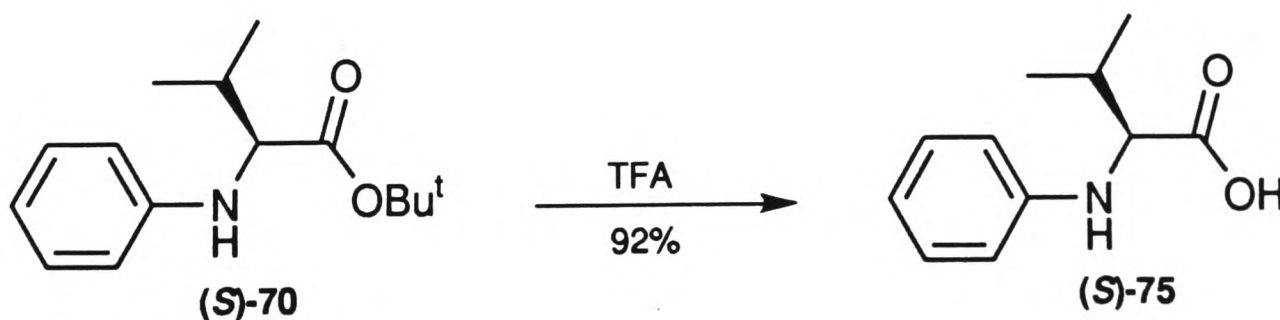
Preparation of (S)-[N-phenylvaline *t*-butyl ester] chromium tricarbonyl (S)-69 at 50°C

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.

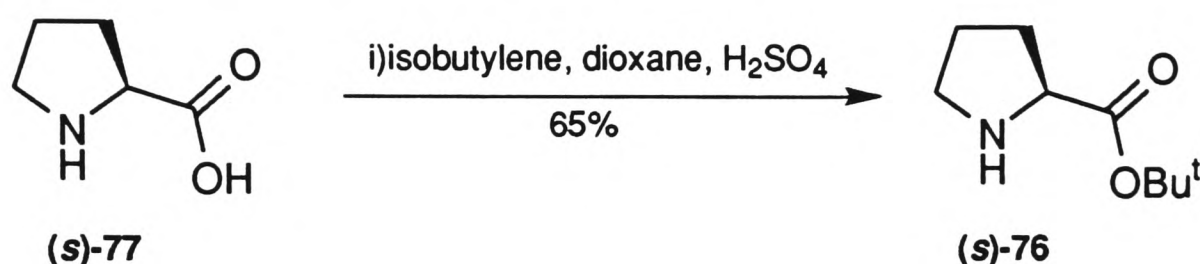
Preparation of (S)-N-phenylvaline (S)-75



(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

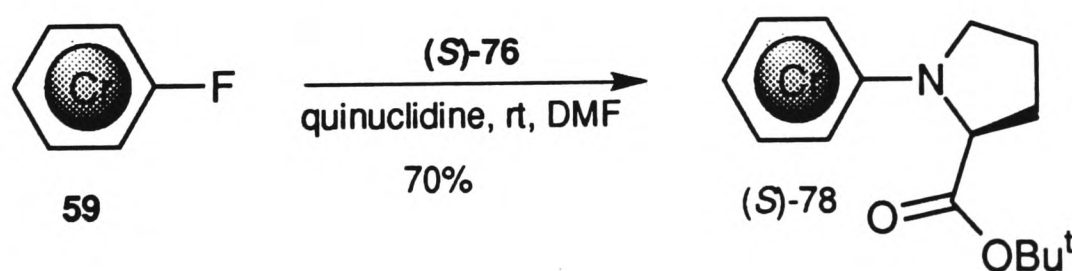
acid was subsequently removed *in vacuo* and the resultant oil dissolved in a minimum amount of CHCl_3 and basified with 1 N NaOH. The aqueous solution was then extracted twice with CHCl_3 and then acidified with concentrated hydrochloric acid to pH 4. At this pH, the free acid crystallised out and was 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; $[\alpha]_{\text{D}}^{22}$ -86.77 (c 0.31, EtOH); {lit.⁶, $[\alpha]_{\text{D}}^{22}$ -86.0 (1.2% EtOH)}; δ_{H} (300 MHz; CD_3OD) 7.11 (2H, m, Ph), 6.65 (3H, m, Ph), 3.74 (1H, d, J 6.4, CHCO_2), 2.16 (1H, m, CH_3CH), 1.09 (3H, d, J 7.1, CHCH_3) 1.03 (3H, d, J 7.1, CHCH_3).

Preparation of (*S*)-proline *t*-butyl ester⁴ (*S*)-**76**



To a 500 cm^3 round bottom flask containing a solution of (*S*)-**77** (5.09 g, 43.43 mmol) in dioxane (80 cm^3) and concentrated H_2SO_4 (8 cm^3) at -78°C, was bubbled isobutylene gas (85 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 and the reaction mixture poured into a cold mixture of diethyl ether (200 cm^3) and 1N NaOH (125 cm^3). The aqueous phase was extracted with diethyl ether (3 x 50 cm^3) and the organic phase dried over MgSO_4 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%); $[\alpha]_{\text{D}}^{22}$ -40.8 (c 1.61, EtOH); {lit.⁷, $[\alpha]_{\text{D}}^{25}$ -41.5 (c 1.8, EtOH)}; δ_{H} (300 MHz; CDCl_3) 3.61 (1H, dd, J 4.8, 5.5, CHCO_2), 3.06–2.85 (2H, m, CH_2CH), 2.05 (2H, m, CH_2CH_2), 1.73 (2H, m, CH_2CH_2), 1.45 (9H, s, $\text{C}(\text{CH}_3)_3$).

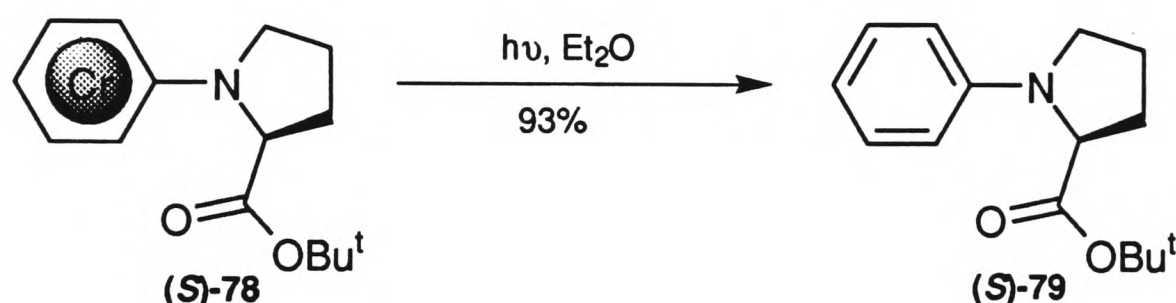
Preparation of (*S*)-[*N*-phenylproline *t*-butyl ester] chromium tricarbonyl (*S*)-**78**



To a DMF (0.3 cm^3) 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

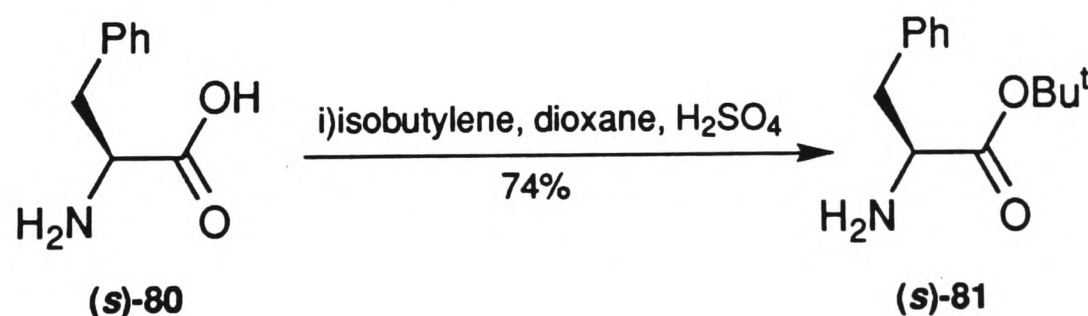
(S)-**78** (0.29 g, 70%), as a yellow solid, which was recrystallised from petrol/diethyl ether; m.p. 74-75°C. $[\alpha]_{\text{D}}^{25}$ -241.71 (*c* 0.70, CHCl₃); ν_{max} (KBr)/cm⁻¹ 2982 (N-H), 1946, 1849 (C≡O), 1736 (C=O), 1370 (N-C); δ_{H} (300 MHz; CDCl₃) 5.57 (2H, m, ArCr(CO)₃), 4.77 (2H, m, ArCr(CO)₃), 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); δ_{C} (125 MHz, CDCl₃) 234.61 (Cr(CO)₃), 171.62 (CO₂), 131.69 (ArCr(CO)₃:C_{ipso}), 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* (CI) 384 (MH⁺, 100%), 248 (MH⁺-Cr(CO)₃, 30), 146 (MH⁺-Cr(CO)₃-C₅H₁₀O₂, 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%); $[\alpha]_D^{22}$ -132.31 (c 0.78, CHCl₃); ν_{max} (CHCl₃)/cm⁻¹ 1734 (C=O), 1369 (N-C), 1245 (C-N), 1216 (C=O); δ_{H} (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); δ_{C} (125 MHz, CDCl₃) 173.78 (CO₂), 146.85 (Ph:C_{ipso}), 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 (CI) 248.165026. C₁₅H₂₂NO₂ (MH⁺) requires 248.165054; *m/z* (CI) 248 (MH⁺, 73%), 192 (MH⁺-Bu^t, 30).

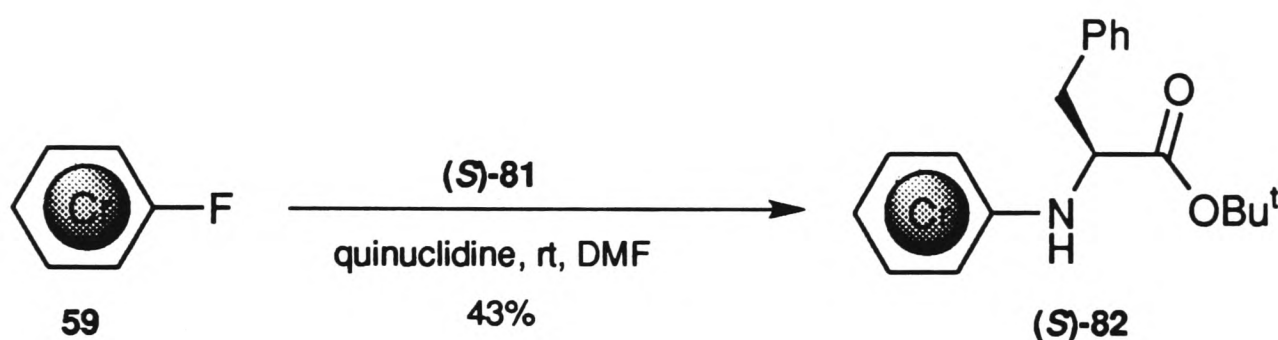
Preparation of (S)-phenylalanine *t*-butyl ester⁴ (S)-81



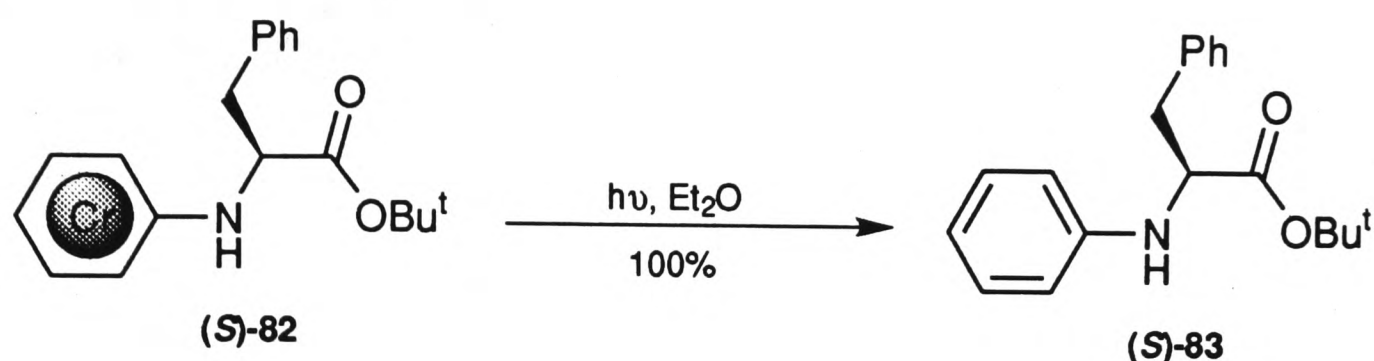
To a 250 cm³ round bottom flask containing a solution of (*S*)-**80** (5.0 g, 30.27 mmol) in dioxane (80 cm³) and concentrated H₂SO₄ (5 cm³) at -78°C, was bubbled

isobutylene gas (50 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 flask and the reaction mixture poured into a cold mixture of diethyl ether (200 cm³) and 1N NaOH (125 cm³) and the aqueous phase was extracted with diethyl ether (3 x 50 cm³). The organic phase was then dried over MgSO₄ and concentrated *in vacuo*, to give an oil. Purification of the oil by column chromatography on silica gel (50% petrol/ethyl acetate) afforded (*S*)-**81** as a yellow oil (4.97 g, 74%); [α]_D²² +24.2 (neat); {lit.⁷, [α]_D²⁵ +24.6 (neat)}; δ_{H} (300 MHz; CDCl₃) 7.35-7.21 (5H, m, Ph), 3.62 (1H, dd, *J* 7.7, 5.7, CH₂CH), 3.06, 2.85 (2H, AB of ABX system, *J*_{AB} 13.5, *J*_{AX} 7.8, *J*_{BX} 5.6, CH₂Ph), 1.57 (2H, s, NH₂), 1.43 (9H, s, C(CH₃)₃).

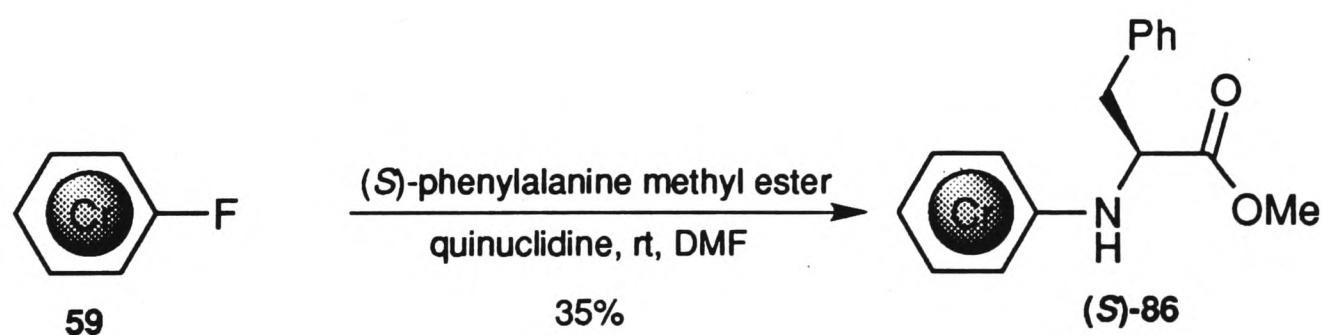
Preparation of (*S*)-[η^6 -*N*-phenyl(phenylalanine *t*-butyl ester)] chromium tricarbonyl (*S*)-82****



To a DMF (0.2 cm³) 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. [α]_D²² +75.12 (*c* 1.17, CHCl₃); ν_{max} (KBr)/cm⁻¹ 3020 (N-H), 1961, 1882 (C≡O), 1729 (CO₂); δ_{H} (500 MHz; CDCl₃) 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, CHCO₂), 3.05 (2H, AB of ABX system, *J*_{AB} 13.9, *J*_{AX} 6.2, *J*_{BX} 6.5, CH₂Ph), 1.40 (9H, s, C(CH₃)₃); δ_{C} (125 MHz; CDCl₃) 234.18 (Cr(CO)₃), 170.61 (CHC(=O)₂), 135.83 (Ph), 131.50 (ArCr(CO)₃:C_{ipso}), 129.56, 128.51, 127.12 (Ph), 96.44, 96.23, 83.15 (ArCr(CO)₃:C), 82.98 (C(CH₃)₃), 76.46, 74.82 (ArCr(CO)₃:C), 57.57 (NHCH), 39.13 (CH₂Ph), 27.80 (C(CH₃)₃); *m/z* (CI) 434 (MH⁺, 59%), 298 (MH⁺-Cr(CO)₃, 93), 293 (100), 196 (MH⁺-Cr(CO)₃-C₅H₁₀O₂, 20); (Found C, 60.77; H, 5.12; N, 3.18. C₂₂H₂₃NO₅Cr requires C, 60.97; H, 5.35; N, 3.22%).

Preparation of (S)-N-phenylphenylalanine *t*-butyl ester (S)-83

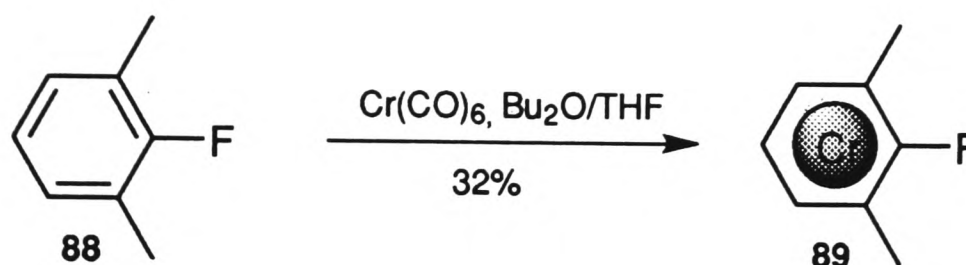
An ether solution of (S)-82 (0.10 g, 0.23 mmol) was allowed to stand in direct sunlight for 2 days, after which it was filtered through deactivated alumina, the solvent removed *in vacuo* to yield the product (S)-83 as a white solid (0.67 g, 100%), m.p. 81–82°C. $[\alpha]_{\text{D}}^{22} +21.43$ (*c* 0.63, CHCl_3); ν_{max} (KBr)/ cm^{-1} 3359 (N-H), 1705 (CO_2), 1305 (N-H); δ_{H} (500 MHz; CDCl_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_2), 4.15 (1H, br s, NH), 3.11 (2H, d, *J* 6.4, PhCH_2), 1.35 (9H, s, $\text{C}(\text{CH}_3)_3$); δ_{C} (125 MHz, CDCl_3) 172.24 (CO_2), 146.62 (Ph: C_{ipso}), 136.70 (Ph: C_{ipso}), 129.50, 129.25, 128.33, 126.81, 118.19, 113.63 (Ph), 81.73 ($\text{C}(\text{CH}_3)_3$), 58.17 (NHCH), 38.66 (CH_2Ph), 27.90 ($\text{C}(\text{CH}_3)_3$); *m/z* (CI) 298 (MH^+ , 100), 242 $\text{MH}^+ - t\text{-Bu}$, 48); Accurate mass (CI) 298.1815. $\text{C}_{19}\text{H}_{23}\text{NO}_2$ (MH^+) requires 298.18070.

Preparation of (S)-[η^6 -N-phenyl(phenylalanine methyl ester)] chromium tricarbonyl (S)-86

To a DMF (0.5 cm^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. $[\alpha]_{\text{D}}^{22} +60.33$ (*c* 0.31, CHCl_3); ν_{max} (KBr)/ cm^{-1} 3027 (N-H), 1942, 1855 ($\text{Cr}(\text{CO})_3$), 1723 ($\text{C}=\text{O}$); δ_{H} (500 MHz; CDCl_3) 7.32–7.16 (5H, m, Ph), 5.47 (2H, m, $\text{ArCr}(\text{CO})_3$), 4.78 (2H, m, $\text{ArCr}(\text{CO})_3$), 4.53 (1H, m, $\text{ArCr}(\text{CO})_3$), 4.18 (1H, d, *J* 6.4, NH), 4.08 (2H, m, CHCO_2), 3.74 (3H, s, OCH_3), 3.13, 3.06, (2H, AB of ABX system, *J*_{AB} 13.6, *J*_{AX} 6.6, *J*_{BX} 5.9, CH_2Ph); δ_{C} (125 MHz, CDCl_3) 234.05 ($\text{Cr}(\text{CO})_3$), 172.07 ($\text{C}=\text{O}$), 135.49

(ArCr(CO)₃:C_{ipso}), 130.80 (ArCr(CO)₃:C_{ipso}), 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**

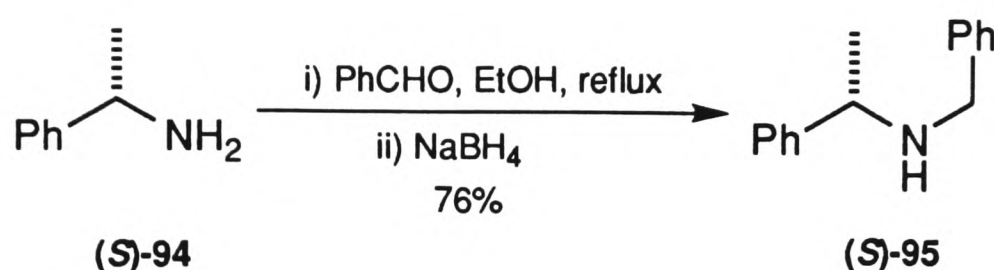


To a solution of **88** (3 g, 24.16 mmol) in Bu₂O:THF (10:1, 110 cm³) was added chromium hexacarbonyl (8.0 g, 36.24 mmol) and the reaction mixture heated to reflux under nitrogen for 48 h. The reaction was then cooled and filtered under nitrogen, through a short column of active alumina and washed with 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; ν_{max} (KBr)/cm⁻¹ 1951, 1855 Cr(CO)₃; δ_{H} (200 MHz; CDCl₃) 5.21 (2H, dd, *J* 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.

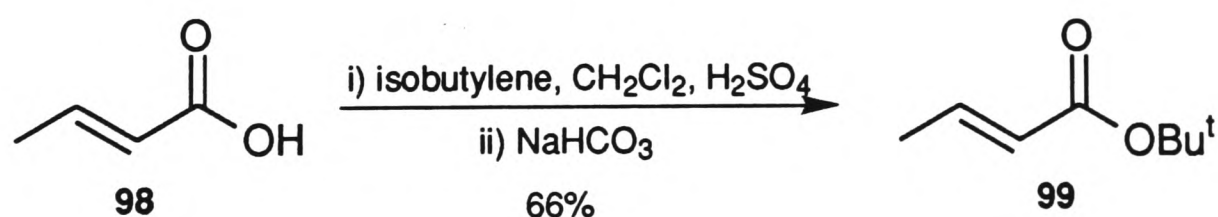
Attempted Synthesis of [(*R*)-*N*-(methyl 2-methylacetate)-2,6-dimethylbenzene] chromium tricarbonyl (*R*)-**91**



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-benzyl-N- α -methylbenzylamine) (*S*)-95

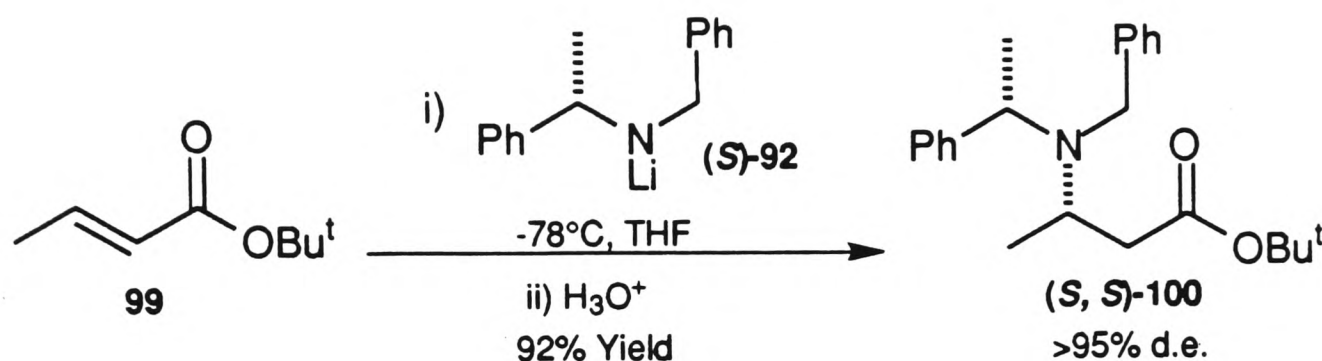
Freshly distilled benzaldehyde (8.94 g, 84.2 mmol) was added to a solution of (*S*)-94 (10 g, 82.52 mmol) in ethanol (500 cm³) and the mixture heated at reflux for 6h. The resultant solution was cooled to 0°C, sodium borohydride (2.4 g, 63.44 mmol) was added cautiously, and the resultant turbid solution 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%); [α]_D²² -53.8 (c 3.2, EtOH); {lit.⁸, [α]_D²² -53.6 (3.86 EtOH)}; δ_{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, *J*_{AB} 13.1, NCH₂Ph), 1.69 (1H, br s, NH), 1.39 (3H, d, *J* 6.6, NCHCH₃).

Preparation of (*E*)-*t*-butyl crotonate⁹ 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 through 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

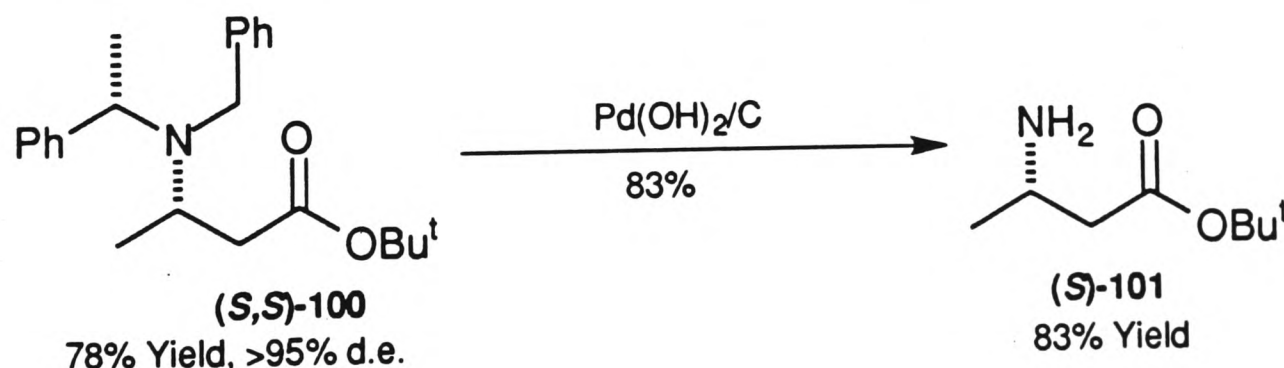
magnesium sulphate, filtered and concentrated to give a crude oil which was purified by flash chromatography [silica; petrol/diethyl ether, 10:1] to give **99** as a colourless oil (5.6 g, 66%); δ_{H} (CDCl_3 ; 300 MHz) 6.87 (1H, dq, J 15.5, 6.7, CH_3CH) 5.75 (1H, dq, J 15.5, 1.7, CHCO_2), 1.85 (3H, dd, J 6.7, 1.7, CH_3CH), 1.50 (9H, s, $\text{C}(\text{CH}_3)_2$).

Preparation of (3*S*, α *S*)-*t*-butyl 3-(*N*-benzyl-*N*- α -methylbenzyl)aminobutanoate (3*S*, α *S*)-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 (3*S*, α *S*)-**100** as a colourless oil (14.6 g, 92%, > 95% d.e.); $[\alpha]_{\text{D}}^{22} +4.36$ (c 0.90, CHCl_3), {lit.,⁸ $[\alpha]_{\text{D}}^{25} -4.3$ (c 1.06, CH_2Cl_2)}; δ_{H} (300 MHz; CDCl_3) 7.41-7.18 (10H, m, Ph), 3.87 (1H, q, J 6.7, PhCHN), 3.75, 3.60 (2H, AB system, J_{AB} 15.0, PhCH_2N), 3.46-3.39 (1H, m, CH_3CHN), 2.28, 1.97 (2H, AB of ABX system, J_{AB} 14.1, J_{AX} 4.7, J_{BX} 9.1, CH_2CO_2), 1.39 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.32 (3H, d, J 6.8, PhCHCH_3), 1.12 (3H, d J 6.7, CHCH_3).

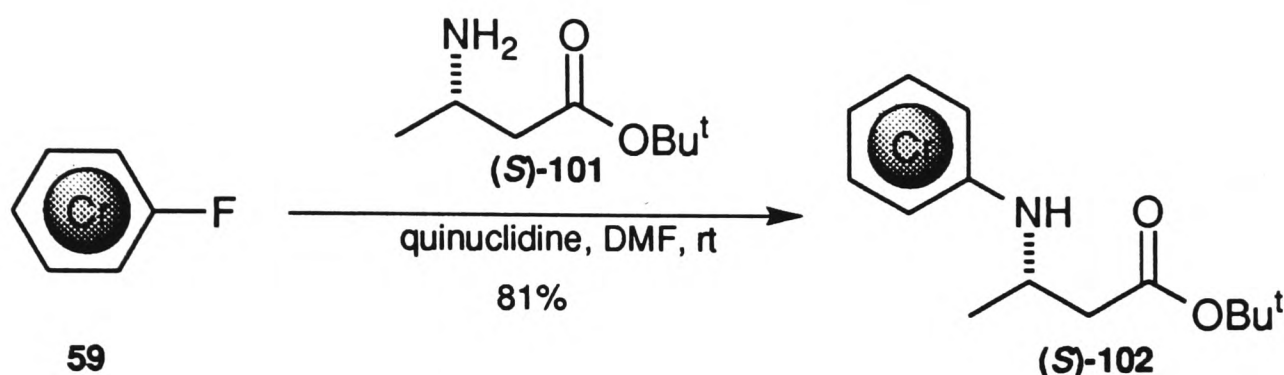
Preparation of (3*S*)-*t*-butyl 3-aminobutanoate (3*S*)-101



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

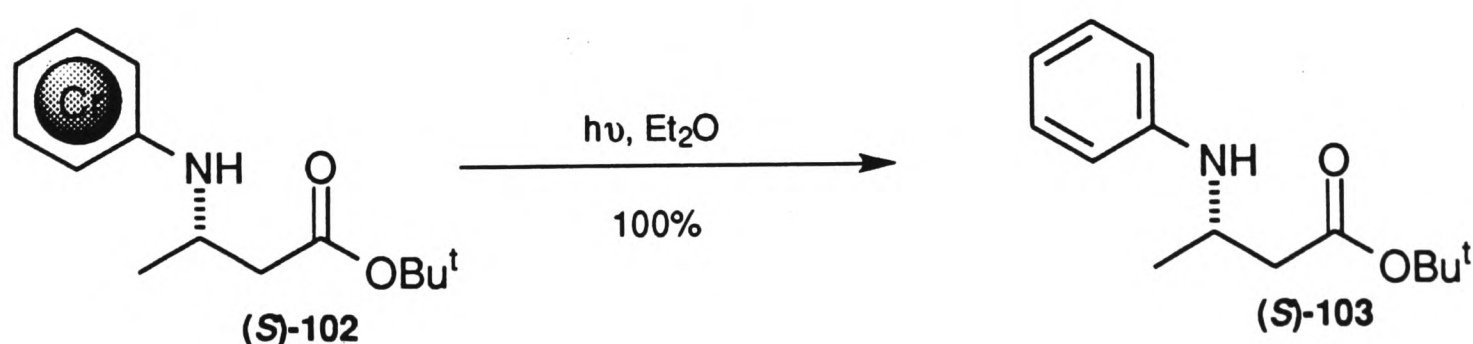
was then filtered through Celite® and the solvent removed *in vacuo* to give a crude oil which was purified by flash chromatography [methanol/ethyl acetate 10:1] giving (*S*)-**101** as a colourless oil (0.75 g, 83%) [α]_D²² -35.03 (*c* 1.73, CHCl₃) δ_{H} (300 MHz; CDCl₃) 3.37 (1H, m, CH₃CH), 2.39-2.21 (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 [(3*S*)-*N*-(*t*-butyl 3-butanoate) aniline] chromium tricarbonyl (*S*)-**102**



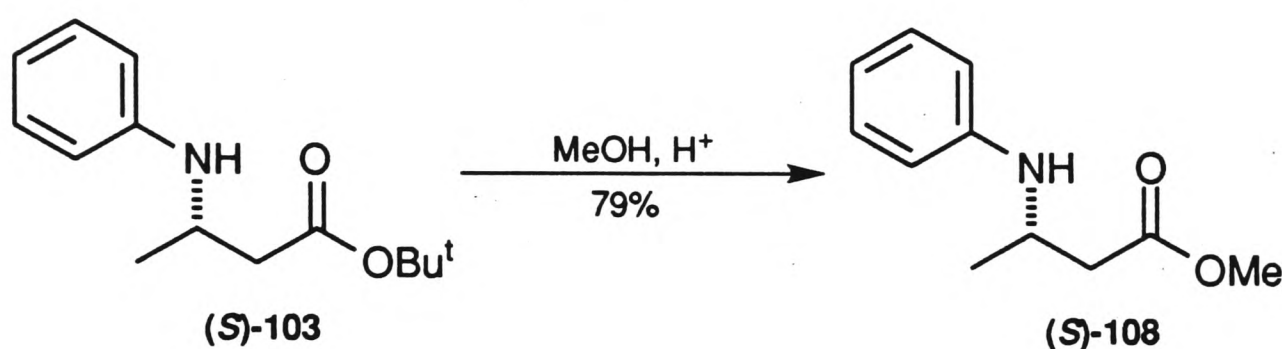
To a DMF (0.5 cm³) solution of **59** (1.5 g, 6.46 mmol) and quinuclidine (0.70 g, 6.30 mmol) was added (*S*)-**101** (2.0 g, 12.56 mmol) and the reaction was allowed to stir at room temperature for 14 days. Dichloromethane was then added to the reaction and the reaction mixture was then filtered through 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. [α]_D²⁵ -9.23 (*c* 0.46, CHCl₃); ν_{max} (KBr)/cm⁻¹ 1963, 1823 (C≡O), 1703 (CO₂), 1369 (N-C), 1309 (C-N); δ_{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, CHCH₃); δ_{C} (125 MHz, CDCl₃) 234.59 (Cr(CO)₃), 171.19 (CH₂CO₂), 132.17 (ArCr(CO)₃:C_{ipso}), 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* (CI) 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 (3*S*)-*N*-(*t*-butyl 3-butanoate) aniline (*S*)-**103**



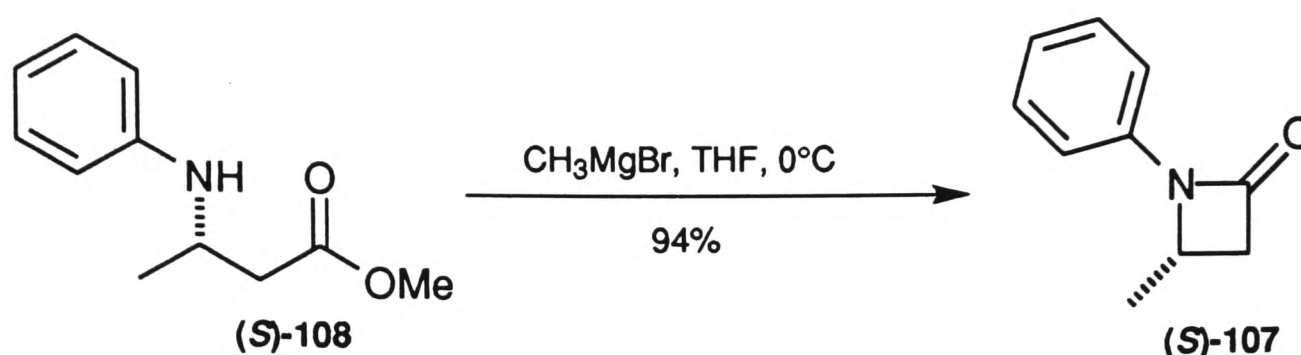
An ether solution of (*S*)-**102** (1.36 g, 3.66 mmol) was allowed to stand in direct sunlight for 2 days, after which it was filtered through deactivated alumina, the solvent was removed *in vacuo* and purified by column chromatography [silica, petrol/diethyl ether, 10:1] to yield (*S*)-**103** as a colourless oil (0.862 g, 100%). $[\alpha]_{\text{D}}^{25} + 4.38$ (*c* 0.85, CHCl_3); ν_{max} (CHCl_3)/ cm^{-1} 1718 (C=O), 1369 (N-C), 1303 (C-N); δ_{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_3CH), 2.56, 2.36 (AB of ABX system, *J*_{AB} 14.7, *J*_{AX} 5.2, *J*_{BX} 6.8, CH_2CO_2), 1.46 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.29 (3H, d, *J* 6.4, CHCH_3); δ_{C} (125 MHz, CDCl_3) 171.19 (CO_2), 146.90 (Ph:C_{ipso}), 129.29, 117.45, 113.47 (Ph), 80.71 ($\text{C}(\text{CH}_3)_3$), 46.12 (NHCH), 42.26 (CH_2CO_2), 28.07 ($\text{C}(\text{CH}_3)_3$), 20.46 (CHCH_3). *m/z* (CI) 236 (MH^+ , 100), 180 (39), 120 (42); Accurate mass 236.1654. $\text{C}_{14}\text{H}_{21}\text{NO}_2$ requires 236.1651.

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



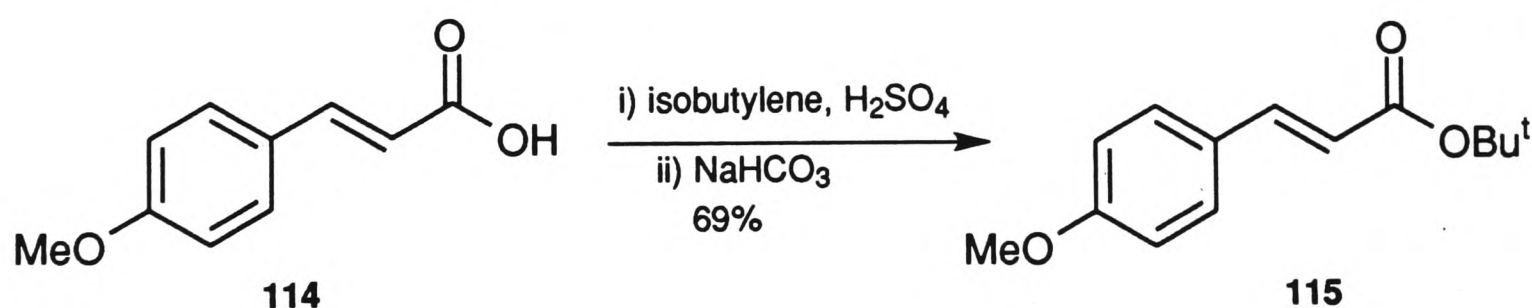
A methanolic solution of (*S*)-**103** (0.71 g, 3.03 mmol) was allowed to stir at room temperature overnight. The next day the solvent was removed *in vacuo* and the resulting solid was taken up in aqueous sodium bicarbonate (50 cm^3), extracted with dichloromethane (2 X 100 cm^3). The combined organic 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%). $[\alpha]_{\text{D}}^{21} + 7.51$ (*c* 0.95, CHCl_3) {lit.,⁴ for *R* $[\alpha]_{\text{D}}^{21} - 7.0$ (*c* 2.0, CHCl_3)}; ν_{max} (CHCl_3)/ cm^{-1} 1729 (C=O), 1504 (N-H), 1367 (N-C, 1299 (C-N); δ_{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_2CO_2), 3.87 (3H, d, *J* 6.3, CHCH_3); δ_{C} (125 MHz, CDCl_3) 172.25 (CO_2), 146.70 (Ph:C_{ipso}), 129.36; 117.75; 113.64 (Ph), 51.62 (OCH_3), 46.01 (NHCH), 40.73 (CH_2CO_2), 20.62 (CHCH_3); *m/z* (CI) 194 (MH^+ , 100), 120 (17).

Preparation of (S)-4-methyl-N-phenylazetidin-2-one (S)-107



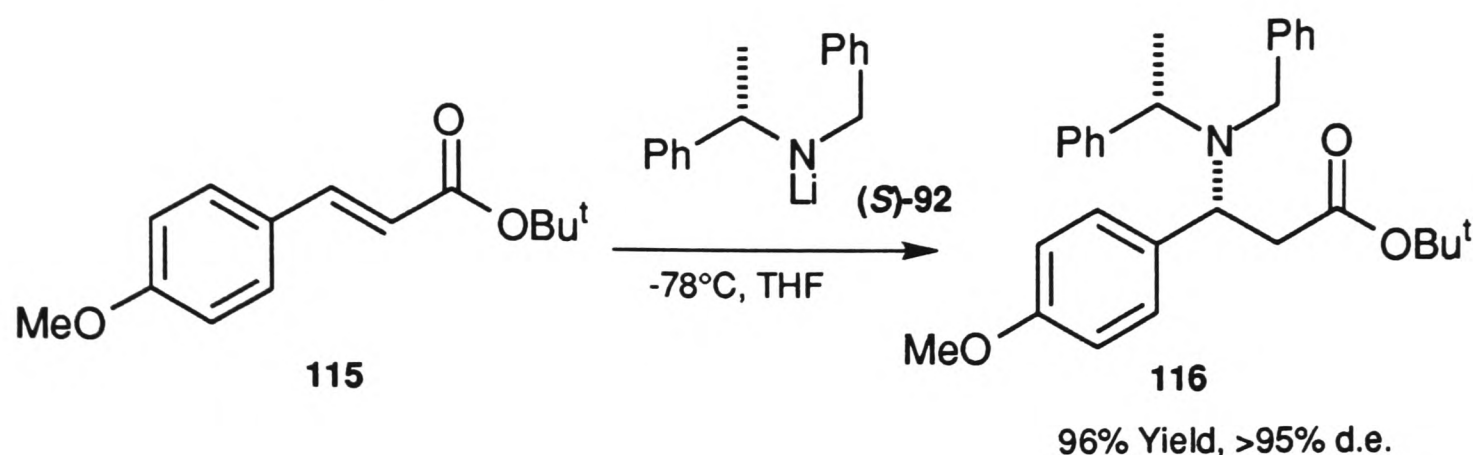
3.0 M Methyl magnesium bromide (0.25 cm³, 0.75 mmol) was added dropwise to a diethyl ether solution (2 cm³) of (*S*)-**108** (0.096 g, 0.497 mmol) at 0°C, whereupon a white precipitate formed. The reaction was stirred at 0°C for 1 h and then quenched with phosphate buffer (pH 7, 2 cm³) and warmed to room temperature. The mixture was then extracted with brine (2 x 50 cm³), 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%); [α]_D²² +113.9. (*c* 0.61, CHCl₃) {lit.¹⁰ for (*R*)-**107**, [α]_D²⁵ -117.5, (*c* 1.34, CHCl₃); δ_{H} (300 MHz; CDCl₃) 7.40-7.31 (4H, m, Ph), 7.11-7.06 (1H, m, Ph), 4.22-4.13 (1H, m, CH₃CH), 3.27; 2.71 (2H, AB of ABX system, J_{AB} 15.1, J_{AX} 2.5, J_{BX} 5.5, CH₂CO), 1.53 (3H, d, J 6.1, CH₃).

Preparation of (*E*)-*t*-butyl 4-methoxycinnamate 115



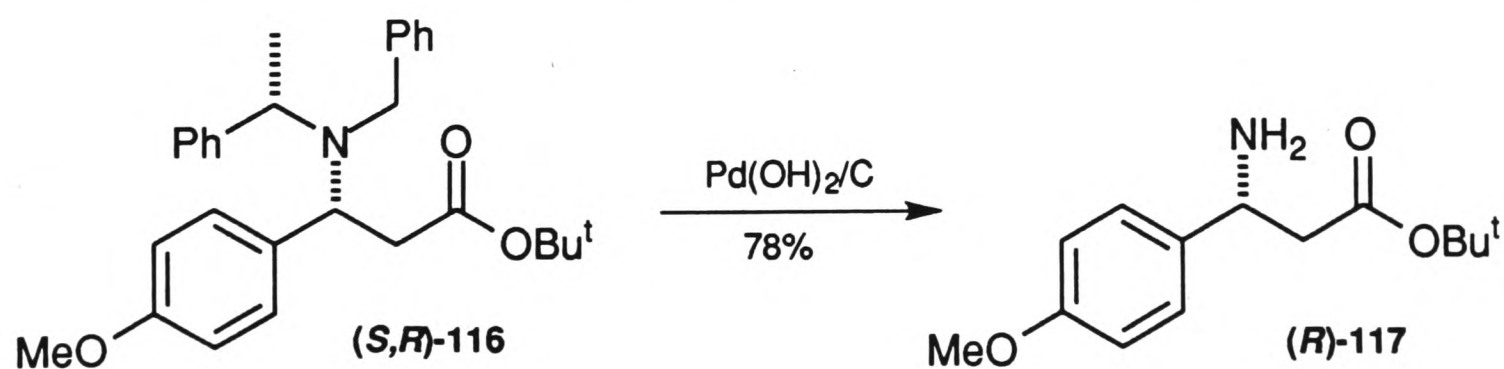
To a stirred suspension of **114** (5.0 g, 28.05 mmol) in dichloromethane (50 cm³) at -78°C was added concentrated sulphuric acid (2 cm³). Isobutylene gas (20 cm³) was then bubbled through the solution and the resultant suspension allowed to warm to room temperature overnight. The acidic suspension was 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; δ_{H} (300 MHz; CDCl₃) 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, CHCO₂), 3.84 (3H, s, OCH₃), 1.53 (9H, s, C(CH₃)₃).

Preparation of (3*R*, α *S*)-*t*-butyl 3-(*N*-benzyl-*N*- α -methylbenzyl)amino-3-(4-methoxyphenyl)propionate **116**



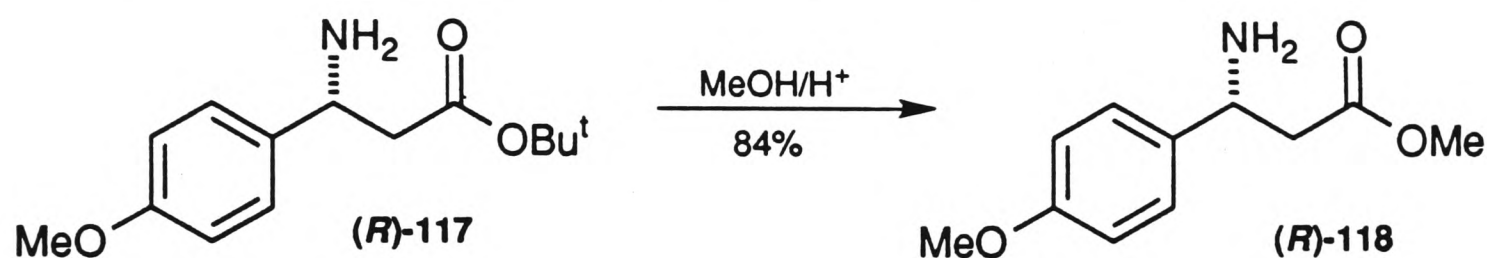
To a THF solution (100 cm³) of (*S*)-**95** (5.38 g, 25.50 mmol) at -78°C was added 1.6M butyllithium (14.6 cm³, 23.37 mmol) to generate the amide (*S*)-**92** and the resulting pink solution was stirred at -78°C for 30 min. To this was added a THF solution of **115** (5.0 g, 21.25 mmol) at -78°C and 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 cm³) 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]_D²² - 2.69 (c 1.41, CHCl₃); ν_{max} (CHCl₃)/cm⁻¹ 1716 (C=O), 1369 (C-N); δ_{H} (500 MHz; CDCl₃) 7.41 (2H, d, *J* 8.5, Ar), 7.33-7.23 (5H, m, Ph), 6.87 (2H, d, *J* 8.5, Ar), 4.37-4.34 (1H, m, CH₃CHN), 3.99 (1H, q, *J* 6.8, CHCH₃), 3.81 (3H, s, OCH₃), 3.67 (2H, s, CH₂Ph), 2.53-2.47 (2H, AB of ABX system, *J*_{AB} 14.5, *J*_{AX} 5.0 and *J*_{BX} 10.2, CH₂CO₂), 1.26 (3H, d, *J* 6.8, CHCH₃), 1.24 (9H, s, C(CH₃)₃); δ_{C} (125 MHz, CDCl₃) 171.19 (CO₂), 158.60; 144.30; 141.85; 133.86; (Ph:C_{ipso}), 129.30; 128.07; 127.95; 127.83; 126.75; 126.44; 113.41 (Ph), 80.08 (C(CH₃)₃), 59.12; 57.06 (CHN), 55.20 (OCH₃), 50.77 (CH₂N), 38.62 (CH₂CO₂), 27.83 (C(CH₃)₃), 16.46 (CH₃CH); *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. C₂₉H₃₅NO₃ requires C, 78.17; H, 7.92; N, 3.14%).

Preparation of (3*R*) 3-(4-methoxyphenyl)-3-aminopropionate (3*R*)-**117**

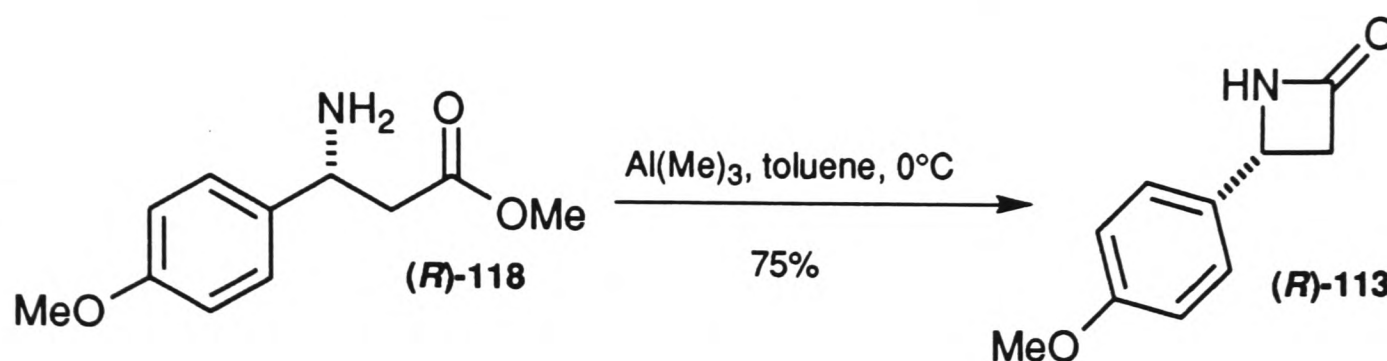


To an ethanolic solution of the β -amino ester **116** (4.0 g, 8.98 mmol) in a Fischer-Porter bottle, was added palladium hydroxide on carbon (2.0 g, 50% by weight) and the suspension stirred overnight at 50°C and under 5 atm of hydrogen. The reaction mixture was then filtered through Celite® and the 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%) [α]_D²² +10.41 (c 0.73, CHCl₃); $\nu_{\max}$ (CHCl₃)/cm⁻¹ 1718 (CO₂), 1612 (N-H), 1302 (C-N); δ_{H} (500 MHz; CDCl₃) 7.27 (2H, d, *J* 8.7, Ar), 6.86 (2H, d, *J* 8.7, Ar), 4.35-4.32 (1H, m, NH₂CH), 3.80, (3H, s, OCH₃), 2.57-2.53 (2H, m, CH₂CO₂), 1.43 (9H, s, C(CH₃)₃); δ_{C} (125 MHz, CDCl₃) 171.42 (CO₂), 158.77; 136.96; (Ar:C_{ipso}), 127.36; 113.85 (Ph), 80.66 (C(CH₃)₃), 55.27 (NHCH), 52.15 (OCH₃), 45.44 (CH₂CO₂), 28.07 (C(CH₃)₃); *m/z* (CI) 252 (MH⁺, 18%), 235 (46), 179 (27), 136 (100); (Found C, 66.79; H, 8.27; N, 5.39. C₁₄H₂₁NO₃ requires C, 66.91; H, 8.42; N, 5.57%).

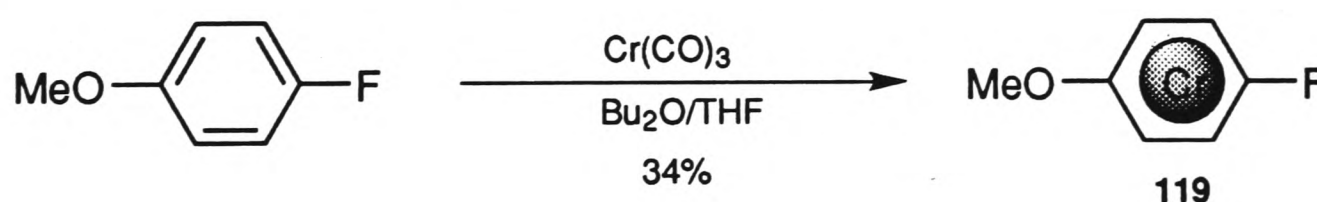
Preparation of (3*R*) methyl 3-(4-methoxyphenyl)aminopropionate (*R*)-118



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 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%); $\nu_{\max}$ (CHCl₃)/cm⁻¹ 1731 (C=O), 1520 (N-H), 1303 (C-N), 1251 (C-O-C); δ_{H} (500 MHz; CDCl₃) 7.31 (2H, m, Ar), 6.89 (2H, m, Ar), 4.39 (1H, t, *J* 6.8, NH₂CH), 3.81, (3H, s, CH₃OAr), 3.69 (3H, s, CO₂CH₃), 2.65 (2H, d, *J* 6.9, CH₂CO₂), 1.71 (2H, br s, NH₂); δ_{C} (125 MHz; CDCl₃) 172.53 (CO₂), 158.86; 136.78; (Ar:C_{ipso}), 127.23, 113.96, (Ar) 55.27 (NHCH), 51.99 (ArOCH₃), 51.63 (CO₂CH₃), 44.06 (CH₂CO₂); *m/z* (CI) 210 (MH⁺, 55%), 193 (100), 136 (83); (Found C, 63.49; H, 7.68; N, 6.66. C₁₁H₁₅NO₃ requires C, 63.14; H, 7.23; N, 6.69. The compound (*R*)-**118** was converted to its 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; [α]_D²² -90.2 (c 1.40, MeOH) {lit.¹¹, [α]_D²⁴ -91.5 (c 1.42, MeOH)}.

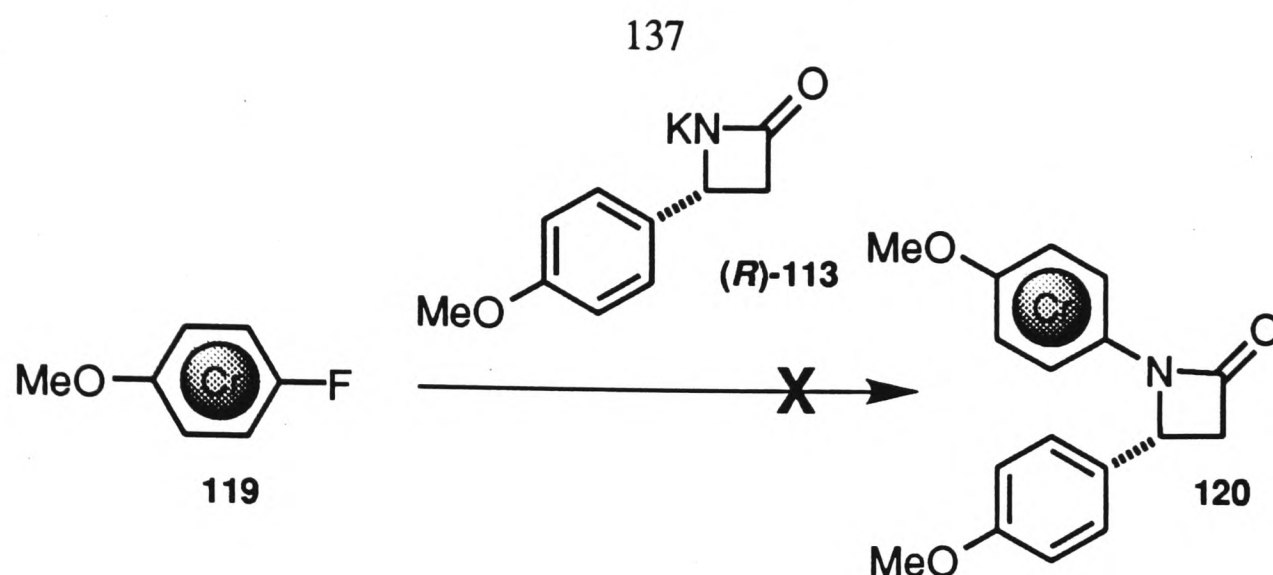
Preparation of (4*R*)-4-(4-methoxyphenyl)-2-azetidinone (*R*)-113

2.0 M Trimethylaluminium (0.43 cm³, 0.86 mmol) was added dropwise to a toluene solution (1 cm³) 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 Et₂O 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; $[\alpha]_{\text{D}}^{22} +131.3$ (*c* 0.12, CHCl₃); ν_{max} (KBr)/cm⁻¹ 1750 (C=O) δ_{H} (500 MHz; CDCl₃) 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, CH₂CH), 3.81 (3H, s, CH₃OAr), 3.41-2.81 (2H, AB of ABX system, *J*_{AB} 15.0, *J*_{AX} 2.4, *J*_{BX} 5.2, CH₂CO); δ_{C} (125 MHz, CDCl₃) 168.13 (CO₂), 159.55, 147.75 (Ar:C_{ipso}), 126.91, 114.18 (Ar), 55.33 (CHCH₂), 49.97 (CH₃OAr), 48.05 (CH₂CH); *m/z* (CI) 178 (MH⁺, 100%); Found C, 67.57; H, 6.57; N, 7.80. C₁₀H₁₁NO₂ requires C, 67.78; H, 6.26; N, 7.90%.

Preparation of (4-fluoroanisole) chromium tricarbonyl 119¹²

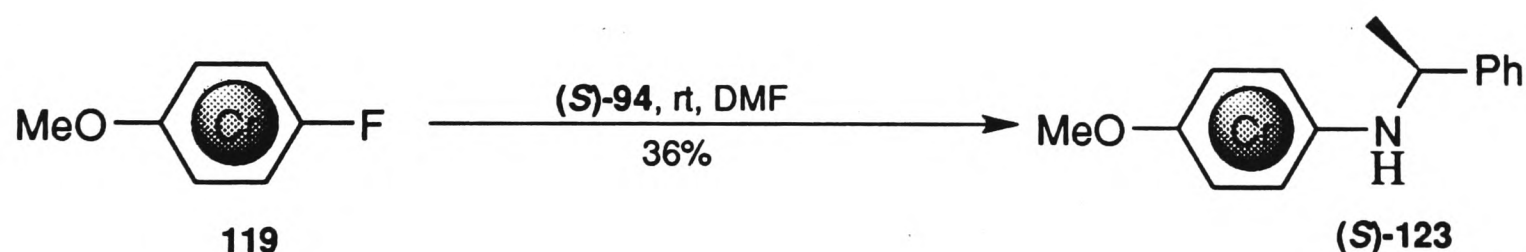
To a solution of 4-fluoroanisole (4.2 g, 33.30 mmol) in Bu₂O:THF (10:1, 110 cm³) was added chromium hexacarbonyl (4.0 g, 18.2 mmol) and the reaction mixture heated to reflux under nitrogen for 48 h. The reaction mixture was then cooled, filtered under nitrogen through a short column of active alumina and washed with petrol to remove all the Bu₂O 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; CDCl₃) 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(OCH₃)).

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 CH₂Cl₂ and filtered through deactivated alumina. The solution was then concentrated to give a crude yellow solid. ¹H nmr spectroscopic analysis of the crude reaction product showed only starting material.

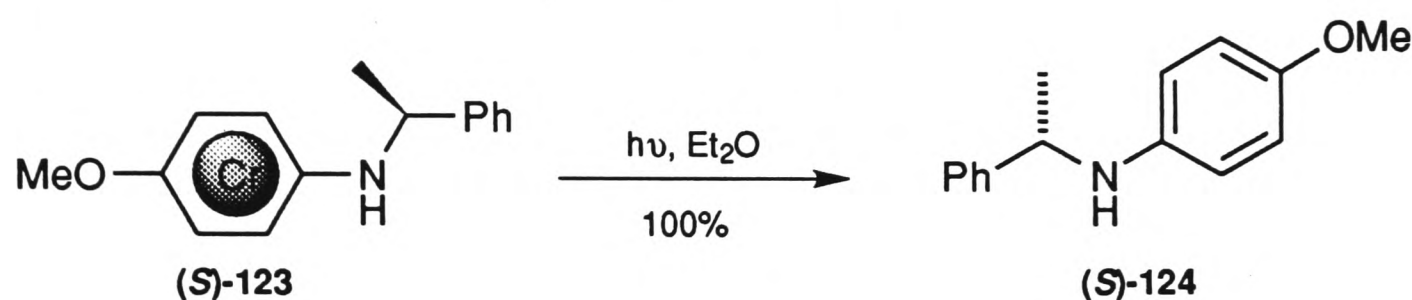
Preparation of (*S*)-[η^6 -*N*--(α -phenylethyl)4-methoxyaniline] chromium tricarbonyl 123



To a DMF (0.5 cm³) 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; $[\alpha]_{\text{D}}^{25}$ -275.2 (c 0.48, CHCl₃); ν_{max} (KBr)/cm⁻¹ 1943, 1839 (C $\equiv$ O), 1514 (N-H), 1368 (N-C), 1321 (C-N), 1272 (C-N), 1243 (C-O-C), 1029 (C-O-C); δ_{H} (300 MHz; CDCl₃) 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, CHCH₃), 4.15 (3H, s, OCH₃), 1.46 (3H, d, *J* 6.7, CHCH₃); δ_{C} (125 MHz, CDCl₃) 235.11 (Cr(CO)₃), 143.54 (Ar:C_{ipso}), 134.51 (ArCr(CO)₃:C_{ipso}), 128.99, 127.52 (Ph), 125.84

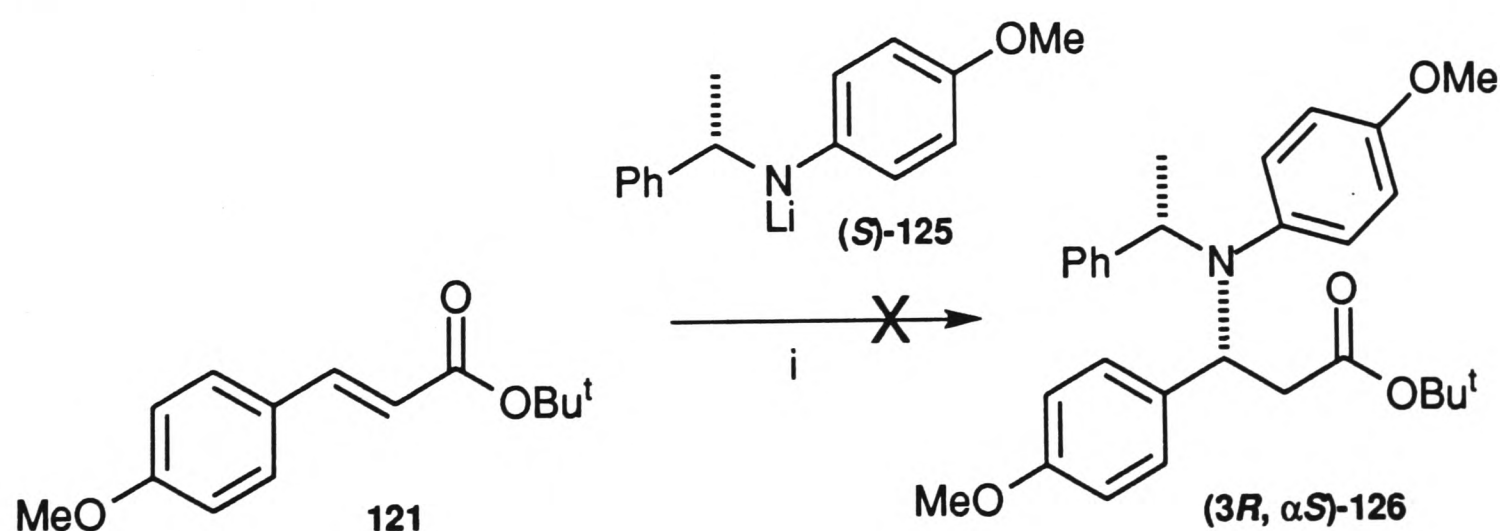
(ArCr(CO)₃:C_{ipso}), 125.58 (Ph), 82.93, 81.30, 78.07, 75.27 (ArCr(CO)₃), 56.45 (OCH₃), 54.88 (CHCH₃), 25.00 (CHCH₃); m/z (EI) 363 (M, 100%), 279 (M-(CO)₃, 100), 227 (M-Cr(CO)₃); Found C, 59.77; H, 4.94; N, 3.93. C₁₈H₁₇NO₄Cr requires C, 59.50; H, 4.72; N, 3.86%).

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%); $[\alpha]_{\text{D}}^{25}$ -8.83 (c 1.67, MeOH); ν_{max} (CHCl₃)/cm⁻¹ 3426, 1513 (N-H), 1374 (N-C), 1236 (C-N), 1224 (C-O-C), 1039 (C-O-C); δ_{H} (200 MHz; CDCl₃) 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), 3.81 (1H, br s, NH), 3.71 (3H, s, OCH₃), 1.53 (3H, d, *J* 6.7, CHCH₃); δ_{C} (125 MHz, CDCl₃) 151.85 (Ar:C_{ipso}), 145.46 (Ph :C_{ipso}), 141.55 (Ar:C_{ipso}), 128.58, 126.79, 125.86 (Ph), 114.72, 114.50 (Ar), 55.71 (CHCH₃), 54.21 (CH₃OAr), 25.12 (CHCH₃); *m/z* (CI) 228 (M⁺, 100%), 124 (30), 105 (23).

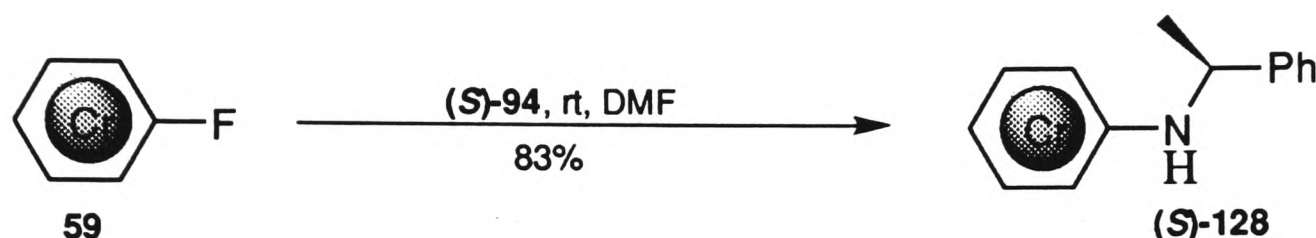
The Attempted Asymmetric Synthesis of *N*-Phenyl β -Amino Ester 126



To a THF solution (10 cm³) of (*S*)-**124** (0.112 g, 0.49 mmol) at -78°C was added 1.6M butyllithium (0.27 cm³, 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

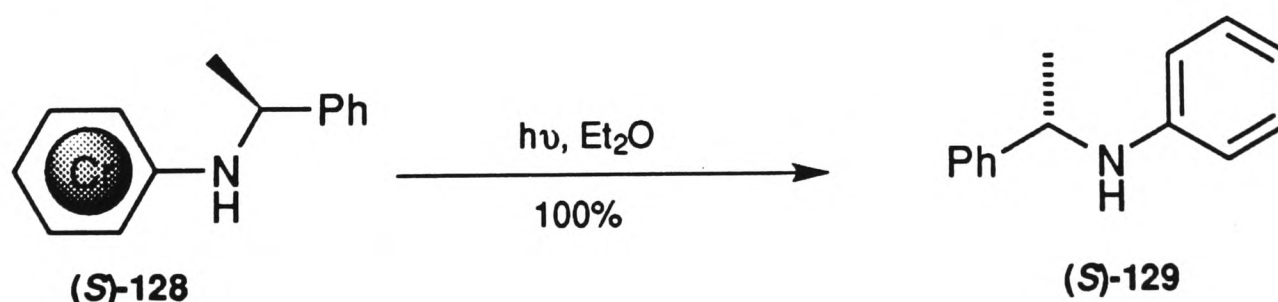
ammonium chloride (10 cm³), whereupon the solution turned yellow. The reaction mixture was extracted twice with diethyl ether. The organic extracts were combined, dried over magnesium sulphate and concentrated to give a crude brown oil. ¹H spectroscopic analysis of the crude reaction product indicated only starting material. The reaction was also repeated at a higher temperature (0°C), however only starting material was identified by analysis of the ¹H nmr spectrum.

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



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; $[\alpha]_{\text{D}}^{25}$ -369.04 (c 1.98, CHCl₃); ν_{max} (KBr)/cm⁻¹ 3410 (N-H), 1941, 1844 (Cr(CO)₃), 1493 (N-H), 1377 (N-C), 1320 (C-N), 1268 (C-N); δ_{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, d, *J* 2.5, CHNH), 1.52 (3H, d, *J* 6.8, CHCH₃); δ_{C} (125 MHz; CDCl₃) 234.58 (Cr(CO)₃), 143.38 (Ph:C_{ipso}), 131.85 (ArCr(CO)₃:C_{ipso}), 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%.

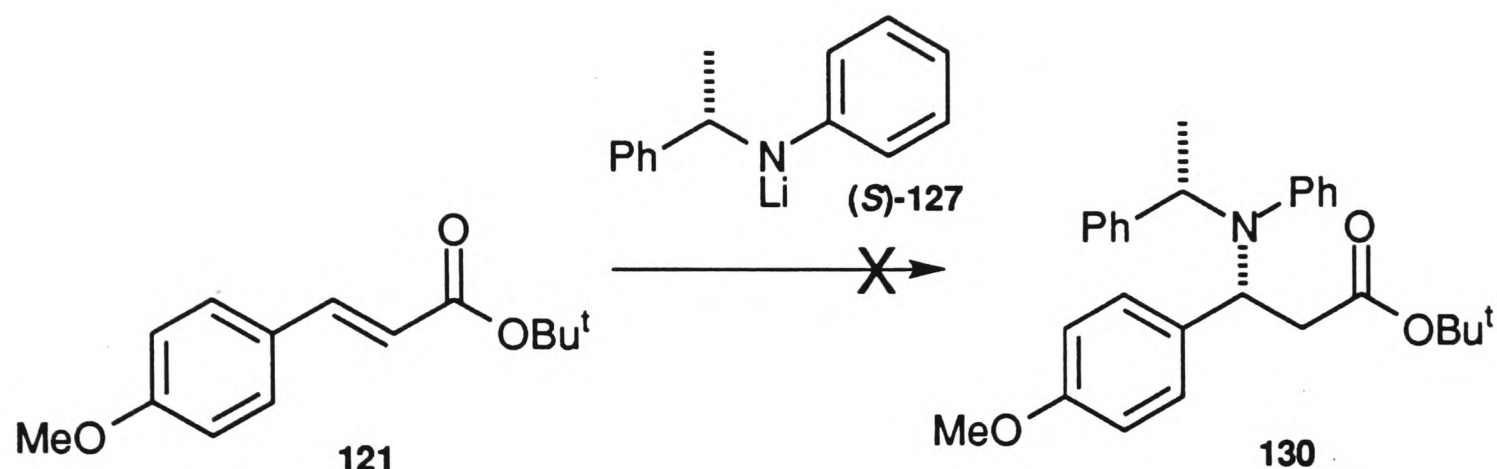
Preparation of (S)-η⁶-N--(α-phenylethyl)aniline]¹³ (S)-129



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**

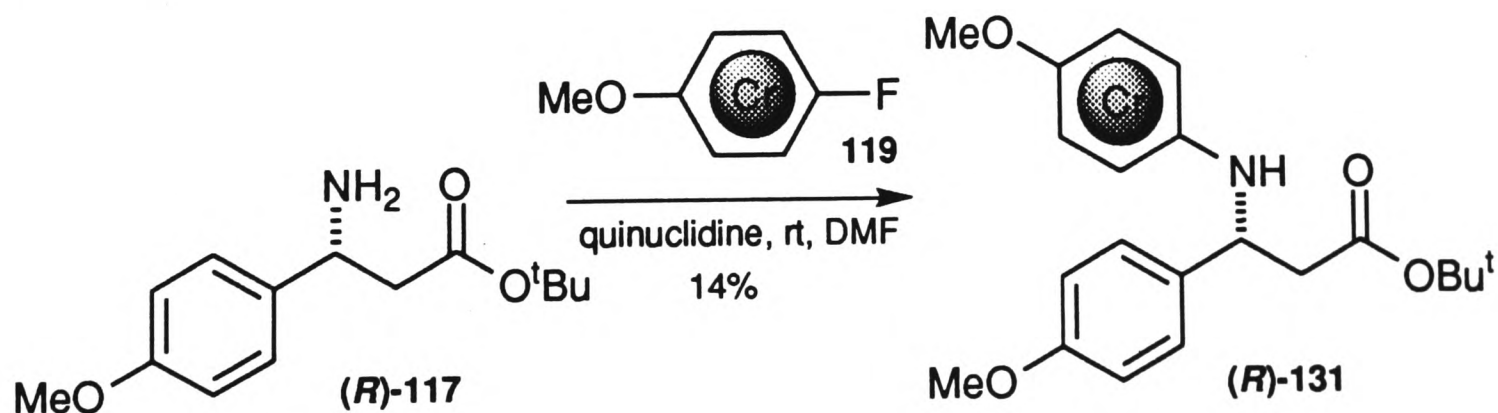
as a white solid (0.35 g, 100%); m.p. 43-45°C; $[\alpha]_{\text{D}}^{25} +20.9$ (c 0.76, MeOH) {lit.¹³, $[\alpha]_{\text{D}}^{24} +18.5$ (c 1, MeOH)}; ν_{max} (KBr)/ cm^{-1} 3410, 1503 (N-H), 1371 (N-C), 1279 (C-N); δ_{H} (200 MHz; CDCl_3) 7.39-7.23 (5H, m, Ph), 7.12 (2H, m, Ph), 6.66 (1H, m, Ph), 6.52 (2H, m, Ph), 4.52 (1H, q, J 6.7, CHCH_3), 4.03 (1H, br s, NH), 1.55 (3H, d, J 6.8, CHCH_3).

The Attempted Asymmetric Synthesis of *N*-Phenyl β -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. ^1H 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 ^1H nmr spectrum.

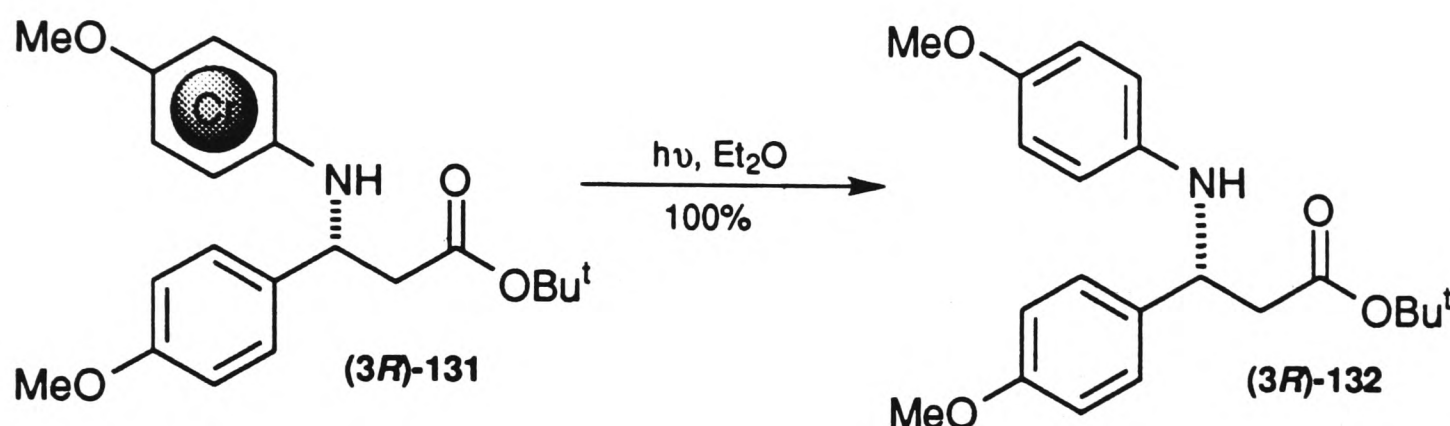
Preparation of (*3R*)-[η^6 -*N*-(*t*-butyl 3-propanoate-3-*p*-methoxybenzene) *p*-methoxyaniline] chromium tricarbonyl (*3R*)-**131**



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

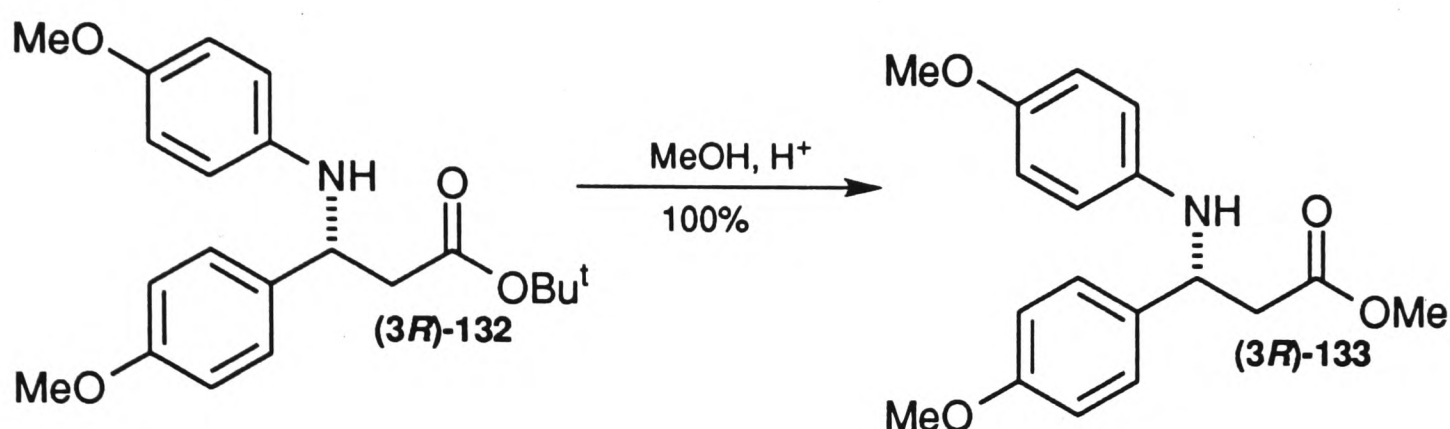
room temperature for 14 days. Dichloromethane was then added to the reaction and the reaction mixture was then filtered through basic alumina and concentrated to give a crude yellow oil. Purification by column chromatography yielded **131** as a yellow solid (0.16 g, 14%). The compound rapidly decomplexed and only satisfactory ^1H nmr spectroscopy could be secured; δ_{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, $\text{ArCr}(\text{CO})_3$), 5.15 (1H, dd, J 7.3, 2.4, $\text{ArCr}(\text{CO})_3$), 4.95 (1H, dd, J 7.2, 2.6, $\text{ArCr}(\text{CO})_3$), 4.65 (1H, m, $\text{ArCr}(\text{CO})_3$), 4.63 (1H, d, J 2.5, NH), 4.38 (1H, m, NHCH), 3.80 (3H, s, OCH_3), 3.56 (3H, s, OCH_3), 2.61 (2H, m, CH_2CO_2), 1.39 (9H, s, $\text{C}(\text{CH}_3)_3$).

Preparation of (3*R*)- η^6 -*N*-(*t*-butyl 3-propanoate-3-*p*-methoxybenzene) *p*-methoxyaniline (3*R*)-132



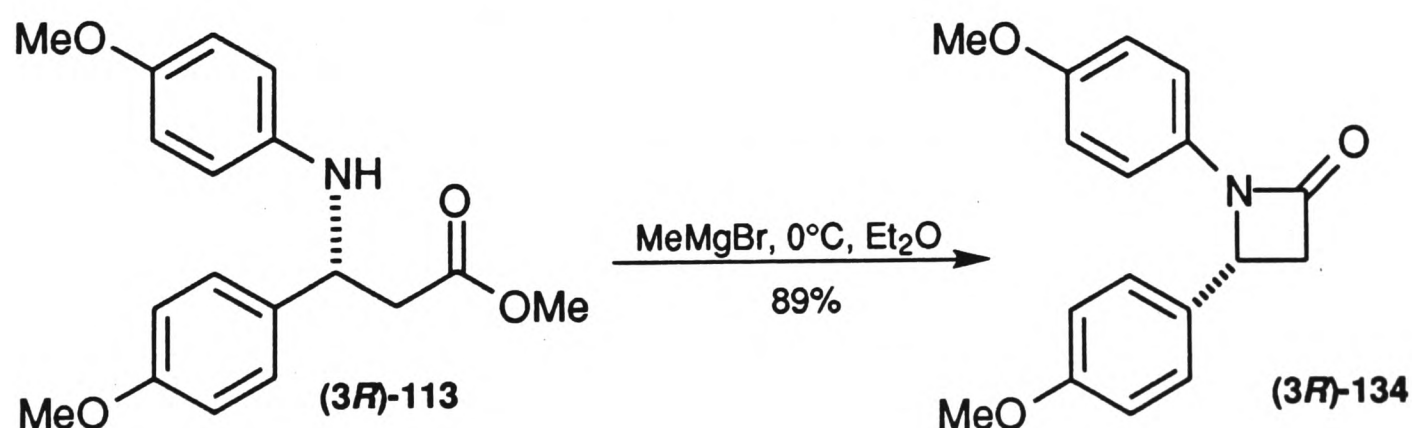
An ether solution of **(3*R*)-131** (0.15 g, 0.30 mmol) was allowed to stand in direct sunlight for 2 days, after which it was filtered through deactivated alumina to yield **(3*R*)-132** as a colourless solid (0.108 g, 100%); m.p. 95-96°C. $[\alpha]_{\text{D}}^{22} + 16.25$ (c 0.72, CHCl_3); ν_{max} (KBr)/ cm^{-1} 1708 (C=O), 1516 (N-H), 1368 (C-N), 1254 (C-O-C), 1093 (C-O-C); δ_{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), 3.79 (3H, s, $\text{CH}_3\text{OC}_6\text{H}_4$), 3.71 (3H, s, $\text{CH}_3\text{OC}_6\text{H}_4$), 2.69 (2H, d, J 7.4, CH_2CO_2), 1.39 (9H, s, $\text{C}(\text{CH}_3)_3$); δ_{C} (125 MHz; CDCl_3) 170.62 (CO_2), 158.74, 152.17, 141.26, 134.60 (Ph: C_{ipso}), 127.46, 115.01, 114.73, 113.96 (Ph), 81.00 ($\text{C}(\text{CH}_3)_3$), 55.67, 55.58 (CH_3O), 55.20 (NHCH), 44.15 (CH_2CO_2), 28.00 ($\text{C}(\text{CH}_3)_3$). m/z (CI) 358 (MH^+ , 28%), 242 (22), 235 (100), 179 (29), 124 (83); Accurate mass 358.2016. $\text{C}_{21}\text{H}_{27}\text{NO}_4$ (CI, MH^+) requires 358.2018.

Preparation of (3*R*)- η^6 -*N*-(methyl 3-propanoate-3-*p*-methoxybenzene) *p*-methoxyaniline (3*R*)-133



A methanolic solution of (3*R*)-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 a crude oil which was purified by flash chromatography on silica gel (10:1; petrol/ethyl acetate] to afford (3*R*)-133 as a yellow oil (0.115 g, 100%). [α]_D²² +11.78 (c 0.28, CHCl₃); ν_{max} (CHCl₃)/cm⁻¹ 1733 (C=O), 1511 (N-H), 1261 (C-N), 1103 (C-O-C); δ_{H} (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, *J*_{AB} 7.4, *J*_{AX} 1.21, *J*_{BX} 2.5, CH₂CO₂); δ_{C} (125 MHz, CDCl₃) 171.14 (CO₂), 158.87, 152.39, 141.01, 134.41 (Ar:C_{ipso}), 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.

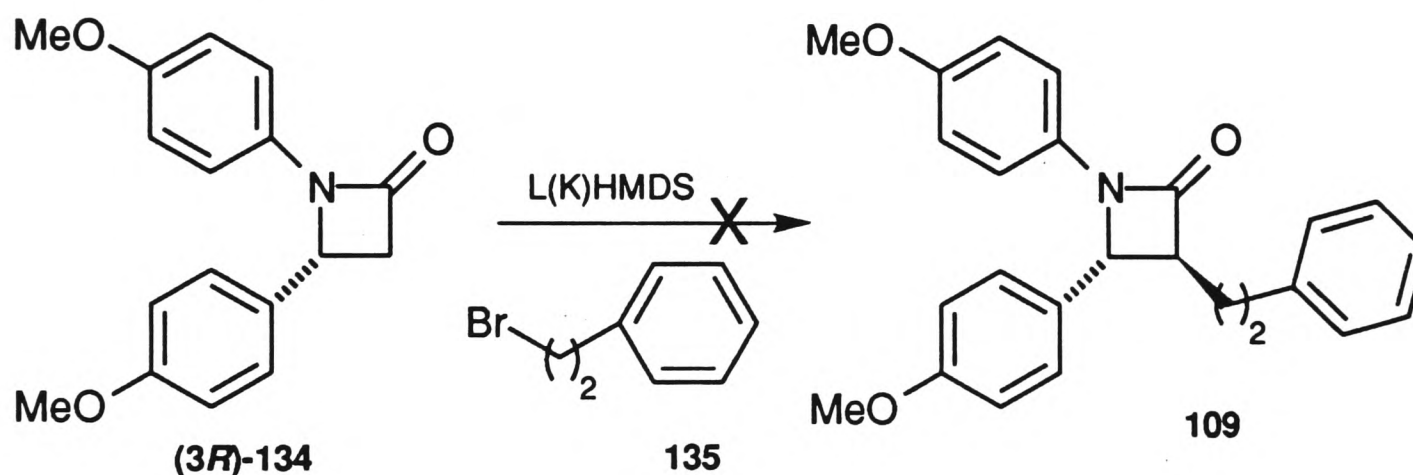
Preparation of (4*R*)-1,4-bis(4-methoxyphenyl)-2-azetidinone (4*R*)-134



3.0 M Methyl magnesium bromide (0.042 cm³, 0.127 mmol) was added dropwise to a diethyl ether solution (2 cm³) of (3*R*)-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 cm³) and warmed to room temperature. The mixture was then extracted with brine (2 x 10 cm³), 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 (3*R*)-**134** as an oil (0.016 g, 89%). Although pure by ¹H nmr spectroscopy, satisfactory elemental analysis for (3*R*)-**134** could not be secured; [α]_D²² +98.46 (*c* 0.065, CHCl₃); ν_{max} (CHCl₃)/cm⁻¹ 1737 (C=O) δ_H (500 MHz; CDCl₃) 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, CH₂CH), 3.81, 3.75 (3H, s, CH₃OAr), 3.53, 2.90 (2H, AB of ABX system, *J*_{AB} 15.0, *J*_{AX} 2.5, *J*_{BX} 5.6, CH₂CO); δ_C (125 MHz, CDCl₃) 164.18 (CO₂), 159.74, 155.94, 131.51, 130.20 (Ph:C_{ipso}), 127.22, 118.17, 114.54, 114.28 (Ph), 55.43 (CH₃OC₆H₄), 55.31 (CH₃OC₆H₄), 53.80 (NHCH), 47.07 (CH₂CH); *m/z* (CI) 284 (MH⁺, 72%), 149 (14), 134 (100).

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



A freshly prepared THF (1 cm³) solution of (3*R*)-**134** (0.019 g, 0.07 mmol) was added to a THF solution of LHMDS (0.09 mmol) and the reaction stirred at -78°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. ¹H nmr spectroscopic analysis showed disappearance of the β-lactam starting material (3*R*)-**134**, however no product **109** was observed. The reaction was repeated using KHMDS as a base, however still no product was observed.

References

1. C. A. Mahaffy, P. L. Pauson, *Inorg. Synth.*, 1979, **19**, 154.
2. A. Abiko, S. Masamune, *Tetrahedron Lett.*, 1992, **33**, 5517.
3. *Aldrich Catalogue Handbook of Fine Chemicals*, 1994, 5, 90.
4. R. Roeske, *J. Org. Chem.*, 1963, **28**, 1251.
5. N. Ikota, K. Achira, S. Yamada, *Chem. Pharm. Bull.*, 1983, **31**, 887.
6. J. F. Klebe, H. Finkbeiner, *J. Am. Chem. Soc.*, 1968, **90**, 7255.
7. G. Anderson, F. Callahan, *J. Am. Chem. Soc.*, 1960, **82**, 3359.
8. Dr. A. J. Burke, personal communication.
9. Dr. M. E. Bunnage, D. Phil. Thesis, Oxford, 1993.
10. J. Sakaki, S. Kobayashi, M. Sato, C. Kaneko, *Chem. Pharm. Bull.*, 1989, **37**, 2952.
11. K. Chu, G. Negrete, J. Konopelski, *J. Org. Chem.*, 1991, **56**, 5196.
12. J. Hamilton, C. Mahaffy, *Synth. React. Inorg. Metal-Org. Chem.*, 1986, **16**, 61.
13. G. Wittig, U. Thiele, *Liebigs Ann. Chemie.*, 1969, **726**, 1.

Experimental: Chapter 3

General Procedures

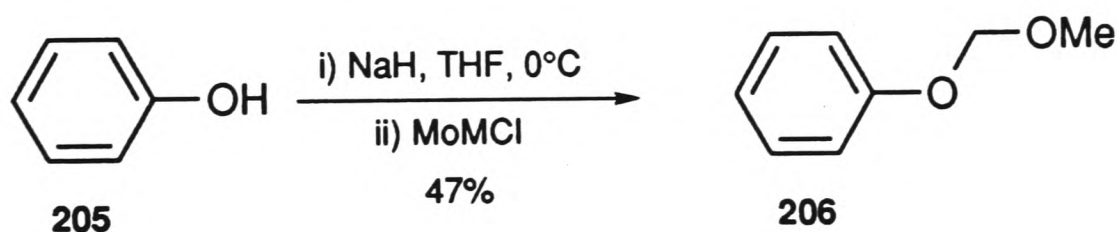
General procedure for the silylation of (arene)chromium tricarbonyl complexes

To a THF solution of the (arene)chromium tricarbonyl complex at -78°C was added the required alkyllithium 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 CH_2Cl_2 and then filtered through alumina (grade v). The CH_2Cl_2 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 CD_3OD (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 CH_2Cl_2 and filtered through alumina (grade v). The CH_2Cl_2 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.

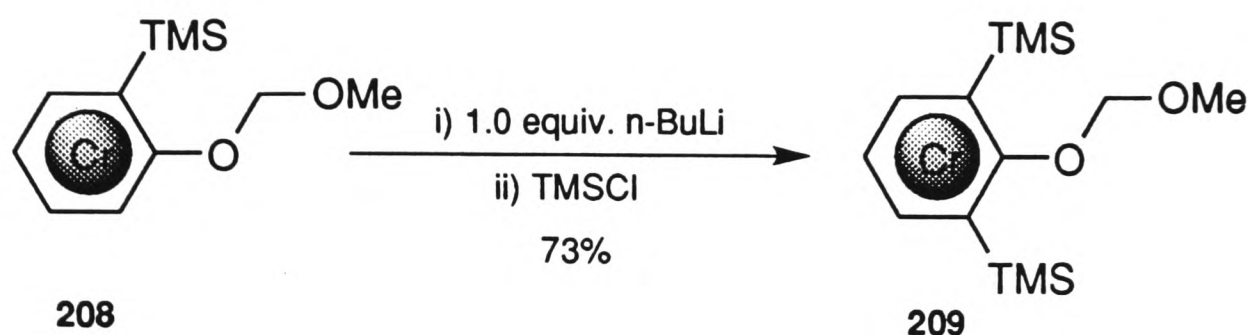
Preparation of methoxymethoxy benzene¹ 206



To a THF solution (10 cm^3) 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 CH_2Cl_2 , 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%); δ_{H} (300 MHz; CDCl_3) 7.36 - 7.28 (2H, m, Ph), 7.09 - 7.00 (3H, m, Ph), 5.21 (2H, s, OCH_2O), 3.51 (3H, s, OCH_3).

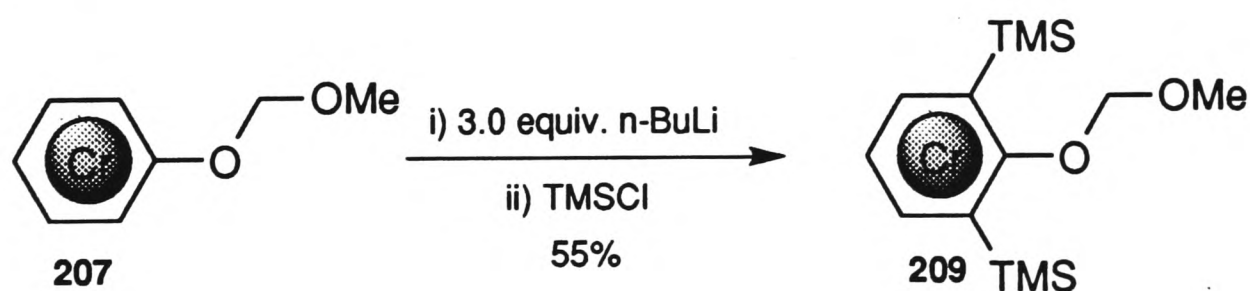
To a THF solution (8 cm³) of **207** (0.23 g, 0.85 mmol) at -78°C, was added 1.2 equivalents of *n*-BuLi (1.3 M, 0.78 cm³, 1.02 cm³) and the reaction mixture stirred for 3 hours. Silylation was then carried out under the standard conditions for the silylation of (arene)chromium tricarbonyl complexes. 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; ν_{max} (KBr)/cm⁻¹ 1953, 1859 (C≡O), 1249, 1074 (Ar-O-C); δ_{H} (300 MHz; CDCl₃) 5.66 (1H, m, ArCr(CO)₃), 5.57 (1H, dd, *J* 1.4, 6.2, ArCr(CO)₃), 5.30 (1H, d, *J* 6.9, ArCr(CO)₃), 5.16, 4.99 (2H, AB system, *J*_{AB} 7.1, OCH₂O), 4.80 (1H, m, ArCr(CO)₃), 3.49 (3H, s, OCH₃), 0.33 (9H, s, TMS); δ_{C} (125.77 MHz, CDCl₃) 234.1 (Cr(CO)₃), 145.0 (ArCr(CO)₃:C_{ipso}), 101.20, 95.9, 94.4 (ArCr(CO)₃:C), 88.2 (ArCr(CO)₃:C_{ipso}), 85.2 (ArCr(CO)₃:C), 77.3 (OCH₂), 56.40 (OCH₃), 0.6 (TMS); *m/z* (EI) 346 (M⁺, 18%), 262 (M⁺-3(CO), 100); (Found C, 48.70; H, 4.95. C₁₄H₁₈O₅CrSi requires C, 48.55; H, 5.24%).

Monosilylation of (2-trimethylsilyl methoxymethoxybenzene)chromium tricarbonyl **208**



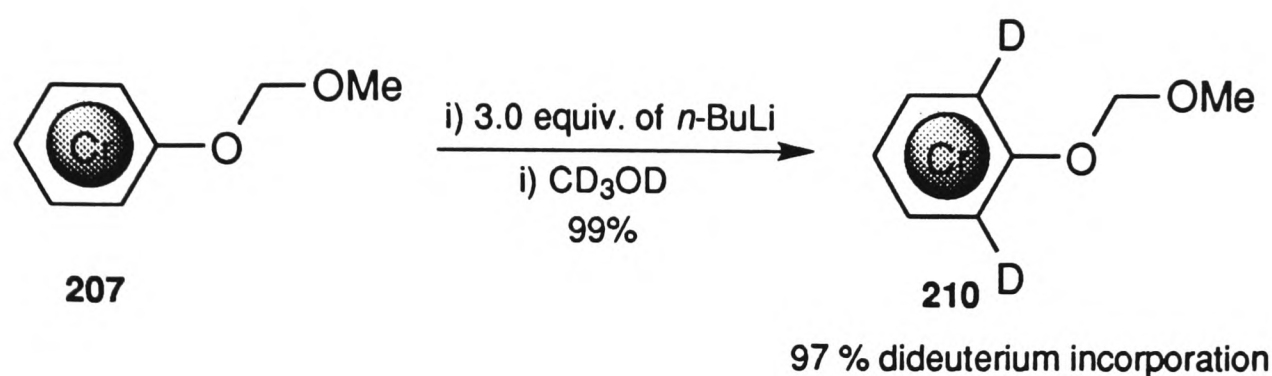
To a THF solution (10 cm³) of **208** (0.089 g, 0.26 mmol) at -78°C was added 1.0 equivalents of *n*-BuLi (1.3M, 0.20 cm³, 0.26 mmol) and the reaction mixture stirred for 3 hours. Silylation was then carried out under the standard conditions for the silylation of (arene)chromium tricarbonyl complexes. 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} (KBr)/cm⁻¹ 1960, 1883 (C≡O), 1251, 1057 (Ar-O-C); δ_{H} (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); δ_{C} (125.77 MHz, CDCl₃) 233.9 (Cr(CO)₃), 149.8 (ArCr(CO)₃:C_{ipso}), 101.8, 101.0, (ArCr(CO)₃:C), 92.2 (ArCr(CO)₃:C_{ipso}), 87.7 (OCH₂), 57.3 (OCH₃), 0.2 (TMS); *m/z* (EI) 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**



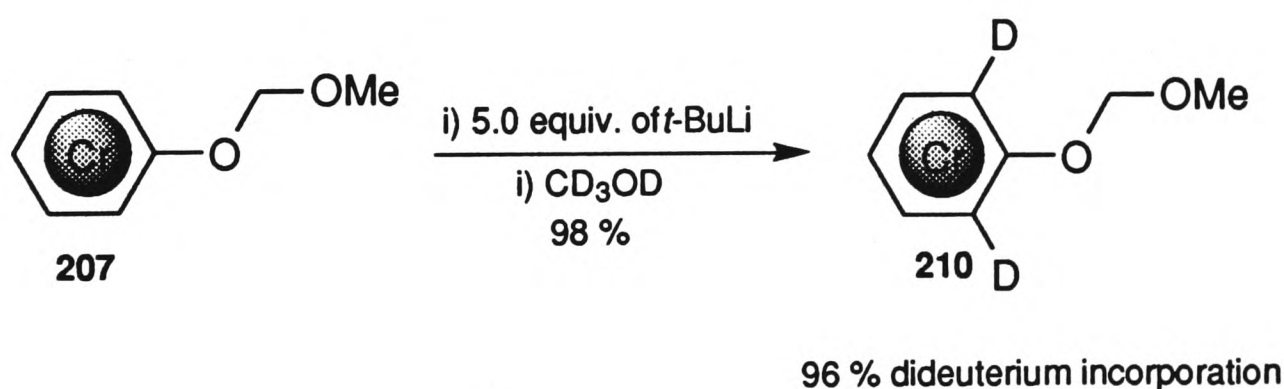
To a THF solution (8 cm³) of **207** (0.23 g, 0.84 mmol) at -78°C was added 3.0 equivalents of *n*-BuLi (1.3 M, 1.9 cm³, 2.52 mmol) and the reaction mixture stirred for 3 hours. Silylation was then carried out under the standard conditions for the silylation of (arene)chromium tricarbonyl complexes. 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.

Dideuteration of (methoxymethoxy benzene)chromium tricarbonyl **207** with 3.0 equiv. of *n*-BuLi

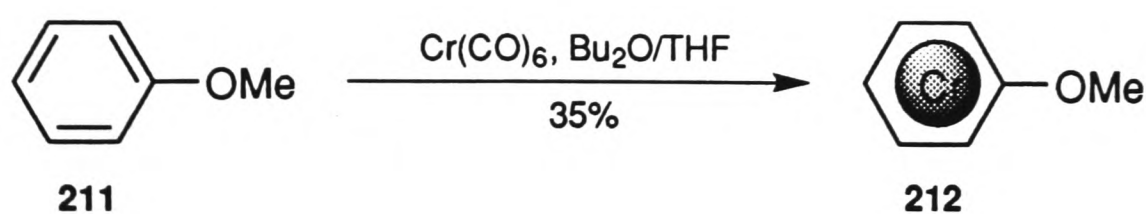


To a THF solution (10 cm³) of **207** (0.11 g, 0.40 mmol) was added 3 equivalents of *n*-BuLi (1.3M, 0.93 cm³, 1.20 mmol) and the reaction was allowed to stir at -78°C for 3 hrs. Deuteration was then carried out under the standard conditions for the deuteration of (arene)chromium tricarbonyl complexes, to afford **210** (0.11g, 99%); m.p. 77-78°C. The ¹H 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* (EI) 276. δ_{H} (300 MHz; CDCl₃), 5.32 (2H, d, *J* 6.2, ArCr(CO)₃), 5.06 (2H, s, OCH₂O), 4.91 (1H, t, *J* 6.2, ArCr(CO)₃), 3.49 (3H, s, OCH₃); *m/z* (EI) 276 (M⁺, 34%), 192 (M⁺-3(CO), 58), 147 (M⁺-Cr(CO)₃).

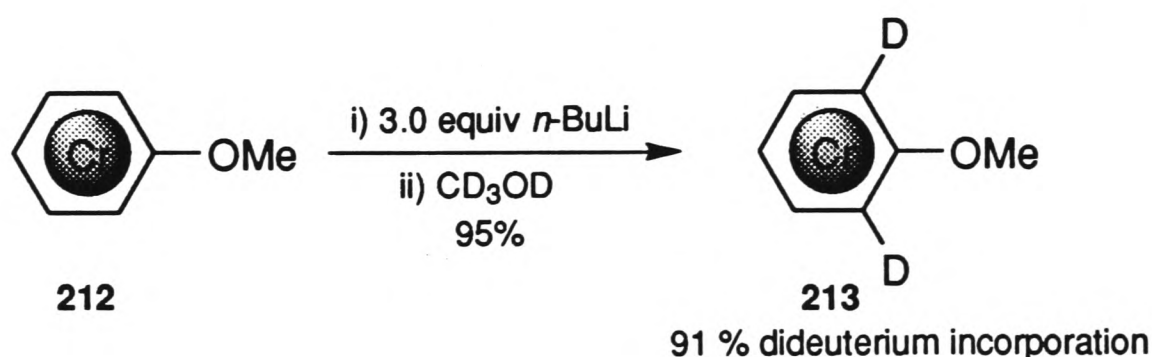
Dideuteration of (methoxymethoxy benzene)chromium tricarbonyl **207** with 5.0 equivalents of *t*-BuLi



The same procedure was repeated, as described above. **207** (0.11g, 0.39 mmol) was deprotonated with 5 equivalents of *t*-BuLi (1.7 M, 1.3 cm³, 1.93 mmol) to afford **210** (0.1g, 98%) upon deuterium quench with CD₃OD. The ¹H nmr and mass spectra were identical to that shown above, except that product contained 96% deuterium incorporation at the 2,6-position.

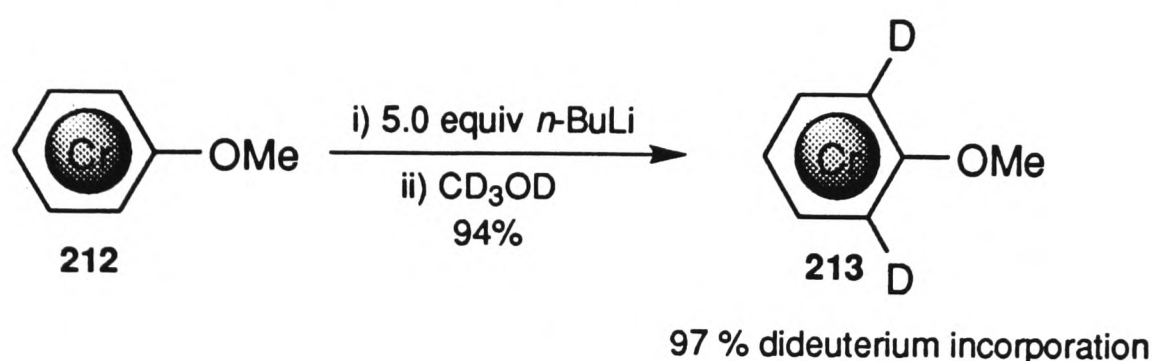
Preparation of (anisole)chromium tricarbonyl² **212**

To a solution of **211** (2.0 g, 18.49 mmol) in Bu₂O:THF (10:1, 110 cm³) 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 Bu₂O 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; δ_{H} (300 MHz; CDCl₃) 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, OCH₃).

Dideuteration of (anisole)chromium tricarbonyl **212** with 3 equiv. of *n*-BuLi

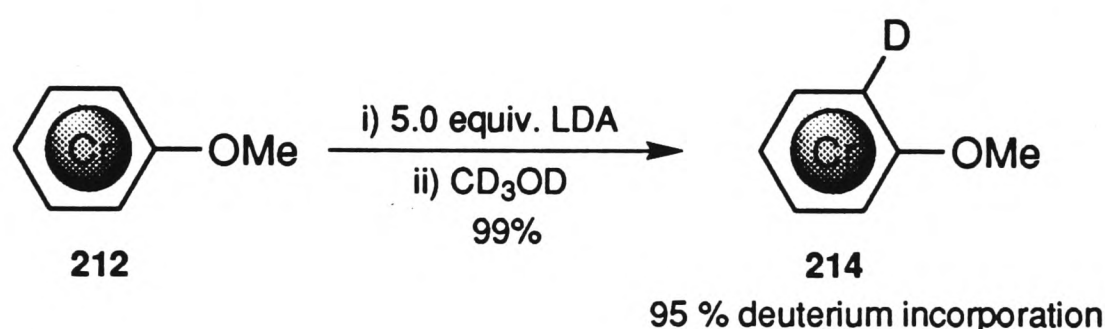
To a THF solution (10 cm³) of **212** (0.11g, 0.46 mmol) was added 3 equivalents of *n*-BuLi (1.3 M, 1.1 cm³, 1.38 mmol) and the reaction was allowed to stir at -78°C for 3 hrs. Deuteration was carried out under the standard conditions for the deuteration of (arene)chromium tricarbonyl complexes to afford **213** (0.11g, 95%). The ¹H 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**; δ_{H} (300 MHz; CDCl₃) 5.58 (2H, d, *J* 6.2, ArCr(CO)₃), 3.71 (3H, s, OCH₃).

Dimetallation of (anisole)chromium tricarbonyl **212** with 5.0 equiv. of *t*-BuLi



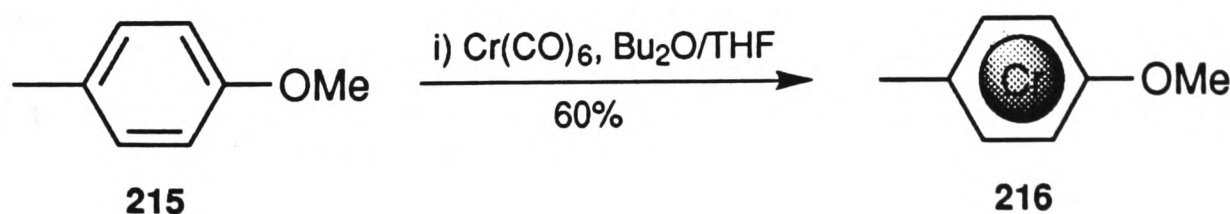
The procedure was repeated as described above, **212** (0.1g, 0.39 mmol) was deprotonated with 5.0 equivalents of *t*-BuLi (1.7 M, 1.1 cm³, 1.95 mmol) to afford **213** (0.09g, 94%), upon deuterium quench with CD₃OD. The ¹H nmr and mass spectra were identical to that shown for **213** above, except that product contained 97% deuterium incorporation at the 2,6-position.

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



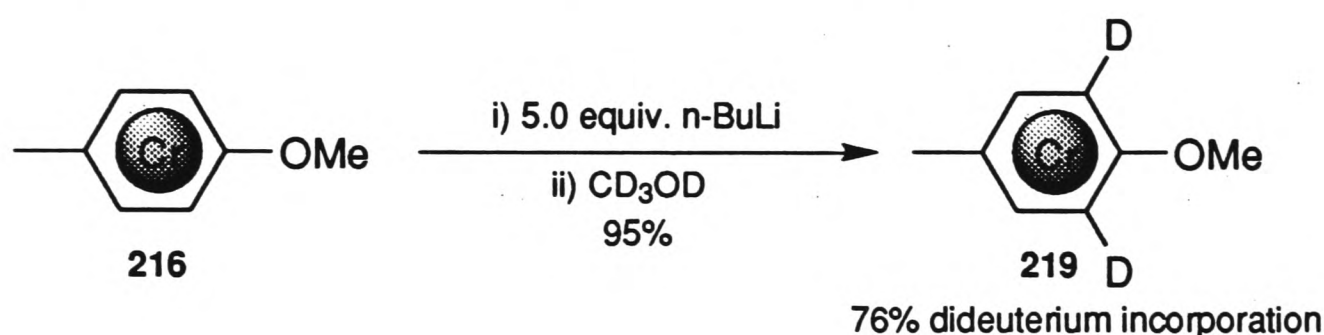
To a THF solution of LDA (5 equiv.) at -78°C was added **212** (0.08 g, 0.33 mmol) and the reaction was allowed to stir at -78°C for 3 hrs. Deuteriation was carried out under the standard conditions for the deuteriation of (arene)chromium tricarbonyl complexes to afford **214** (0.08 g, 99%) which contained 95% deuterium incorporation at the 2-position. The ¹H 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; δ_H (300 MHz; CDCl₃) 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, OCH₃); *m/z* (EI) 245 (M⁺, 48%), 161 (M⁺-3(CO)).

Preparation of (4-methylanisole)chromium tricarbonyl **216**



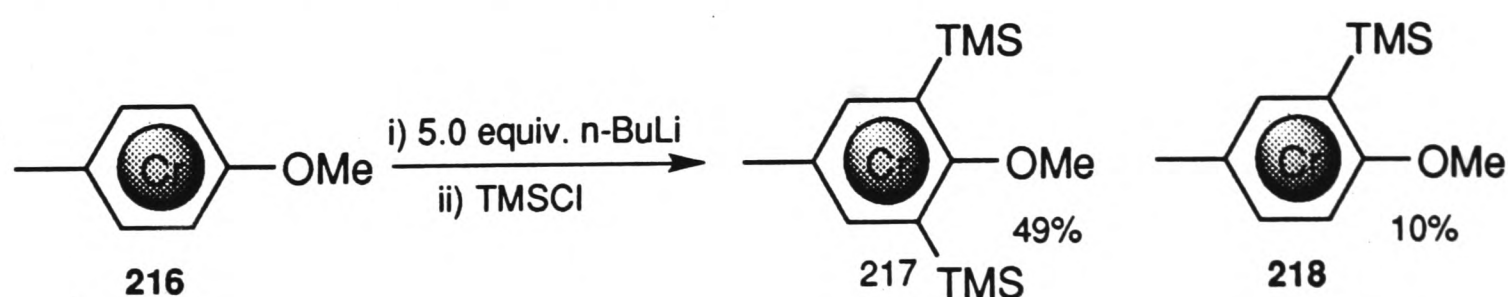
To a solution of **215** (11.5 cm³, 98.0 mmol) in Bu₂O:THF (10:1, 110 cm³) was added chromium hexacarbonyl (4 g, 18.2 mmol) and the reaction mixture heated to reflux, under nitrogen, for 48 hr. The reaction was then cooled and filtered under nitrogen, through a short column of alumina (grade v) and washed with petrol to remove all the Bu₂O 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; ν_{max} (KBr)/cm⁻¹ 1953, 1860 (C≡O), 1241, 1020 (C-O-C); δ_{H} (300 MHz; CDCl₃) 5.41 (2H, d, *J* 6.9, ArCr(CO)₃), 5.13 (2H, d, *J* 6.9, ArCr(CO)₃), 3.67 (3H, s, OCH₃), 2.08 (3H, s, CH₃); δ_{C} (125.77 MHz, CDCl₃) 234.0 (Cr(CO)₃), 141.5, 101.4 (ArCr(CO)₃:C_{ipso}), 95.4, 78.9 (ArCr(CO)₃:C), 55.2 (OCH₃), 19.3 (CH₃); *m/z* (EI) 258 (M⁺, 7%), 174 (M⁺-3(CO), 25), 52 (Cr, 100); (Found C, 51.18; H, 3.63. C₁₁H₁₀O₄Cr requires C, 51.17; H, 3.90%).

Dideuteration of (4-methylanisole)chromium tricarbonyl **216**



To a THF solution (5 cm³) of **216** (0.05 g, 0.21 mmol) was added 5 equivalents of *n*-BuLi (1.3 M, 0.78 cm³, 1.03 mmol) and the reaction was allowed to stir at -78°C for 3 hrs. Deuteration was carried out under the standard conditions for the deuteration of (arene)chromium tricarbonyl complexes to afford **219** (0.05 g, 95%), which contained 76% 2,6-dideuterium incorporation. Analysis of the ¹H 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**; δ_{H} (300 MHz; CDCl₃) 5.41 (2H, br s, ArCr(CO)₃), 3.67 (3H, s, OCH₃), 2.08 (3H, s, CH₃).

Silylation of (4-methylanisole)chromium tricarbonyl **216**

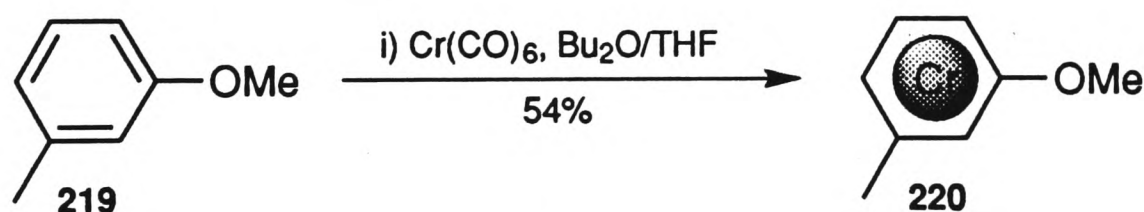


To a THF solution (10 cm³) of **216** (0.24 g, 0.95 mmol) at -78°C was added 5.0 equivalents of *n*-BuLi (1.7M, 2.8 cm³, 4.73 mmol) and the reaction mixture stirred for 3 hours. Silylation was then carried out under the standard conditions for the silylation of (arene)chromium tricarbonyl complexes. 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** (0.03g, 10%).

217 was recrystallised from *n*-pentane/diethyl ether, m.p. 174-176°C; $\nu_{\max}$ (KBr)/cm⁻¹ 1968, 1898 (C≡O), 1250, 1011 (Ar-O-C); δ_{H} (300 MHz; CDCl₃) 5.55 (2H, s, ArCr(CO)₃), 3.69 (3H, s, OCH₃), 2.01 (3H, s, CH₃), 0.39 (18H, s, 2(TMS)); δ_{C} (125.77 MHz, CDCl₃) 234.2 (Cr(CO)₃), 152.1 (ArCr(CO)₃:C_{ipso}), 103.0, (ArCr(CO)₃:C), 102.6, 91.7 (ArCr(CO)₃:C_{ipso}), 63.2 (OCH₃), 19.7 (CH₃), 0.4 (TMS); *m/z* (CI) 403 (MH⁺, 100%), 267 (MH⁺-Cr(CO)₃, 5); (Found C, 50.91; H, 6.79. C₁₇H₂₆O₄CrSi₂ requires C, 50.72; H, 6.51%).

218 was recrystallised from *n*-pentane/diethyl ether, m.p. 112-113°C; $\nu_{\max}$ (KBr)/cm⁻¹ 1962, 1887 (C≡O), 1250, 1024 (Ar-O-C); δ_{H} (300 MHz; CDCl₃) 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, OCH₃), 2.04 (3H, s, CH₃), 0.32 (9H, s, TMS); δ_{C} (125.77 MHz, CDCl₃) 234.0 (Cr(CO)₃), 146.3 (ArCr(CO)₃:C_{ipso}), 102.8, (ArCr(CO)₃:C) 100.4 (ArCr(CO)₃:C_{ipso}), 96.8 (ArCr(CO)₃:C), 88.8 (ArCr(CO)₃:C_{ipso}), 73.1 (ArCr(CO)₃:C), 55.4 (OCH₃), 19.9 (CH₃), -0.6 (TMS); *m/z* (EI) 330 (M⁺, 20%), 246 (M⁺-3(CO), 100); (Found C, 51.10; H, 5.23. C₁₄H₁₈O₄CrSi requires C, 50.90; H, 5.49%).

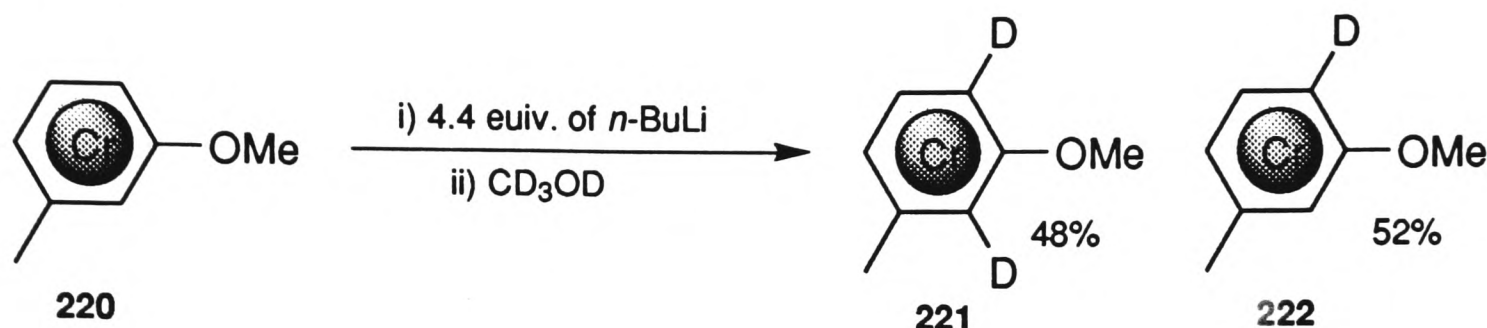
Preparation of (3-methylanisole)chromium tricarbonyl **220**



To a solution of **219** (11.5 cm³, 98.0 mmol) in Bu₂O:THF (10:1, 110 cm³) 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 Bu₂O 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; $\nu_{\max}$ (KBr)/cm⁻¹ 1945, 1847 (C≡O), 1269, 1039 (C-O-C); δ_{H} (300 MHz; C₆D₆) 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, Ar(Cr(CO)₃), 3.72 (3H, s, OCH₃), 2.26 (3H, s, CH₃); δ_{C} (125.77 MHz, CDCl₃) 233.5 (Cr(CO)₃), 143.70, 110.7 (ArCr(CO)₃:C_{ipso}), 94.9, 86.7, 80.3, 75.8 (ArCr(CO)₃:C), 55.5 (OCH₃), 20.9 (CH₃);

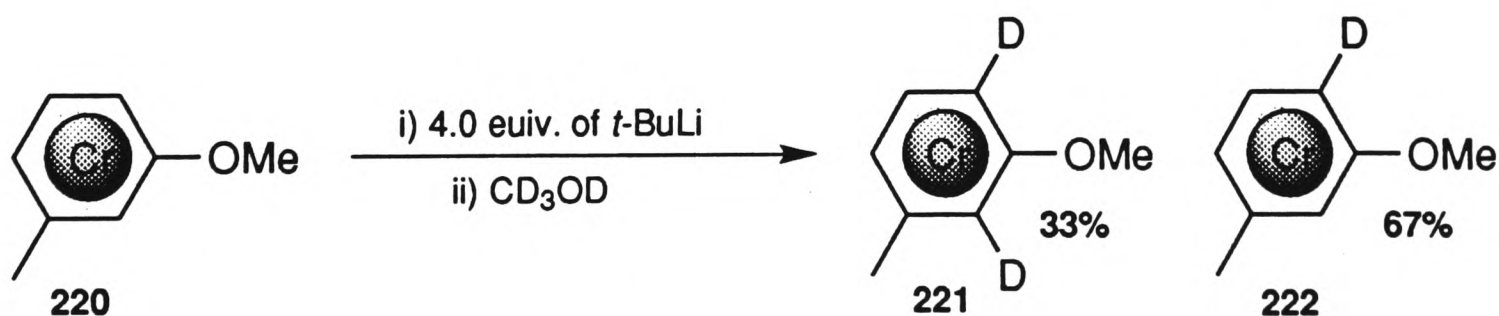
m/z (EI) 258 (M^+ , 6%), 122 ($M^+ - Cr(CO)_3$, 6), 52 (Cr, 100); (Found C, 51.38; H, 3.98. $C_{11}H_{10}O_4Cr$ requires C, 51.17; H, 3.90%).

Deuteration 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 $-78^\circ C$, was added 4.4 equiv. of *n*-BuLi (1.5 M, 1.3 cm^3 , 1.89 mmol) and the reaction was allowed to stir at $-78^\circ C$ for 3 hrs. Deuteration was carried out under the standard conditions for the deuteration of (arene)chromium tricarbonyl complexes to afford a mixture of inseparable products **221** and **222**. The 1H 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 dideuterated compound and monodeuterated compound. Therefore from the 1H nmr spectrum it was calculated that the deuteriated reaction product mixture contained 48% of the dideuterated species **221** and 52% of the monodeuterated species **222**. δ_H (300 MHz; C_6D_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); 2H nmr (76.75 MHz; C_6H_6 spiked with C_6D_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%).

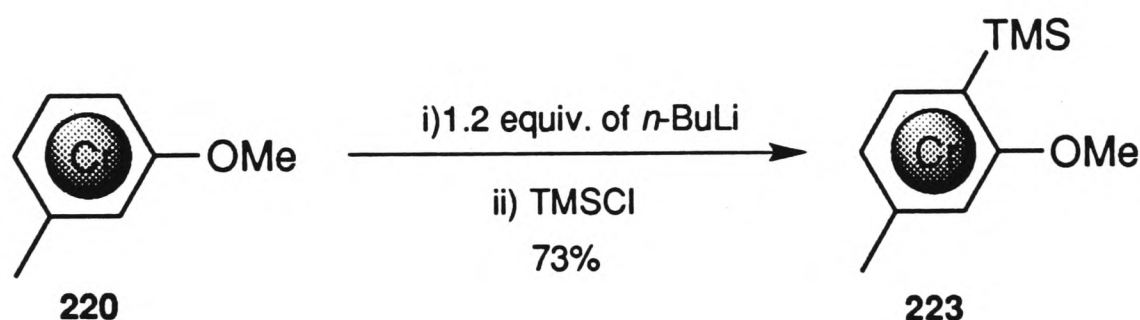
Deuteration of (3-methylanisole)chromium tricarbonyl **220 with 4.0 equiv. of *t*-BuLi**



Compound **220** (0.05g, 0.21 mmol) was deprotonated with 4.0 *t*-BuLi (1.7M, 0.49 cm^3 , 0.84 mmol) and deuteration was carried out under the standard conditions for the deuteration of (arene) $Cr(CO)_3$, to afford a mixture of inseparable products **221** and **222**.

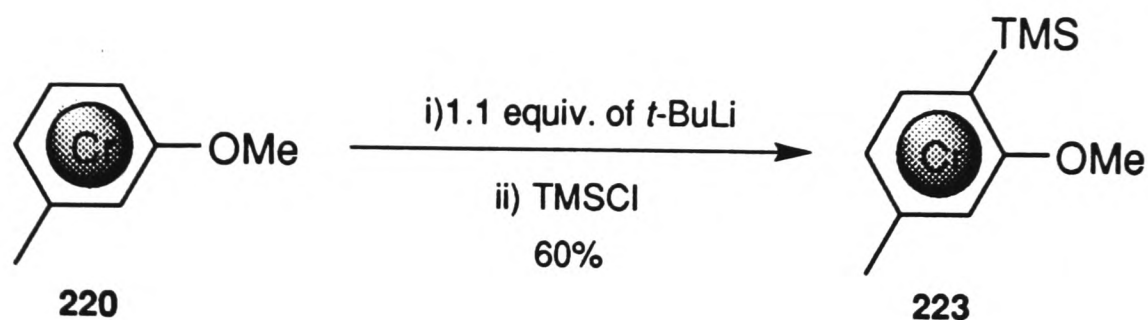
The ^1H nmr spectrum of the crude reaction products was similar to **220**, except for a 31% decrease in the resonance peak at 4.41 ppm, due to deuterium incorporation at the 2-position, and a 93% decrease in the resonance peak at 4.20 ppm, due to deuterium incorporation at the 6-position, and collapse 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 ^1H nmr spectrum it was calculated that the deuterium reaction products contained 33% of the dideuteriated species **221** and 67% of the monodeuteriated species **222**. δ_{H} (300 MHz; C_6D_6) 4.69 (1H, d, J 6.0, $\text{ArCr}(\text{CO})_3$), 3.86 (1H, d, J 6.0, $\text{ArCr}(\text{CO})_3$), 2.94 (3H, s, OCH_3), 1.62 (3H, s, CH_3); ^2H nmr (76.75 MHz; C_6H_6 spiked with C_6D_6) 4.39 (br s), 4.19 (br s); m/z (EI) 260 (M^+ , 10%), 259 (M^+ , 23%), 176 ($\text{M}^+ - 3(\text{CO})$, 43), 175 ($\text{M}^+ - 3(\text{CO})$, 74), 52 (Cr, 100%).

Monosilylation of (3-methylanisole)chromium tricarbonyl **220 with 1.2 equiv. of $n\text{-BuLi}$**



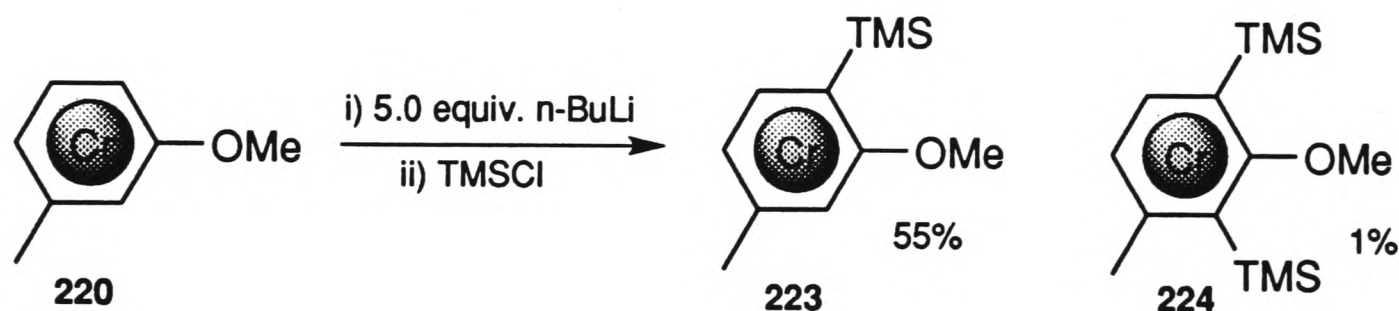
To a THF solution (2 cm^3) of **220** (0.24 g, 0.95 mmol) at -78°C was added 1.2 equivalents of $n\text{-BuLi}$ (1.6 M, 0.7 cm^3 , 1.13 mmol) and the reaction mixture stirred for 3 hours. Silylation was then carried out under the standard conditions for the silylation of (arene)chromium tricarbonyl complexes. 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. $126\text{--}127^\circ\text{C}$; ν_{max} (KBr)/ cm^{-1} 1943, 1867 ($\text{C}\equiv\text{O}$), 1250, 1031 (C-O-C); δ_{H} (300 MHz; CDCl_3) 5.54 (1H, d, J 6.2, $\text{ArCr}(\text{CO})_3$), 4.91 (1H, s, $\text{ArCr}(\text{CO})_3$), 4.70 (1H, d, J , 5.4, $\text{ArCr}(\text{CO})_3$), 3.74 (3H, s, OCH_3), 2.29 (3H, s, CH_3), 0.29 (9H, s, TMS); δ_{C} (125.77 MHz, CDCl_3) 233.9 ($\text{Cr}(\text{CO})_3$), 147.6, 111.0, 109.9 ($\text{ArCr}(\text{CO})_3\text{:C}_{\text{ipso}}$), 101.4, 86.7, 76.0 ($\text{ArCr}(\text{CO})_3$), 55.2 (OCH_3), 21.1 (CH_3), -0.6 (TMS); m/z (CI) 331 (MH^+ , 100%), 195 ($\text{MH}^+ - \text{Cr}(\text{CO})_3$, 12); (Found C, 50.60; H, 5.30. $\text{C}_{14}\text{H}_{18}\text{O}_4\text{CrSi}$ requires C, 50.90; H, 5.49%).

Monosilylation of (3-methylanisole)chromium tricarbonyl **220** with 1.1 equiv. of *t*-BuLi



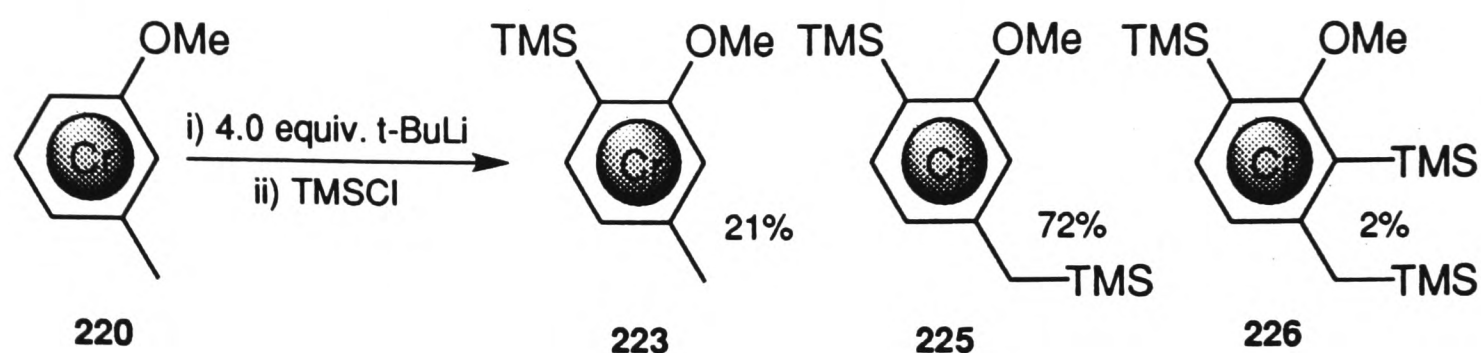
To a THF solution (4 cm³) of **220** (0.21 g, 0.81 mmol) at -78°C was added 1.1 equivalents of *t*-BuLi (1.7 M, 0.52 cm³, 0.88 mmol) and the reaction mixture stirred for 3 hours. Silylation was then carried out under the standard conditions for the silylation of (arene)chromium tricarbonyl complexes. 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



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%); δ_{H} (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

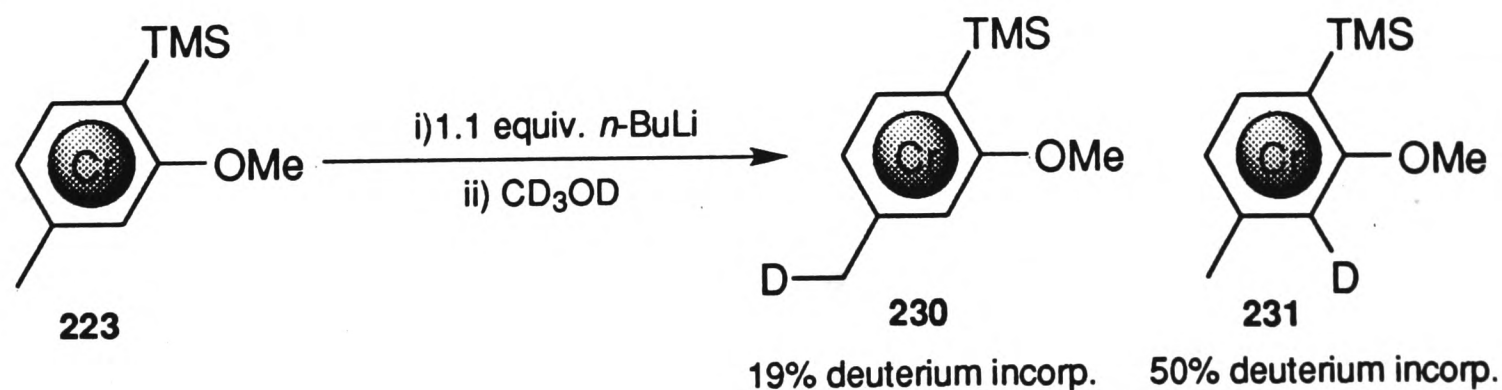


To a THF solution (5 cm³) of **220** (0.22 g, 0.85 mmol) at -78°C was added 4.0 equivalents of *t*-BuLi (1.7 M, 2.0 cm³, 3.41 mmol) and the reaction mixture stirred for 3 hours. Silylation was then carried out under the standard conditions for the silylation of (arene)chromium tricarbonyl complexes. 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, 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(CO)₃), 147.9, 116.1 (ArCr(CO)₃:C_{ipso}), 101.5, 85.7, 75.0 (ArCr(CO)₃:C), 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, CH₂TMS), 0.48, 0.35, 0.07 (9H, s, TMS).

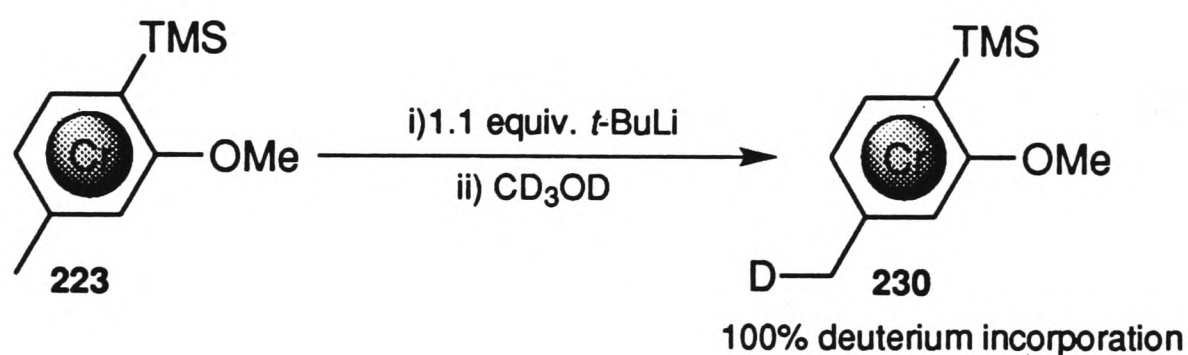
Deuteration of (2-trimethylsilyl 5-methylanisole)chromium tricarbonyl **223** with 1.1 equiv. of *n*-BuLi



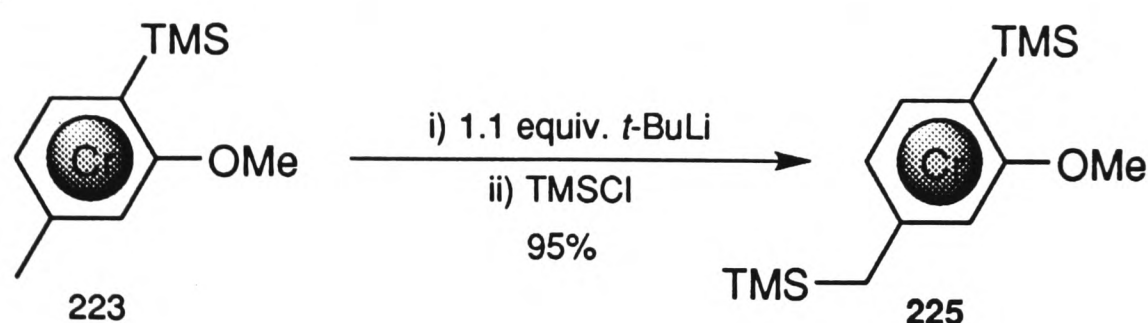
To a THF solution of **223** (0.05 g, 0.15 mmol) at -78°C, was added 1.1 equivalents of *n*-BuLi (1.6 M, 0.1 cm³, 0.17 mmol) and the reaction was allowed to stir at -78°C for 3 hrs. Deuteration was carried out under the standard conditions for the deuteration of

(arene)chromium tricarbonyl complexes to afford an inseparable mixture of **230** and **231** and some starting material **223**. The ^1H 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. ^2H 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**. δ_{H} (300 MHz; CDCl_3) 5.54 (1H, d, J 6.2, $\text{ArCr}(\text{CO})_3$), 4.70 (1H, d, J , 6.2, $\text{ArCr}(\text{CO})_3$), 3.74 (3H, s, OCH_3), 2.18 (2H, m, CH_2D), 0.29 (9H, s, TMS); ^2H 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 ($\text{M}^+ - 3(\text{CO})$, 100%), 52(Cr, 51%).

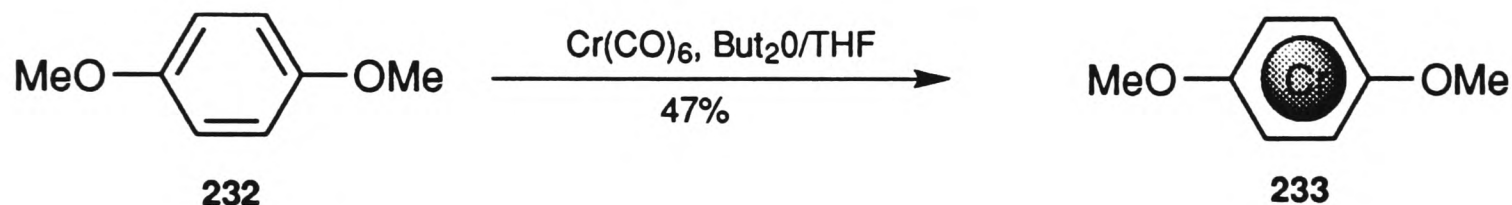
Reaction of (2-trimethylsilyl 5-methylanisole)chromium tricarbonyl **223 with 1.1 equiv. of $t\text{-BuLi}$**



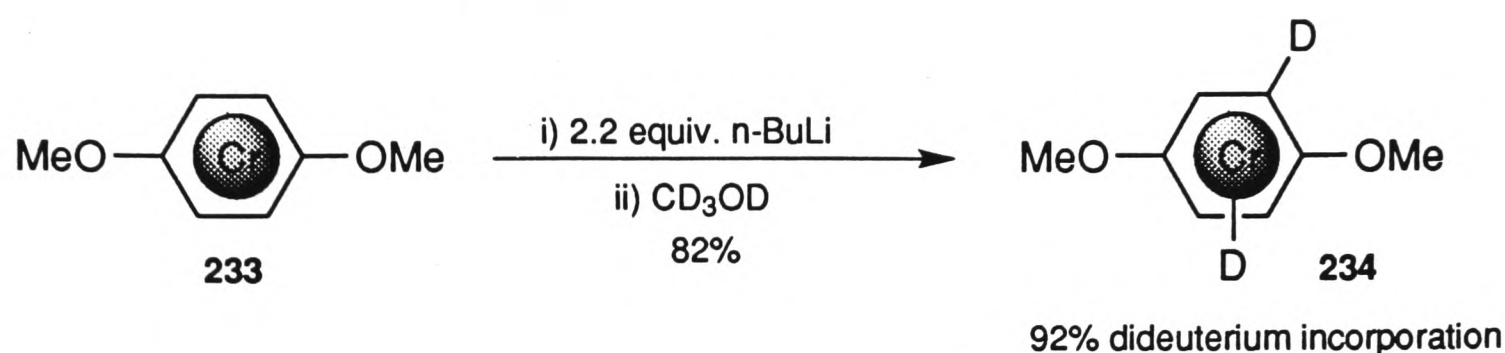
To a THF solution of **223** (0.05 g, 0.15 mmol) at -78°C , was added 1.1 equivalents of $t\text{-BuLi}$ (0.1 cm^3 , 0.17 mmol) and the reaction was allowed to stir at -78°C for 3 hrs. Deuteriation was carried out under the standard conditions for the deuteriation of (arene)chromium tricarbonyl complexes to afford **230**. The ^1H 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. ^2H 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**; δ_{H} (300 MHz; CDCl_3) 5.54 (1H, d, J 6.4, $\text{ArCr}(\text{CO})_3$), 4.92 (1H, s, $\text{ArCr}(\text{CO})_3$), 4.70 (1H, d, J , 6.4, $\text{ArCr}(\text{CO})_3$), 3.74 (3H, s, OCH_3), 2.27 (2H, m, CH_2D), 0.29 (9H, s, TMS); ^2H nmr (76.75 MHz; CHCl_3 spiked with CDCl_3) 2.31 (br s); m/z (EI) 331(M^+ , 9%) 247 ($\text{M}^+ - 3(\text{CO})$, 100%), 52(Cr, 46%).

Silylation of (2-trimethylsilyl 5-methylanisole)chromium tricarbonyl **223**

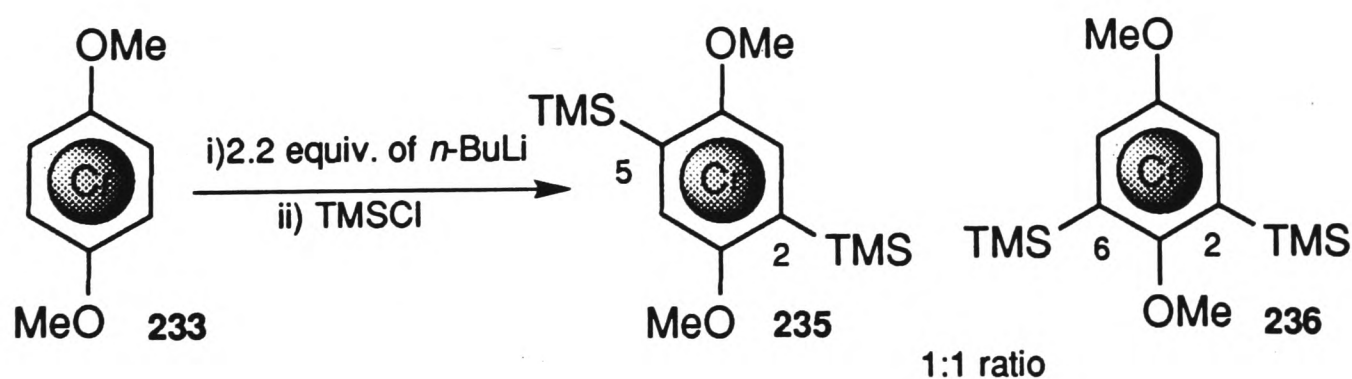
To a THF solution (5 cm³) of **223** (0.14 g, 0.42 mmol) at -78°C was added 1.1 equivalents of *t*-BuLi (1.7 M, 0.27 cm³, 0.47 mmol) and the reaction mixture stirred for 3 hours. Silylation was then carried out under the standard conditions for the silylation of (arene)chromium tricarbonyl complexes. 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**

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; ν_{max} (KBr)/cm⁻¹ 1942, 1860 (C≡O), 1243, 1028 (C-O-C); δ_{H} (300 MHz; CDCl₃) 5.26 (4H, s, ArCr(CO)₃), 3.63 (6H, s, 2(OCH₃)); δ_{C} (125.77 MHz, CDCl₃) 234.4 (Cr(CO)₃), 136.8 (ArCr(CO)₃:C_{ipso}), 79.6 (ArCr(CO)₃), 55.8 (OCH₃); *m/z* (CI) 275 (MH⁺, 100%), 138 (M-Cr(CO)₃, 25); (Found C, 48.25; H, 3.38. C₁₁H₁₀O₅Cr requires C, 48.19; H, 3.68%).

Dideuteration of (1,4-dimethoxybenzene)chromium tricarbonyl **233**

To a THF solution of **233** (0.22 g, 0.80 mmol) at -78°C , was added 2.2 equivalents of $n\text{-BuLi}$ (1.3M, 1.35 cm^3 , 1.75 mmol) and the reaction was allowed to stir at -78°C for 3 hrs. Deuteration was carried out under the standard conditions for the deuteration of (arene)chromium tricarbonyl complexes to afford **234** (0.18 g, 83%), as a yellow solid (m.p. $95\text{--}97^\circ\text{C}$). Since the compound is symmetrical, it is not possible to assign the exact position of the deuterium atoms in the molecule. The ^1H 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; δ_{H} (300 MHz; CDCl_3) 5.26 (2H, s, ArCr(CO)_3), 3.63 (6H, s, $2(\text{OCH}_3)$); m/z (CI) 277 (MH^+ , 100%).

Disilylation of (1,4-dimethoxybenzene)chromium tricarbonyl **233** with 2.2 equiv. of $n\text{-BuLi}$ 

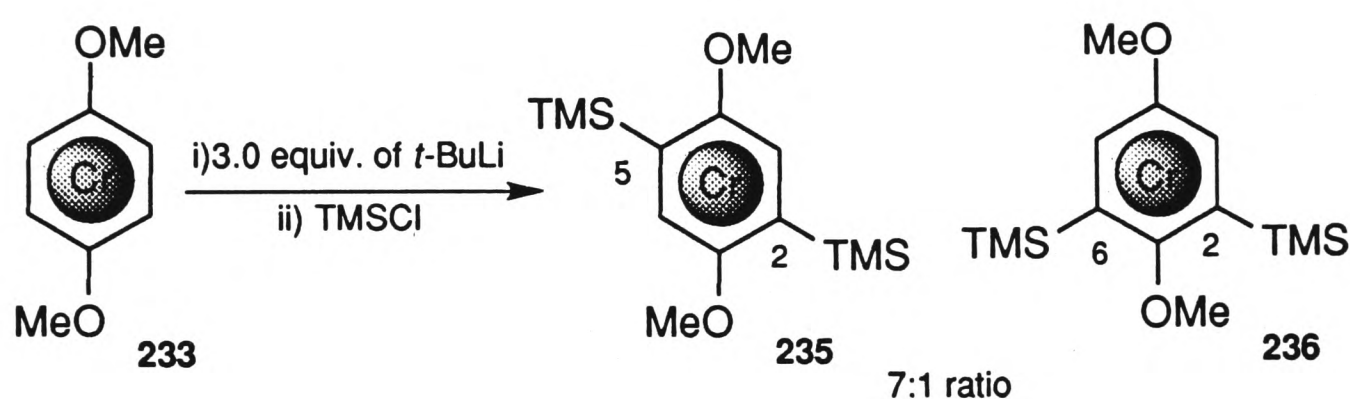
To a THF solution (20 cm^3) of **233** (0.21 g, 0.75 mmol) at -78°C was added 2 equivalents of $n\text{-BuLi}$ (1.3 M, 1.26 cm^3 , 1.65 mmol) and the reaction mixture stirred for 3 hours. Silylation was then carried out under the standard conditions for the silylation of (arene)chromium tricarbonyl complexes. 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. $106\text{--}107^\circ\text{C}$; ν_{max} (KBr)/ cm^{-1} 1940, 1856 ($\text{C}\equiv\text{O}$), 1254, 1036 ($\text{C}-\text{O}-\text{C}$); δ_{H} (300 MHz; CDCl_3) 5.06 (2H, s, ArCr(CO)_3), 3.63 (6H, s, $2(\text{OCH}_3)$), 0.35 (18H, s, $2(\text{TMS})$); δ_{C} (125.77 MHz, CDCl_3) 234.6 (Cr(CO)_3), 140.8, 91.1 ($\text{ArCr(CO)}_3\text{:C}_{\text{ipso}}$), 81.1 ($\text{ArCr(CO)}_3\text{:C}$), 56.2 (OCH_3), -0.8 (TMS); m/z (EI)

418 (M^+ , 8%), 334 ($M^+ - 3(\text{CO})$, 100); (Found C, 48.77; H, 6.05. $\text{C}_{17}\text{H}_{26}\text{O}_5\text{CrSi}_2$ requires C, 48.78; H, 6.26%).

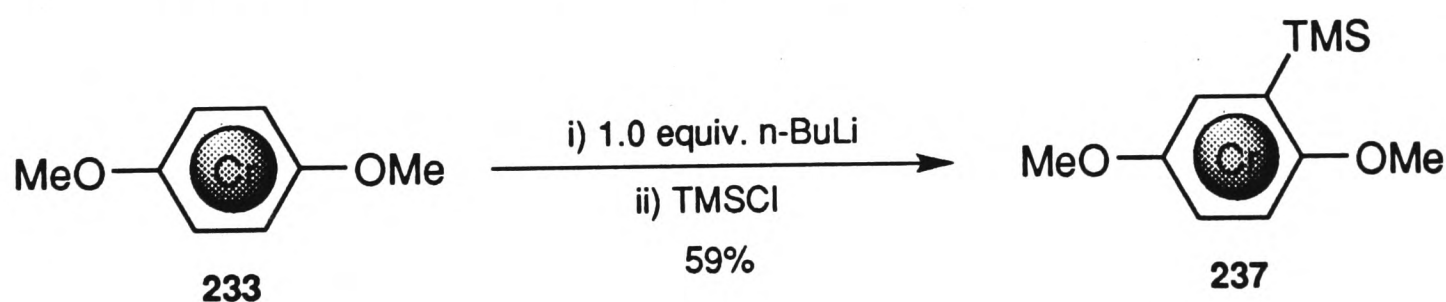
236 was recrystallised from petrol/diethyl ether, m.p. 107-109°C; ν_{max} (KBr)/ cm^{-1} 1942, 1865 ($\text{C}\equiv\text{O}$), 1253, 1041 ($\text{C}-\text{O}-\text{C}$); δ_{H} (300 MHz; CDCl_3) 5.47 (2H, s, $\text{ArCr}(\text{CO})_3$), 3.67 (3H, s, OCH_3), 3.59 (3H, s, OCH_3), 0.40 (18H, s, 2(TMS)); δ_{C} (125.77 MHz, CDCl_3) 234.6 ($\text{Cr}(\text{CO})_3$), 149.3, 135.6, 91.4 ($\text{ArCr}(\text{CO})_3:\text{C}_{\text{ipso}}$), 88.9 ($\text{ArCr}(\text{CO})_3:\text{C}$), 63.4 (OCH_3), 55.7 (OCH_3), 0.3 (TMS); m/z (EI) 418 (M^+ , 10%), 334 ($M^+ - 3(\text{CO})$, 100); (Found C, 48.92; H, 6.47. $\text{C}_{17}\text{H}_{26}\text{O}_5\text{CrSi}_2$ 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 cm^3) of **233** (0.21 g, 0.78 mmol) at -78°C was added 3 equivalents of *t*-BuLi (1.37 cm^3 , 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** (0.87 g, 27%) and **236** (0.01 g, 4%) as yellow solids.

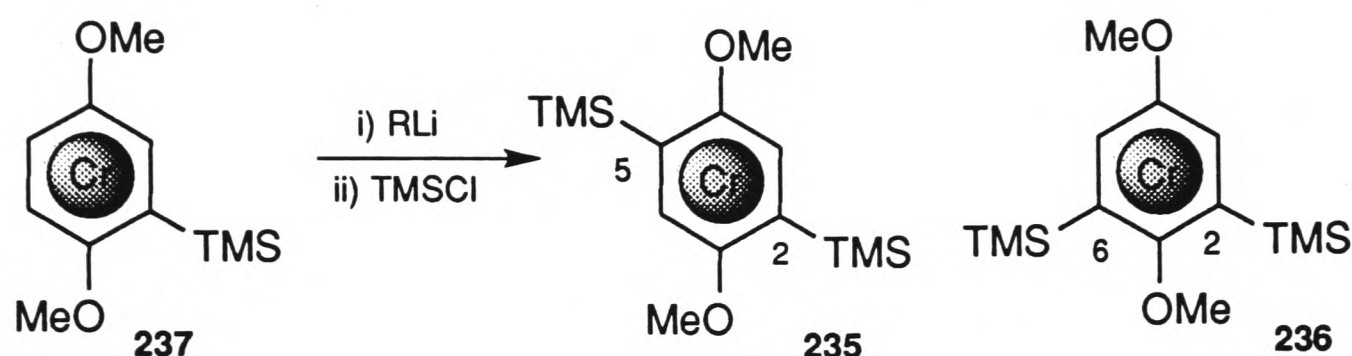
Monosilylation of (1,4-dimethoxybenzene)chromium tricarbonyl **233**



To a THF solution (20 cm^3) of **233** (0.35 g, 1.28 mmol) at -78°C , was added 1 equivalent of *n*-BuLi (1.3 M, 0.98 cm^3 , 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

(C≡O), 1257, 1031 (C-O-C); δ_{H} (300 MHz; CDCl₃) 5.49 (1H, dd, J 2.5, 7.3, ArCr(CO)₃), 5.42 (1H, d, J 2.5, ArCr(CO)₃), 4.97 (1H, d, J 7.3, ArCr(CO)₃), 3.68 (3H, s, OCH₃), 3.61 (3H, s, OCH₃), 0.32 (9H, s, TMS); δ_{C} (125.77 MHz, CDCl₃) 234.8 (Cr(CO)₃), 143.1, 134.5, 128.3 (ArCr(CO)₃:C_{ipso}), 88.2, 82.4, 73.1 (ArCr(CO)₃:C), 56.3 (OCH₃), 55.4 (OCH₃), -0.7 (TMS); m/z (EI) 346 (M⁺, 23%), 262 (M⁺-3(CO), 100); (Found C, 48.74; H, 5.33. C₁₄H₁₈O₅CrSi requires C, 48.55; H, 5.24%).

Silylation of (2-trimethylsilyl 4-methoxyanisole)chromium tricarbonyl **237**

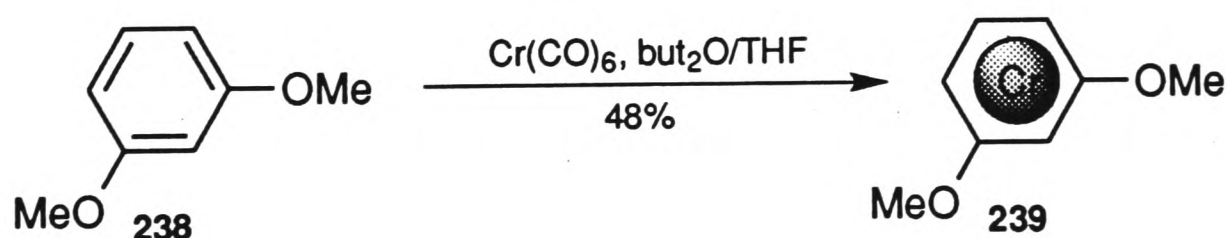


To a THF solution (20 cm³) of **237** (0.10 g, 0.30 mmol) at -78°C was added the required alkyllithium base (1 or 1.1 equiv.) and the reaction mixture stirred for 3 hours. Silylation was then carried out under the standard conditions for the silylation of (arene)chromium tricarbonyl complexes. ¹H nmr 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

Entry	RLi (equiv.)	Ratio	
		235	236
1	<i>n</i> -BuLi (1.0)	2	1
2	<i>t</i> -BuLi (1.0)	2	1

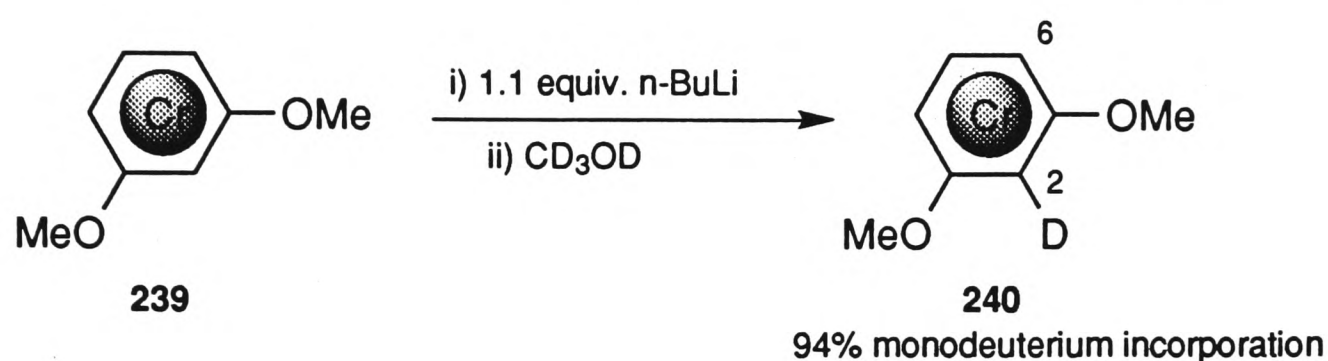
Preparation of (1,3-dimethoxybenzene)chromium tricarbonyl **239**



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

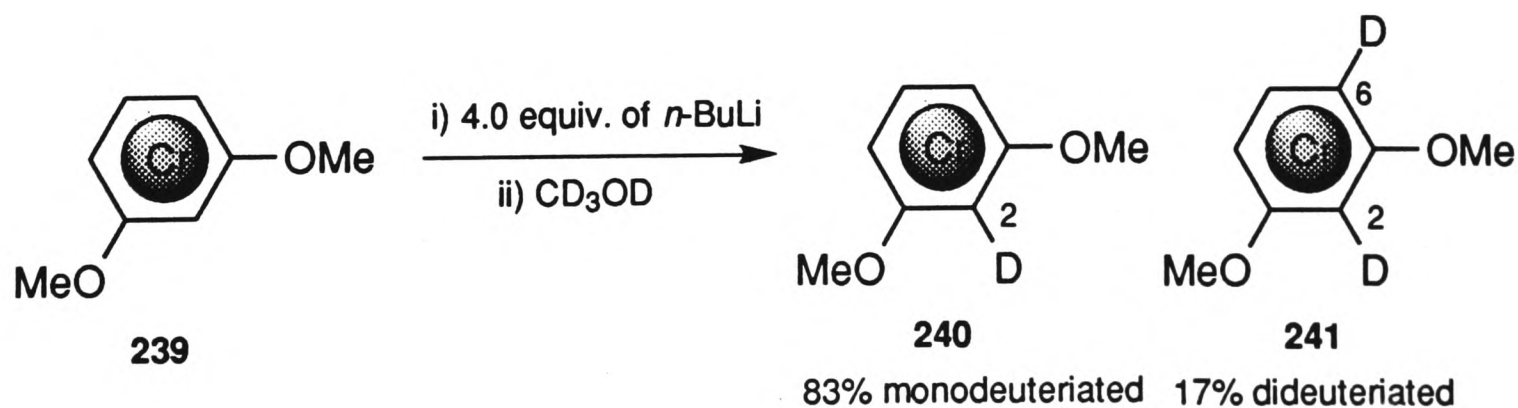
solution was removed *in vacuo* to afford **239** as a yellow solid (1.5 g, 48%), which was then recrystallised from petrol/diethyl ether; m.p. 121-123°C; ν_{max} (KBr)/cm⁻¹ 1972, 1849 (C≡O), 1274, 1034 (C-O-C); δ_{H} (300 MHz; CDCl₃) 5.57 (1H, t, *J* 6.7, ArCr(CO)₃), 5.18 (1H, m, ArCr(CO)₃), 4.82 (2H, dd, *J* 1.7, 6.7, ArCr(CO)₃), 3.74 (6H, s, 2(OCH₃)); δ_{C} (125.77 MHz, CDCl₃) 233.5 (Cr(CO)₃), 143.9 (ArCr(CO)₃:C_{ipso}), 93.1, 72.9, 69.3 (ArCr(CO)₃:C), 55.7 (OCH₃); *m/z* (EI) 274 (M⁺, 28%), 190 (M⁺-3(CO), 100) (Found C, 47.87; H, 3.40. C₁₁H₁₀O₅Cr requires C, 48.19; H, 3.68%).

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



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 cm³, 0.24 mmol) and the reaction was allowed to stir at -78°C for 3 hrs. Deuteration was carried out under the standard conditions for the deuteration of (arene)chromium tricarbonyl complexes to afford **240**. The ¹H 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 monodeuterated species **240**; δ_{H} (300 MHz; CDCl₃) 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(OCH₃)); *m/z* (EI) 275 (M⁺, 39%), 191 (M⁺-3(CO), 100).

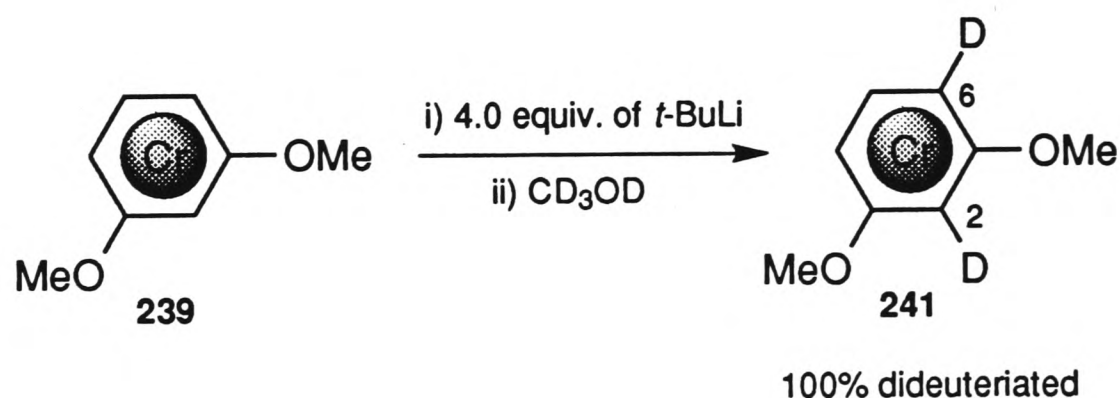
Dideuteration of (1,3-dimethoxybenzene)chromium tricarbonyl **239** with 4.0 equiv. of *n*-BuLi



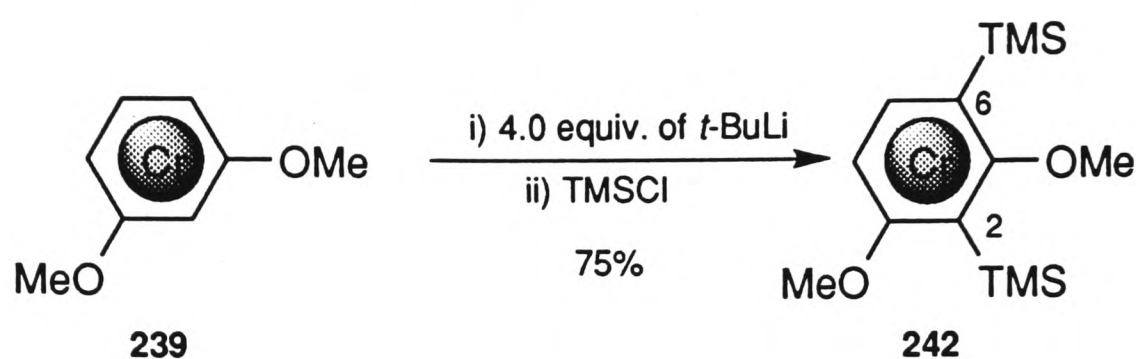
To a THF solution of **239** (0.07 g, 0.26 mmol) at -78°C, was added 4.0 equivalents of *n*-BuLi (1.6 M, 0.64 cm³, 1.02 mmol) and the reaction was allowed to stir at -78°C for 3

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 ^1H 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 ^1H 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**; δ_{H} (300 MHz; CDCl_3) 5.57 (1H, m, $\text{ArCr}(\text{CO})_3$), 3.74 (6H, s, 2(OCH_3); ^2H 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 ($\text{M}^+ - 3(\text{CO})$, 25), 191 ($\text{M}^+ - 3(\text{CO})$, 50), 52 (Cr, 100).

Dideuteriation of (1,3-dimethoxybenzene)chromium tricarbonyl **239 with 4.0 equiv. of $t\text{BuLi}$**



The standard procedure for the deuteriation of (arene) $\text{Cr}(\text{CO})_3$ was used. **239** (0.09 g, 0.32 mmol) was deprotonated with 4.0 equivalents of $t\text{-BuLi}$ (1.7 M, 0.75 cm^3 , 1.27 mmol) and quenched with CD_3OD to afford the dideuteriated product **241**. The ^1H 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**; δ_{H} (300 MHz; CDCl_3) 5.57 (1H, m, $\text{ArCr}(\text{CO})_3$), 4.82 (1H, d, J 6.7, $\text{Ar}(\text{Cr}(\text{CO})_3)$), 3.74 (6H, s, 2(OCH_3); ^2H 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 ($\text{M}^+ - 3(\text{CO})$, 82), 52 (Cr, 100).

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

To a THF solution (4 cm³) of **239** (0.20 g, 0.73 mmol) at -78°C, was added 4 equivalents of *t*-BuLi (1.7 M, 1.7 cm³, 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; ν_{max} (KBr)/cm⁻¹ 1942, 1865 (C≡O), 1251, 1067 (C-O-C); δ_{H} (300 MHz; CDCl₃) 5.67 (1H, d, *J* 6.9, ArCr(CO)₃), 4.75 (1H, d, *J* 6.9, ArCr(CO)₃), 3.72 (3H, s, OCH₃), 3.67 (3H, s, OCH₃), 0.42 (9H, s, TMS), 0.33 (9H, s, TMS); δ_{C} (125.77 MHz, CDCl₃) 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 (OCH₃), 55.5 (OCH₃), 1.8, 0.3 (TMS); *m/z* (EI) 418 (M⁺, 9%), 334 (M⁺-3(CO), 100); (Found C, 48.53; H, 6.22. C₁₇H₂₆O₅CrSi₂ requires C, 48.78 H, 6.26%).

References

1. R. R. Ronald, M. Winkle, *Tetrahedron*, 1983, **39**, 21.
2. B. Nichols, M. C. Whiting, *J. Chem. Soc.* 1959, 551.

