1999

Asymmetric reactions of (arene)tricarbonylchromium acetal complexes.

Maurice Kevin. McKay
University of Windsor

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Asymmetric Reactions of (Arene)tricarbonylchromium Acetal Complexes

by

Maurice Kevin McKay

A dissertation

submitted to the College of Graduate Studies and Research

through the Department of Chemistry and Biochemistry

in partial fulfillment

of the requirements for the degree of Doctor of Philosophy

at the University of Windsor

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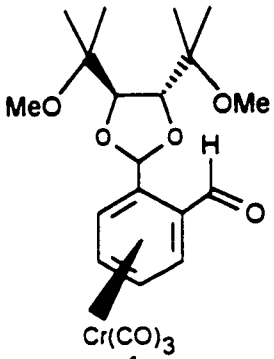
May 1999

ABSTRACT

Chapter 1

The nucleophilic addition of alkyl and arylmetals to **1** was examined. When the reaction was mediated by $Ti(O^iPr)_4$, diastereomeric excesses ranged from 77% to >94%. X-ray crystallography suggested that the major diastereomer had the absolute configuration of *S*. Conjugate addition of alkylmetal nucleophiles was attempted on **2** and **3** without success.



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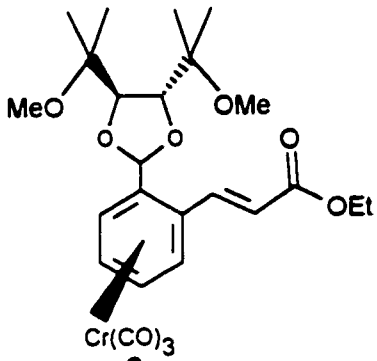

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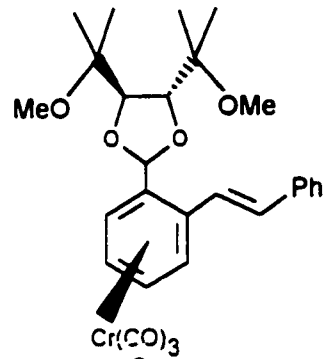
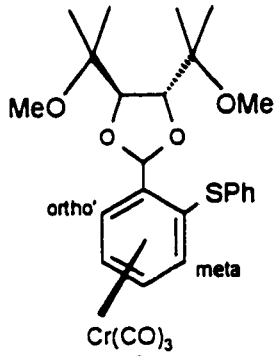


3

Chapter 2

The preparation of meta-disubstituted arenechromium tricarbonyl complexes was attempted. The initial phase of this research involved the directed ortho lithiation of **4**, with thioether directing groups. In the case of the **4**, carrying out the reaction in Et_2O led

to the metallation in the *ortho'* position. In THF lithiation occurred in both the *meta* and *ortho'* position. Desulfurization was attempted on the unsubstituted thiophenyl complex **4**. The use of both Raney Nickel and Nickel Boride led to the formation of the desulfurized complex and its decomplexed analogue in equal proportions.



4

Chapter 3

A series of chromium tricarbonyl complexes with benzylic and non-benzylic alcohol functionalities were subjected to DMSO-TFAA and DMSO/SO_3-pyridine. Yields of carbonyl complexes ranged from 61-80% for the DMSO-TFAA oxidation and from 60-81% for the DMSO/SO_3.pyridine oxidation.

The most exciting phrase to hear in science, the one that heralds new discoveries, is not "Eureka!" (I found it!) but "That's funny ..."

Isaac Asimov

ACKNOWLEDGEMENTS

I would like to take his opportunity to thank my academic supervisor, Dr. J.R. Green for his help, guidance and especially his patience during my prolonged stay at grad school. Without his timely intervention, my colleagues would have endured even more of my stress-induced tirades.

I also wish to thank the rest of Organic Group; Drs. J.M. McIntosh and P. J. Dutton, and the numerous post-docs, grad students and undergrads who passed through. The Organic Group Meetings were an excellent opportunity for information exchange as well as skin-thickening. My co-workers that merit special mention are Anne Charlton, Nikki Swan, Mike Siwek and Jay Kiser.

My parents and family are thanked for encouraging my graduate studies

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

Chapter 1

Chapter 2

Chapter 3

LIST OF ABBREVIATIONS

^{n}BuLi	normal butyllithium
^{s}BuLi	secondary butyllithium
^{t}BuLi	tertiary butyllithium
°C	degrees Celsius
$CDCl_3$	deuterated chloroform
CH_2Cl_2	dichloromethane
cm^{-1}	wavenumbers (IR)
d	doublet (NMR)
de	diastereomeric excess
DMSO	dimethyl sulfoxide
ee	enantiomeric excess
e^-	electron
Et_2O	diethyl ether
EtOAc	ethyl acetate
equiv	equivalents
g	grams
h	hours
Hz	hertz
IR	infrared
LDA	lithium diisopropylamide
m	multiplet (NMR)

M	moles per litre
MHz	megahertz
min	minutes
mL	millilitres
mmol	millimoles
MS	mass spectrometer
mp	melting point
NMR	nuclear magnetic resonance
Ph	phenyl
ppm	parts per million
q	quartet (NMR)
s	singlet (NMR)
t	triplet (NMR)
TMS	trimethylsilyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine

Chapter 1

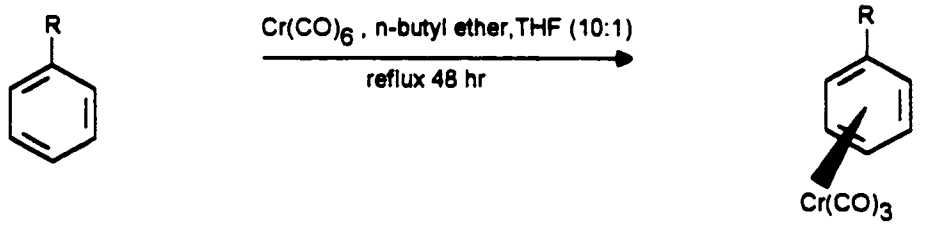
1.1 Introduction

Much attention has been focused on the use of arenechromium tricarbonyl complexes in organic synthesis[1]. They are easily prepared and handled and complexation of the chromium tricarbonyl moiety imparts unique reactivity properties to the arene. The steric effect of the chromium tricarbonyl group on one face of the arene ring can be exploited in the induction of asymmetry.

1.1a Ease of Preparation

(η^6-Arene)$Cr(CO)_3$ complexes are prepared by several convenient methods under rather mild conditions. The simplest and most widely used method is direct ligand exchange with $Cr(CO)_6$. This process takes place best in the presence of a donor solvent. The most effective solvent for this reaction has been found to be a 10:1 mixture of n-

butyl ether and THF [2] (Scheme 1). Other methods of complexation include thermolysis of $Cr(CO)_3L_3$ [L= NH_3[3], RCN (R = Me, Et[4]), or pyridine[5]] with the arene or arene exchange with (naphthalene)chromium tricarbonyl[6]. Complexation of chromium tricarbonyl to an aromatic ring is affected by substituents on the ring[6]. Strongly electron-withdrawing groups such as NO_2 and CN are incompatible with complexation. π-Electron withdrawing substituents (CHO, CO_2H and CO_2R) inhibit complexation and should be protected prior to complexation. Electron donating substituents increase the rate of complexation[7, 8].



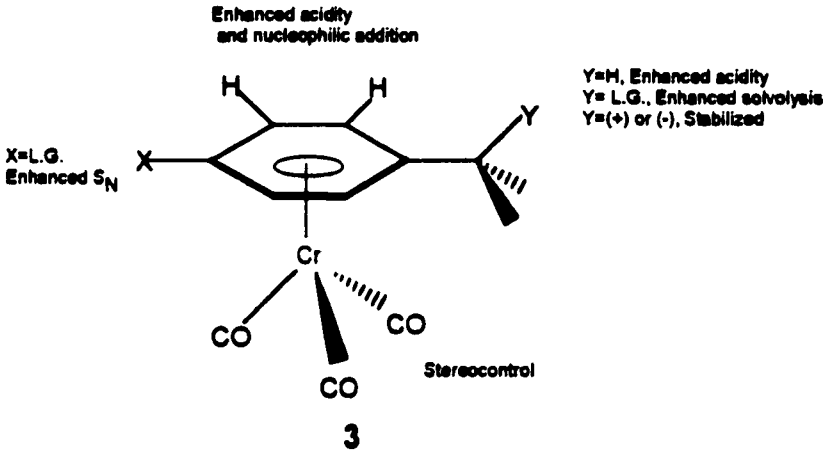
1 **2**

Scheme 1

1.1b Unique Properties

Complexation of the chromium tricarbonyl complex to an aromatic ring imparts unique reactivity properties to the ring (**Figure 1**). The effect of the complexation is the net lowering of electron density in the ring. There is an increased ability of the ring to undergo both ring and benzylic deprotonation, and nucleophilic addition (or substitution

if a leaving group is present[9]). Spatially, the metal occupies one face of the ring and the attack of any reagent on the ring is restricted to an approach only from the side *anti* to the metal[10]. Additionally, ionization of a benzylic leaving group occurs antiperiplanar to the metal atom.

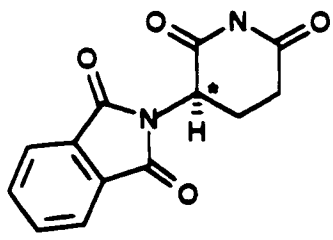


3

Figure 1: Unique Reactivity of Arene as a Result of Complexation

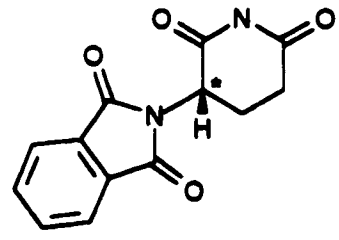
1.1c Chirality in Arene Chromiumtricarbonyl Complexes

Many naturally occurring compounds are chiral and optically pure and the biological activity of one enantiomer is completely different from that of its mirror image. Examples of this include the terpene, carvone, whose (+) enantiomer has the odor of spearmint, whereas the (-) enantiomer has the odor of caraway seed. The *R* enantiomer of asparagine is bitter, while the *S* enantiomer is sweet. The most dramatic example of the differing effects was seen in the case of thalidomide. The *S* form was found to be extremely teratogenic while the *R* form could have been administered to pregnant women without adverse effect. It is necessary to produce many substances in their optically pure form. Drugs, food additives, flavouring agents, pheromones and pesticides are examples of this.



(*R*)-Thalidomide

4

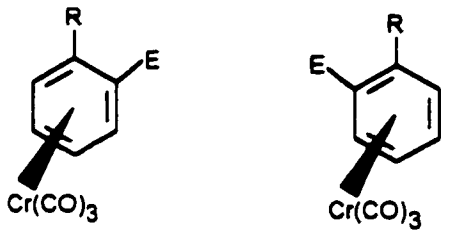


(*S*)-Thalidomide

5

Figure 2: Enantiomers of Thalidomide

Since the chromium tricarbonyl moiety destroys the symmetry that lies in the plane of the aromatic ring, it is possible for *ortho* and *meta* disubstituted arene chromiumtricarbonyl complexes to exist as pairs of enantiomers (assuming the substituents do not contain a chiral center)



6 **7**

Scheme 2

That the products are enantiomers may not be immediately evident, since the chiral centers in these compounds are not of classical tetrahedral geometry. In fact each of the two compounds are mirror images and each of the substituted arene carbons can be thought of as tetrahedral (**Figure 3**). To assign *R* and *S* stereodescriptors, the same method used for classical carbons is applied; thus the arene carbon bearing the methoxy group would be designated *R*.

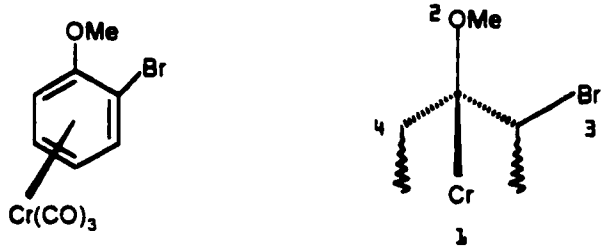


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Figure 3: Assignment of Stereochemistry in Chromium Complexes

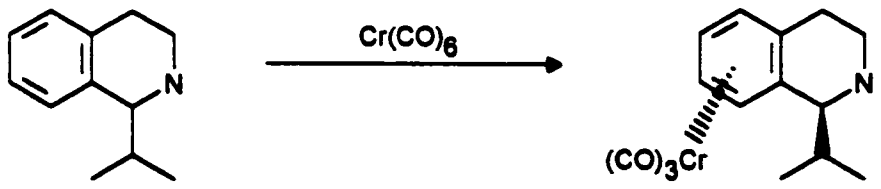
1.1.2 Asymmetry in Reactions of (Arene) Chromium Tricarbonyl Complexes

Arenechromium tricarbonyl complexes have been found useful for the introduction of asymmetry into a reaction. The relatively large steric demands of the chromium tricarbonyl moiety have been exploited for the stereoselectivity in cycloadditions, biaryl cross-coupling and addition of nucleophiles to benzylic sites. The tendency for the chromium tricarbonyl group to stabilize benzylic anions, cations and radicals as well as the addition of some rigidity to the transition state has also been widely utilized. Following, is a description of asymmetric reactions involving arene chromium tricarbonyl complexes.

1.1.2a Diastereoselective Complexation

It is possible to prepare chiral chromium tricarbonyl complexes by the complexation of the chromium tricarbonyl to one of the diastereotopic faces of an arene. For an aromatic molecule bearing a chiral substituent, facial selectivity is governed by steric and electronic effects[11].

The steric effect is evident in the complexation of N-methyl-1-isopropyl-1,2,3,4-tetrahydroisoquinoline **(9)** to chromium tricarbonyl (Scheme 3)[12]. This reaction yields a single diastereomer where the isopropyl group and the chromium tricarbonyl group are on opposite faces of the molecule.



9 **10**

Scheme 3

There have been numerous reports of benzyl alcohol derivatives favoring the addition of chromium tricarbonyl on the same face as the hydroxyl (or ether) group[13,14,15,16]. A mechanism has been proposed [17,18] for this preference in which the first step is coordination of the chromium to an oxygen lone pair. The chromium tricarbonyl is then delivered to the nearest face of the arene (**Figures 4,5**).

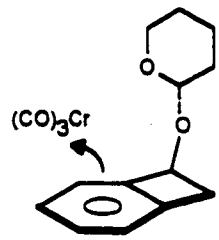
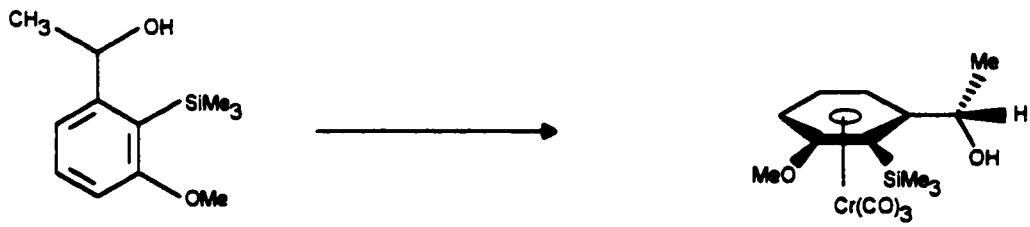


Figure 4: Diastereoselective Complexation via Coordination

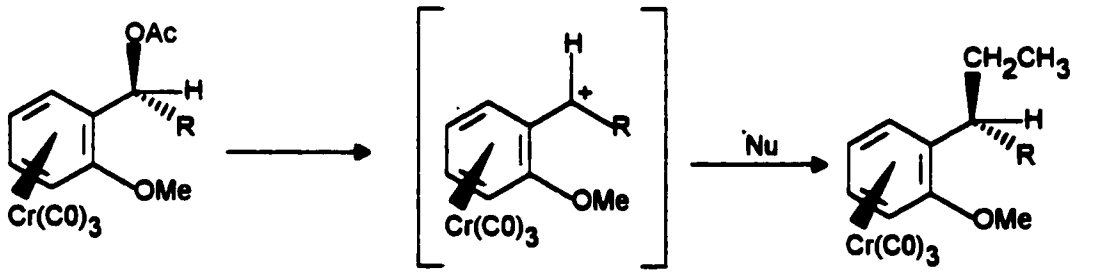


11 **12**

Figure 5: A Diastereoselective Complexation

1.1.2b Benzylic Cations

Reactions of nucleophiles with benzylic cations of (arene)tricarbonylchromium complexes take place with a high degree of stereoselectivity. For example, the reactivity of the chromium tricarbonyl complexes of *ortho*-methoxy-substituted benzyl acetates with alkylaluminum nucleophiles to generate and trap the benzylic cation intermediates has been studied (**Scheme 4**)[19]. It was found that the reaction proceeded with the formation of a single diastereomer. Loss of the acetate group from the *exo* face of the complex shown below yielded a cation in the *syn* conformation. (The use of the other diastereomer of the complex yielded a cation in the *anti* conformation.) The formation of a single conformation of the cation intermediate can be attributed to two factors. First, the leaving group must be in an orientation *anti* to the chromium-arene centroid axis. Secondly, the cation is stabilized by delocalization of the positive charge by overlap of the filled d-orbitals of the metal and the empty p-orbital of the benzylic carbon. This can be represented by a resonance structure in which there is substantial exocyclic double bond character, which implies hindered rotation about the C_{α}-C_{ipso} bond.

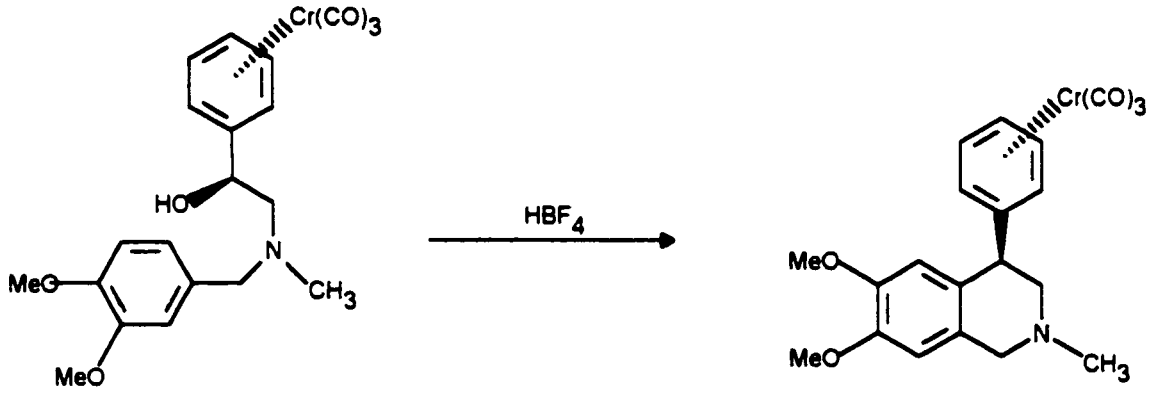


R= CH_3, Nu = $(CH_3CH_2)_3Al$

Scheme 4

Typically, the substrates used to generate benzylic carbocations have hydroxyl groups in the benzylic position. Other benzylic leaving groups include acetates, halides and acetal alkoxy groups. Generation of the cations occurs in the presence of various Brönsted and Lewis acids. The range of nucleophiles used to capture these benzylic cations includes thiols[20], alcohols[21], amines[22], Grignard reagents[23], electron-rich arenes and β-dicarbonyl compounds[19].

This method has been used to prepare several pharmacologically important compounds, including tetrahydroquinoline **(16)** via the cyclization reaction of the chromium tricarbonyl complex of a chiral benzylic alcohol **(15)** (**Scheme 5**)[24].



ee > 98% (67%)

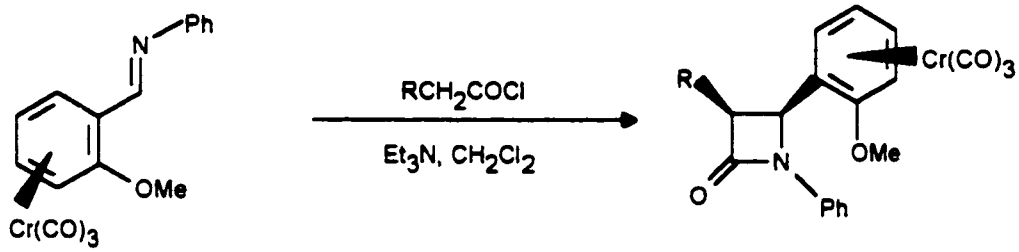
15 **16**

Scheme 5

1.1.2c Asymmetric Cycloadditions

(Arene)tricarbonylchromium compounds have been successfully utilized as chiral auxiliaries in stereoselective cycloaddition reactions. Asymmetric [2 + 2] cycloadditions, 1,3-dipolar cycloadditions and Diels-Alder reactions have been performed in this manner.

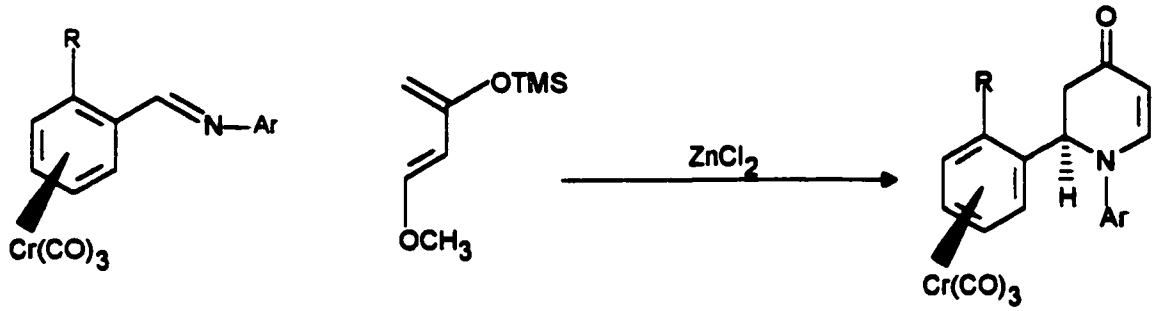
Buttero *et al* has used the [2+ 2] cycloaddition between the chromium tricarbonyl complexes of *ortho*-substituted aryl imines **(17)** and ketenes to synthesize chiral β-lactams **(18) (Scheme 6)**[25].



17 **18**

Scheme 6

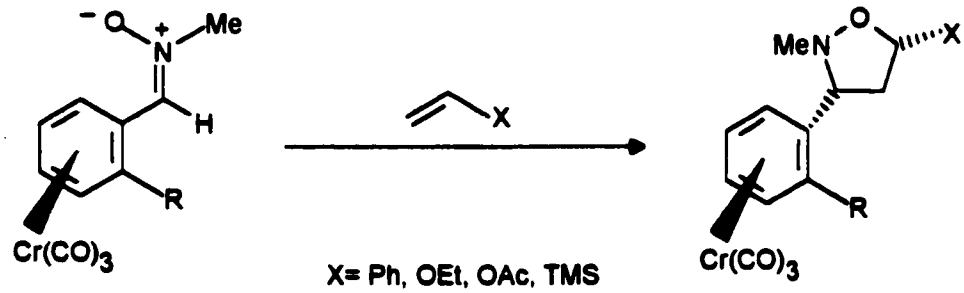
Using the asymmetric Diels-Alder cycloaddition between chiral chromium tricarbonyl complexes of *ortho*-substituted benzylimine **(19)** and Danishefsky's diene **(20)**, Maiorana and co-workers were able to achieve the stereoselective synthesis of 2,3-dihydro-4-pyridone derivatives **(21) (Scheme 7)** [26].



19 **20** **21**

Scheme 7

Hanaoka used the 1,3-dipolar cycloaddition reaction for the preparation of *cis*-3,5-disubstituted isoxazolidines **(23).** Electron rich olefins were reacted with chromium tricarbonyl complexed aryl nitrones **(22)** to afford the corresponding cycloadducts (**Scheme 8**). *Cis-trans* ratios were typically in the 98:2 range[27]. Selectivity has been rationalized on the basis of a concerted mechanism via a transition state that places the electron releasing substituent of the dipolarophile close to the electron-deficient aromatic ring. In such a position, it was postulated that there was an attractive effect between the two groups.

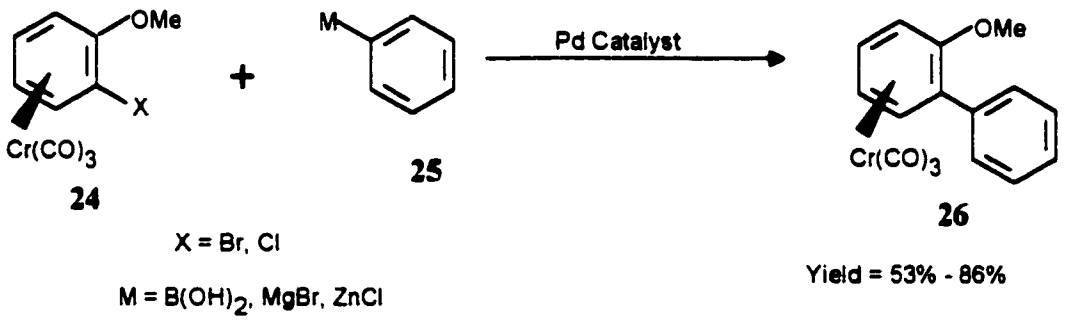


22 **23**

Scheme 8

1.1.2d Asymmetric Biaryl Cross-Coupling Reactions

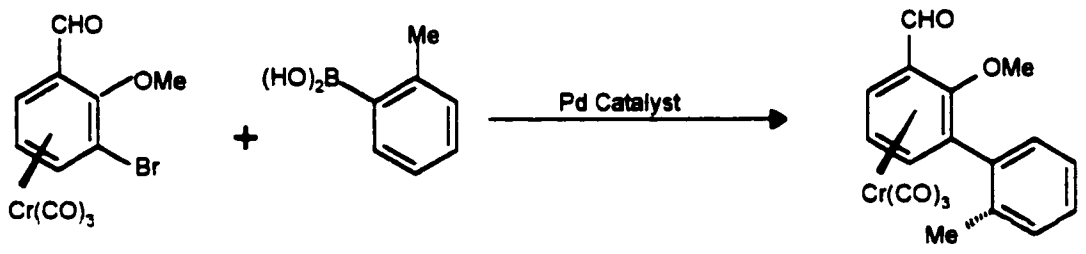
Palladium(0) catalyzed cross coupling reactions of (arylhalide)tricarbonyl-chromium complexes with arylmetals provide an efficient route to mono-chromium tricarbonyl complexes of biphenyl compounds in good yields. *Ortho*-chloro and *ortho*-bromo substituted (anisole)tricarbonylchromium complexes were reacted with phenyl Grignard reagents, phenylboronic acids and phenylzinc chlorides with yields ranging from 53% to 86% (Scheme 9)[28].



Scheme 9

In the cross coupling reactions between *ortho* disubstituted (haloarene)tricarbonyl chromium complexes with *ortho* substituted arylboronic acids, mono-$Cr(CO)_3$ complexes of biphenyl compounds are obtained which have hindered rotation about the aryl-aryl bond. This results in the product having both planar and axial chirality. The coupling reaction between (2-methoxy-3-formyl-bromobenzene)$Cr(CO)_3$ (**27**) and *ortho*-

methylphenylboronic acid **(28)** gave the coupling product **(29)** in 82% yield as a single stereoisomer (**Scheme 10**)[28].

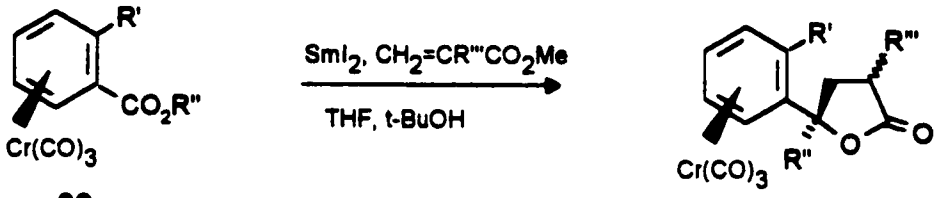


27 **28** **29**

Scheme 10

1.1.2e Samarium Iodide Mediated Couplings

Uemura *et al* have reported the samarium iodide mediated coupling reactions of the planar chiral chromium tricarbonyl complexes of benzaldehyde and benzaldimine to give the corresponding *threo* 1,2-diols or 1,2-diamines, respectively[29]. Chromium tricarbonyl complexes of *ortho* substituted benzaldehydes and acetophenones **(30)** were coupled with methyl acrylate in the presence of samarium iodide to give a single diastereomer of γ-butyrolactones **(31)** in moderate to good yields (**Scheme 12**). Stereoselection has been rationalized on the basis of a proposed ketyl radical intermediate that possesses considerable exocyclic double bond character. Rotation about the C_{α}-C_{ipso} bond is hindered and the radical intermediate reacts with the acrylate approaching from the face opposite the chromium tricarbonyl group.



30

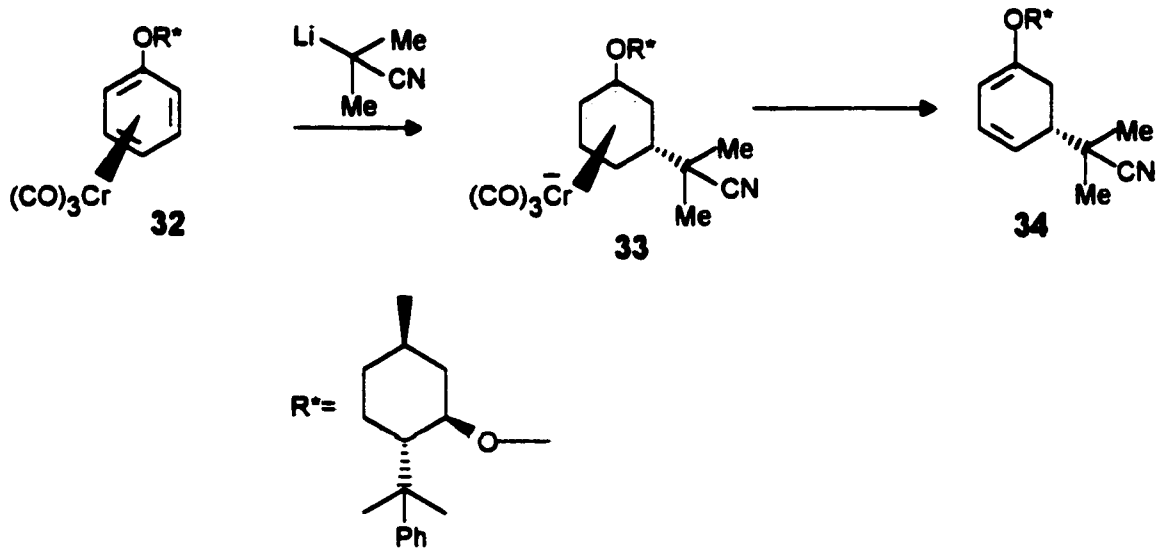
R' = OMe, Me, Br
R" = H, Me
R'" = H, Me

31

Scheme 12

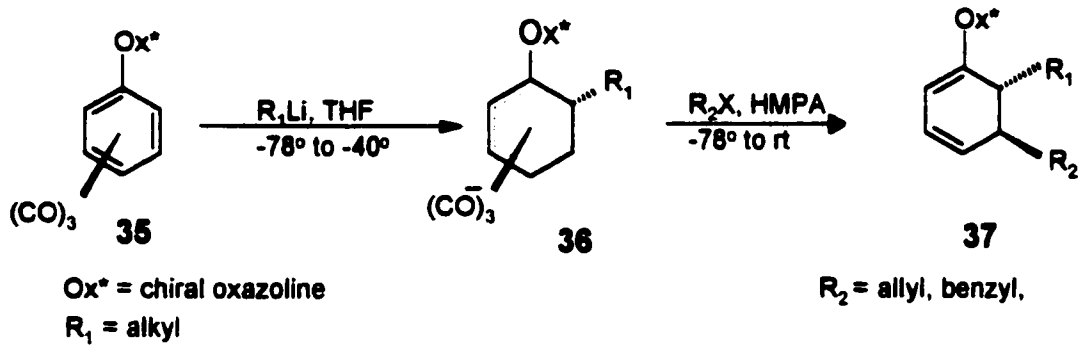
1.1.2f Asymmetric Nucleophilic Additions to Arene Rings

It is well established that nucleophiles will add to electron-poor aromatic rings[30]. The complexation of the electron withdrawing chromium tricarbonyl group to an aromatic ring also renders that ring susceptible to nucleophilic substitution. Chiral alkoxy groups have been exploited as auxiliaries in the asymmetric addition of nucleophiles to arene chromium tricarbonyl complexes[31,32]. Addition of 2-methylpropionitrile to the chromium tricarbonyl complex of 8-phenylmenthylphenyl ether **(32)** gave 1,5 disubstituted cyclohexadienes **(34)** in up to 48% de (**Scheme 13**).



Scheme 13

Using oxazolines as chiral auxiliaries, it is possible to get regio and stereoselective transformation of arenes into *trans* disubstituted cyclohexadienes [33,34]. The combined effects of the *ortho* directing oxazoline group and the electron withdrawing chromium tricarbonyl result in the addition of the nucleophile in the *ortho* position on the arene ring (**Scheme 14**). The subsequent addition of an electrophile to the resulting cyclohexadienyl complex results in the formation of a *trans*-disubstituted cyclohexadiene. Initial coordination of the electrophile to the chromium atom followed by delivery to the proximal face of the cyclohexadienyl unit provides the *trans*-orientation of the two substituents. A variation on this methodology involves the addition of nucleophiles to the arene in the presence of chiral ligands such as sparteine and some C_2 symmetric vicinal diols[35].



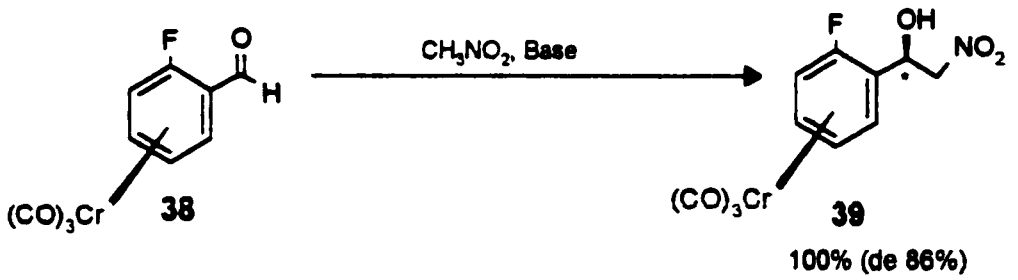
Scheme 14

1.1.2g Asymmetric Addition of Nucleophiles to Aryl Carbonyl Groups

The chromium tricarbonyl group on these complexes can be used to cause stereochemical bias by blocking one face of the molecule from the approach of a reagent. One of the most common uses of this tactic is the addition to an electrophilic benzylic site of a chromium tricarbonyl complex. Typically, the electrophilic site is an aldehyde carbonyl group, although imines have been used in this role. A wide variety of aldol-type reactions have been successfully carried out in a stereoselective manner.

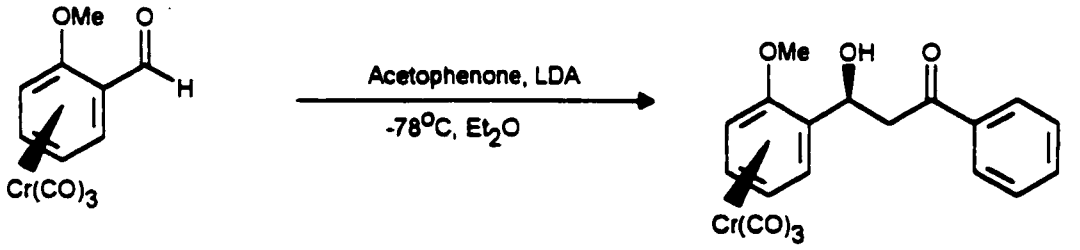
In an effort to synthesize ephedrine analogues, Solladié- Cavallo *et al* have investigated the reaction of nitroalkanes with *o*-substituted benzaldehyde chromium tricarbonyl complexes. Using (*o*-fluorobenzaldehyde)chromium tricarbonyl complex **(38)** with nitromethane in the presence of potassium fluoride, a quantitative yield of β-nitroalcohol **(39)** was obtained with a de of 86% [36] **(Scheme 15)**. With (*o*-

methylbenzaldehyde)chromium tricarbonyl as the substrate, the β-nitroalcohol was formed in 90% yield with 94% de [37].



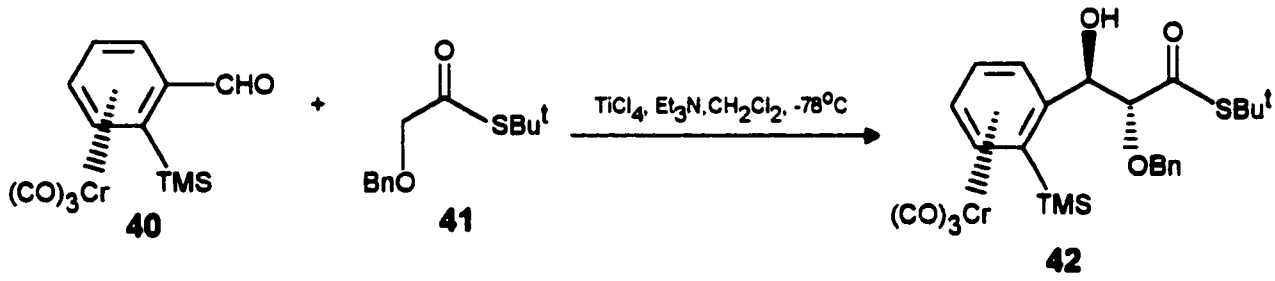
Scheme 15

Brocard *et al* have studied the addition of the lithium enolates of methyl ketones and esters with the chromium tricarbonyl complexes of *ortho* substituted benzaldehydes [38]. Diastereomeric excesses (de) ranged from a low value of 78% to 98%, the higher stereoselection observed with the use of LDA in diethyl ether at -78°C. The reaction of acetophenone with (*o*-methoxybenzaldehyde)chromium tricarbonyl in the presence of LDA gave the addition product in 98% de (**Scheme 16**).



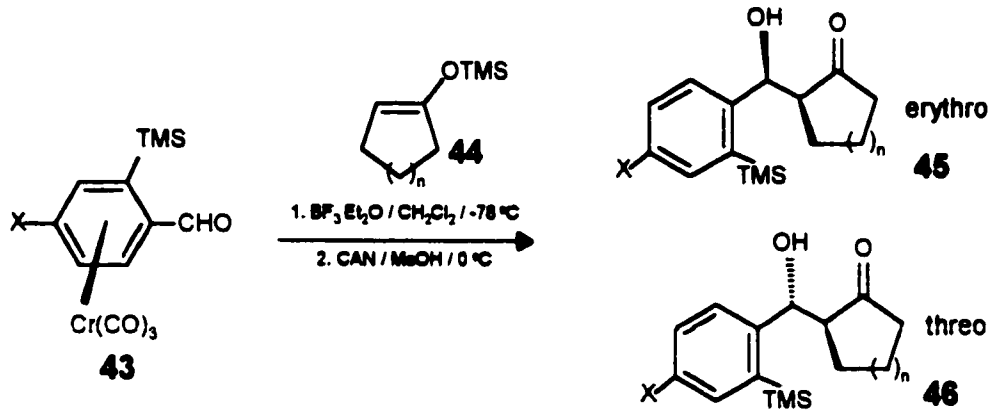
Scheme 16

In the syntheses of (+)-Goniofurone [39], a titanium enolate of a thioester was added to a chromium tricarbonyl complexed benzaldehyde in a selective manner. (*o*-Trimethylsilylbenzaldehyde) chromium tricarbonyl **(40)** was treated with the titanium enolate of t-butyl ethanethioate **(41)** to afford the *anti* aldol condensation product. (**Scheme 17**). The same methodology was applied successfully in the synthesis of (2*R*,3*S*)-(-)-*N*-benzoyl-3-phenylisoserine methyl ester **(42)**, a taxol side chain analogue [40].



Scheme 17

The high π-facial selectivity of arene chromium tricarbonyl complexes has been exploited by Mukai and Hanaoka in imparting asymmetry on the Lewis acid mediated addition of silyl enol ethers to *o*-substituted benzaldehydes. [41, 42] It was found that high *erythro* selectivity was obtained for the addition of cyclic silyl enol ethers with (*o*-trimethylsilylbenzaldehyde)chromium tricarbonyl complexes. For the reaction between with (o-trimethylsilylbenzaldehyde) chromium tricarbonyl **(43)** and trimethylsilyloxycycloheptane **(44)**, a 98:2 *syn:anti* ratio was obtained. Changing the ring size of the nucleophile had little effect on *syn* selectivity. Varying the *para*-substituent on the aldehyde also had little effect on isomer ratios (**Scheme 18**).



Scheme 18

Selectivity for this type of reaction is a consequence of two factors. First, the nucleophile must approach the carbonyl group from the face opposite the chromium tricarbonyl group. The coordination of the Lewis acid to both the trimethylsilyl group and the carbonyl oxygen causes the carbonyl group to adopt the rotational conformation that places the carbonyl oxygen close to the *ortho* substituent. Also, the orientation of the nucleophile determines which isomer is produced. **Figure 6** shows transition states to depict the addition of the silyl enol ether to the Lewis acid-catalyzed carbonyl group. Transition state **A** shows the nucleophile situated in such a manner that the trimethylsiloxy group is held away from other fragments. Transition state **B** depicts the nucleophile adopting an orientation such that the trimethylsiloxy group is in relatively close proximity to other substituents, which through steric interactions between the aldehyde function and the silyl enol ether would destabilize the transition state.

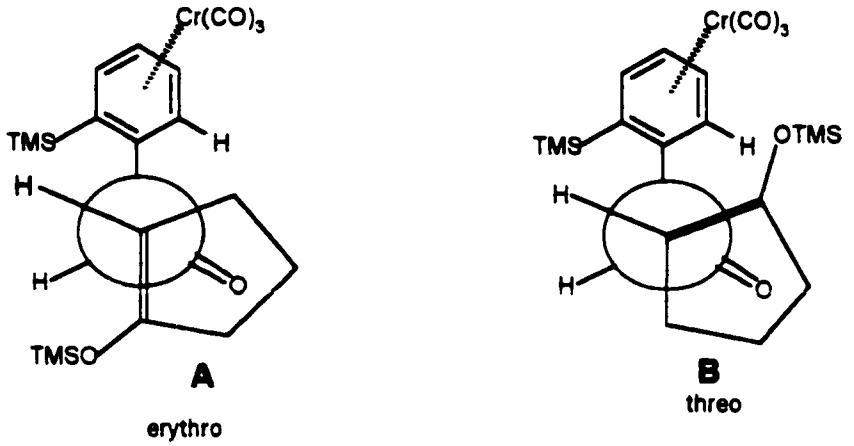
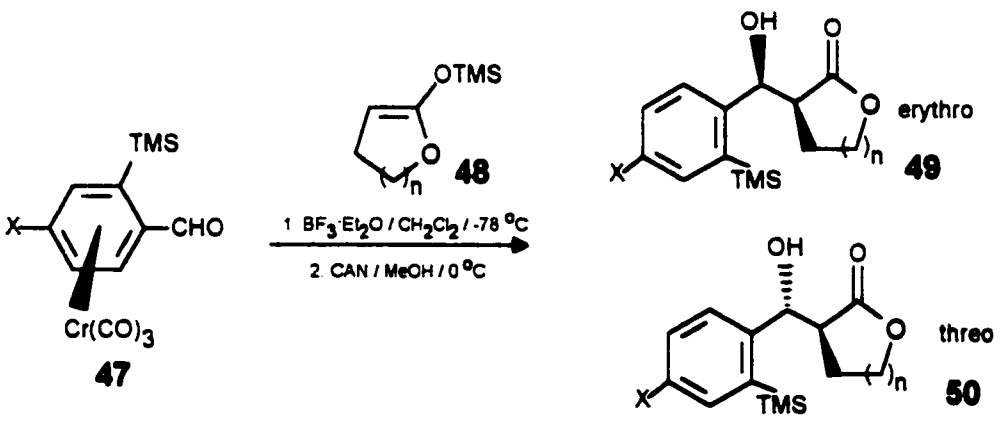


Figure 6: Proposed Transition States to Rationalize *Erytho* Selectivity in the Addition of Cyclic Silyl Enol Ethers to *o*-substituted Benzaldehydes

Mukai *et al* extended their study to include the examination of cyclic silyl ketene acetals as nucleophiles[43]. **(Scheme 18)**



Scheme 18

The addition reaction exhibited highest selectivity when the *ortho* substituent on the aldehyde was a silyl group. Seven-membered silyl ketene acetals added to the aldehydes in the most *erythro* selective manner. Transition states that explain the diminished selectivity as compared to the silyl enol ethers have been proposed. (**Figure 7**).

In a manner similar to the case of the silyl enol ethers, the preferred conformations for both the *threo* and *erythro* additions have hydrogen atom on the double bond on the nucleophile in the most sterically demanding position. Since it is the smallest substituent, repulsive interaction with the bulky TMS group is minimized. With silyl ketene acetals, there is another factor that must be considered. There may be an unfavorable dipole-dipole interaction between the ether oxygen of the nucleophile and the aldehyde oxygen. It is more likely, than with the silyl enol ethers, that the addition of the silyl ketene acetals may proceed through other transition states less affected by this dipole-dipole interaction.

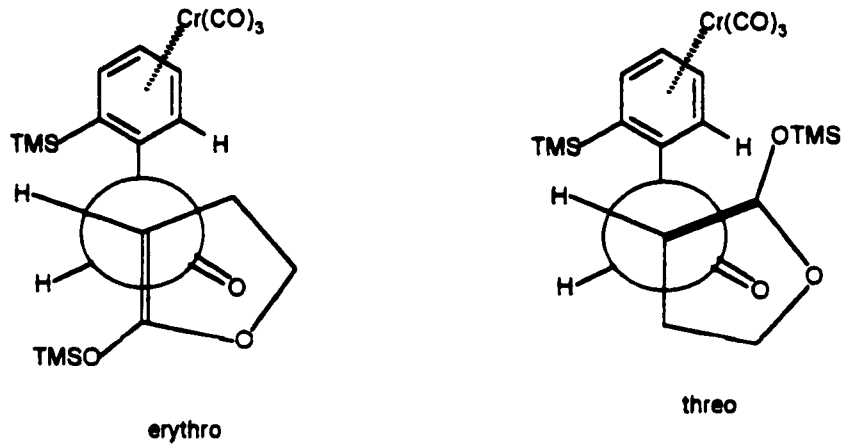
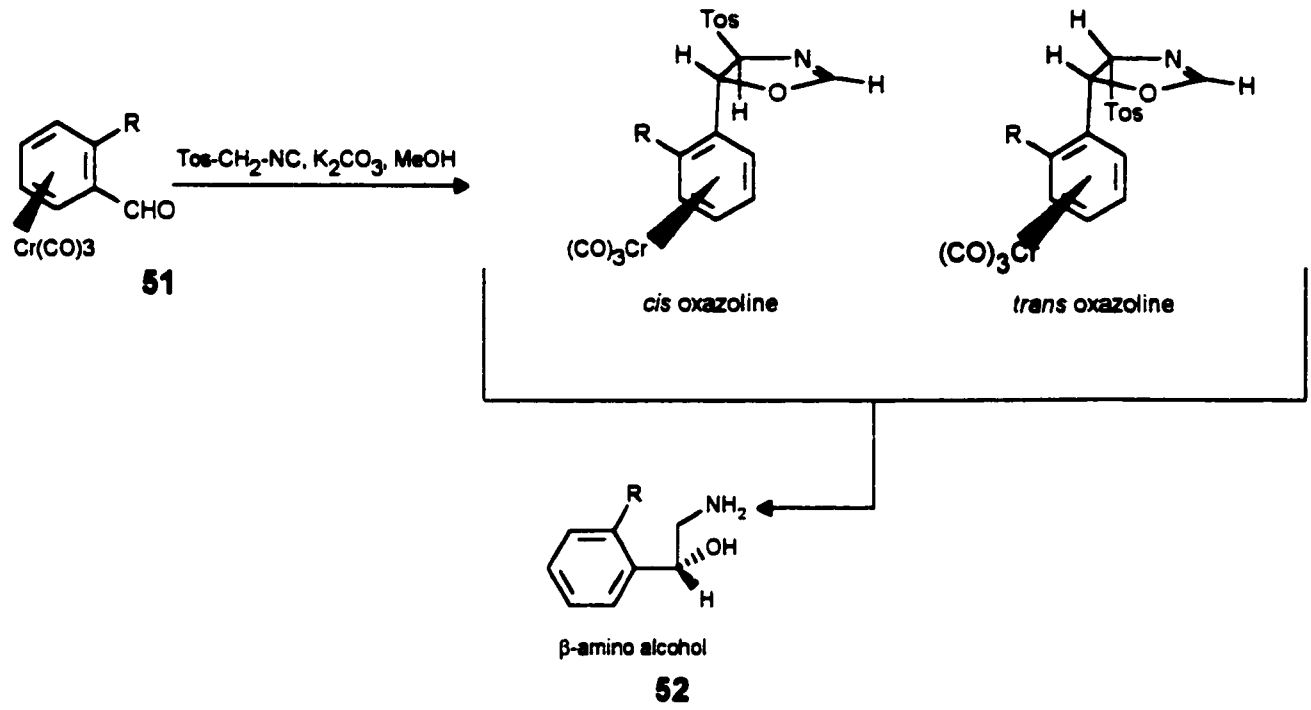


Figure 7: Proposed Transition States to Rationalize *Erytho* Selectivity in the Addition of Cyclic Silyl Ketene Acetals to *o*-substituted Benzaldehydes

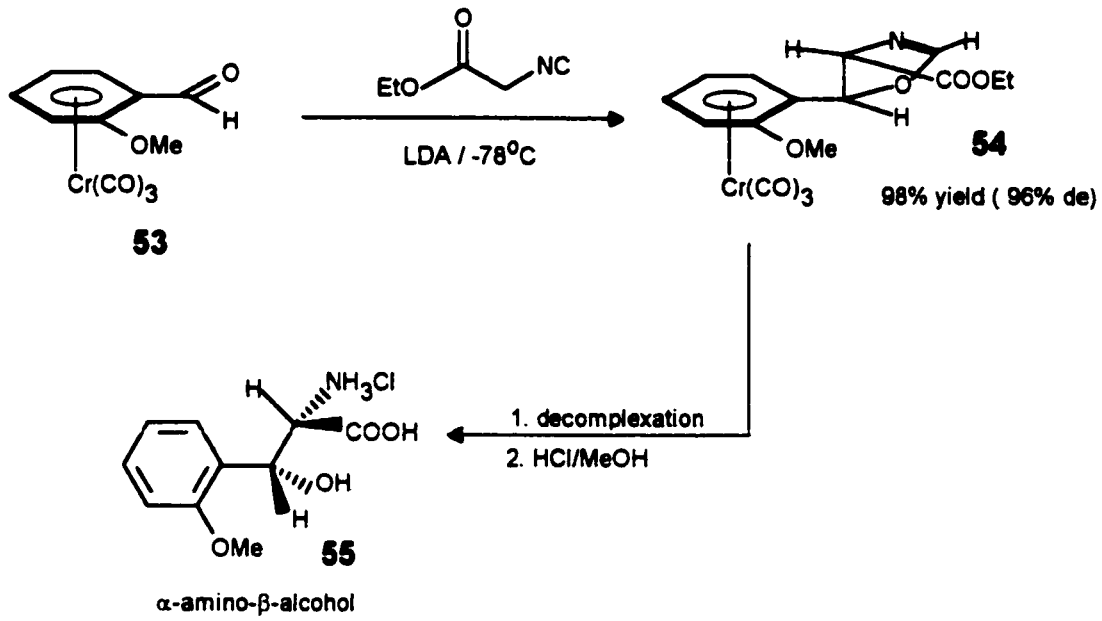
Isocyanide additions to aldehydes

Solladié-Cavallo *et al* have examined the reaction of tosylmethyl isocyanide with *ortho* substituted benzaldehyde chromium tricarbonyl complexes (**51**) as a method to prepare optically pure β-amino alcohols (**52**), en route to their synthesis of halostachin[44,45]. It was found that a single diastereomer of the oxazoline was formed from the reaction of (*o*-tolualdehyde)chromium tricarbonyl with tosylmethyl isocyanide. Upon decomplexation and reduction, (+)-halostachin was obtained. (**Scheme 19**)



Scheme 19

The anion of ethyl cyanoacetate has also been added to *ortho* substituted benzaldehyde chromium tricarbonyl complexes to give carboxylate-substituted oxazolines[46] (**Scheme 20**). When ethyl cyanoacetate was reacted with (o-anisaldehyde) chromium tricarbonyl (**53**), in the presence of LDA at –78°C, one diastereomer was produced predominantly. Upon decomplexation and reduction, optically pure α-amino-β-hydroxyacids (**54**) were obtained.

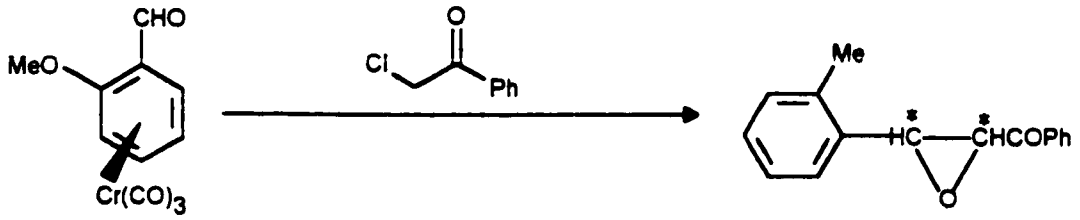


Scheme 20

Darzens' condensation reactions

The Darzens' condensation reaction between the chromium tricarbonyl complexes of *o*-substituted benzaldehydes with α-halo nucleophiles has been used in the preparation of chiral epoxides [47,48]. Using *ortho*-methoxy and *ortho*-chlorobenzaldehyde(tricarbonyl)

chromium complexes **(55)** , Baldoli *et al* obtained very high ee values of styrene oxides **(56)** following decomplexation (**Scheme 21**).

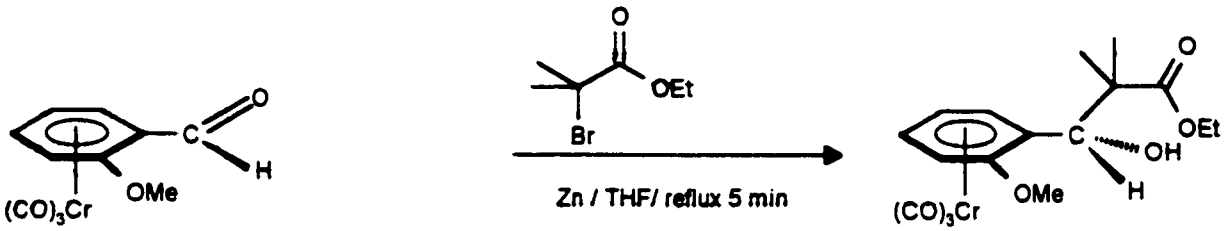


55 **56**

Scheme 21

Reformatsky Reactions

Zinc ester, nitrile and ketone enolates have been used as nucleophiles in the addition to chromium tricarbonyl complexes of *ortho*-substituted benzaldehyde [49,50]. The reaction of methyl-2-bromo-2-methylpropanoate with (*o*-methoxybenzaldehyde) chromium



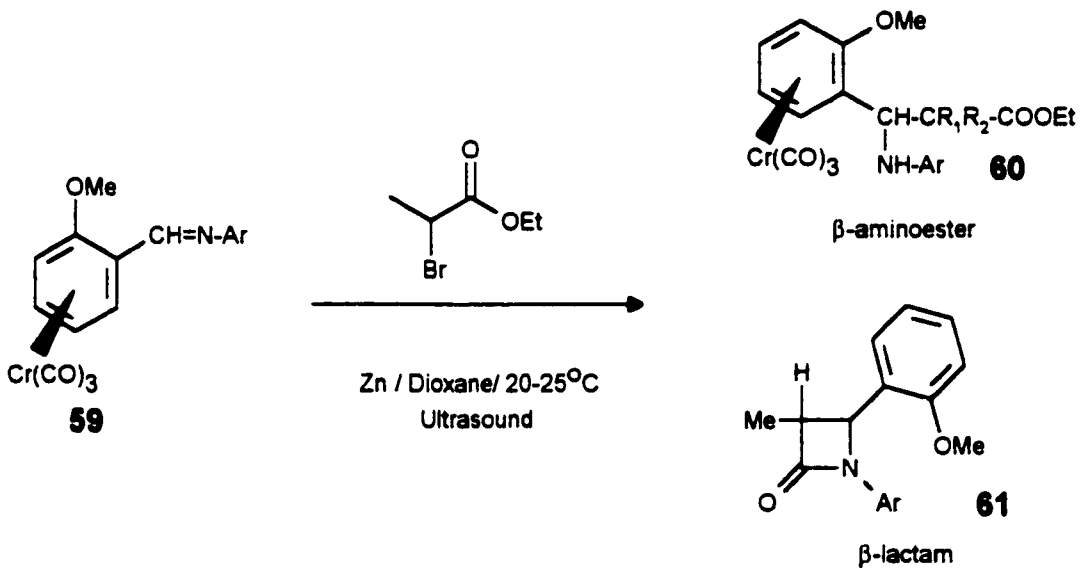
57 **58**

Scheme 22

tricarbonyl (**57**) afforded the corresponding β-hydroxyester (**58**) with good diastereoselectivity (**Scheme 22**). The examples exhibiting the best selectivity are those in which there is an *ortho* methoxy substituent. Regardless of the nature of the electron withdrawing group or the α-substituent on the nucleophile, complete diastereoselectivity was observed. Transition states have been proposed in which there is coordination of the zinc atom to both the aldehyde carbonyl and the enolate heteroatom. The rotational conformation of the formyl group is such that the carbonyl oxygen is oriented away from the methoxy substituent.

Baldoli *et al* used Reformatsky methodology in their attempts to prepare optically active β-lactams [51] (**Scheme 23**). In this investigation, the electrophilic species were arylimino derivatives of chromium tricarbonyl complexes of *ortho*-substituted benzaldehydes.

Preparation of the zinc enolate of the ester was assisted by the use of ultrasound. Reaction of ethyl 2-bromopropionate with [N-(2-methoxybenzylidene)aniline]chromium tricarbonyl **(59)** in the presence of zinc afforded a mixture of the corresponding β-lactam and β-aminoester **(60)** **(Scheme 23.)** The β-lactam was obtained in a 40:18 *cis: trans* ratio. Upon decomplexation, the aminoester was converted to the β-lactam **(61)** in the presence of LDA in a 39:17 *cis:trans* ratio.



Scheme 23

Aminoalcohol Chiral Catalysts

An arene chromium tricarbonyl based chiral catalyst has been developed for the addition of dialkylzincs to aldehydes [52,53]. Its structure, at the active species, is a zinc

alkoxide, derived from one of a series of chromium tricarbonyl complexed amino alcohols (**62**) (**Figure 8**). It has been effective in mediating the addition of dialkyl zincs to aldehydes giving alcohols in up to 99% ee (**Scheme 24**)[54]. For catalysts without chromium tricarbonyl fragments, inferior selectivities were observed.

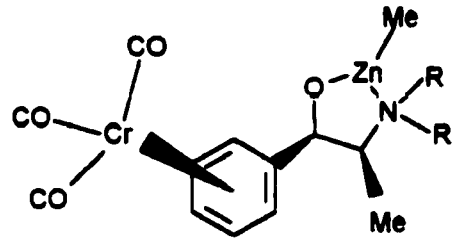


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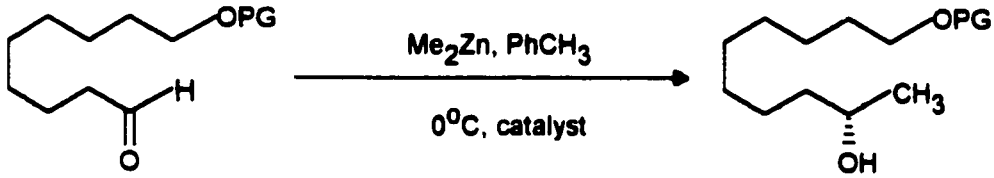
Figure 8: Jones' β-Amino Alcohol Based Catalysts

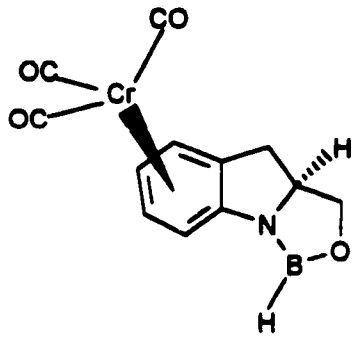


63 **64**

Scheme 24

Jones has also developed a series of chromium complexed tricyclic oxazaborolidine catalysts [55] (**65**) (**Figure 9**). These catalysts have found application in the borane reduction of ketones. Enantiomeric excesses of up to 91% have been observed for the reduction of ketones.

Enantioselectivity is a function of the preference of the larger of the substituents on the carbonyl carbon to adopt an orientation *anti* to the bulky upper portion of the catalyst; thereby inducing intramolecular delivery to one enantiotopic face of the ketone.

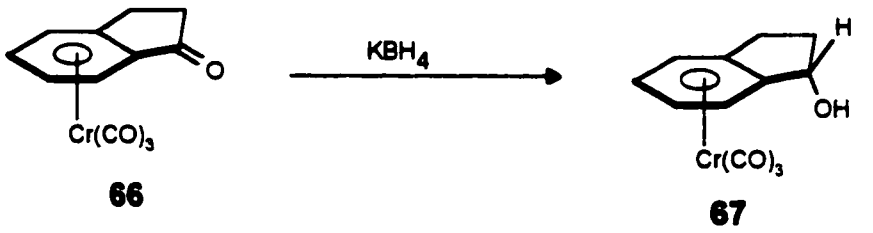


65

Figure 9: Jones' Oxazaborolidine Catalyst

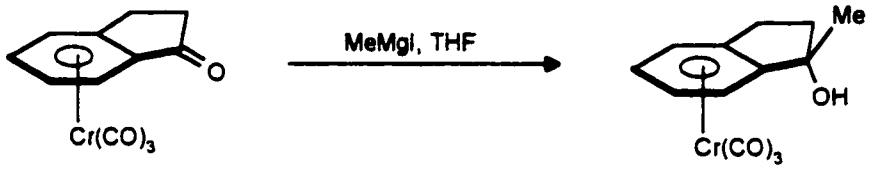
Alkylmetals as Nucleophiles

Alkyllithiums have been found to add stereoselectively to a carbonyl bearing arenechromium tricarbonyl complexes. Early research in this area demonstrated that KBH_4 reductions of chromium tricarbonyl complexes of indanones and tetralones (**Scheme 25**) [56, 57, 58] gave exclusively *endo* indanols and tetralols respectively. For the case of these bicyclic ketones, with its skeleton imposing high conformational restriction, it is not surprising that almost total stereoselectivity has been realized. Grignard reagents as well as alkyllithiums have also been successfully used to alkylate indanones[59], resulting in the formation of *endo* indanols (**Scheme 26**).



66 **67**

Scheme 25

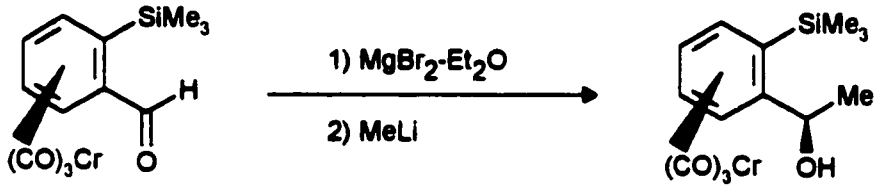


68 **69**

Scheme 26

Arene chromium tricarbonyl complexes bearing aldehyde functionality have also been used as substrates for nucleophilic additions. With the appropriate *ortho* substituent, highly stereoselective nucleophilic additions are possible. The *ortho* methoxy group has been utilized to this end. For example, Solladié-Cavallo *et al* have made extensive use of the *ortho* methoxy-arenechromiumtricarbonyl compounds as substrates for asymmetric alkylations with alkyllithium and alkyl Grignard nucleophiles [60]. Perfluoroalkyllithiums and perfluoroalkylzinc nucleophiles have also been used by the Solladié-Cavallo group [60,61]. Other *ortho* substituents that have been included on the substrate include fluoro, methyl and trifluoromethyl. Addition of lithium acetylides and Grignards to chiral *ortho*-substituted benzaldehyde tricarbonyl chromium complexes provide a stereoselective route to optically pure propargyl alcohols[62].

Davies *et al* has shown that the incorporation of the trimethylsilyl group in the *ortho* position of the chromium tricarbonyl complex of benzaldehyde also leads to stereoselective nucleophilic additions to the carbonyl [63] (**Scheme 27**). Pre-treatment of the aldehyde with $MgBr_2 \cdot Et_2O$ ensured that there was a sufficient bias in the rotation of the carbonyl group such that nucleophilic addition occurred predominantly on the preferred rotamer which has the carbonyl oxygen pointing away from the TMS group.



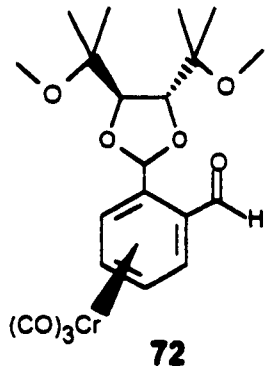
70 **71**

Scheme 27

With the numerous examples of nucleophilic additions arenechromium tricarbonyl complexes bearing prochiral benzylic carbonyl groups, there seemed ample precedent to predict asymmetric nucleophilic additions to the carbonyl group of the *ortho*-formyl complex (**Figure 10**). This compound is readily prepared with methodology developed in this research group[64].

1.2 Results and Discussion

The recent development of tartrate-derived benzaldehyde acetal tricarbonylchromium complexes as substrates for highly stereoselective *ortho* substitution reactions has revealed the unit to be promising in the field of asymmetric synthesis [64]. As such, the systematic investigation of the reactions of prochiral centers attached to the ring is warranted. In the field of *ortho*-disubstituted arenetricarbonylchromium complexes, study of the additions to the aldehyde function has become the standard of this ability therefore *ortho*-benzaldehyde complex (**72**) was chosen for this examination.



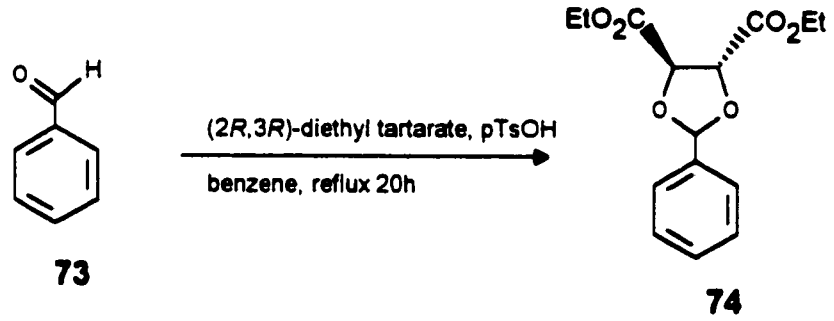
72

Figure 10: *o*-Formyl Complex

1.2.1 Preparation of the o-Formyl Complex (72)

The chiral acetal was selected for the ease of preparation of the acetal unit and its demonstrated ability in directing asymmetric lithiations. The *ortho* formyl complex was

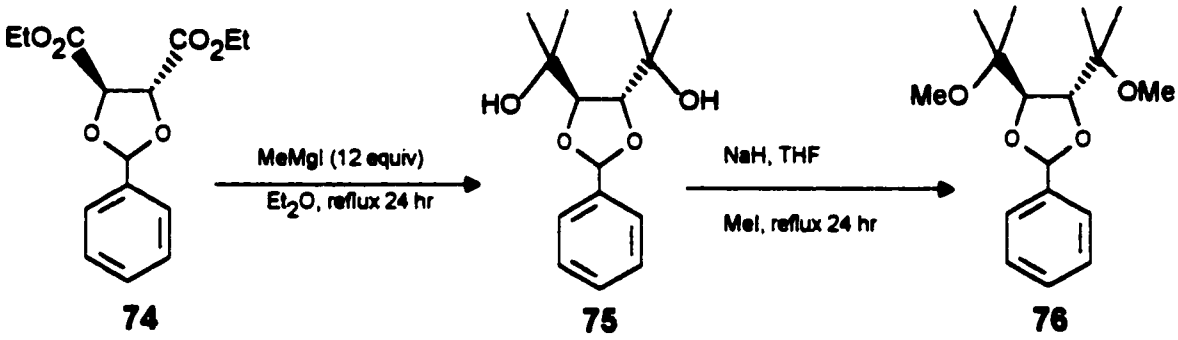
prepared via the following synthetic pathway. A modification of the previously reported procedure was found to be more straightforward for the preparation of the acetal. First, benzaldehyde was protected as an acetal using diethyl tartrate and *p*TsOH (**Scheme 28**). This reaction was a modification of an existing procedure in which the diethyl acetal of benzaldehyde was prepared *in situ* using triethyl orthoformate[65]. It was found that preparing the tartrate acetal directly had no deleterious effect on yield. It was also found that it was not necessary to separate the product using Kugelrohr distillation as prescribed by literature. It was sufficient to remove any remaining starting materials by filtration since they are liquids.



73 **74**

Scheme 28

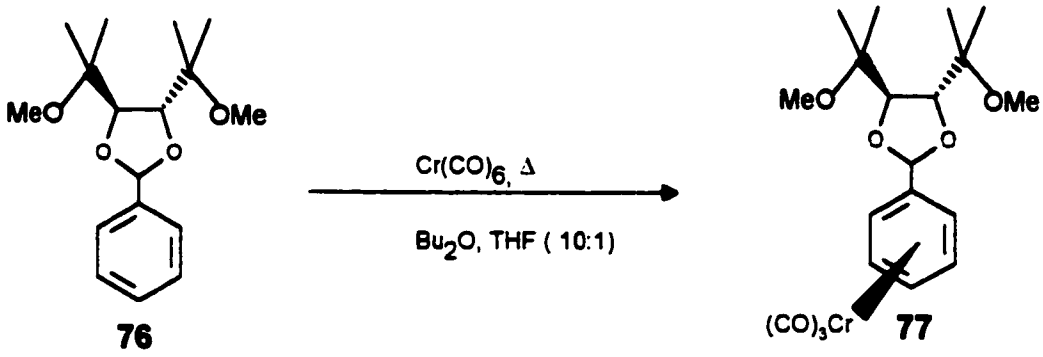
The resulting acetal (**74**), which bears two ethyl esters, was treated with excess methylmagnesium iodide to convert the esters to tertiary alcohols (**75**) (**Scheme 29**). Deprotonation of these alcohols followed by reaction with iodomethane gave the bis(dimethyl ether) compound (**76**)



Scheme 29

Thermolysis of the diether (**76**) with chromium hexacarbonyl led to the formation of the chiral acetal chromium complex (**77**) (**Scheme 30**). Yields of complexation products were typically in the 60-70% range after chromatography. Unreacted compound was easily recovered by column chromatography. During the course of the reaction it was necessary to remove sublimed chromium hexacarbonyl from the inside of the reflux condenser. Failure to do so resulted in an accumulation of solvent above the blockage in

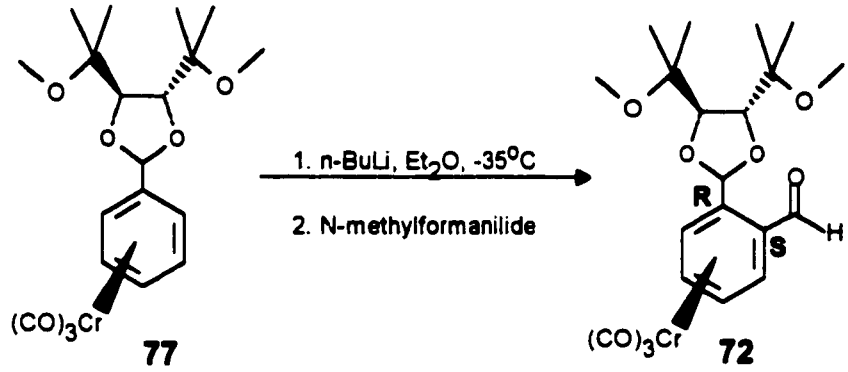
the reflux condenser and thus a loss of solvent in the reaction flask. The reaction failed outright under such circumstances.



Scheme 30

Using the directed metallation methodology developed for this particular substrate[64], it was possible to introduce a formyl group exclusively into one of the *ortho* positions of the ring by *pro*-R deprotonation **(Scheme 31).** The chiral acetal **(77)** was lithiated at –35°C in Et_2O by the addition of n-BuLi over 1.5 h, using a syringe pump, followed by stirring for 3 h at –35°C. After the addition of the electrophile, the reaction was allowed to stir for an additional hour at which point it was quenched with H_2O. Initially, DMF was used as the electrophile and yields of 70 % were typical of this reaction. Use of N-methylformanilide as the electrophile led to an improvement in yield to approximately 80 %. The ^1H NMR spectrum of the crude product showed no evidence of a minor diastereomer; thus the de for the reaction was estimated at > 94%. The stereochemical assignment at the ring carbons of *R* for the carbon bearing the acetal and *S* for the carbon bearing the formyl group, as depicted in **Scheme 31,** is based on the

known stereochemical disposition of this reaction with other electrophiles. An additional benefit of this modification was that it was unnecessary to distill the electrophile prior to its use in the reaction.



Scheme 31

1.2.2 Nucleophilic Addition to the *o*-Formyl Complex (72)

With the diastereomerically and enantiomerically pure aldehyde **(72)** in hand, its electrophilic reactivity was examined. The nucleophiles used for this phase of the study are shown below **(Figure 11)**. Two criteria were considered when selecting potential nucleophiles; ready availability and ease of preparation. Methyllithium, n-butyllithium, t-butyllithium, phenyllithium and 2-propylmagnesium chloride were commercially available as solutions and were used as received. Methylmagnesium iodide, ethylmagnesium iodide, phenylmagnesium bromide and 2-bromomagnesiothiophene were prepared from the corresponding halide and magnesium metal in diethyl ether. 1-Hexynyllithium was prepared by the reaction of 1-hexyne with n-butyllithium[66]. The commercially available lithium nucleophiles were titrated with 2,5-

dimethoxybenzylalcohol[67] whereas the preparation of the Grignard reagents was assumed to be near quantitative.

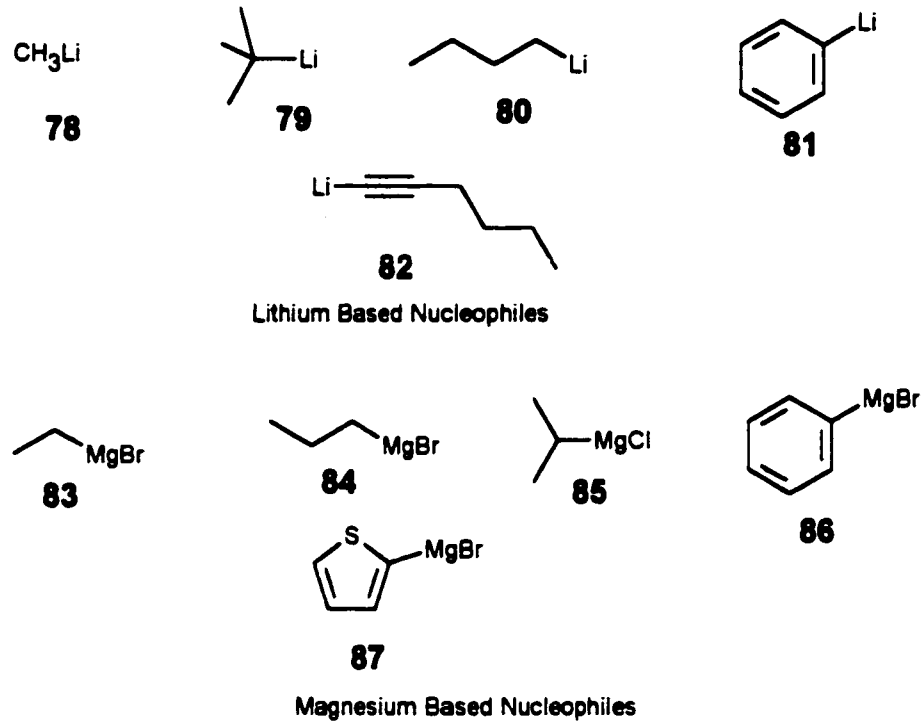
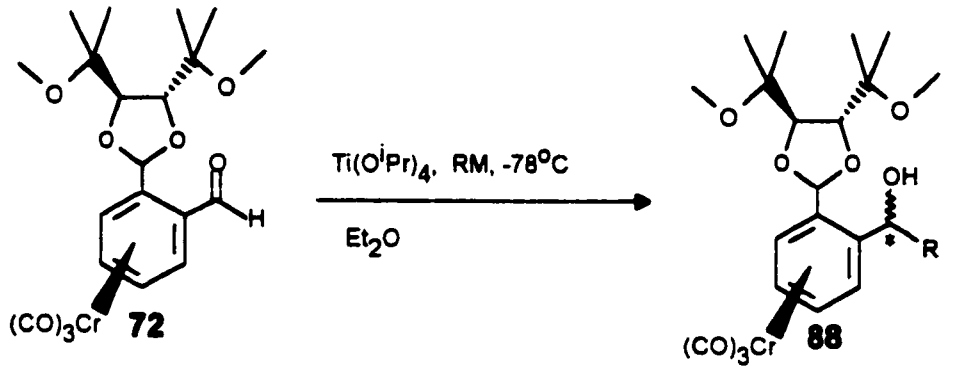


Figure 11: Nucleophiles Chosen For Study

The initial phase of this research involved the optimization of the conditions for nucleophilic addition to the *o*-formyl complex. Methyllithium was chosen for this purpose based on its ready availability and anticipated success in reactions of this type. The reaction was typically performed by the dropwise addition of three equivalents of methyllithium to a cooled solution of the *o*-formyl complex (**72**). The colour of the solution underwent a change from dark orange to yellow, indicating that the conjugation between the aromatic ring and the formyl group had been interrupted, as in the

conversion of the carbonyl group to an alkoxide. The reaction was stirred for 3 h, at which time it was quenched with water.



Scheme 32

To choose a suitable solvent for the reaction, the addition was carried out in THF and diethyl ether at -78°C. **(Scheme 32)** It was found that in both solvents, the colour of the solution changed almost immediately, indicating a very rapid reaction. Chemical yields were similar for these reactions, typically 75% after chromatography. Determination of the diastereomeric excess was determined by examination of the ^{1}H NMR spectrum of the crude reaction products. In all cases, it was possible to determine the ratio of diastereomers by comparing the integrations of the signals from the acetal protons that typically occurred at about 6 ppm. The resonance for the minor diastereomer occurred slightly downfield from the resonance from the major diastereomer. For the reaction of methyllithium with the aldehyde **(72)**, the peak for the acetal proton of the major diastereomer occurred at δ 6.02 whereas the corresponding peak for the minor diastereomer occurred at δ 6.26.

Superior diastereoselectivity was observed for the addition using diethyl ether as a solvent. At –78°C, the diastereomeric ratio for the addition of methyllithium was 4.6:1 in Et_2O as opposed to 2.9:1 in THF. This may be attributed to the fact that as a better coordinating solvent, THF is better able to facilitate the formation of lower order oligomers of lithium base/ solvent composition [68] . In other words, the reacting species in the case of the THF solvent is smaller in size than the reacting species in the diethyl ether. The smaller reactive THF/alkyllithium aggregate species should be more reactive and thus less selective than the Et_2O/alkyllithium aggregate.

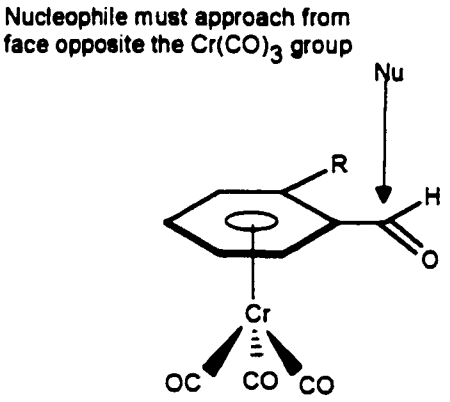


Figure 12: Factors Governing the Stereoselectivity of Nucleophilic Addition to Carbonyl Group

Reaction temperature was the next parameter to be examined. Methyllithium was added to the substrate in diethyl ether at -35°C, -78°C and -110°C. At -35°C and -78°C, the addition of the nucleophile was almost instantaneous, whereas at -110°C the colour change of the solution took approximately 1 min. After 3 h, the reactions were quenched with water. Not surprisingly, the best selectivity was observed with decreased

temperatures. At –35°C the ratio was 2.41:1, at –78°C there was a 4.6: 1 ratio of diastereomers and at –110°C the ratio was 4.9:1. This can be explained by considering the origin of the minor diastereomer. It is assumed that the nucleophile attacks the aldehyde from the face opposite the chromium tricarbonyl group and that there is a preferred rotational conformer that places the aldehyde oxygen in a position away from the bulky acetal group. (**Figure 13**) The less favoured rotamer places the aldehyde oxygen close to the acetal group.

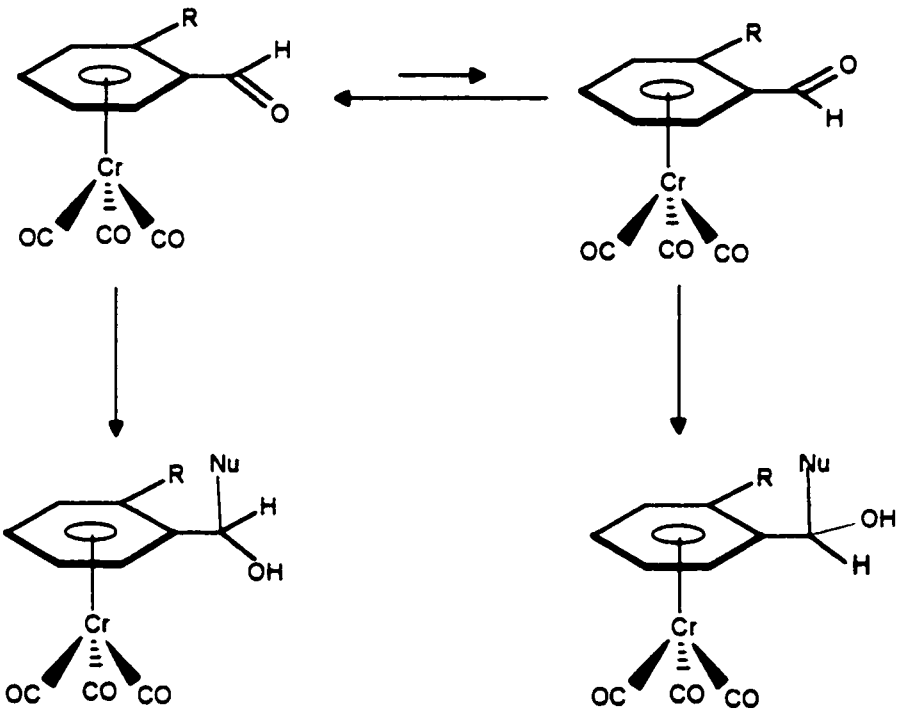
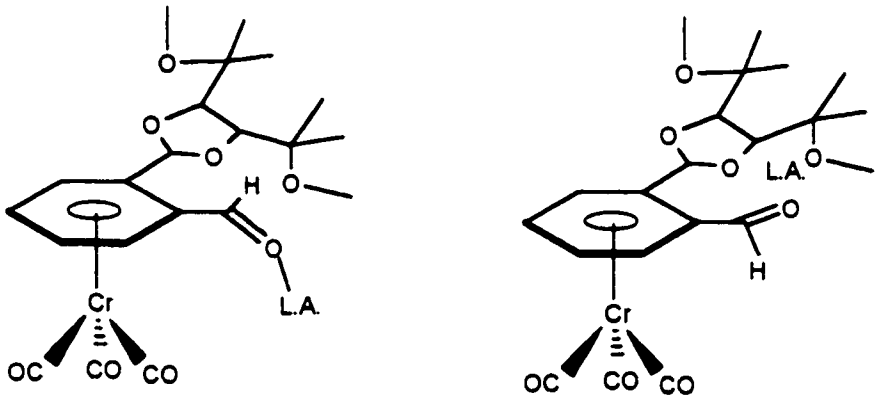


Figure 13: Rotamer Effect on Stereochemistry of Addition Product

A study of the effect of the mediation of Lewis acids on the addition of nucleophiles to the aldehyde was undertaken. It was expected that the Lewis acid would affect the reaction in two ways (**Figure 14**). First, it was anticipated that the reaction rate

would increase due to the ability of the Lewis acid to coordinate to the aldehyde oxygen and increase the polarization of the carbonyl bond. It was also envisioned that it might be possible to reverse the stereochemistry of the nucleophilic addition by shifting the rotamer population. In principle it is possible for the metal center of some Lewis acids to bind to more than one oxygen atom on the substrate. By participating in bidentate coordiation, the Lewis acid would require the aldehyde to adopt the previously "less favoured" conformation. Successful additions to the aldehyde under these conditions would lead to the formation the "minor diastereomer" and thus access to both isomers would be possible.



Monodentate chelation to *o*-formyl complex allows for favoured conformation of carbonyl

Bidentate chelation to *o*-formyl complex places carbonyl group in "less favoured" comformation

Figure 14: Possible Modes of Lewis Acid Coordination

The Lewis acids chosen for this study were BF_3 etherate, titanium(IV) isopropoxide, titanium(IV) *n*-propoxide and zinc chloride. No addition products were detected when BF_3 etherate was used to mediate the reaction of methyllithium and the o-formyl complex; the effect of BF_3 etherate on the reaction was the complete decomplexation of the *o*-formyl compound. Using $ZnCl_2$ to mediate the reaction led to

the formation of the major diastereomer found in the unmediated reaction. The yield was somewhat diminished due to the presence of decomplexed substrate. That there was decomplexation of the substrate was not especially surprising since previous studies in our group have demonstrated that the presence of halide ion in an acidic medium leads to the removal of chromium tricarbonyl groups in donor solvents, such as ether and THF, possibly through a ligand exchange mechanism. Fortunately, the addition of methyllithium to the substrate was successfully accomplished in the presence of titanium(IV) isopropoxide and titanium(IV) *n*-propoxide. With the use of both Lewis acids, chemical yields improved slightly over the non-mediated reaction and diastereoselectivity improved significantly toward the formation of the major diastereomer. With $Ti(O^iPr)_4$ mediating the MeLi reaction at –78°C, the ratio of isomers was 16:1 or 88% de. Although both of theses Lewis acids had similar effect on the reaction and it would be incorrect to state that one was better than the other consistently, titanium(IV) isopropoxide was chosen since it was easier to handle. Titanium (IV) n-propoxide had a higher viscosity than titanium(IV) isopropoxide and was more difficult to transfer. This is not a trivial consideration since exposure to the air and especially atmospheric moisture has a detrimental effect on reactions involving alkyllithiums.

Having chosen the proper temperature, solvent and additive, we endeavoured to expand the range of nucleophiles that could be added to the *o*-formyl complex in a highly diastereoselective manner. The results are summarized in **Table 1.**

Table 1: Results of Nucleophilic Addition to o-Formyl Complex 72 in the Presence of $Ti(O^iPr)_4$

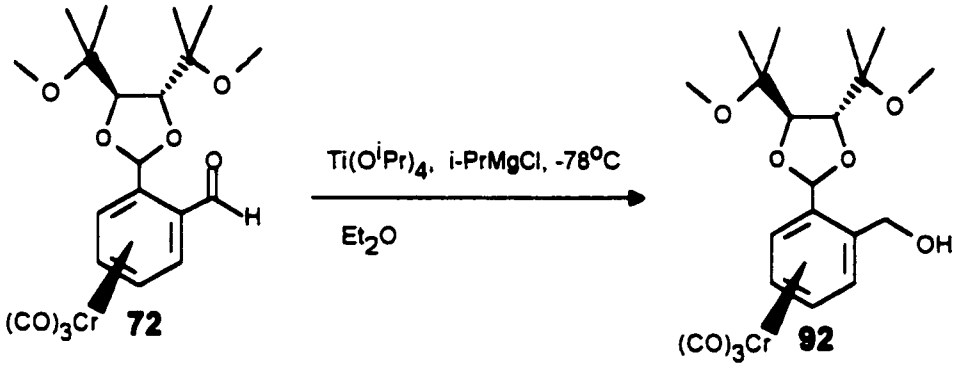
Nucleophile	Yield (%)	Diastereomeric excess (%)
MeLi (**89a,b**)	75	88
EtLi (**90a,b**)	73	85
n-PrMgBr (**91a,b**)	77	87
i-PrMgI (**92**)	56	reduction
n-BuLi (**93a,b**)	72	86
t-BuLi (**94a,b**)	61	85
1-hexynyllithium (**95a,b**)	Not isolated	94
Phenyllithium (**96 a,b**)	60	77
PhenylMgBr (**96a,b**)	63	82
2-bromomagnesiothiophene (**97a,b**)	70	86

The optimized conditions for the addition of methyllithium to (**72**) did not prove to be the best for all nucleophiles. While the small alkyllithiums and Grignard reagents exhibited good reactivity and diastereoselectivity under the conditions developed for

methyllithium, the aryl nucleophiles and the 2° and 3° alkylmetals reacted relatively sluggishly. For example, very little t-BuLi reacted by the end of three hours at -78°C as observed by TLC. It was necessary to allow the reaction to proceed overnight while warming to room temperature. For these longer reactions, it was necessary to protect the reaction flask from light; or else there was significant decomplexation of the chromium tricarbonyl complexes.

Several of the benzyl alcohols proved to be unstable under 'normal conditions'. Some compounds such as the methyl and n-butyl derivatives proved to be extremely robust and survived storage for several months. Others, such as the phenyl derivative decomplexed during purification unless strict control was exerted over temperature and light. It was necessary to carry out TLC at 0° C. Even more fragile was the hexynyl derivative which decomplexed during purification regardless of the precautions taken. The ^{1}H NMR spectrum of the crude reaction material was much cleaner than that of the post chromatographic fractions, the latter of which exhibit peaks in the δ 7.0 to 7.5 region. Decomplexation of the chromium complexes can be detected in two ways: the appearance of green precipitate in the solution and the appearance of extraneous peaks in the ^{1}H NMR spectrum in the δ 7 range (protons on complexed aromatic rings appear at approximately δ 5). In general, the chromium tricarbonyl complexes that were crystalline were less susceptible to decomplexation than those that were oils.

In the attempted addition of 2-propylmagnesium chloride to the *o*-formyl complex, the only product recovered was the alcohol (**92**) resulting from the reduction of the aldehyde function (**Scheme 33**). The alcohol proved to be very unstable, rapidly decomplexing while in $CDCl_3$ solution as an NMR sample.

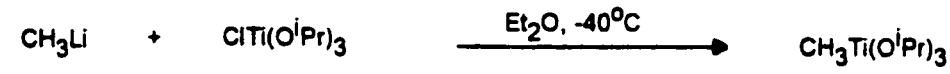


Scheme 33

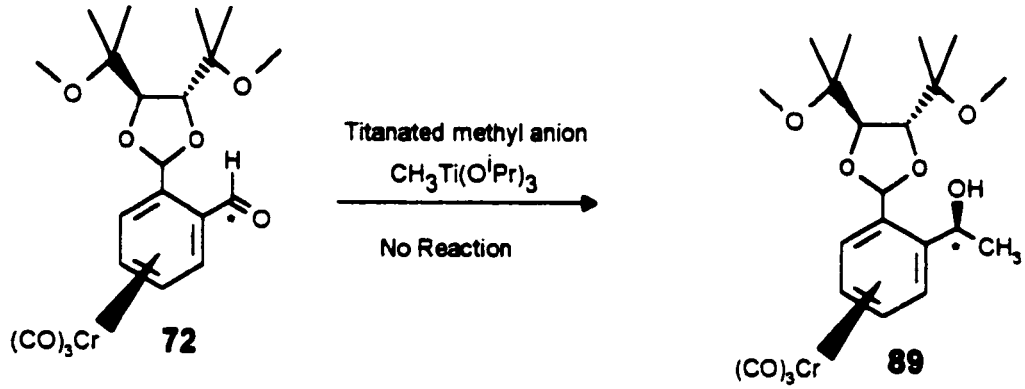
It was possible to crystallize the addition product between n-butyllithium and the *o*-formyl complex (**93a**) in order to determine the crystal structure by X-ray diffraction. It is apparent from the ORTEP diagram of the crystal structure (**Figure 15**) that the newly formed chiral center at the benzylic carbon is of the (*S*)-configuration. This is consistent with the addition of the nucleophile to an aldehyde function with the oxygen atom *anti* to the acetal unit, and from the face *anti* to the tricarbonylchromium unit. Based on this and the precedented pattern of the reactivity of other *ortho*- substituted arylaldehyde tricarbonyl chromium complexes, the analogous stereochemical assignments have been made to the other addition products (**89a-97a**).

The observed stereoselectivies also imply that the added $Ti(OiPr)_4$ is complexed solely in the transition state to the carbonyl oxygen, and does not coordinate with any of the oxygen atoms of the acetal moiety (see **Figure 14**). In the process, the effective size of the carbonyl group is increased such that the conformational bias in favour of that *anti* to the tartrate is enhanced. For the n-alkylmetals and alkynylmetals, the observed stereoselectivities also give a preference for the most favoured transition state of 4.1 – 5.6 kJ/ mol (1.0 – 1.4 kcal/mol) over the closest alternative favouring the minor diastereomer. Such an analysis is not possible with the other nucleophiles given the uncertainty of the temperature at which the reaction occurs. This and the lower aggregation states for more bulky organolithium reagents, makes a discussion of de versus nucleophile size difficult.

Other alternatives are possible for the role that is played by the titanium. Aside from acting as a Lewis acid merely coordinating to the oxygen of the aldehyde carbonyl, there exists the possibility of the intervention of either a titanium ate complex ($[RTi(O^iPr)_4]^-$) or an alkyltitanium triisopropoxide ($RTi(O^iPr)_3$) in the reaction. In order to evaluate this, $CH_3Ti(O^iPr)_3$ was prepared by reacting MeLi with $ClTi(OiPr)_3$ [69]. **(Scheme 34)** Addition of an ether solution of the $CH_3Ti(O^iPr)_3$ to a solution of the o-formyl complex under the usual reaction conditions (i.e. -78°C, stirring for 3 h followed by quenching at -78°C) showed no evidence of addition taking place (**Scheme 35**). The ^1H NMR spectrum of the crude reaction mixture showed mostly starting material.

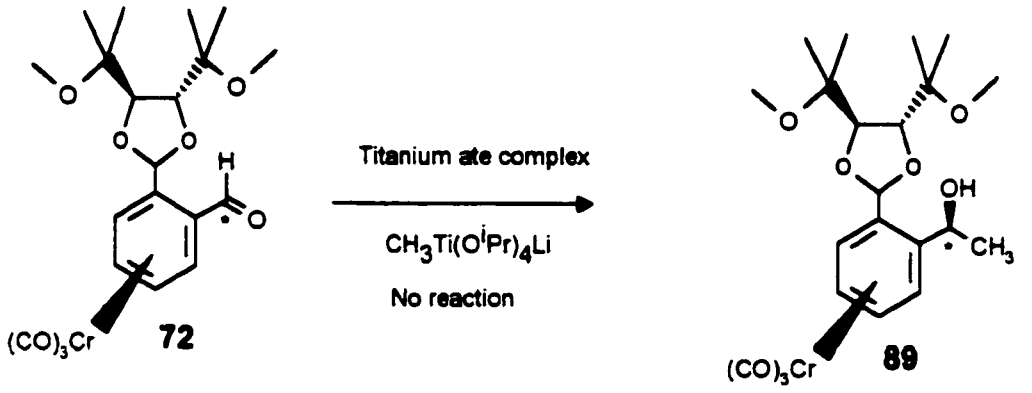


Scheme 34



Scheme 35

Similar results were obtained when the *o*-formyl complex **(72)** was reacted with the titanium ate complex, $CH_3Ti(O^iPr)_4Li$. Addition of $Ti(O^iPr)_4$ to an ether solution of methyllithium produced the clear yellow solution of the ate complex at -30°C [70]. Addition of an ether solution of the *o*-formyl complex to the solution of the ate complex also resulted in no addition to the carbonyl group of the *o*-formyl complex. (**Scheme 36**) Failure of either the methyltitanium triisopropoxide or the methyl titanium ate complex to add to the aldehyde is dramatically different from the rapid reaction of methyllithium with the o-formyl complex in the presence of $Ti(O^iPr)_4$. It can be deduced that the formation of either the methyl titanium ate complex of the titanated methyl anion does not occur to a significant extent during the $Ti(O^iPr)_4$ mediated addition of methyllithium to the *o*-formyl complex. Further discounting formation of the ate complex is the necessity for its formation at -30°C.

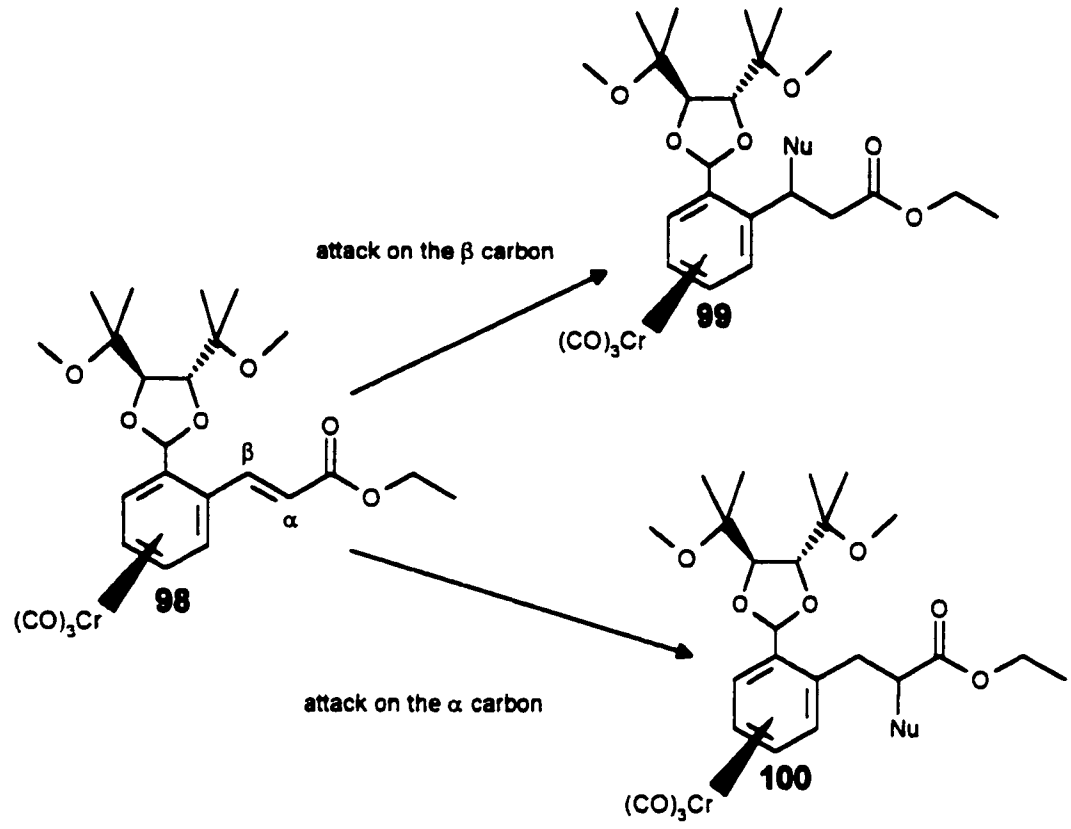


Scheme 36

1.2.3 Investigation of 1,4 Additions

With the nature of the 1,2-additions at the benzylic site of compound **72** established, the possibility of other asymmetric, Michael-type, additions at other prochiral benzylic sites of arylacetal chromium tricarbonyl complexes was investigated. Substrates chosen for the conjugate addition studies were the cinnamate **98** and the stilbene **107** are shown below. The cinnamate was selected more for its structural features than its ease of preparation. For arene chromium tricarbonyl complexes bearing an α,β-unsaturated ester, there are four potential sites for nucleophilic attack: i), the carbonyl carbon of the ester function; ii), the aromatic ring; iii) the carbon in the α position of the ester; iv), the benzylic carbon which is β to the ester. Nucleophilic addition to this compound was considered interesting since there was precedent to support the prediction that attack would occur in the β– position, as is customary for Michael additions[71]. It is also known that arene chromium tricarbonyl complexes stabilize negative charges in the benzylic position [72]; such a situation would result from addition of a nucleophile to the

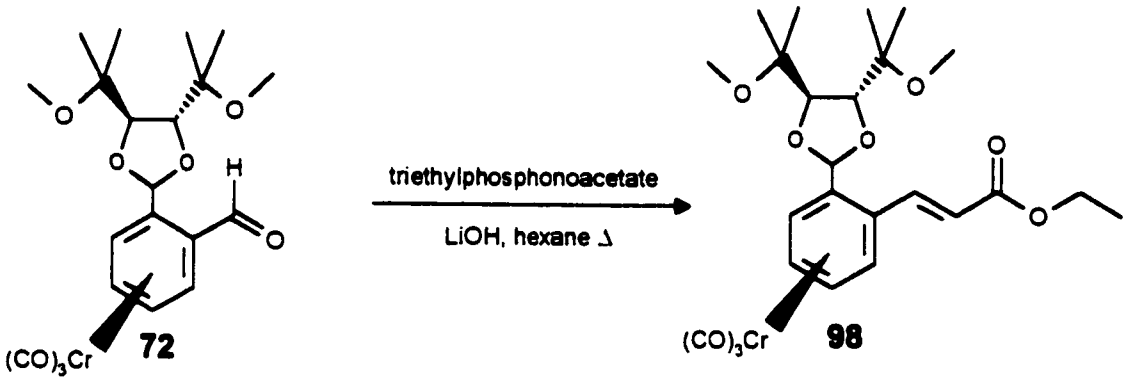
α– carbon of the ester. (**Scheme 37**) Therefore there were regiochemical issues that needed to be addressed as well as stereochemical ones.



Scheme 37

Preparation of compound **98** was attempted initially by Peterson olefination [73], using ethyl trimethylsilylacetate and LDA. This technique was chosen for its relatively mild conditions, as it was thought that heating solutions of arene chromium tricarbonyl complexes would lead to rapid decomplexation. Unfortunately, the Peterson olefination gave mixtures of the intended product and starting material, usually at approximately a 45% conversion rate as determined by ^{1}H NMR spectroscopy. Although the mixtures

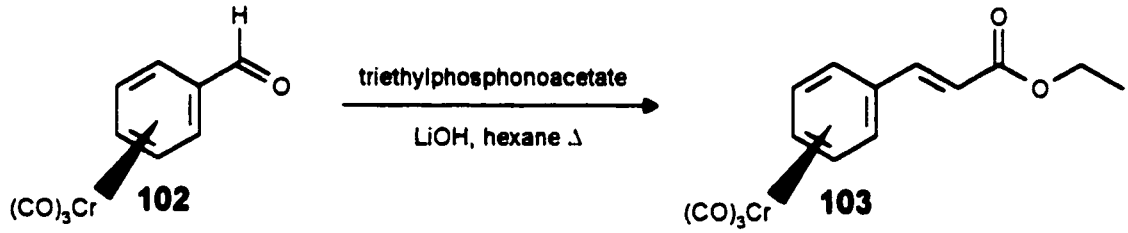
were separable by column chromatography, a more efficient preparation was sought. It was decided to try Horner Emmons methodology[74] to prepare the substrate. Triethyl phosphonoacetate, lithium hydroxide and the *o*-formyl complex were heated under reflux under phase transfer conditions to afford **98** in quantitative yield **(Scheme 38)**[75]. There was no evidence of decomplexation of either the *o*-formyl complex or the product. The *E*-configuration of the olefin double bond was determined by ^{1}H NMR spectroscopy, with coupling constants for olefinic protons of 16 Hz.



Scheme 38

With the cinnamate complex (**98**) in hand, a study of its electrophilic properties was undertaken. The addition of methyllithium was attempted. Methyllithium was added to diethyl ether solutions of the cinnamate complex at -78°C, -35°C and 0°C . In all cases there was only starting material recovered. In an attempt to increase the electrophilicity of the substrate, $Ti(O^iPr)_4$ was incorporated . It was expected that the complexation of the Lewis acid to the α,β-unsaturated ester would increase the polarization of the carbonyl bond. Adding three equivalents of the Lewis acid to the reaction mixture did not result in the addition of methyllithium under any circumstances and only starting material was recovered. It was suspected that the inability for the nucleophiles to react with the

cinnamate complex was due to the extreme steric bulk of the β-substituent of the olefin double bond; the chromium tricarbonyl complexed arene ring bearing the chiral acetal. To lessen this effect on the system compound **103** was prepared using the same method as with the preparation of **98 (Scheme 39).**

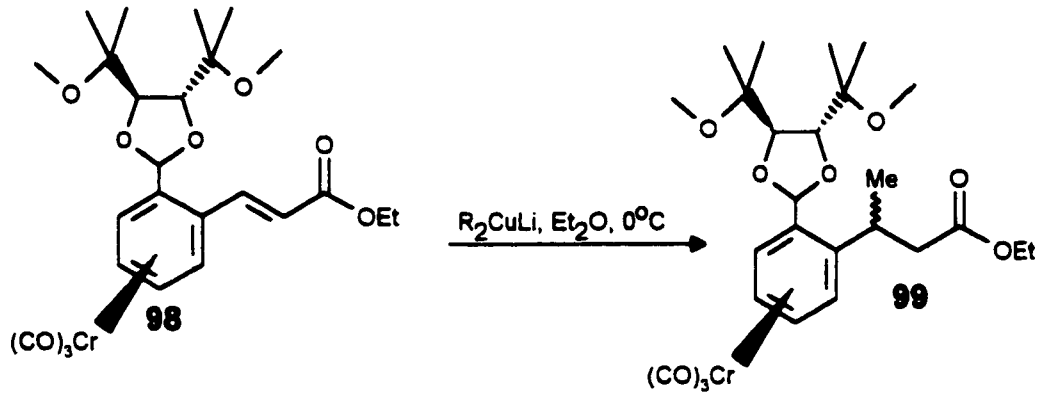


Scheme 39

Using **103** as a substrate for nucleophilic additions gave similar results to those obtained with the use of **98** as a substrate. No nucleophilic addition was observed under any conditions attempted. Apparently the steric bulk of the arene chromium tricarbonyl substituent on the β-carbon rendered nucleophilic addition to the double bond impossible.

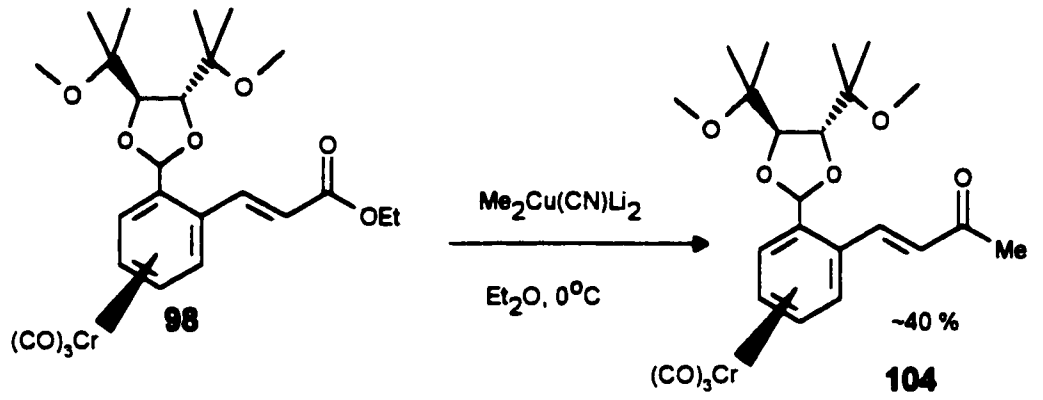
Attention was then turned to organocuprates as nucleophiles. The cuprates are softer nucleophiles and thus the expected mode of reactivity for these compounds with α,β-unsaturated carbonyl systems is at the softer β carbon. Lithium dimethylcuprate

was the first organocopper nucleophile to be investigated (**Scheme 40**). Addition of this reagent to cinnamate **98** did result in a reaction but gave multiple reaction products, including those involving decomplexation, as evidenced by analytical TLC and ^{1}H NMR spectroscopy. Chromatographic separation of these products was not successful.



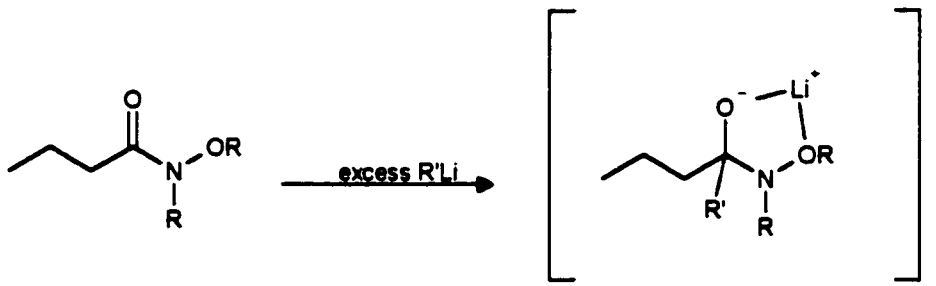
Scheme 40

The lithium cyanocuprate $Me_2Cu(CN)Li_2$ was then investigated in its reaction with **98**. Here the reaction pathway was cleaner. In this case, the nucleophile apparently ignored the β- site of the cinnamate, preferring the ester carbonyl instead, and an approximately 40% yield of methyl ketone **104** could be isolated (**Scheme 41**). Apparently, the (areneacetal)tricarbonylchromium group imposes enough steric hindrance at the β-site of the cinnamate to preclude nucleophilic attack there. What is also curious is that, in the presence of five equivalents of cyanocuprate nucleophile, only one methyl group added to the ester, and that the ketone did not undergo further nucleophilic attack to afford a tertiary alcohol.



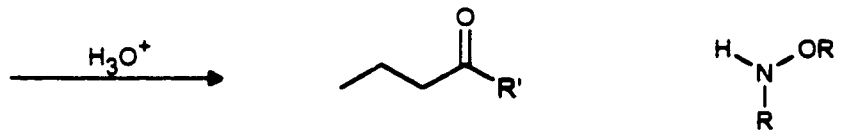
Scheme 41

This feature is reminiscent of the reaction patterns of N-methoxy-N-methyl amides, or 'Weinreb amides'[76], in which the tetrahedral intermediate stemming from nucleophilic attack **105** is stabilized by chelation of the metal cation by the alkoxide oxygen and the N-methoxy oxygen atoms (**Scheme 42**). As a result, the tetrahedral intermediate does not collapse until aqueous workup, and over-alkylation can be avoided. In the case of cinnamate complex **98**, it is conceivable that the tetrahedral intermediate would be stabilized by chelation involving one or more oxygen atoms of the acetal unit, again preventing ketone formation prior to workup and thus preventing tertiary alcohol formation. The exact nature of this chelate is not known, and it must be recognized that the chelate must be a minimum of a nine membered ring **106** (**Scheme 43**).

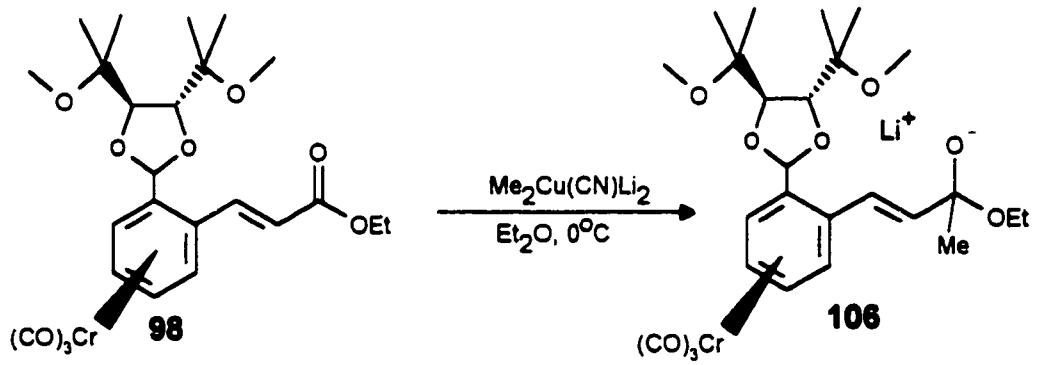


Tetrahedral intermediate stabilized by coordination to cation

105



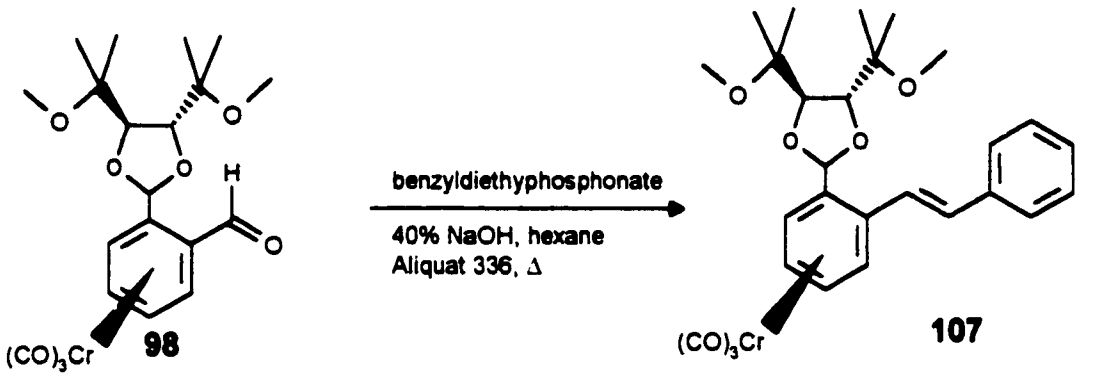
Scheme 42



Scheme 43

In view of the apparent difficulty in Michael-type additions in these systems, a substrate was chosen that did not possess the same competitive polarization on the side chain. With this in mind it was decided to prepare the stilbene derivative. With the

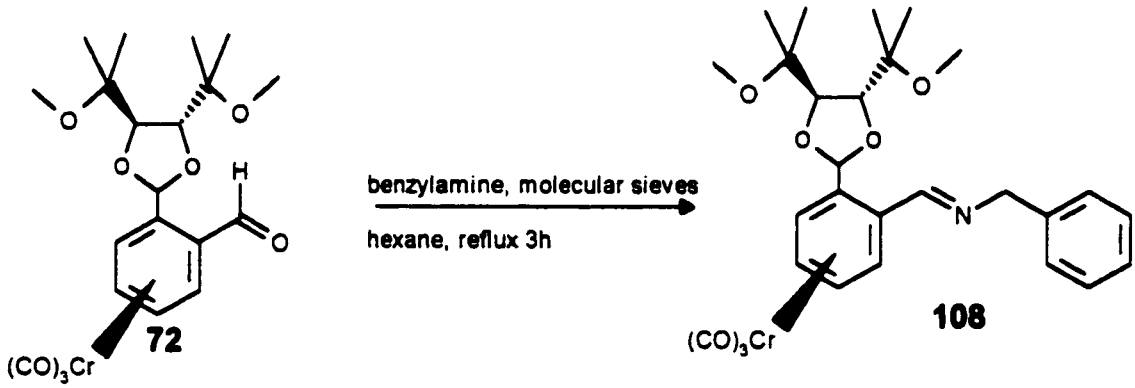
knowledge that heating the complex did not necessarily lead to decomplexation, preparation of the stilbene derivative was attempted using Horner-Emmons methodology under phase-transfer conditions. (**Scheme 44**) Refluxing a hexane solution *o*-formyl complex with diethylbenzylphosphonate in the presence of 40% aqueous NaOH and Aliquat 336 (a phase-transfer catalyst) gave the **107** in quantitative chemical yield.



Scheme 44

Nucleophilic additions to **107** were attempted under a number of conditions including MeLi, MeLi in the presence of $Ti(O^iPr)_4$, lithium dimethylcuprate and lithium methylcyanocuprate. No addition product was observed in any of these cases therefore this area was no longer investigated.

Having met with little success performing conjugate additions on the vinyl substituted arenechromium tricarbonyl complexes, attention was turned to the addition of nucleophiles to benzylimine derivative of **72**. The benzylimine derivative of the o-formyl compound **108** was prepared simply by refluxing the *o*-formyl complex with the benzylamine in the presence of 3Å molecular sieves. (**Scheme 45**) The benzylimine derivative was formed in relatively high purity as indicated by the lack of extra peaks in the ^{1}H NMR spectrum of the crude product. This was fortunate since the benzylimine proved to be incompatible with silica gel chromatographic conditions; attempted chromatography gave back the aldehyde and benzylamine.



Scheme 45

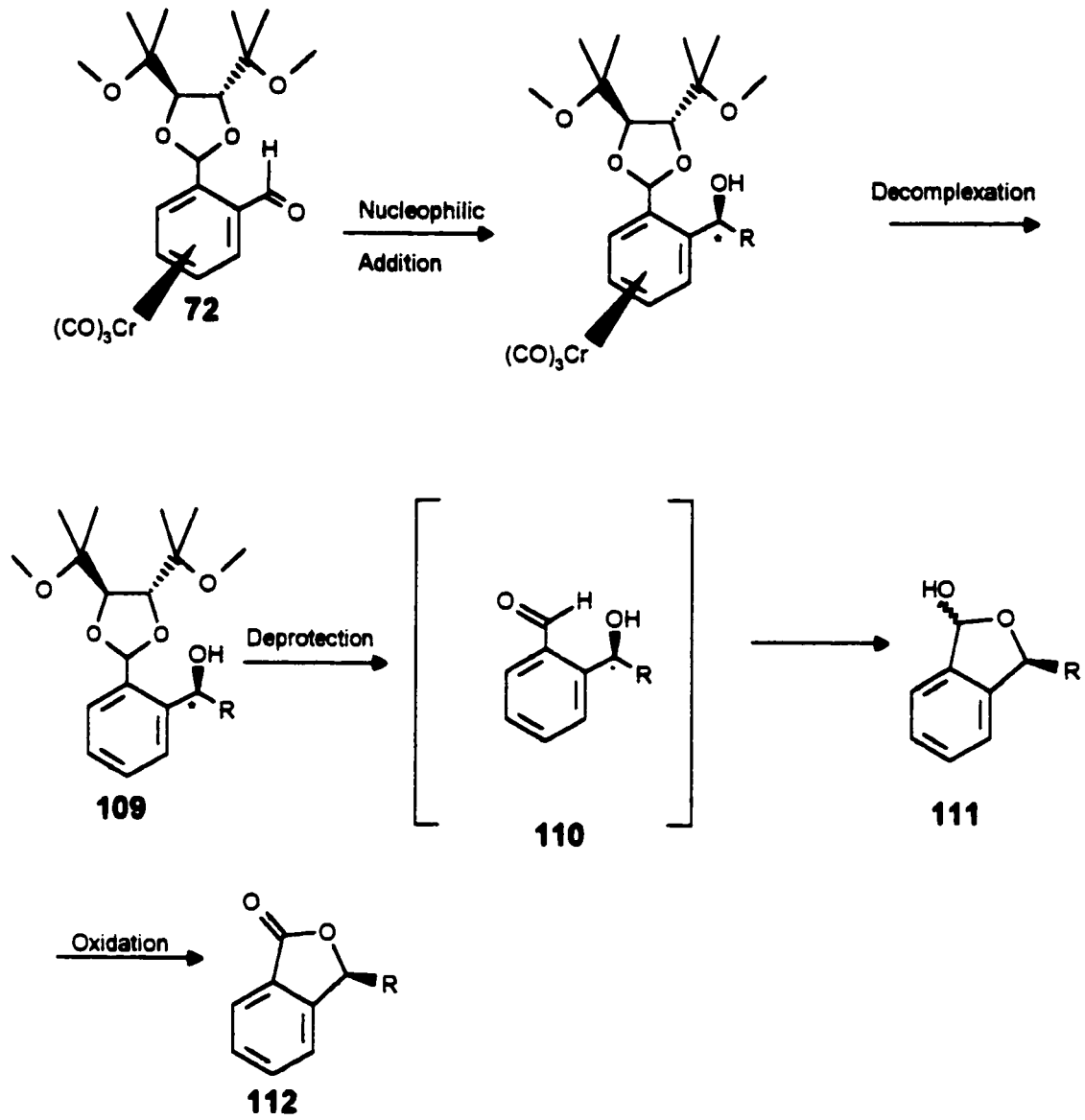
Attempts were made to add nucleophiles to the imino derivative **108**. Using the same approach as with the stilbene and the cinnamate, the initial attempts at addition were with methyllithium. Regardless of reaction times and temperatures, there was no evidence for addition of methyllithium to the imine. In order to increase the polarity and thus the electrophilicity of the double bond, the addition of $Ti(O^iPr)_4$ to mediate the

reaction was examined. Again there was no evidence of addition. Only starting material was recovered. Failure of the imines to react with nucleophiles and to stay intact was surprising given the extreme tendency toward hydrolysis on silica gel.

Future Work

A possible application of the research is the preparation of optically active phthalides. The phthalide skeleton is found in many natural products, many of which exhibit pharmacological activity. The 3-butyl derivative, a component of celery oil, is used as a flavouring agent and in Korea it has found use in the treatment of anemia. The 3-alkylidenyl phthalides include antispasmodic, herbicidal and insecticidal activities. 3-Arylidines have also been used extensively as intermediates in the synthesis of drugs and naturally occuring compounds[77]. Phthalide-isoquinoline alkaloids have been investigated for their potential as GABA antagonists[78].

The diastereospecific addition of a nucleophile to the carbonyl group of the *o*-formyl complex results in the formation of optically active benzyl alcohols. Deprotection of the masked aldehyde group by hydrolysis of the tartrate acetal would lead to a compound that upon ring closure would form a lactol. Oxidation of this lactol to a lactone yields the phthalides (**Scheme 46**)


Nucleophilic
Addition
Decomplexation
Deprotection
Oxidation
72
109
110
111
112

Scheme 46

A problem that needs to be addressed is inherent in the removal of the tartrate acetal. Typically, acetal removal is accomplished by acid catalyzed hydrolysis and it is a possibility that under acidic conditions the alcohol function may epimerize. This is a probable since arene chromium tricarbonyl complexes are known to stabilize benzylic cations. To circumvent this occurrence it may be possible to decomplex the alcohol prior to acetal removal to minimize the possibility of ionization of the alcohol. It is the influence of the chromium tricarbonyl group that enhances the rate of ionization relative to the non-complexed analogues by stabilizing the resulting cation.

This research could be extended to include the study of the electrophilic behavior of the α,β- unsaturated aldehyde derivative of the chiral acetal arenechromiumtricarbonyl complexes.(**Figure 17**) A study of the electrophilic behavior of this substrate would provide information regarding the ability of the $Cr(CO)_3$ moiety to induce asymmetry γ- to the aromatic ring.

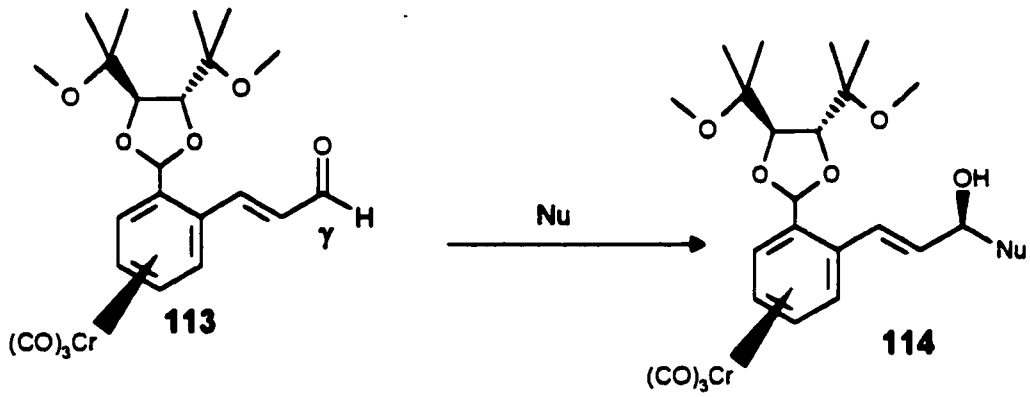


Figure 17: γ-Asymmetric Induction

1.3 Experimental

General Methods

All solvents were used after distillation from the appropriate drying agent. Diethyl ether and tetrahydrofuran were distilled from benzophenone ketyl immediatedly prior to use. Butyl ether and dichloromethane were distilled from calcium hydride.

All column chromatography was performed using Merck Kieselgel 230-400 mesh silica gel, while all preparative thin layer chromatography was performed using Uni-Plate™ 1000 micron silica gel GF plates. Analytical thin layer chromatography was performed using Merck precoated silica gel 60 F254 aluminium sheets. Flash chromatography followed the protocol described by Still [79].

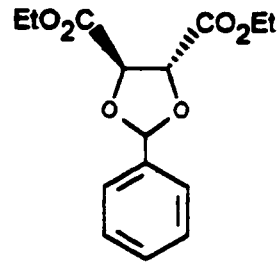
Infrared spectra were run on a Nicolet 5DX Spectrometer or a Bomem Michelson 100. NMR spectra, chemical shifts given in ppm and coupling constants given in Hz, were run on a Bruker AC300 spectrometer at 300 MHz for ^{1}H and 75 MHz for ^{13}C, or on a Bruker Avance 500 spectrometer at 500 MHz for ^{1}H and 125 MHz for ^{13}C, in $CDCl_3$ solution at 25 °C. Mass spectra were run on a Varian Kratos Profile instrument in electron impact mode. Gas chromatographic analyses were performed on a Shimadzu GC-9A instrument using a fused silica glass capillary column and a Shimadzu C-R6A recorder.

Melting points were obtained from a Thomas-Hoover, Uni-Melt* capillary melting point apparatus. Boiling points refer to bulb to bulb distillation.

A standard aqueous work-up refers to extraction of the organic product from the aqueous phase with three portions of diethyl ether or dichloromethane, drying the combined layers with anhydrous magnesium sulfate followed by filtration and evaporation of the solvent under reduced pressure to afford the crude product.

All reactions were performed under nitrogen or argon unless otherwise noted. Diastereomeric ratios were determined by integration of the relevant ^{1}H NMR resonances of the crude reaction products.

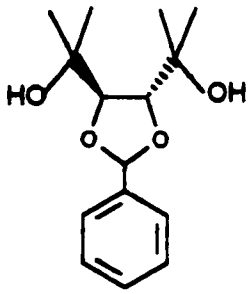
Diethyl (4*R*, 5*R*)-2-phenyl-1,3-dioxolane-4,5-dicarboxylate (74)



74

A mixture of benzene (150 mL), benzaldehyde (15 g, 0.14 mol), (+)-diethyl tartrate (22 g, 0.14 mol) and pTsOH (250 mg) was placed in a 250 mL round bottomed flask fitted with a Dean Stark apparatus. The solution was maintained at reflux for 20 h. After cooling, the solution was diluted with CH_2Cl_2 and washed with 1M $NaHCO_{3(aq)}$ (30 mL x 2). The aqueous layer was extracted with CH_2Cl_2 and the combined organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure and the resulting residue was distilled under reduced pressure (1.2 Torr, 155°C). The distillate crystallized to afford **74**, (36.704 g, 0.1247 mol 88%), which was found to be spectroscopically identical to literature [65].

(4*R*,5*R*)-4,5-Bis(1-hydroxy-1-methylethyl)-2-phenyl-1,3-dioxolane (75)

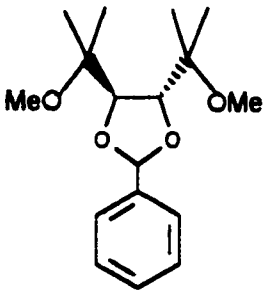


75

Magnesium turnings (11.9 g, 0.49 mol, 12 equiv) were placed in an oven dried 500mL 2- necked round bottomed flask fitted with a septum and a reflux condenser under nitrogen. The flask was charged with 150 mL of freshly distilled diethyl ether and the flask was immersed in a cooling bath containing ice water and NaCl. Iodomethane (69.5 g, 0.49 mol, 12 equiv) was added dropwise to the flask at such a rate that the reaction mixture did not overflow the condenser. After the addition of the iodomethane was complete, the flask was removed from the cooling bath and the reaction was allowed to proceed for 30 min at room temperature at which time the magnesium was completely consumed. A diethyl ether solution (60 mL) containing **74** (12.00 g, 40.1 mmol) was added dropwise to the reaction flask. After the addition of the ether solution, the reaction was heated to reflux for 24 h. The contents of the flask were poured slowly over a mixture of ice and water. Aqueous 3M HCl was added to the flask until all of the solids were dissolved. The layers were separated and the aqueous layer was extracted with three 50 mL portions of diethyl ether. The ether layers were combined and washed with saturated sodium bicarbonate solution and distilled water. The ether layer was dried over magnesium sulfate and then concentrated under reduced pressure to afford **75** (9.94g,

92%) as a white solid which was spectroscopically identical to literature . mp 103-104°C (lit.[80] 105-106°C). This solid was used without further purification.

(4*R*,5*R*)-[4,5-Bis(1-methoxy-1-methylethyl)-2-phenyl-1,3-dioxolane] (76)

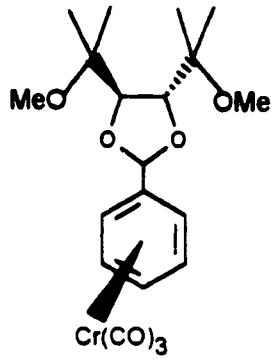


76

Sodium hydride (60% suspension in mineral oil) (6.02 g, 0.15 mol, 4 equiv) was placed in a 500 mL 2-necked round bottomed flask fitted with a septum and a reflux condenser. The sodium hydride was washed with three 20 mL portions of diethyl ether to remove mineral oil. The flask was charged with 150 mL of freshly distilled THF. A THF solution (60 mL) containing **75** (10 g, 0.042mol) was added dropwise to the reaction flask. The reaction was allowed to proceed for 30 min at room temperature. Iodomethane (21 g, 0.15 mol, 4 equiv) was added to the flask and the reaction was refluxed for 24 hr. The reaction was cooled to room temperature and the THF was removed under reduced pressure. The residue was dissolved in 75 mL of CH_2Cl_2. Distilled water (75 mL) was added and the layers were separated. The aqueous layer was extracted three times with CH_2Cl_2 and the organic layers were combined and dried over magnesium sulfate. The CH_2Cl_2 was removed under reduced pressure and the residue crystallized to give **76**

(8.72g, 79%) as colourless prisms, which were found to be identical to literature mp.75-78°C (lit.[80] 78-79°C) .

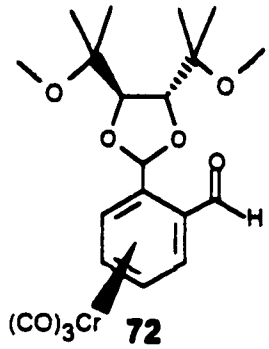
(4*R*,5*R*)-[4,5-Bis(1-methoxy-1-methylethyl)-2-phenyl-1,3-dioxolane] tricarbonylchromium(0) (77)



77

Compound 77 was prepared according to the literature[64] procedure in 63% yield, mp 80-82°C, (lit.[81] 81-83°C).

(1'*R*,2'*S*,4*R*,5*R*)-[4,5-Bis(1-methoxy-1-methylethyl)-2-(2'-formyl)phenyl)-1,3-dioxolane]tricarbonylchromium(0) (72)



72

Chiral acetal **77** (1.50 g, 3.49 mmol) was placed in an oven dried two necked 250 mL round bottomed flask fitted with a septum and gas adapter. Freshly distilled diethyl ether (150 mL) was added and the flask was cooled to -35°C in a dry ice/ ethanol-water (1:1) cooling bath. n-BuLi (3.78 mL, 2.21M, 8.364 mmol, 2.4 equiv) was added to the flask over 90 min using a syringe pump. After addition of the n-BuLi, the reaction was kept at -35°C for 3h, at which point N-methylformanilide (1.03 mL, 8.36 mmol, 2.4 equiv) was added. The reaction mixture was stirred for another 60 min. Standard aqueous workup afforded a red viscous oil which was purified by column chromatography using petroleum ether:ethyl acetate (5:1) as the eluent to afford **72** (1.246g, 78 %) as a red crystalline solid, mp=104-105°C (hexanes), $[\alpha]_D$=296° (C=0.6, Et_2O), IR (KBr pellet) ν_{max} 2987, 2934, 2830, 1984, 1924, 1692 cm^{-1}; ^1H NMR δ 9.91 (s, 1H), 6.42 (s, 1H), 6.06 (d, 1H, J = 6.5 Hz), 5.63 (m, 2H), 5.26 (t, 1H, J=6.0 Hz), 4.22, (d, 1H,J =3.3 Hz,), 4.05 (d, 1H, J=3.3 Hz), 3.22 (s, 3H), 3.13 (s, 3H), 1.31 (s. 3H), 1.14 (s, 3H), 1.12 (s, 3H), 1.03 (s, 3H); ^{13}C NMR δ 230.1, 187.2, 110.9, 99.7, 94.1, 93.6, 92.4, 92.3, 88.6, 86.7, 85.0, 83.1, 75.3, 49.3, 49.2, 22.1, 21.1, 20.9, 19.3; MS m/e 458 (M+); HRMS m/e for $C_{21}H_{26}O_8Cr$ calculated 458.1032 found 458.1031.

Nucleophilic Additions to the *o*-Formyl Complex (72)

Standard Nucleophilic Additions Procedure (I)

o-Formyl complex **72** (0.075g – 0.100g) was placed in an oven-dried 50 mL round bottomed flask containing a stirring bar and fitted with a septum. After 6 h under high vacuum, the flask was flushed with nitrogen. Freshly distilled Et_2O (10 mL) was added to the flask and the solution was cooled to –78°C. $Ti(O^iPr)_4$ (3 equiv) was added and the solution was allowed to stir for 20 min. The nucleophile (3 equiv) was added dropwise by syringe and stirring was continued for 3 h at –78°C. The reaction was quenched by the addition of distilled water (approx. 2 mL). A standard aqueous work-up resulted in a crude product whose ^1H NMR spectrum was examined to determine the diastereomeric ratio.

Reaction of *o*-Formyl complex 72 with Titanium-Based Nucleophiles

Preparation of $ClTi(O^iPr)_3$

A two-necked 50 mL round-bottomed flask was fitted with a septum and gas adapter. The flask was charged with $Ti(O^iPr)_4$ (5.0 mL, 4.809 g, 17 mmol, 3 equiv) and cooled to 0°C. $TiCl_4$ (1.062g, 5.599mmol) was added to the flask dropwise. The flask was allowed to warm to room temperature. The reaction mixture was distilled to give $ClTi(OiPr)_3$ as a viscous white oil (3.16g, 12.12 mmol, 72% yield). Bp 72-75°C at 0.3 torr (lit.[82] 65°C at 0.1 torr)

Preparation of $CH_3Ti(O^iPr)_3$

A two-necked 50 mL round bottomed flask was fitted with a gas adapter and a septum. $ClTi(OiPr)_3$ (2.00 g, 7.69 mmol) was added to the flask and the flask was cooled to -40°C. Methyllithium (7.69 mL, 1.00 M, 7.69 mmol, 1 equiv) was added to the flask dropwise and the reaction was allowed to warm to room temperature. The result was a 0.40 M solution of $CH_3Ti(OiPr)_3$ in diethyl ether that was used without further treatment for nucleophilic additions.

Addition of $CH_3Ti(O^iPr)_3$ to o-formyl complex 72

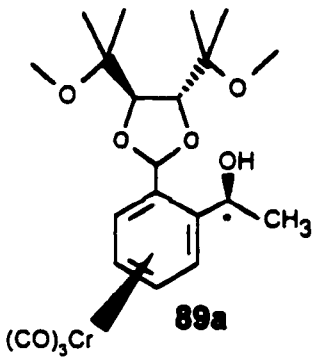
The *o*-formyl complex **72** (0.100g, 0.2183mmol) was placed in a two-necked 50 mL round-bottomed flask was fitted with a gas adapter and a septum. The flask was flushed

with nitrogen and diethyl ether was added (10 mL). The solution was cooled to -78°C and allowed to stir for 15 min. $CH_3Ti(OiPr)_3$ (1.64 mL, 0.40 M in Et_2O, 0.66 mmol, 3 equiv) was added as an ether solution in a dropwise manner. The reaction was allowed to proceed for 3 h, at which time H_2O (10 mL) was added. A standard aqueous work-up afforded a red residue (0.084g) which was determined to be starting material, **72**.

Addition of the ate complex [$CH_3Ti(O^iPr)_4Li$] to *o*-formyl complex 72

THF (10 mL) was placed in a 2-necked round bottomed flask fitted with a septum and gas adapter. The flask was cooled to -78°C and MeLi (0.66 mL, 1.0 M, 0.66 mmol, 3 equiv) was added. The solution was allowed to stir for 30 min and then $Ti(O^iPr)_4$ (0.19 mL, 0.66 mmol, 3equiv) was added dropwise. After 30 min, The o-formyl complex **72** (0.100 g, 0.218 mmol)was added as a solution in THF (2.0mL). The solution was warmed to -30°C and allowed to stir for 1 h, at which point distilled water (10 mL) was added. A standard aqueous work-up afforded a red residue (0.075g) which was determined to be **72.**

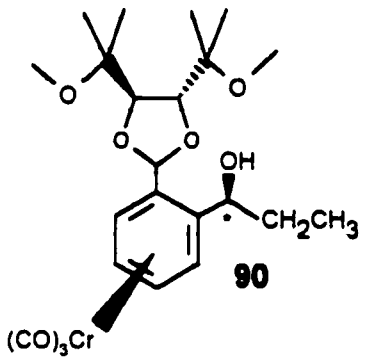
(1'*R*,2'*S*,4*R*,5*R*)-[4,5-Bis(1-methoxy-1-methylethyl)-2-(2''-(*S*-1-hydroxyethyl)phenyl)-1,3-dioxolane]tricarbonylchromium(0) (89) (methyl derivative)



89a

o-Formyl complex **72** (0.0983 g, 0.2146 mmol) was subjected to procedure (I) with MeLi (0.43 mL, 1.5 M, 0.64 mmol, 3 equiv) as the nucleophile. A standard aqueous work-up resulted in a crude product whose ^{1}H NMR spectrum revealed a resonance at δ 5.99 **89a** and δ 6.26 **89b** with a relative integral of 15.6:1 (88% de). Purification by silica gel chromatography using petroleum ether:ethyl acetate (5:1) as eluent gave **89a** (76mg, 75%) as a yellow solid. Mp 77-78 °C (pentane); $[\alpha]_D$ = -36° (C=0.5, Et_2O); IR (KBr pellet) ν_{max} 3436, 1966, 1886 cm^{-1}; ^{1}H NMR, δ, 5.99 (s, 1H), 5.73 (d, 1H, J=6.0 Hz), 5.66 (d, 1H, J=6.1 Hz), 5.34 (m, 2H), 4.82 (q, 1H, J=2.7 Hz), 4.16 (d,1H, J=3.2 Hz), 3.98 (d, 1H, J=3.2 Hz), 3.22 (s, 3H), 3.16 (s, 3H), 2.02 (s, 1H), 1.48 (d, 3H, J=6.3 Hz), 1.26 (s, 3H), 1.17 (s, 3H), 1.13 (s, 3H), 1.03 (s, 3H); ^{13}C NMR, δ, 232.9, 117.6, 105.6, 99.7, 92.4, 91.8, 90.1, 89.0, 84.7, 82.7, 75.5, 64.5, 49.6, 49.4, 25.9, 22.4, 21.2, 19.2; MS m/e 474 (M+); HRMS m/e calcd for $C_{22}H_{30}CrO_8$ (M+) 474.1346, found 474.1357

(1'*R*,2'*S*,4*R*,5*R*)-[4,5-Bis(1-methoxy-1-methylethyl)-2-(2''-(*S*-1-hydroxypropyl)phenyl)-1,3-dioxolane]tricarbonylchromium(0) (90) (ethyl derivative)

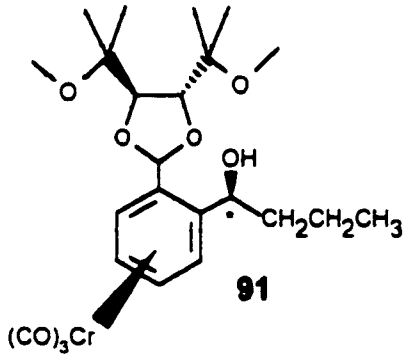


90

o-Formyl complex **72** (0.0890g, 0.1943 mmol) was subjected to procedure (I) with EtLi (0.49 mL, 1.2 M, 0.58mmol, 3 equiv) as the nucleophile. A standard aqueous work-up resulted in a crude product whose ^{1}H NMR spectrum revealed a resonance at δ 6.00 (**90a**) and δ 6.26 (**90b**) with a relative integral of 12.4:1 (85% de). Purification by silica gel chromatography using petroleum ether:ethyl acetate (5:1) as eluent gave **90a** (77mg, 73%). $[\alpha]_D$ = -40.4° (C = 0.54, Et_2O); IR (NaCl, neat) ν_{max}3452, 1966, 1892 cm^{-1}; ^{1}H NMR, δ, 6.00 (s, 1H), 5.77 (d, 1H, J=5.9 Hz), 5.61 (d, 1H, J=5.9 Hz), 5.33 (m, 2H), 4.61 (d, 1H, J=6.0 Hz), 4.17 (d, 1H, J=3.1 Hz), 3.98 (d, 1H, J=3.1 Hz), 3.23 (s, 3H), 3.17 (s, 3H), 1.94 (m, 3H), 1.31 (s, 3H), 1.14 (s, 3H), 1.12 (s, 3H), 1.03 (m, 6H);^{13}C NMR, δ, 232.9, 116.8, 106.0, 99.6, 91.6, 90.4, 89.3, 84.7, 82.7, 75.5, 69.3, 49.6, 49.4, 32.5, 22.5,

21.3, 19.3, 10.5; MS m/e 488 (M+); HRMS m/e calcd for $C_{23}H_{32}CrO_8$ (M+) 488.1502, found 488.1517

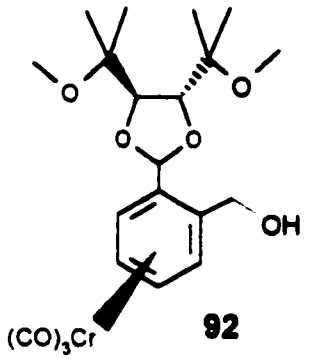
(1'*R*,2'*S*,4*R*,5*R*)-[4,5-Bis(1-methoxy-1-methylethyl)-2-(2''-(*S*-1-hydroxybutyl)phenyl)-1,3-dioxolane]-tricarbonylchromium(0) (91) (^{n}propyl derivative)



91

o-Formyl complex **72** (0.1102 g, 0.2406 mmol) was subjected to procedure (I) with PrMgBr (0.56 mL, 1.14 M, 0.63 mmol, 3 equiv) as the nucleophile. A standard aqueous work-up resulted in a crude product whose ^{1}H NMR spectrum revealed a resonance at δ 6.00 (**91a**) and δ 6.24 (**91b**) with a relative integral of 14.4:1 (87% de). Purification by silica gel chromatography using petroleum ether:ethyl acetate (5:1) as eluent gave **91a** (92mg, 77%). $[\alpha]_D$ = -55° (C=0.50, Et_2O), IR (NaCl, neat) ν_{max} 3457, 1966, 1886 cm^{-1}; ^{1}H NMR, δ, 6.00 (s, 1H), 5.77 (d, 1H, J=6.7Hz), 5.61 (d, 1H, J=6.4Hz), 5.33 (m, 2H), 4.67 (d, 1H, J=8.6Hz), 4.17(d, 1H, J=3.3Hz), 3.97 (d, 1H, J=3.3Hz), 3.22

(s, 3H), 3.18 (s, 3H), 1.93 (s, 1H), 1.57 (m, 2H), 1.47 (m, 2H), 1.31 (s, 3H), 1.22 (s, 3H), 1.12(s, 3H), 1.06 (s, 3H), 0.92 (t, 3H, J=4.4 Hz); ^{13}C NMR, δ, 232.9, 117.1, 105.8, 99.5, 92.3, 91.6, 90.3, 89.2, 84.7, 82.6, 75.5, 67.9, 65.9, 49.6, 49.4, 41.7, 22.5, 21.3, 19.5, 19.3, 15.4, 13.8; MS m/e 502 (M+); HRMS m/e calcd for $C_{24}H_{34}CrO_8$ (M+) 502.1659, found 502.1667

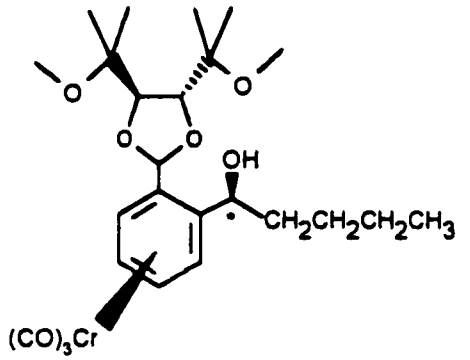


92

***o*-Formyl complex with ^{i}PrMgCl**

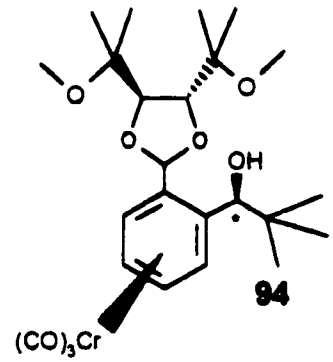
o-Formyl complex **72** (0.1102g, 0.2406 mmol) was subjected to procedure (I) with ^{i}PrMgBr (0.63mL, 1.14 M, 0.6332 mmol, 3 equiv) as the nucleophile. A standard aqueous work-up resulted in a crude product whose ^{1}H NMR spectrum revealed a resonance at δ 6.6. Purification by silica gel chromatography using petroleum ether:ethyl acetate (5:1) as eluent gave **92** (72mg, 70%) which was identified spectroscopically. IR (NaCl, neat) ν_{max} 3461, 1967, 1890 cm^{-1}; ^{1}H NMR, δ, 6.12 (s, 1H), 5.76 (m, 1H), 5.39 (m, 1H), 5.32 (m, 2H), 4.67 (dd, 2H, J=12.9, 3.0 Hz), 4.14(d, 1H, J=3.3 Hz) 4.00 (d, 1H, J=3.3 Hz) 3.25 (s, 3H), 3.17 (s, 3H), 2.04 (s, 1H), 1.31 (s, 3H), 1.19 (s, 3H), 1.09 (s, 3H) 1.06 (s, 3H), ^{13}C NMR, δ, 232.2,108.1, 106.5, 100.9, 93.8, 92.3, 90.8, 90.4, 85.0, 82.6, 75.5, 62.0, 60.4, 49.3, 21.8, 21.3, 21.0, 20.7, 19.5 ; MS m/e 461 (M+)

(1'*R*,2'*S*,4*R*,5*R*)-[4,5-Bis(1-methoxy-1-methylethyl)-2-(2'-(*S*-1-hydroxy-2,2-pentyl)phenyl)-1,3-dioxolane]tricarbonylchromium(0) (93) (^{n}butyl derivative)



o-Formyl complex **72** (0.0823g, 0.1797 mmol) was subjected to procedure (l) with n-BuLi (0.24mL, 2.21 M, 0.54 mmol, 3 equiv) as the nucleophile. A standard aqueous work-up resulted in a crude product whose ^{1}H NMR spectrum revealed a resonance at δ 5.99 (**93a**) and δ 6.26 (**93b**) with a relative integral of 13.2:1 (86% de). Purification by silica gel chromatography using petroleum ether:ethyl acetate (5:1) as eluent gave **93a** (67mg, 72%). Mp 93-94 °C (pentane); $[\alpha]_D$ = -50.6 (C=0.48, Et_2O) IR (KBr pellet) ν_{max} 3489, 1968, 1893 cm^{-1}; ^{1}H NMR, δ, 5.99 (s,1H), 5.77 (d, 1H, J=6.7 Hz), 5.62 (d, 1H, J=8.1 Hz), 5.34 (m, 2H), 4.66 (m, 1H), 4.16 (d, 1H, 3.3), 3.98 (d, 1H, J=3.3), 3.22 (s, 3H), 3.17 (s, 3H) 1.98 (s, 1H),1.47 (m, 6H), 1.35 (s, 3H),1.14 (s, 3H), 1.11 (s, 3H), 1.04(s, 3H), 0.88 (m, 3H); ^{13}C NMR, δ, 233.0, 117.1, 105.8, 99.5, 92.3, 91.6, 90.3, 89.2, 84.7, 82.6, 75.5, 68.1, 49.6, 49.4, 39.3, 28.3, 22.5, 21.3, 19.3, 14.0; MS m/e 516 (M+); HRMS m/e calcd for $C_{25}H_{36}CrO_8$ (M+) 516.1815, found 516.1812

(1'*R*,2'*S*,4*R*,5*R*)-[4,5-Bis(1-methoxy-1-methylethyl)-2-(2'-(*S*-1-hydroxy-2,2-dimethylpropyl)phenyl)-1,3-dioxolane]tricarbonylchromium(0) (94) (t-butyl derivative)

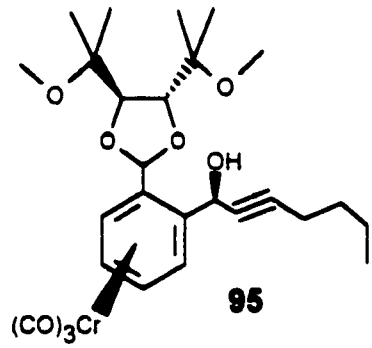


94

o-Formyl complex **72** (0.0753g, 0.1644 mmol) was subjected to procedure (I) with t-BuLi (0.22 mL, 1.5 M, 0.49 mmol, 3 equiv) as the nucleophile. A standard aqueous work-up resulted in a crude product whose ^{1}H NMR spectrum revealed a resonance at δ 6.12 (**94a**) and δ 6.48 (**94b**) with a relative integral of 12.3:1 (85% de). Purification by silica gel chromatography using petroleum ether:ethyl acetate (5:1) as eluent gave **94a** (52mg, 61%). $[\alpha]_D$ = -14.7° (C = 0.3, Et_2O); IR (NaCl, neat) ν_{max} 3480, 1968, 1891 cm^{-1}; ^{1}H NMR, δ, 6.12 (s, 1H), 5.74 (d, 1H, J=5.9 Hz), 5.58 (d, 1H, J=6.6 Hz), 5.33 (m, 2H), 4.57 (d, 1H, J=2.0 Hz), 4.16 (d, 1H, J=3.6Hz), 3.94 (d, 1H, J=3.7 Hz), 3.22 (s, 3H), 3.20 (s, 3H), 1.67 (s, 1H), 1.34 (s, 3H), 1.17 (s, 3H), 1.14 (s, 3H), 1.10 (s, 3H), 0.97 (s, 9H); ^{13}C NMR, δ, 232.7, 115.9, 99.3, 92.6, 91.3, 90.6, 90.5, 84.7, 82.3,

75.7, 73.7, 65.9, 49.4, 49.3, 36.7, 26.5, 22.8, 21.7, 21.1, 19.2, 15.3 ; MS m/e 516 (M+); HRMS m/e calcd for $C_{25}H_{36}CrO_8$ (M+) 516.1815, found 516.1838

(1'*R*,2'*S*,4*R*,5*R*)-[4,5-Bis(1-methoxy-1-methylethyl)-2-(2'-(*S*-1-hydroxy-2-heptynyl)phenyl)-1,3-dioxolane]-tricarbonylchromium(0) (95) (hexynyl derivative)

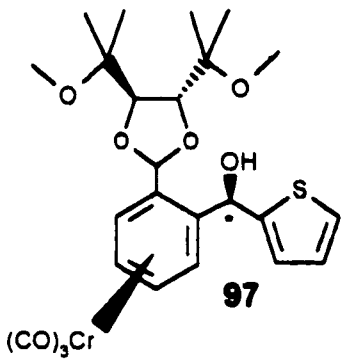


95

o-Formyl complex **72** (0.124 g, 0.2707 mmol) was subjected to procedure (I) with hexynyllithium (0.50 mL, 1.64 M, 0.81 mmol, 3 equiv) as the nucleophile. A standard aqueous work-up resulted in a crude product whose ^{1}H NMR spectrum revealed a resonance at δ 6.52 (**95a**) and δ 6.71 (**95b**) with a relative integral of 15.6:1 (88 % de). Purification attempts by silica gel chromatography using petroleum ether:ethyl acetate (5:1) as eluent resulted in post chromatographic fractions exhibiting extensive decomplexation. Further isolation was not possible ^{1}H NMR δ 6.52 (s, 1H), 5.68 (d, 1H, J=6.4 Hz), 5.63 (d, 1H, J=6.4 Hz), 5.35 (t, 2H, J=6.3 Hz), 5.26 (d, 1H, J=8.1 Hz), 5.20

(t, 1H, J=6.5 Hz), 4.23 (d, 1H, J=3.3 Hz), 4.02 (d, 1H, J=3.4), 3.21 (s, 3H), 3.15 (s, 3H) 2.21 (t, 2H, J=6.8Hz), 1.35-1.57 (m, 4H), 1.30 (s, 3H), 1.15 (s, 3H), 1.13 (s, 3H), 1.06 (s, 3H), 0.87 (t, 3H, J=7.4 Hz)

(1'*R*,2'*S*,4*R*,5*R*)-[4,5-Bis(1-methoxy-1-methylethyl)-2-(2'-(*S*-1-hydroxy-1-thiophene-1-ylmethyl)phenyl)-1,3-dioxolane]-tricarbonylchromium(0) (96) (thiophene derivative)

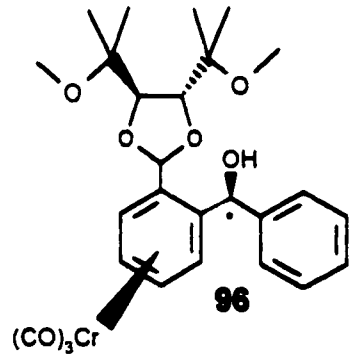


97

o-Formyl complex **72** (0.0763 g, 0.1666 mmol) was subjected to procedure (I) with Bromomagnesiothiophene (0.47mL, 1.14 M, 0.50 mmol, 3 equiv) as the nucleophile. A standard aqueous work-up resulted in a crude product whose ^{1}H NMR spectrum revealed a resonance at δ 6.32 (**97a**) and δ 6.48 (**97b**) with a relative integral of 13.3:1 (86% de). Purification by silica gel chromatography using petroleum ether:ethyl acetate (5:1) as eluent gave **13a** (77mg, 73%). $[\alpha]_D$ = 128.9° (C = 0.58, Et_2O); IR (NaCl, neat) ν_{max} 3480, 3076, 1971, 1897 cm^{-1}; 1H NMR, δ, 7.50 (d,1H,J=4.1 Hz), 7.30 (m, 2H), 6.32 (s, 1H), 5.8 (d, 1H, J=6.5), 5.63 (d, 1H, J=6.6), 5.20 (m, 2H) 5.11 (d, 1H, J=6.3), 4.20 (d, 3H,

J=3.5), 4.04 (d, 1H, J=3.5), 3.24 (s, 3H), 3.17 (s, 3H) 1.32 (m, 3H) 1.15 (s, 3H), 1.13 (s, 3H), 1.09 (s, 3H);^{13}C NMR, δ 232.0, 132.9, 129.4, 128.4, 107.8, 101.0, 95.4, 91.8, 90.4, 90.0, 84.7, 83.0, 76.7, 75.6, 49.5, 49.5, 22.3, 21.5, 21.0, 19.7 MS m/e 406 (M – $Cr(CO)_3$); HRMS m/e calcd for $C_{25}H_{30}CrO_8S$ (M+) 537.1039, found 537.1026

(1'*R*,2'*S*,4*R*,5*R*)-[4,5-Bis(1-methoxy-1-methylethyl)-2-(2'-(*S*-1-hydroxy-1-phenylmethyl)phenyl)-1,3-dioxolane]tricarbonylchromium(0) (97) (phenyl derivative)

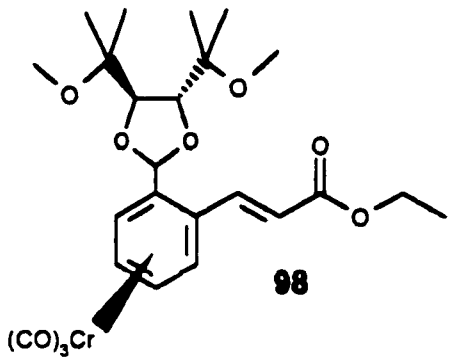


96

ortho-Formyl complex **72** (0.0924g, 0.2017 mmol) was subjected to procedure (I) with phenylmagnesium bromide (0.42mL, 1.44 M, 0.61 mmol, 3 equiv) as the nucleophile. A standard aqueous work-up resulted in a crude product whose ^{1}H NMR spectrum revealed a resonance at δ 6.11 (**96a**) and δ 6.32 (**96b**) with a relative integral of

7.7:1 (77 % de). Purification by silica gel chromatography using petroleum ether:ethyl acetate (5:1) as eluent gave **96a** (67mg, 62%). $[\alpha]_D$ = -49.4° (C = 0.56, Et_2O); IR (NaCl, neat) ν_{max}3421, 1966, 1887 cm^{-1}; ^1H NMR, δ, 7.45 (d, 2H, J=7.0 Hz), 7.29 (m, 3H), 6.11 (s, 1H), 5.88 (s, 1H), 5.73 (m, 2H), 5.32 (t, 2H, J=7.6 Hz), 4.11 (d, 1H, J=3.0 Hz), 3.98 (d, 1H, J=3.0 Hz), 3.21 (s, 3H), 3.15 (s, 3H), 2.32 (s, 1H), 1.34 (s, 3H), 1.11 (s, 3H), 1.08 (s, 3H), 1.04 (s, 3H); MS m/e 536 (M+); HRMS m/e calcd for $C_{27}H_{32}CrO_8$ (M+) 536.1502, found 536.1492

(1'*R*,2'*S*,4*R*,5*R*)-[4,5-Bis(1-methoxy-1-methylethyl)-2-(2'-(2-carboxyethyl-*E*-ethenyl)phenyl)-1,3-dioxolane]tricarbonylchromium(0) (98)



98

o-Formyl complex **72** (0.250 g, 0.5459 mmol) of was placed in a 50 mL round bottomed flask fitted with a reflux condenser. Triethylphosphonoacetate (0.11 mL, 0.55 mmol, 1 equiv) , lithium hydroxide monohydrate (0.0229 g, 0.55 mmol, 1 equiv) and THF (10mL) were added to the flask and solution was allowed to reflux for 3 h.1M HCl (10 mL) was added to the flask. Diethyl ether (5 mL) was added and the layers were separated. A standard aqueous workup afforded a red solid which was purified by flash chromatography on silica gel using petroleum ether:ethyl acetate (5:1) as the eluent Recrystallization from hexanes afforded a red crystalline solid (246 mg, 97%) which was identified spectroscopically as **98** mp 143-144°C IR (NaCl, neat) 1970, 1896, 1712 cm^{-1}; 1H NMR, δ, 7.62 (d,1H, J=15.7), 6.29 (d, 1H, J=15.7), 6.08 (s, 1H), 5.75 (d, 1H, J=6.5), 5.56 (d, 1H, J=6.5), 5.43 (t, 1H, J=6.2) 5.28 (t, 1H, J=6.4), 4.23 (m, 3H), 4.02 (d, 1H, J=3.5), 3.23 (s, 3H), 3.16 (s, 3H) 1.29 (m, 6H) 1.15 (s, 3H), 1.14 (s, 3H), 1.06 (s, 3H); ^{13}C NMR, δ, 231.6, 121.3, 107.9, 99.9, 98.9, 91.9, 90.7, 90.2, 88.9, 87.7, 84.9, 82.7, 75.5, 60.7, 49.3, 49.2, 22.1, 21.2, 20.9, 19.4, 14.2; MS m/e 528 (M+); HRMS m/e calcd for $C_{25}H_{32}CrO_9$ (M+) 528.1451, found 528.1452

Alkylation attempts on the cinnamate complex (98)

Alkylation with MeLi (Method 1)

Cinnamate complex **98** (0. 0750 g, 0.142 mmol), was weighed into a 50 mL round bottomed flask fitted with a septum and gas adapter. The flask was flushed with nitrogen and charged with 10mL of diethyl ether. The reaction flask was cooled to -78°C and then MeLi (0.28 mL, 1.5M, 0.43 mmol, 3 equiv) was added over 10 min. The reaction mixture was allowed to stir for 3 h at -78°C. Addition of 5mL of saturated $NH_4Cl_{(aq)}$ solution was followed by a standard aqueous workup that resulted in a red residue. This residue was identified as **98**.

Alkylation with MeLi and Lewis Acid (Method 2)

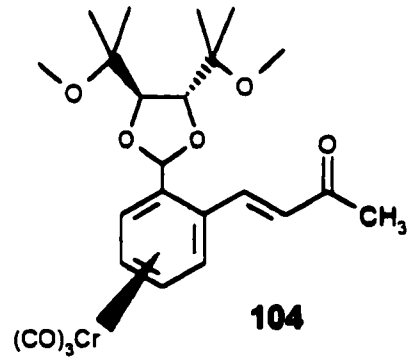
Cinnamate complex **98** (0.0782 g, 1.481 mmol) was weighed into a 50 mL round bottomed flask fitted with a septum and gas adapter. The flask was flushed with nitrogen and then charged with diethyl ether (10 mL). The reaction flask was cooled to -78°C and $Ti(OiPr)_4$ (0.050 mL, 0.042g, 0.44 mmol, 3 equiv) was added. The reaction mixture was allowed to stir for 20 min and then MeLi (0.30 mL, 1.5 M, 0.444 mmol, 3 equiv) was added over 10 min. The reaction mixture was allowed to stir for 3 h at -78°C. Addition of 5mL of saturated $NH_4Cl_{(aq)}$ solution was followed by a standard aqueous workup that resulted in a red residue which was identified as **98.**

Alkylation with lithium dimethylcuprate (Method 3)

Cu(I)I (0.100 g, 0.5251 mmol, 2 equiv with respect to substrate) was placed in 50 mL round bottomed flask fitted with a septum and charged with nitrogen. Diethyl ether (10 mL) was added to the flask and the flask was cooled to 0°C. MeLi (0.700 mL, 1.5 M in Et_2O 1.05 mmol, 4 equiv) was added to the flask over 1 h. The reaction mixture was allowed to stir for 2 h. Cinnamate **98** (0.139 g, 0.263 mmol) was added as a diethyl ether solution (5mL). The reaction mixture was allowed to warm to ambient temperature for 6 h. The addition of 2mL of saturated $NH_4Cl_{(aq)}$ solution was followed by a standard aqueous workup that resulted in a red residue. The residue was identified as **98**.

Alkylation with Methylcyanocuprate (Method 4)

Preparation of methyl ketone (104)



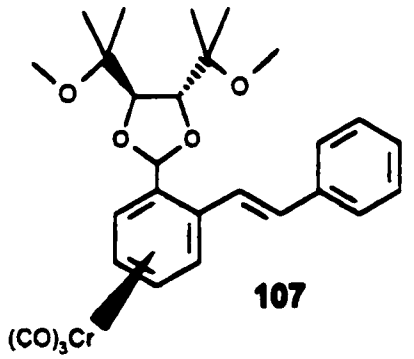
104

CuCN (0.0283 g, 0.316 mmol, 2 equiv with respect to substrate) was weighed into a 50 mL round bottomed flask. THF (20 mL) was added and the flask was cooled to -78°C. MeLi (0.42 mL, 1.5 M in diethyl ether, 0.63 mmol, 4 equiv) was added to the flask over 1 h. The reaction mixture was allowed to stir for 2 h at -78°C. The cinnamate complex **98** (0.0835 g, 0.1581 mmol) was added as a THF solution. The reaction mixture was allowed to warm to -20°C. Addition of saturated $NH_4Cl_{(aq)}$ (5 mL) was followed by a standard

aqueous workup that resulted in a red residue. The residue was purified by chromatography on silica gel using petroleum ether: ethyl acetate (5:1) as an eluent to afford **104** (31 mg, 39%) as a yellow oil which was evidenced by ^{1}H NMR spectroscopy. ^{1}H NMR δ 7.65 (d, 1H, J=16.1 Hz), 6.53 (d, 1H, J=16.1 Hz), 6.10 (s, 1H), 5.76 (d, 1H, J=6.4 Hz), 5.57 (d, 1H, 6.5 Hz), 5.46 (t, 1H, J=6.0 Hz), 5.29 (t, 1H, J=6.2 Hz), 4.17 (d, 1H, 3.0Hz), 3.98 (d, 1H, 3.0 Hz), 3.22 (s, 3H), 3.18 (s, 3H), 2.34 (s, 3H), 1.32 (s, 3H), 1.15 (s, 3H), 1.13 (s, 3H), 1.09 (s, 3H)

Preparation and Conjugate Addition Trials of Stilbene Complex 107

(1'*R*,2'*S*,4*R*,5*R*)-[4,5-Bis(1-methoxy-1-methylethyl)-2-(2'-((*E*)-2-phenyl-ethenyl)phenyl)-1,3-dioxolane]tricarbonylchromium(0) (107)



107

o-Formyl complex **72** (0.250 g, 0.546 mmol) , diethyl benzylphosphonate (0.11 mL 0.1245g, 0.55 mmol, 1 equiv) , tricaprylmethylammonium chloride (0.050 g), hexane (2 mL) and 40% $NaOH_{(aq)}$ solution (1.2 mL) were placed in a 25 mL round bottomed flask fitted with a reflux condenser. The flask was heated to reflux for 3 h. The addition of 5 mL of saturated $NH_4Cl_{(aq)}$ was followed by a standard aqueous workup. Purification by silica gel chromatography using petroleum ether:ethyl acetate (5:1) as an eluent followed by recrystallization from hexane gave **107** (0.272g, 94%) as red needles. Mp = 175-176°C; $[\alpha]_D$ = 303° (C = 0.5, Et_2O); IR ν_{max} 3059, 2974, 2910, 1959, 1861, 1496, 1462 cm^{-1};1H NMR δ, 7.46 (d, 2H, J=7.2), 7.35-7.29 (m, 3H), 7.02 (s, 2H), 6.11 (s, 1H), 5.85 (d, 1H, J=6.6 Hz), 5.62 (d, 1H, J= 6.6 Hz), 5.38 (t, 1H, J=6.0 Hz), 5.30 (t, 1H, J=6.1 Hz), 4.22 (d, 1H, J=3.4 Hz), 4.03 (d, 1H, J=3.5 Hz), 3.22 (s, 3H), 3.17 (s, 3H), 1.33 (s, 3H), 1.18 (s, 3H),1.15 (s, 3H), 1.09 (s, 3H); ^{13}C NMR, δ, 232.8, 136.4, 133.3, 128.8, 128.5, 127.1, 122.5, 100.4, 92.0, 90.6, 89.9, 84.8, 82.7, 75.7, 65.9, 49.5, 22.3, 21.4, 21.2, 19.6, 15.4 ; MS m/e 532 (M+); HRMS m/e calcd for $C_{28}H_{32}CrO_7$ (M+) 532.1554, found 532.1551

Alkylation attempts on the Stilbene complex 107

Alkylation with MeLi

Stilbene complex **107** (0.065g, 0.1222mmol) was weighed into a 50 mL round bottomed flask fitted with a septum and gas adapter. The flask was flushed with nitrogen and then charged with diethyl ether (10 ml). The reaction flask was cooled to -78°C and the MeLi

(0.24 mL, 1.5 M, 0.37 mmol, 3 equiv) was added over 10 min. The reaction mixture was allowed to stir for 3 h at -78°C. Addition of saturated $NH_4Cl_{(aq)}$ solution (5mL) was followed by a standard aqueous workup that afforded a red residue identified as **107**.

Alkylation with MeLi and Lewis Acid

Stilbene complex **107** (0.0763g, 0.1434 mmol) was weighed into a 50 mL round bottomed flask fitted with a septum and gas adapter. The flask was flushed with nitrogen and then charged with 10mL of diethyl ether. The reaction flask was cooled to -78°C and $Ti(OiPr)_4$ (0.13 mL, 0.12 g 0.43 mmol, 3 equiv) was added. The reaction mixture was allowed to stir for 20 min and then MeLi (0.29 mL, 1.5 M, 0.43 mmol, 3 equiv) was added over 10 min. The reaction mixture was allowed to stir for 3 h at -78°C. Addition of saturated $NH_4Cl_{(aq)}$ solution (5 mL) was followed by a standard aqueous workup that resulted in a red residue which was identified as **107**.

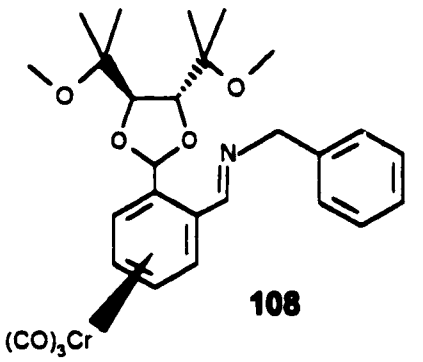
Alkylation with lithium dimethylcuprate

Cu(I)I (0.0823g, 0.4323 mmol, 2 equiv) was placed in 50 mL round bottomed flask fitted with a septum and charged with nitrogen. Diethyl ether (10 mL) was added to the flask and the flask was cooled to 0°C. MeLi (0.58 mL, 1.5M 0.86 mmol, 4 equiv) was added to the flask over 1 h. The reaction mixture was allowed to stir for 2 h. Stilbene complex **107** (0.115 g, 0.2162 mmol) was added as an ether solution (5 mL). The reaction mixture was allowed to warm to room temperature for 6 h. The addition of 2 mL of saturated $NH_4Cl_{(aq)}$ solution was followed by a standard aqueous workup that afforded a brown oil which was found to be an inseparable mixture of compounds.

Alkylation with lithium methylcyanocuprate

CuCN (0.0357g, 0.400 mmol, 2 equiv) was weighed into a 50 mL round bottomed flask.THF (20 mL)was added and the flask was cooled to -78°C. MeLi (0.53 mL, 1.5M in diethyl ether, 0.80 mmol, 4 equiv) was added to the flask over 1 h. The reaction mixture was allowed to stir for 2 h at -78°C. The stilbene complex **107** (0.1063 g, 0.1998 mmol) was added as a THF solution. The reaction mixture was allowed to warm to -20°C. Addition of saturated $NH_4Cl_{(aq)}$ (5 mL) was followed by a standard aqueous workup that resulted in a red residue that was found to contain an inseparable mixture of compounds.

(1'*R*,2'*S*,4*R*,5*R*)-[4,5-Bis(1-methoxy-1-methylethyl)-2-(2'-phenylmethylimino)phenyl)-1,3-dioxolane]tricarbonylchromium(0) (108)



108

o-Formyl complex **72** (0.250 g, 0.546 mmol), benzylamine (0.058g, 0.060mL, 0.55mmol, 1equiv), p-TsOH (10 mg, cat.), 4Å molecular sieves (1 g) and hexane (10 mL) were placed in a 50 mL round-bottomed flask fitted with a reflux condenser. The reaction mixture was heated to reflux for 3 h. After cooling to room temperature and filtration, the solution was subjected to a standard aqueous workup that afforded a red solid (0.281g,

94%). This solid was identified spectroscopically as **108** ; $[\alpha]_D$ = -50.6 (C=0.48, Et_2O) IR (NaCl, neat) ν_{max} 3489, 1979, 1886, 1672 cm^{-1}; ^1H NMR, δ, 8.36 (s, 1H), 7.35-7.24 (m, 5H), 6.22 (s, 1H), 5.72 (d, 1H, 6.1 Hz), 5.45 (t, 1H, J=6.0 Hz), 5.30 (t, 2H, J=6.2 Hz), 4.79 (d, 2H, J=4.2 Hz), 4.19 (d, 1H, J=3.2 Hz), 4.03 (d,1H, J= 3.2 Hz), (s, 3H), 3.14 (s, 3H), 1.33 (s, 3H), 1.21 (s, 3H), 1.19 (s, 3H), 1.04 (s, 3H); ^{13}C NMR, δ, 232.0,156.4, 138.9, 128.6, 128.0, 127.2, 108.6, 100.1, 99.2, 92.7, 91.3, 90.7, 88.4, 85.1, 83.0, 75.6, 65.9, 64.7, 49.5, 22.2, 21.3, 21.1, 19.4; MS m/e 547 (M+); HRMS m/e calcd for $C_{28}H_{33}CrO_7N$ (M+) 547.1662, found 547.1651

Alkylation attempts on the Benzylimine complex (108)

Alkylation with MeLi

Benzylimine complex **108** (0.128g, 0.2340 mmol) was weighed into a 50 mL round bottomed flask fitted with a septum and gas adapter. The flask was flushed with nitrogen and then charged with diethyl ether (10 mL). The reaction flask was cooled to -78°C and the MeLi (0.47 mL, 1.5 M, 0.7020 mmol, 3 equiv) was added over 10 min. The reaction mixture was allowed to stir for 3 h at -78°C. Addition of 5 mL of saturated $NH_4Cl_{(aq)}$ solution was followed by a standard aqueous workup resulted in a brown residue that was identified as **108**.

Alkylation with MeLi and Lewis Acid

Benzylimine complex **108** (0.0932g , 0.1704 mmol) was weighed into a 50 mL round bottomed flask fitted with a septum and gas adapter. The flask was flushed with nitrogen

and then charged with diethyl ether (10 mL). The reaction flask was cooled to -78°C and $Ti(OiPr)_4$ (0.15 mL, 0.15 g, 0.51 mmol, 3 equiv) was added. The reaction mixture was allowed to stir for 20 min and then MeLi (0.34 mL, 1.5 M, 0.51 mmol, 3 equiv) was added over 10 min. The reaction mixture was allowed to stir for 3 h at -78°C. Addition of saturated $NH_4Cl_{(aq)}$ solution (5mL) was followed by a standard aqueous workup that resulted in a brown residue that was identified as **108**

Alkylation with lithiumdimethylcuprate

Cu(I)I (0.0791g, 0.415 mmol, 2 equiv) was placed in 50 mL round bottomed flask fitted with a septum and charged with nitrogen. 10 mL of diethyl ether was added to the flask and the flask was cooled to 0°C. MeLi (0.55 mL, 1.5 M in Et_2O 0.83 mmol, 4 equiv) was added to the flask over 1 h. The reaction mixture was allowed to stir for 2 h. Benzylimine complex **108** (0.1136 g, 0.2076 mmol) was added as a solution in ether (5 mL). The reaction mixture was allowed to warm to ambient temperature for 6 h. The addition of saturated $NH_4Cl_{(aq)}$ (2 mL) was followed by a standard aqueous workup which resulted in a brown residue of inseparable products.

Alkylation with methylcyanocuprate

CuCN (0.0345g, 0.385 mmol, 2 equiv with respect to substrate) was weighed into a 50 mL round bottomed flask. 20 mL THF was added and the flask was cooled to -78°C. MeLi (0.51 mL, 1.5 M in diethyl ether, 0.77 mmol, 4 equiv) was added to the flask over 1 h. The reaction mixture was allowed to stir for 2 h at -78°C. The benzylimine complex **108** (0.1053g, 0.1925 mmol) was added as a THF solution (5 mL). The reaction mixture

was allowed to warm to -20°C. Addition of 5 mL of saturated $NH_4Cl_{(aq)}$ was followed by a standard aqueous workup that resulted in a reddish-brown residue identified as **108**

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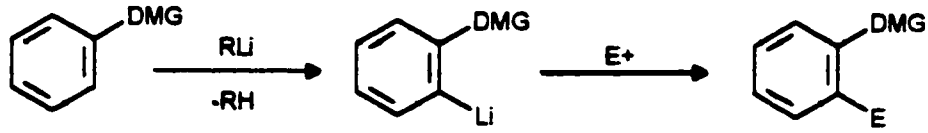
Chapter 2

2.1 Introduction

There are many methods at the modern synthetic chemist's disposal for the *ortho* functionalization of substituted aromatic compounds based on directed *ortho*-metallation (DOM) followed by the reaction of the metallated aromatic ring with electrophiles[1,2]. Preparation of enantiomerically pure *meta*-disubstituted aromatic compounds is less straightforward. The goal of this part of the project was to develop a technique for the preparation of enantiomerically pure *meta* substituted chromium tricarbonyl complexes of aromatic aldehydes (**Scheme 1**). The general strategy involves the preparation of an optically pure *ortho*-thioether derivative of the chromium tricarbonyl complex of a diethyl tartrate acetal protected benzaldehyde. Next, the thioether group will be used as an *ortho* director in a second metallation of the chromium complex. The final stage of this strategy involves the removal of the thioether substituent, resulting in a *meta* disubstituted compound.

2.1.1 Directed *Ortho* Metallation (DOM)

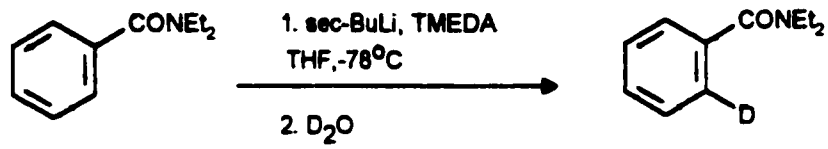
The DOM process involves the deprotonation of a site *ortho* to a heteroatom containing directed metallation group (DMG) **1** by a strong base, normally an alkyllithium reagent, leading to an *ortho* lithiated species **2**. This aryllithium species, upon treatment with an electrophile, yields 1,2-disubstituted products **3**. (**Scheme 1**)



1 **2** **3**

Scheme 1

Typically the pKa's of the *ortho* protons on the aromatic ring are in the 36-42 range, and thus the DOM process occurs in the presence of alkyllithium bases. In organic solvents in which alkyllithiums exhibit high solubility there is a tendency to form aggregates, typically hexamers (in hydrocarbons) or tetramers-dimers (in basic solvents)[1]. Coordinating solvents such as THF and diethyl ether cause dissociation of the alkyllithium aggregates. THF coordination to $(n\text{-BuLi})_6$ gives solvated $(n\text{-BuLi})_4$. The addition of TMEDA, a bidentate ligand, breaks down aggregates to form monomers and dimers in solution, thus increasing their kinetic basicity[32]. n-Butyllithium, s-butyllithium, t-butyllithium and methyllithium have all been used extensively for DOM reactions. Standard DOM conditions are illustrated below[3]. **(Scheme 2)**



4 5

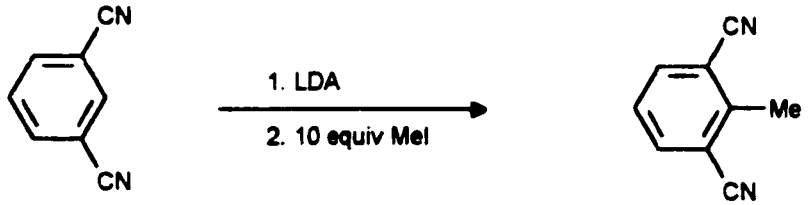
Scheme 2

Regiospecific deprotonation of aromatic compounds is directed by the *ortho* substituent that typically contains a heteroatom. (Exceptions to this include the acetylide anion and the phenyl group.)[1] There are two ways in which the DOM group exerts its influence on the reaction; through induction (CF_3 or F) or coordination (OMe, NR_2). With the most effective DOM groups, both effects enhance the deprotonation ($CONR_2$, SO_2NR_2). Table 1 lists examples of DOM groups, categorized according to their directing abilities. pKa determinations reflecting mainly inductive effects show little variation and given the difference in DMG abilities, this suggest that coordination ability of the DMG under the kinetic conditions normally used in synthesis is a key factor in determining its relative metallation ability.

Table 1: DOM Groups

Carbon -based DMG	pKa	Heteoatom Based DMG	pKa
Strong			
CON^-R		N^-COR	≥40.5
CSN^-R		N^-CO_2R	
$CONR_2$		$OCONR_2$	37.2
CH=NR		OTHP	40.0
		Oph	38.5
Moderate			
CF_3		NR_2	≥40.3
		Ome	39
		$OCH_2=CH_2$	
		F	
		Cl	
Weak			
CH_2O^-		O^-	(≥40.5)
$C\equiv C-$		S^-	
Ph			

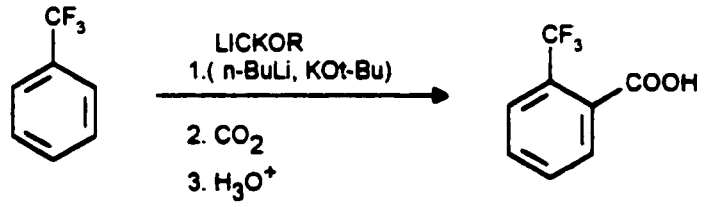
To a lesser extent, lithium amides have also seen use as bases in DOM reactions (**Scheme 3**)[4]. Lithium diisopropylamide (LDA) is the most commonly used lithium amide for DOM reactions, although it has found greater use in remote metallations.



6 **7**

Scheme 3

Recently there has been use of the "super-bases" LICKOR (RLi + KOR)[5] and LIDAKOR (LDA + KOR)[6] (**Scheme 4**), although these have been more extensively utilized for benzylic lithiations.



8 **9**

Scheme 4

The coordination of an aromatic ring to a chromium tricarbonyl complex greatly increases the acidity of the ring protons. For example, the pKa of the *ortho* proton of ansiole is 39.0[2], whereas the pKa of the chromium tricarbonyl complex of anisole is 33.0[7]; thus it is not suprising that arenechromium tricarbonyl complexes are suitable substrates for DOM reactions, and have seen extensive use in this capacity[8].

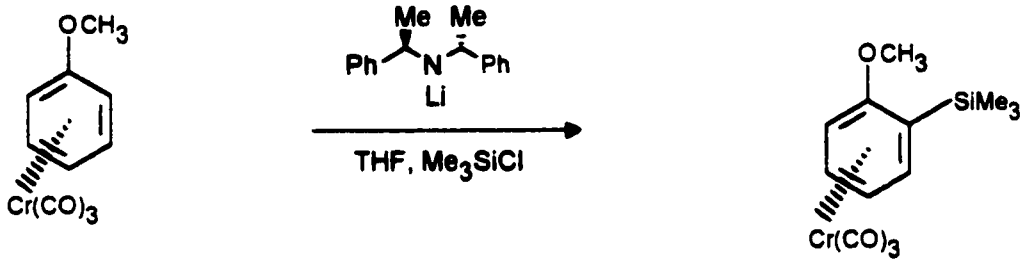
2.1.2 Asymmetric Deprotonations of Arenechromium Tricarbonyl Complexes

Since it is desirable to have a route to obtain a single enantiomer of an arenechromium tricarbonyl complex, several techniques have been developed in which one of the *ortho* protons is abstracted preferentially over the other. Three general strategies have been developed to facilitate diastereoselective *ortho* lithiation of arenechromium tricarbonyl complexes; use of a chiral base for deprotonation, the incorporation of a chiral additive and attachment of a chiral auxiliary to the arene.

2.1.2a Chiral Bases

Using a chiral base for stereoselective deprotonation is an approach used by many research groups. The selectivity stems from the fact that the transition states for the *ortho* and *ortho'* deprotonation with a chiral base are diastereomeric.

Chiral lithium amides have been utilized to prepare optically pure arenechromium tricarbonyl complexes. Simpkins has used chiral lithium diphenethylamide to deprotonate (anisole)chromium tricarbonyl (**Scheme 5**)[9,10]. Upon quenching with TMSCl, the mono silylated product was obtained in 50% yield with >97% de. Aldehydes have been used as electrophiles in this system, although stereoselectivity was found to be modest.

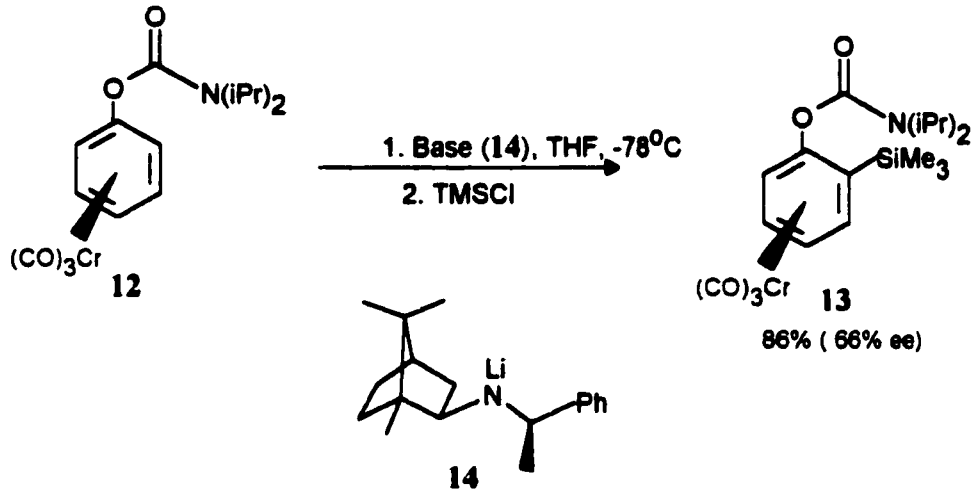


10 **11**

Scheme 5

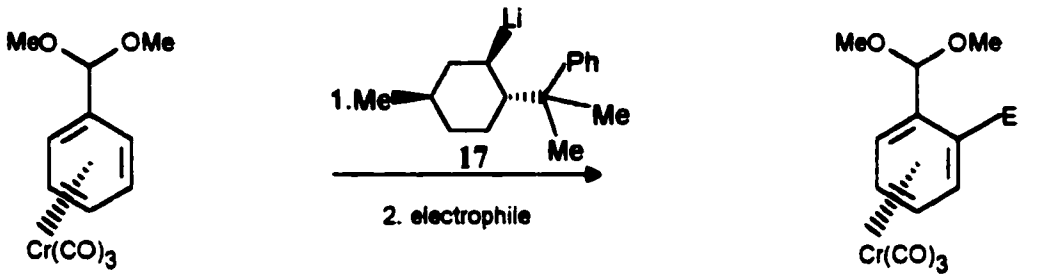
Kundig has employed the same base for the deprotonation of chromium tricarbonyl complexes of acetals of benzaldehyde. With the ethylene glycol derived acetal of benzaldehyde, mostly benzylic deprotonation occurred with the lithium di(phenethyl)amide. Use of a camphor derived lithium amide (**Scheme 6**) resulted in a modest improvement. The proportion of benzyl deprotonation diminished as Kundig employed a technique in which the electrophile was in solution while the deprotonation was taking place. Good levels of regioselectivity and enantioselectivity were never achieved for the deprotonation of acetals with Kundig's lithium amides.

Kundig focused on phenyl carbamates as deprotonation substrates (**Scheme 6**)[11]. With both bases, moderate selectivity (64% to 73% ee) and good yields were observed. With no benzylic proton on the phenyl carbamates, benzylic deprotonation was not an issue.



Scheme 6

Chiral alkyllithiums have been investigated for their effectiveness in stereoselective deprotonations. Organolithium bases derived from (*R*)-menthyl chloride and (*R*)-8-phenylmenthyl chloride were used to deprotonate the chromium tricarbonyl complex of the dimethyl acetal of benzaldehyde (**Scheme 7**)[12]. Both of the bases were somewhat selective in the deprotonation. In the case of the menthyllithium base, the pro-*R* proton was abstracted, while the 8-phenylmenthyllithium abstracted the pro-*S* proton, providing a route to both enantiomers of *ortho* disubstituted arene complexes.



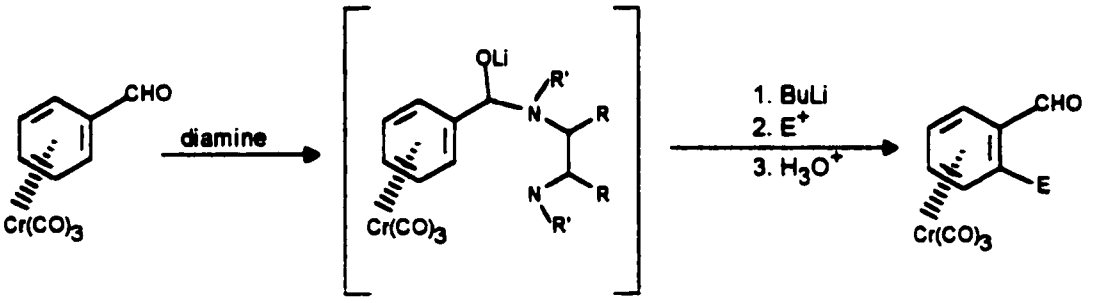
15 **16**

Scheme 7

2.1.2b Chiral Additives

By the addition of a chiral diamine to the aldehyde carbonyl group, Alexakis has made use of a method originated by the Comins group in which the aldehyde is temporarily protected as an amino alcoholate[13]. In principle, the second nitrogen atom in the appendage acts as a coordination site for the lithium base and by doing so, facilitates *ortho* lithiation of the chromium complex. Several pseudo C_2 symmetric diamines were used as additives in the deprotonation. With most of the diamines, complete regioselectivity was not observed. In most cases there was a significant amount of *meta* lithiation that accompanied the *ortho* lithiation. This is evidence that the steric bulk of the nitrogen side chains somewhat interfered with the coordinating effect of the nitrogen atom. When the side chains on the nitrogen contained methoxy groups, there was another

potential chelation site and complete regioselectivity was observed. Stereoselectivity was only about 70% ee (**Scheme 8**).



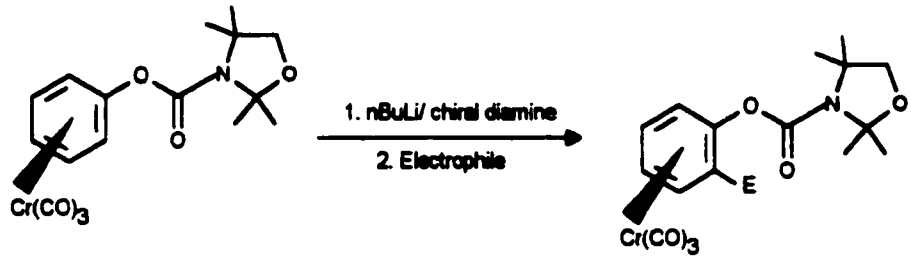
18 **19** **20**

Scheme 8

Uemura *et al* have used chiral diamines as additives in the deprotonation of the chromium tricarbonyl complexes of phenyl carbamates bearing oxazolidine groups (**Scheme 9**)[14]. Promising results were obtained with the use of the additive *N, N,N',N'*-tetramethyl-1,2-diphenylethylenediamine. With methyl chloroformate as an electrophile, an enantiomeric excess of 82% was achieved. The authors contend that in hydrocarbon solvent, the oligomeric structure of alkyllithium, upon the addition of a diamine, changes to a less bulky dimeric structure that abstracts the pro-*R* proton. In diethyl ether, lower enantioselectivities were obtained for the lithiation, due to the fact that butyllithium can coordinate with both the ether oxygen and nitrogen, disrupting the structure of the alkyllithium/ diamine aggregate.

The chiral diamine additive approach was applied to the chromium tricarbonyl complex of *N*-methyl-*N*-Boc-aniline. It is known that N,N-dimethylaniline undergoes deprotonation primarily at the *meta* position with minor amounts of *ortho* and *para* deprotonation. In spite of having the bulky Boc group, in the presence of chiral diamine,

N-methyl-*N*-Boc-aniline deprotonation is highly *ortho* selective. Stereoselectivity was poor to fair, typically in the 50%-60% range.



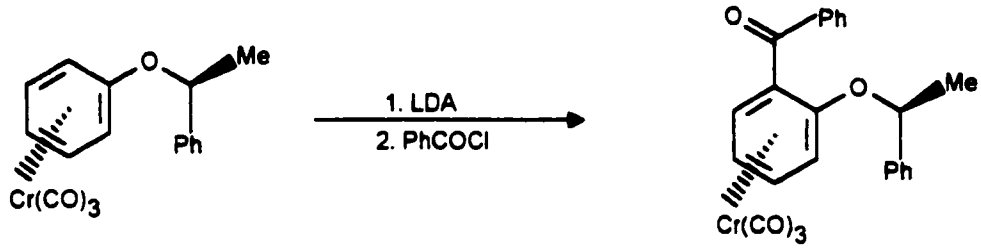
21 **22**

Scheme 9

2.1.2c Chiral Auxiliaries

2.1.2c.i Chiral Ethers

As part of an effort to prepare optically active biaryl alcohols, Davies *et al* has made use of phenethanol based ethers as chiral auxiliaries in the *ortho* lithiation of (arene)chromium tricarbonyl complexes[15]. Deprotonation of the chromium tricarbonyl was achieved with LDA in THF at –78°C and the lithium species was reacted with a series of electrophiles which included benzoyl chloride (67% yield, one diastereomer), DMF (82% yield, single diastereomer) and benzaldehyde (33% de) (**Scheme 10**).



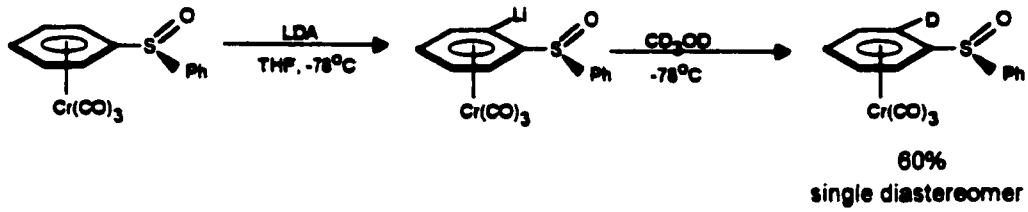
23 **24**

Scheme 10

2.1.2c.ii Chiral Sulfoxides

Davies *et al* has successfully exploited the ability of the phenyl sulfoxide group to induce asymmetry in the deprotonation of (arene)chromium tricarbonyl complexes[16]. Reaction of diphenyl sulfoxide chromium tricarbonyl with LDA in THF at –78°C followed by quenching of the anion with CD_3OD gave the mono *ortho*-deuterated complex as a single diastereomer (**Scheme 11**). It was possible to add an electrophile to the other *ortho* position via the intermediacy of a dianion, which was formed upon the

addition of three equivalents of LDA. Both deprotonations were *ortho*-regioselective with the first being completely stereoselective. Addition of one equivalent of electrophile resulted in the formation of the diastereomer not formed as a result of mono-lithiation.

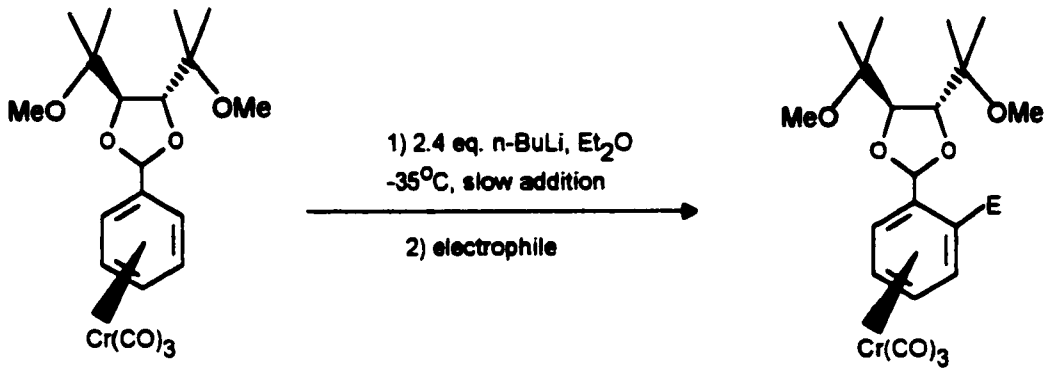


25 **26** **27**

Scheme 11

2.1.2c.iii Chiral Acetals

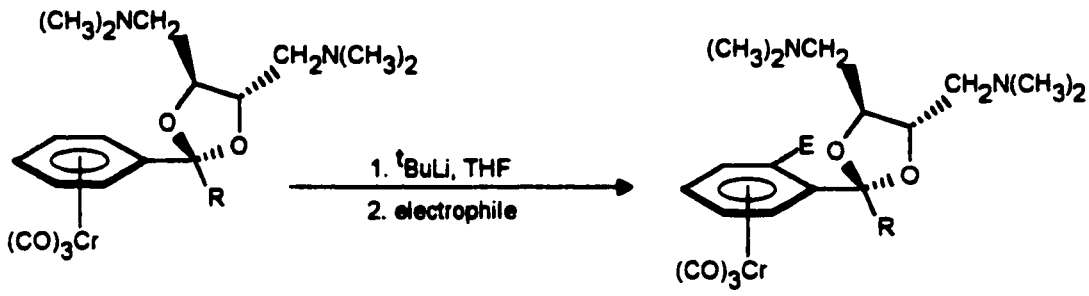
Green *et al* have successfully used chiral acetals as for the preparation of optically enriched 1,2-disubstiuted (arene)chromium tricarbonyl complexes[17]. A modified diethyl tartrate derived acetal of benzaldehyde served the dual purposes of protecting the aldehyde functionality and preferentially directing metallation to one of the *ortho* protons. Deprotonation of the chromium complex with 2.4 equivalents of n-butyllithium resulted in the removal of the pro-*R* proton. This anionic species was quenched with a wide variety of electrophiles in good yields and de's typically in the 85% to 95% range (**Scheme 12**). Deprotection of the aldehyde was achieved by acid catalysed hydrolysis, but is efficient only for small *ortho* substituents.



28 **29**

Scheme 12

The deprotonation of the chromium tricarbonyl complexes of chiral ketals of acetophenone was examined by Aubé[18]. Functionalized derivatives of ethylene glycol were used to prepare a series of ketals bearing side chains in the 4 and 5 positions. Impressive levels of stereoselectivity were achieved for ketals bearing the side chains $CH_2N(CH_3)_2$ in the 4 and 5 position of the ketal ring. Carrying out the deprotonation with t-BuLi in THF at -78°C, and quenching with TMSCl gave the mono-silylated product in 88% de (**Scheme 13**). Ketals with methoxymethyl side chains were also deprotonated although the stereoselectivity was somewhat diminished (~50% de). In the cases with small *ortho* substituents, efficient removal of the auxiliaries was accomplished by acid catalysed hydrolysis to give the optically pure *o*-substituted benzaldehyde chromium complexes.

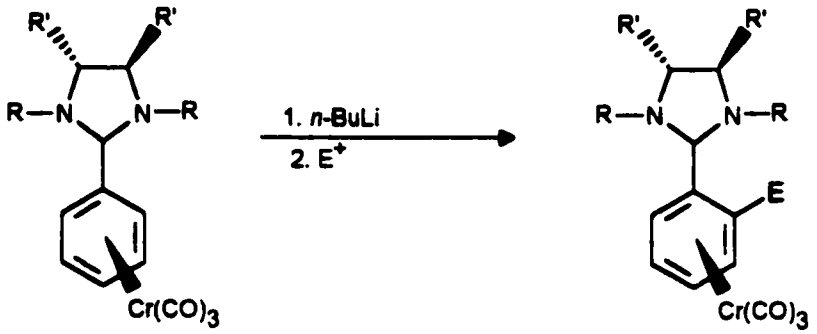


30 **31**

Scheme 13

2.1.2c.iv Chiral Aminals

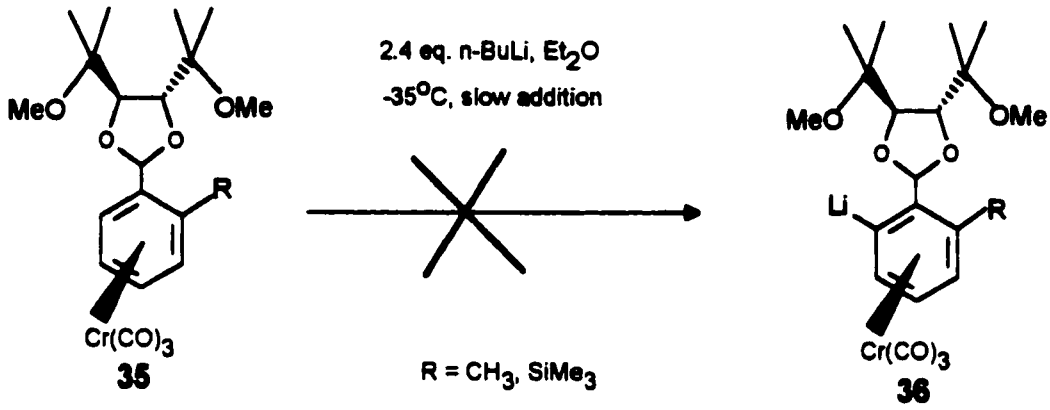
Chiral aminals have been examined as directing groups in the selective *ortho*-lithiation of (arene)chromium tricarbonyl complexes. Alexakis *et al* have prepared a series of aminals by the reaction of (benzaldehyde)chromium tricarbonyl and a series of chiral diamines (**Scheme 14**)[19]. The deprotonations were done in THF at –30 °C and it was found that the regioselectivity depended on the nature of the side chains of the imidazoline nitrogen. Deprotonations performed on aminals with nitrogens having alkyl or aryl side chains occurred preferentially in the *meta* position. The steric bulk of the side chains on nitrogen outweighed the coordinative effect of the nitrogen atom of the imidazoline on the lithium atom. The addition of the methoxy group as part of the nitrogen side chain allows for tight chelation of the metal, thus deprotonations on this compound were *ortho*-selective. Stereoselectivity was greater than 99% *ee* in all cases. Removal of the auxiliary was achieved by acid catalyzed hydrolysis and appeared to occur more readily than for the acetals.



32 **33**

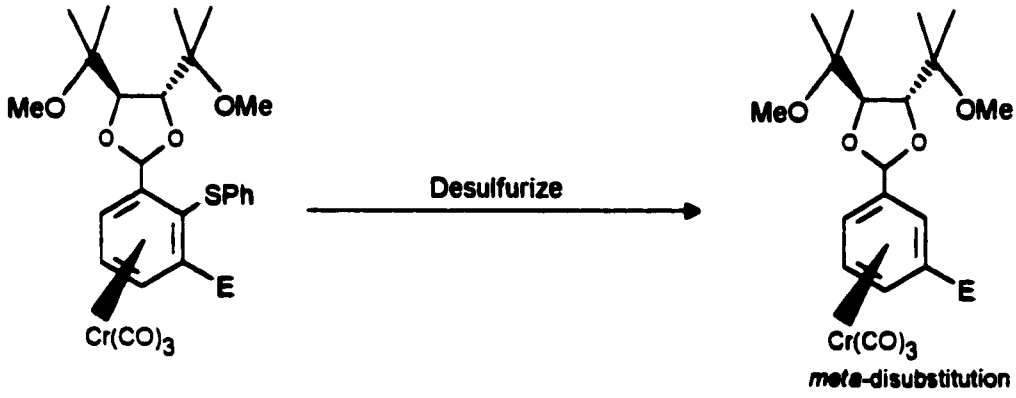
Scheme 14

Despite the increasing number of methods for preparation of chiral *ortho*-disubstituted (arene)chromium tricarbonyl complexes, there has been little emphasis on the preparation of enantiomerically pure *meta*-disubstituted complexes. Using the metallation of an aromatic ring bearing the tartrate acetal derived chiral auxiliary, it was possible to obtain optically pure chiral acetals bearing thioether substituents *ortho* to the chiral directing group. It has been found that the thioether groups are capable of directing metallation to its position *ortho* position[20-23]. Also it is known that compounds **34** and **35** do not lithiate readily in the *ortho'* position[24], suggesting that lithiation of the thioether complexes would occur primarily next to the thioether (**Scheme 15**).



Scheme 15

Further metallation of such compounds followed by reaction with electrophiles would, in principle afford 1,2,3-trisubstituted aromatic rings. Removal of the thioether substituent from the aromatic ring would, in principal give a *meta*-substituted compound (**Scheme 16**). There are several methods available for the removal of thiophenyl groups from aromatic rings. It was deemed useful to pursue an investigation based on this strategy.



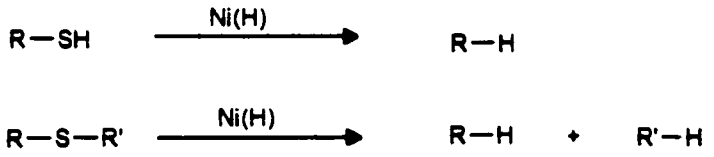
Scheme 16

2.1.3 Desulfurization of Organic Compounds

One of the primary uses of organosulfur compounds in organic chemistry is based on the role of the sulfur moiety which can serve as an auxiliary group that can be removed once it has fulfilled its function. There are therefore a wide variety of methods that have been developed to reduce the carbon-sulfur bond to a carbon-hydrogen bond.[24-27]

2.1.3a Raney Nickel Desulfurization

Several transition metal compounds have proven to be extremely thiophilic. A classical heterogeneous technique for the reduction of organosulfur compounds involves the use of Raney Nickel[28]. Raney Nickel desulfurization involves the breaking of a carbon-sulfur bond and the formation of at least one new carbon hydrogen bond (**Scheme 17**).



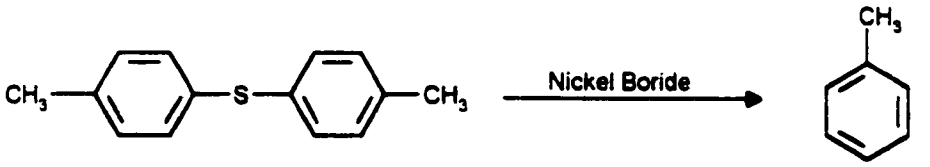
Scheme 17

It has been suggested, the first step of the reaction is the oxidative addition of nickel in the carbon-sulfur bond to form a nickel mercaptide which undergoes hydrogenolysis to form nickel sulfide and a hydrocarbon (**Scheme 18**). The source of hydrogen is the Raney Nickel, which contains large amounts of hydrogen as it is ordinarily prepared. A free radical mechanism for Raney Nickel reduction has also been proposed[28].

Scheme 18

2.1.3b Nickel Boride Desulfurization

An in situ technique for the generation of a reactive nickel compound has been utilized for the desulfurization[29] and deselenization[30] of organic compounds (**Scheme 19**). The reduction of nickel(II) chloride hexahydrate with sodium borohydride yields nickel boride. Nickel boride prepared this way has a Ni:B ratio of ~2:1, contains adsorbed hydrogen in consistent with the formula $(Ni_2B)_2H_3$ and functions as a hydrogenation catalyst. The mechanism of metal boride reduction has not yet been fully elucidated.

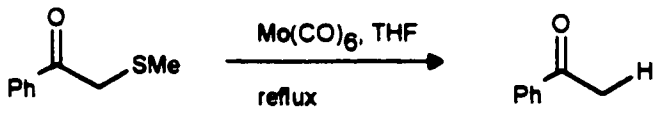


34 **35**

Scheme 19

2.1.3c Molybdenum Hexacarbonyl Desulfurization

By using molybdenum hexacarbonyl to generate molybdenum(II) species in situ, Luh *et al* has been successful in the reduction of sulfides[31]. Reactive carbon-sulfur bonds such as benzylic or α to a carbonyl undergo reductive cleavage with molybdenum carbonyl in refluxing THF (**Scheme 20**). It is possible to reduce allylic sulfides by reaction with $Mo(CO)_6$ in dioxane. Tungsten carbonyl has also been used for the reduction of sulfides. With $W(CO)_6$, the reduction proceeds via a free radical mechanism[32].



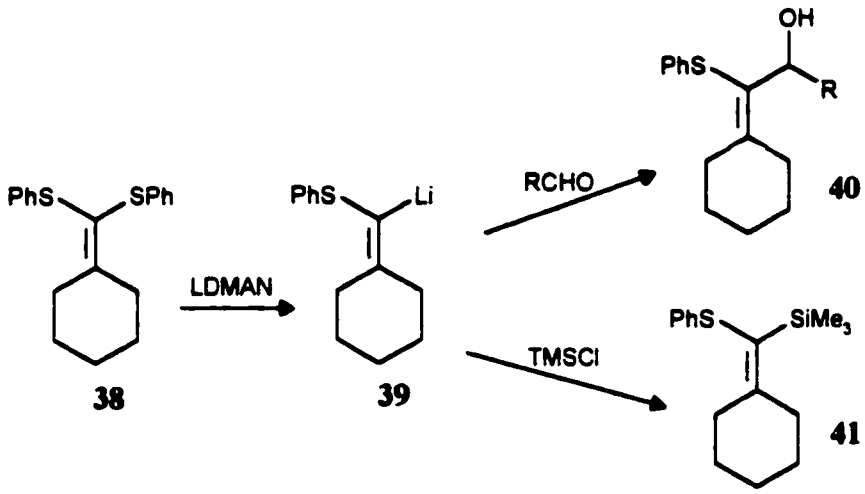
36 **37**

Scheme 20

2.1.3d Radical Anion Desulfurization

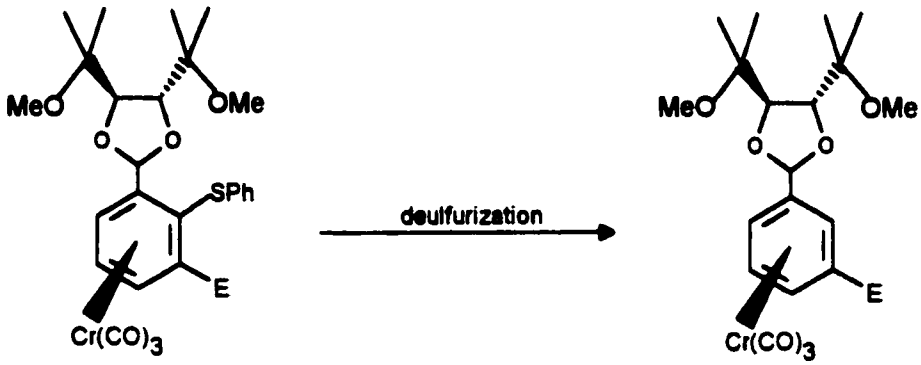
Cohen *et al* has made use of radical anion chemistry in the desulfurization of organic compounds[33]. The focus of Cohen's work is the conversion of phenylthioethers to organolithium compounds by their reaction with LDMAN (lithium - (dimethylamino)-naphthlenide))[34] (**Scheme 21**) or with LDBB (lithium *p,p'*-di'butylbiphenylide). Once the

organolithium compound is formed it can be trapped with a variety of electrophiles. The mechanism of reduction most likely involves two one-electron transfers from the LDMAN to the carbon bearing the thiophenyl group.



Scheme 21

Given the abundance of techniques for desulfurization, especially those targeted to the thiophenyl group, it seemed likely that a suitable method would be found to remove the sulfur-containing DOM group of the substituted thioether derivatives to achieve the goal of this phase of research (**Scheme 22**).

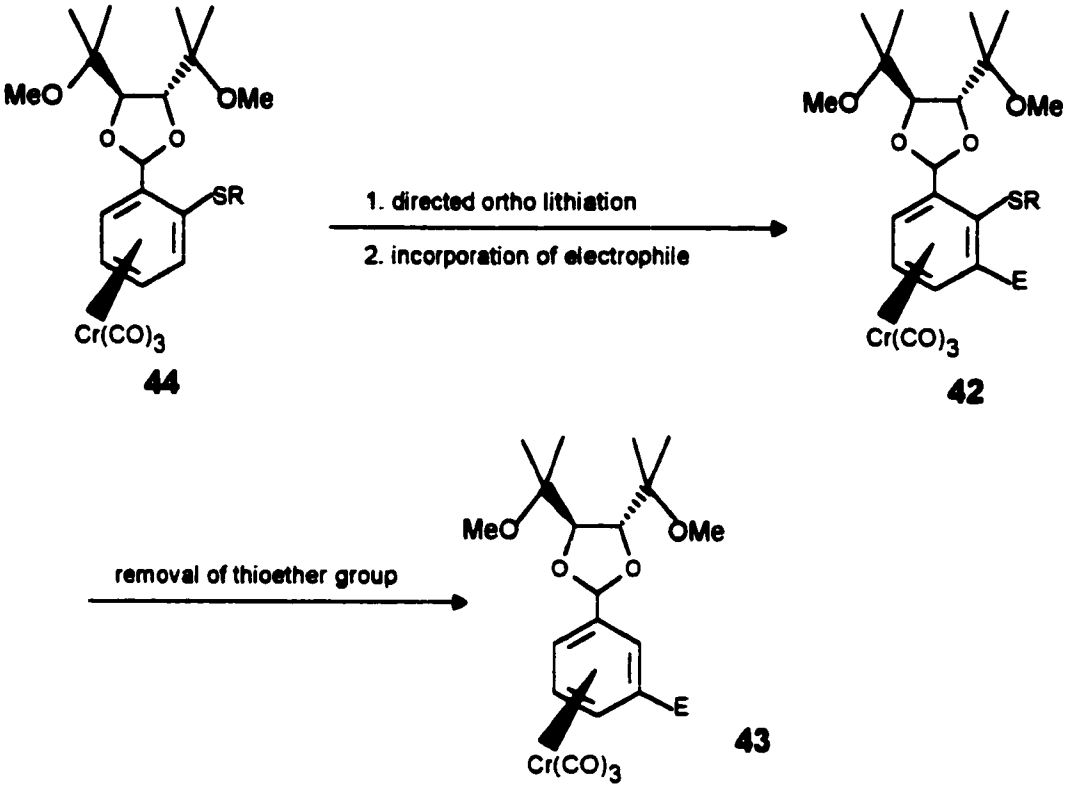


42 **43**

Scheme 22

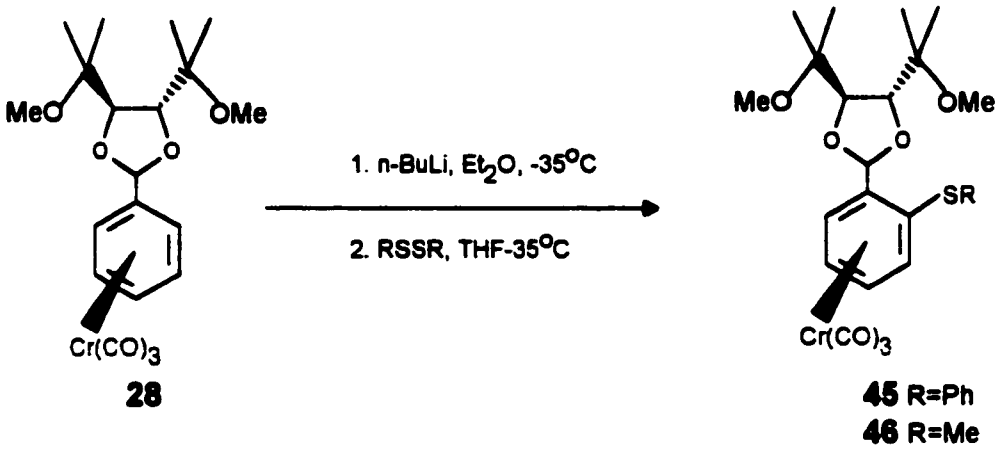
Results and Discussion

With the rapidly evolving set of auxiliaries and protocols for the synthesis of enantiomerically enriched ortho disubstituted arenetricarbonylchromium complexes, we deemed it important to address the question of the synthesis of their rarely encountered *meta*-disubstituted counterparts. The intended strategy involved the exploitation of a removable sulfur-containing group in the *ortho* position with respect to the chiral acetal previously demonstrated to be an effective directed *ortho* metallation group[24]. **(Scheme 21)** Thioether groups have had limited use in directing *ortho* metallation [35,36,37]. Two such thioethers were investigated as removable directing groups; thiophenyl and thiomethyl ethers. In principle, lithiation of the *ortho*-thioether derivatives **44** of the compounds, followed by quenching with an electrophile leads to a 1,2,3-substitution pattern on the chromium complexed aromatic ring **42**. With such a trisubstituted species in hand, removal of the sulfur-containing fragment from between the flanking substituents would result in a *meta*-disubstituted compound **43**.



Scheme 21

Preparation of the thioether substrates required some modification of the conditions for chiral acetal-directed lithiation reactions developed in our laboratory. Initial attempts at the synthesis of the thiophenyl derivative (**45**) made using the standard methodology (-35 °C, Et_2O) failed to give any of the intended compound. The addition of a volume of THF equal to the volume of Et_2O, followed by the addition of diphenyl disulfide as a THF solution, led to the formation of thiophenyl ether **45** in 82% yield after chromatographic purification. This phenomenon has been observed before in directed lithiation reactions[38] and in our system previously with MeI as the electrophile. The thiomethyl derivative **46** was prepared in an analogous manner in 66% yield, with dimethyl disulfide added as a neat liquid to the THF/Et_2O solution of the lithioarene.



Scheme 22

The initial segment of this phase of the research involved the evaluation of the phenylthio ether substituent to act in the role of DOM group. There exists a potential site for competitive lithiation, at the remaining *ortho* position to the acetal unit (referred to as the *ortho'* site henceforth) (**Figure 1**). Deprotonation at this site, however, was found to be exceedingly difficult for both the *ortho*- Me_3Si and *ortho*- methyl compounds.[39] this is not surprising based on two factors governing the course of the reaction.

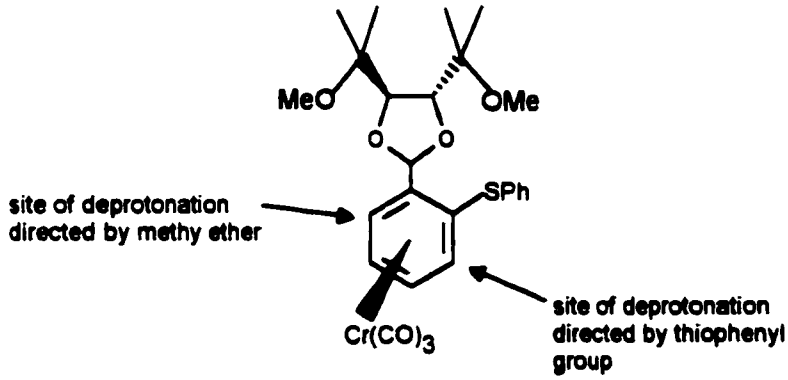


Figure 1: Possible Sites for Deprotonation of Thiophenyl Complex 45

First, in order for the tartrate acetal to operate otimally as an *ortho* director, we believe that there is a necessity for the acetal to adopt a conformation that places the ether oxygen of the dioxolane ring slightly below the plane of the ring. In this conformation, an ether oxygen is also in a position to coordinate to the incoming alkyllithium reagent. **(Figure 2)**

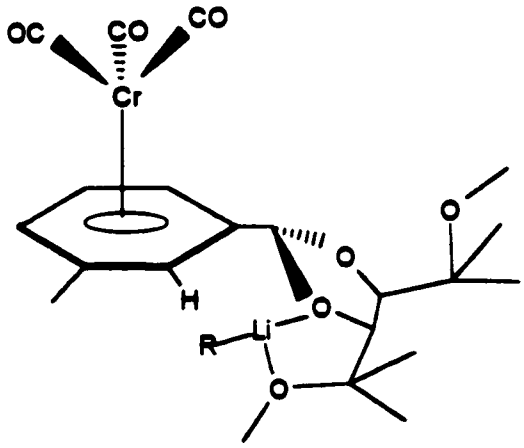


Figure 2: Conformation Favouring *o*-Deprotonation

In order for the acetal to direct to the *ortho'* site, it is necessary for the acetal to undergo rotation to place a methyl ether in proximity to that *ortho'* proton. This rotation would be hindered due to interference by the $Cr(CO)_3$ unit. Furthermore, even if the rotation could occur, the dioxolane oxygen would then be unable to participate in coordination of the alkyllithium reagent while bringing it near the *ortho'* oxygen. **(Figure 3)**. Therefore, it was predicted that even a weak directing group such as thioalkyl or thioaryl should direct preferentially into its *ortho* position, or the *meta* position relative to the acetal.

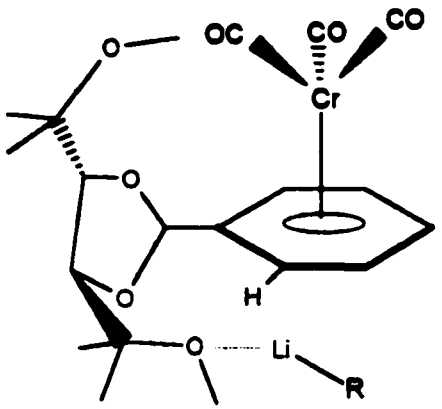
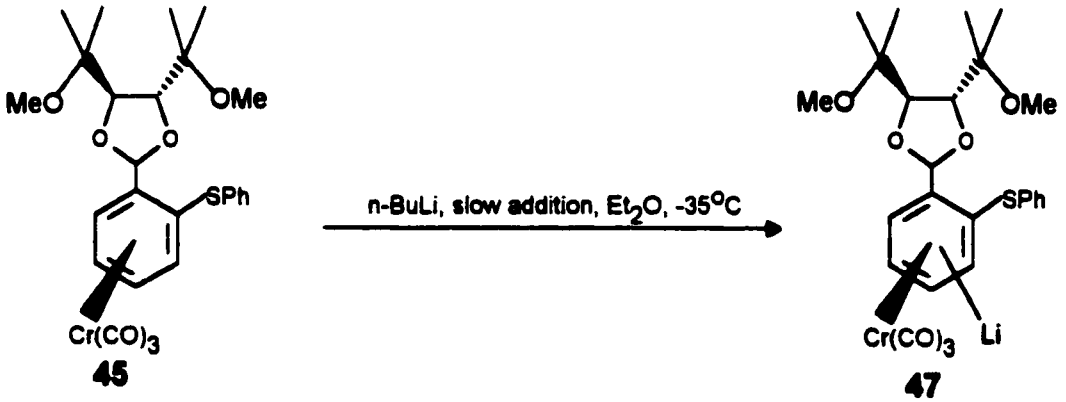


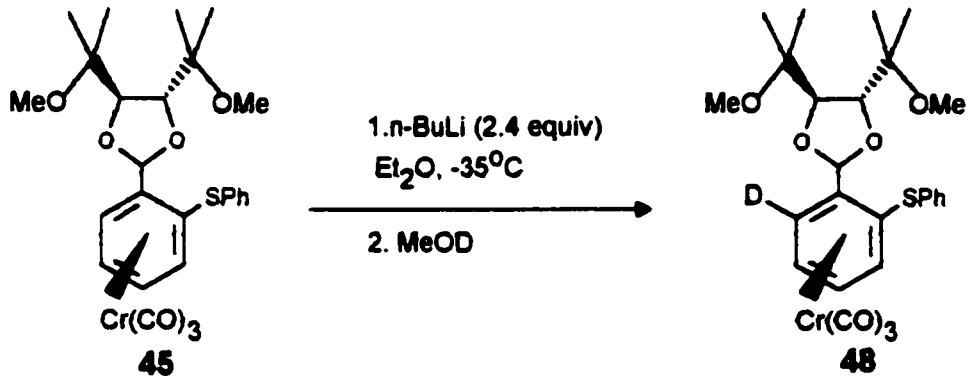
Figure 3: Conformation Necessary for *o*'-Deprotonation

In the case of the thiophenyl substrate **45**, a number of sets of conditions were investigated, using deuteration with MeOD as a probe. The most effective lithiation was found to occur with slow addition of 2.5 equiv of *n*-BuLi at –35 °C in Et_2O. (**Scheme 23**) This resulted in a single regioisomer of deuterated material, in 86% yield. Unfortunately, the disappearance of the furthest downfield arene-$Cr(CO)_3$ resonance in the ^1H NMR spectrum (δ 5.80 ppm) suggested this was the product of deuteration *ortho*- to the acetal group.

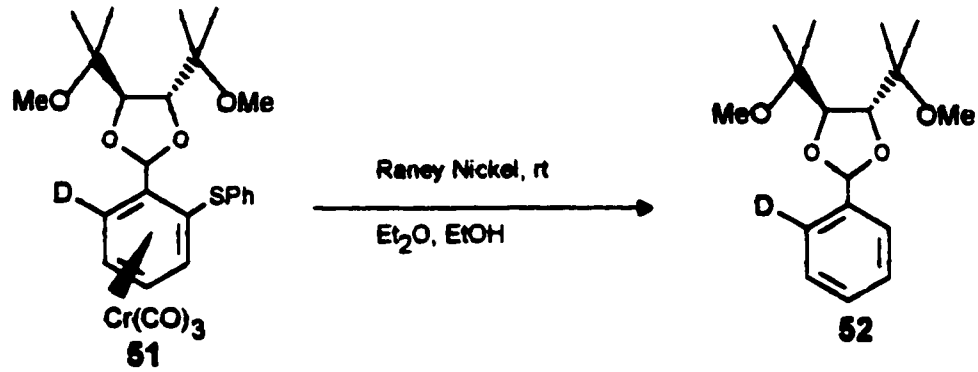


Scheme 23

Deuterium was incorporated in the *ortho'* position to an 86% extent as determined by ^{1}H NMR integration.(**Scheme 24**) This regiochemical assignment was based on examination of the aromatic region of the ^{1}H NMR spectrum. That the complex was mono-deuterated, was determined by the disappearance of the double at δ 5.83 which integrated to 1H in the unsubstituted thiophenyl complex **45**. To determine which proton was abstracted, the deutero-substituted thiophenyl complex **48** was subjected to Raney-Nickel desulfurization. This process resulted in both the removal of the thiophenyl group and the $Cr(CO)_3$ group to afford (**49**) (**Scheme 25**).

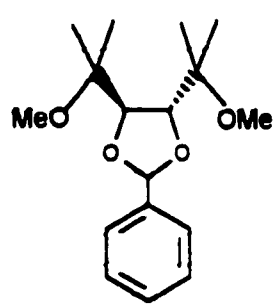


Scheme 24



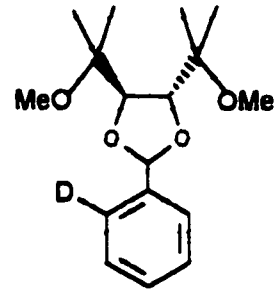
Scheme 25

The aromatic region of the ^{1}H NMR spectrum of **49** was compared to that of its non-deuterated counterpart **50**. The downfield signal (δ 7.5-7.45) integrated to 1 proton whereas the upfield resonance (δ 7.40-7.32) integrated to 3 protons. This indicated that the deuterium was incorporated at the *ortho'* position (**Figure 4**). Also, if the deuterium had been incorporated in the meta position, next to the thiophenyl substituent, the desulfurized complex would exhibit a different splitting pattern in the aromatic region.(**Figure 5**). Homodecoupling confirmed that the deuterium was incorporated in the *ortho'* position.



50

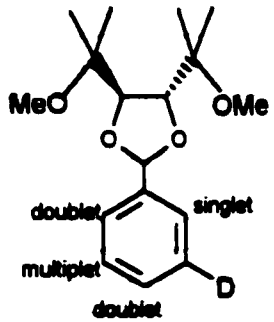
ortho protons integrate to 2H
meta and para protons integrate to 3H



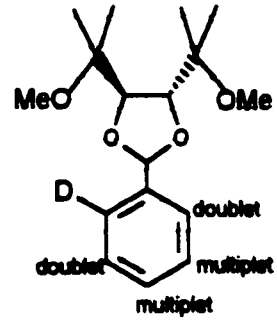
49

ortho protons integrate to 1H
meta and para protons integrate to 3H

Figure 4: Determination of Regioselectivity of Deprotonation



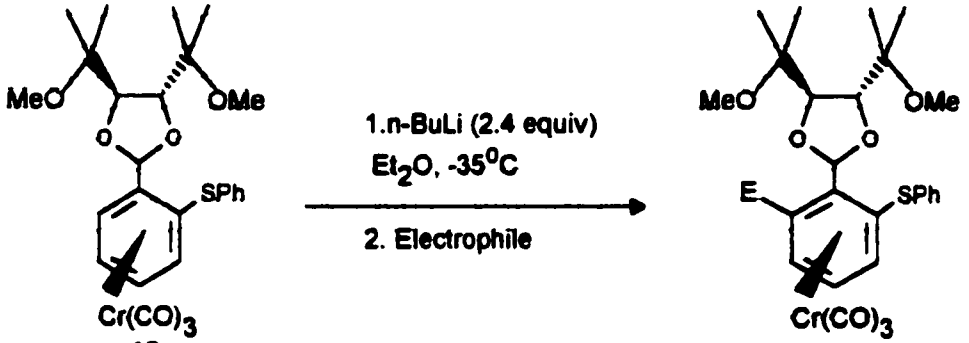
50



49

Figure 5: Multiplicity in Aromatic Resonances of *o* & *m*-Deuterated Compouds

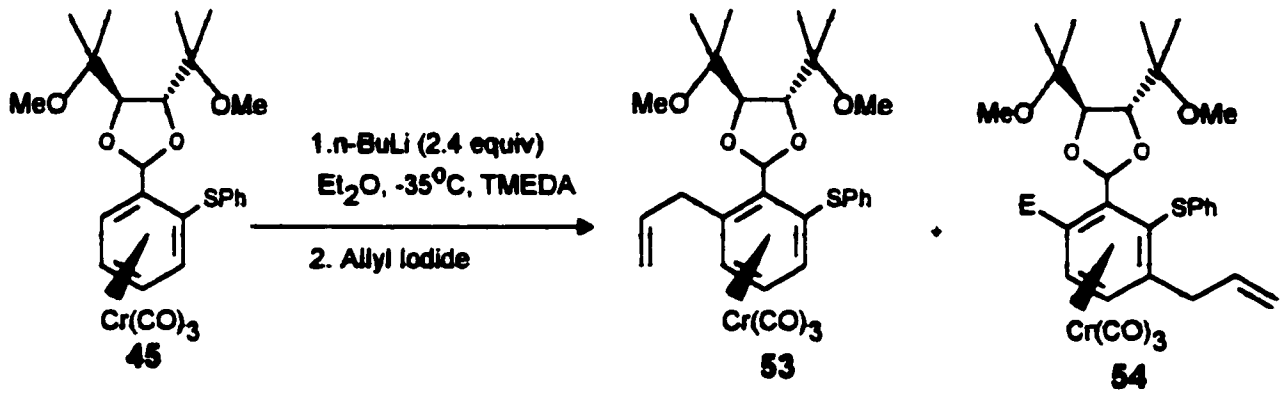
The *ortho'* lithioarene was successfully reacted with allyl iodide, N-methylformanilide and dibromotetrafluoroethane to give the compounds depicted below (**Scheme 26**).



Electrophile	E (% yield)
Dibromotetrafluoroethane	Br (77%) (**51**)
N-methylformanilide	CHO (61%) (**52**)
Allyl Iodide	Allyl (32%) (**53**)

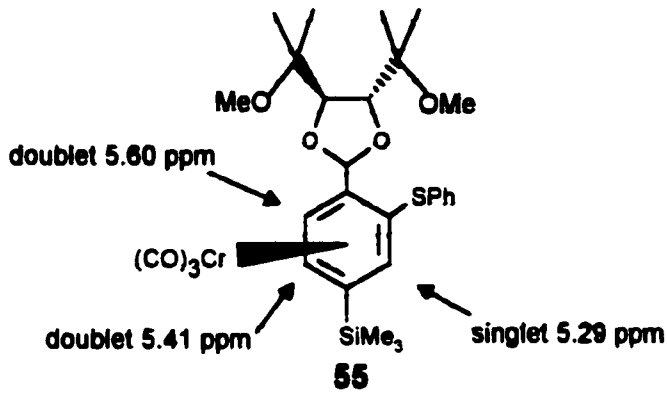
Scheme 26

Carrying out the lithiation in Et_2O in the presence of TMEDA, followed by reaction of the lithioarene with allyl iodide, afforded a 1:1 mixture of *ortho'* (**53**) and *meta* (**54**) allyl substituted thiophenyl complexes (**Scheme 27**).



Scheme 27

Somewhat surprising results were obtained with the use of trimethylsilyl chloride as an electrophile. Lithiation of the thiophenyl compound followed by the reaction of he lithiated arene with trimethylsilyl chloride led to the formation of primarily the *para* TMS derivative **55** (**Figure 6**) In other words, the thiophenyl group acted as a *meta*-director for lithiation of the aromatic ring. *Meta* direction of lithiation is quite uncommon for metallation directing groups, having been observed in very few cases for arenechromium tricarbonyl complexes. Widdowson observed *meta*-direction of lithiation by the triisopropyl ether group[40]. Fukui used the N-methyl-N TBDMS group to cause lithiation at the *meta* site[41]. Assignment of the *para* trimethylsilyl regioisomer was based on the singlet at δ 5.29 representing the *meta* proton and the doublets at δ 5.41 and δ 5.60 representing the *meta'* and *ortho'* protons respectively.



55

Figure 6: *p*-TMS Thiophenyl Complex 55

Incorporation of other electrophiles was attempted but in the remaining cases, the ^1H NMR spectrum of the crude reaction material showed multiple products. For most of the cases, this was determined by the abundance of peaks in the acetal region (δ 6). The unsuccessful electrophiles included CO_2, Bu_3SnCl, Ph_2PCl, diphenyl disulfide, diethylcarbamoyl chloride and iodomethane.

Lithiation of the thiophenyl complex in THF at –35°C leads to the formation of a dilithioarene species which, upon reacting with dibromotetrafluoroethane, led to the formation of the *m, o'*-dibrominated compound **56** (**Figure 7**). The assignment of the regioisomer was based on the disappearance of the aromatic resonances furthest upfield (δ 5.8) and furthest downfield (δ 5.1) representing the *meta'* and *para* protons respectively. The remaining peaks from the aromatic region simplified to two doublets with coupling constants of 6.7 Hz, indicating an *ortho* orientation. Mass Spectrometry verified that there were two bromine atoms added to the ring, by giving an M-3(CO) peak at 610.

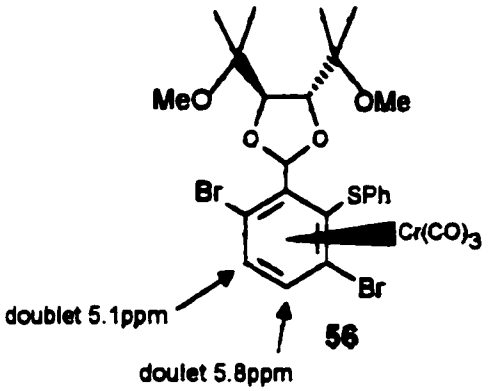


Figure 7: *m,o'*-Dibrominated Thiophenyl Complex 49

Although the lithiation conditions examined for the thiophenyl complex did not give the expected regioisomeric outcome, a route was developed by which it is possible to functionalize the chiral acetal by replacement of he pro-*S* proton. Green *et al* have developed lithiation conditions that result in the replacement of the pro-*R* proton and the work in this chapter provides a complementary route through which the "opposite" regioisomer may be obtained (after desulfurization) (**Figure 8**).

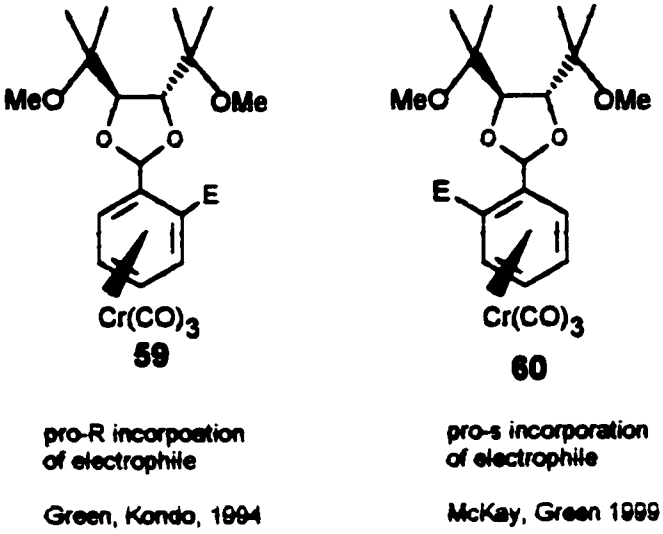
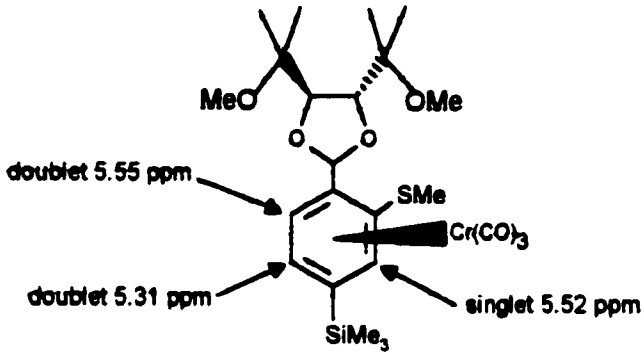


Figure 8: Formation of Both the Ortho and Ortho' Derivatives

For the attempted lithiation of the *ortho*-thiomethyl complex **46** in Et_2O the thiomethyl ether was not effective as a DOM group. Even with the use of CH_3OD as an electrophile, a negligible amount of deuterium was incorporated anywhere on the ring. incorporated *ortho* to the thiomethyl group. This was apparent as the relative integrals of the acetal proton and the *meta* proton did not change appreciably after the attempted reaction. It was only apparent from the mass spectrum that the deuterium was incorporated into the molecule.

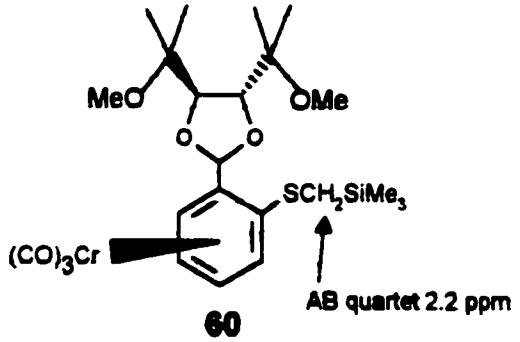
For the reaction between the lithiated thiomethyl compound and Me_3SiCl, several inseparable compounds were formed, although there was ^1H NMR evidence for the predominant formation of two compounds. In the aromatic region, there were doublets observed at δ 5.55 and δ 5.30 as well as a singlet at δ 5.52. It is reasonable to assign these signals to the protons of the *para* TMS compound **59** (**Figure 9**). This is another example of a thioether acting as a *meta* directing group.



59

Figure 9: *p*-TMS Thiomethyl Complex 59

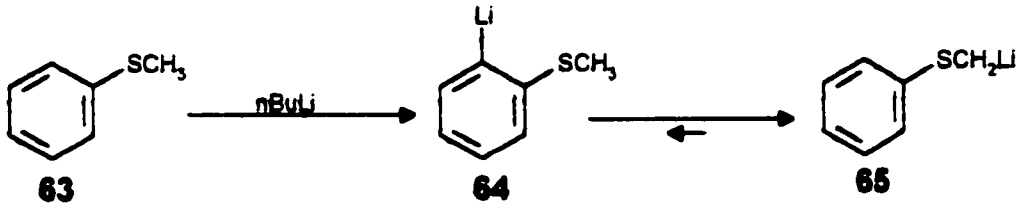
Another feature of the crude ^{1}H NMR spectrum that proved informative was the disappearance of the singlet at δ 2.44 from the thiomethyl ether group. In its place was (among other peaks) was an AB quartet at δ 2.10 and δ 2.20. It is reasonable to attribute this signal to the product derived from the incorporation of the trimethylsilyl group on the thiomethyl substituent as a result of lithiation of the thiomethyl group **60**. **(Figure 10)**.



60

Figure 10: Lithiation of Thiomethyl Methyl Group

The lithiation of the thiomethyl methyl group was not completely unexpected. Although the thiomethethyl group is known to direct deprotonation initially to the *ortho* site with lithium bases in the case of thioanisole, the ortho lithiated species quickly forms the methyl-metallated species[42] (**Scheme 28**). In the case of chromium tricarbonyl complexed aromatic compounds, the aromatic protons are much more acidic than those in non-complexed aromatic rings. It was anticipated that given the increased acidity of the aromatic protons, the equilibrium between the *ortho* lithiated (**62**) and the thiomethyl lithiated compound (**63**) would favour the *ortho* lithiated species rather than the thiomethyl lithiated species.



Scheme 28

With electrophiles including dibromotetrafluoroethane, N-methylformanilide and allyl iodide, ^{1}H NMR showed the presence of several inseparable products resulting from the lithiation and subsequent quenching of the lithiated thiomethyl complex.

With an albeit limited number of electrophiles incorporated into the ring ,attention was turned to the desulfurization of the system. As a model, compound **45** was chosen for study. One of the most common desulfurization reagents, Lithium di-*tert*-butylbiphenylide (LiDBB)[44], is not compatible with the acetal function in **45**. As a result, the use of Raney Nickel[45], cobalt boride[46], nickel boride[46], $(Ph_3P)_2NiCl_2$-^{t}BuMgCl[47], Et_3SiH-Pd/C[48], and lithium naphthalenide[49] were tested. The results of this study are collected in **Table 2.**

Table 1: Desulfurization Trials

Desulfurization Technique	Comments
Raney Nickel	80% desulfurization, 1:1 A:B*
Et_3SiH, Pd-C	No reaction
Nickel Boride	80% desulfurization, 1:1 A:B*
Cobalt Boride	No reaction
LiDBB	Inseparable mixture
$(PPh_3)_2NiCl_2$, ^{t}BuMgCl	No reaction
$Mo(CO)_6$ on SiO_2	Slow decomplexation

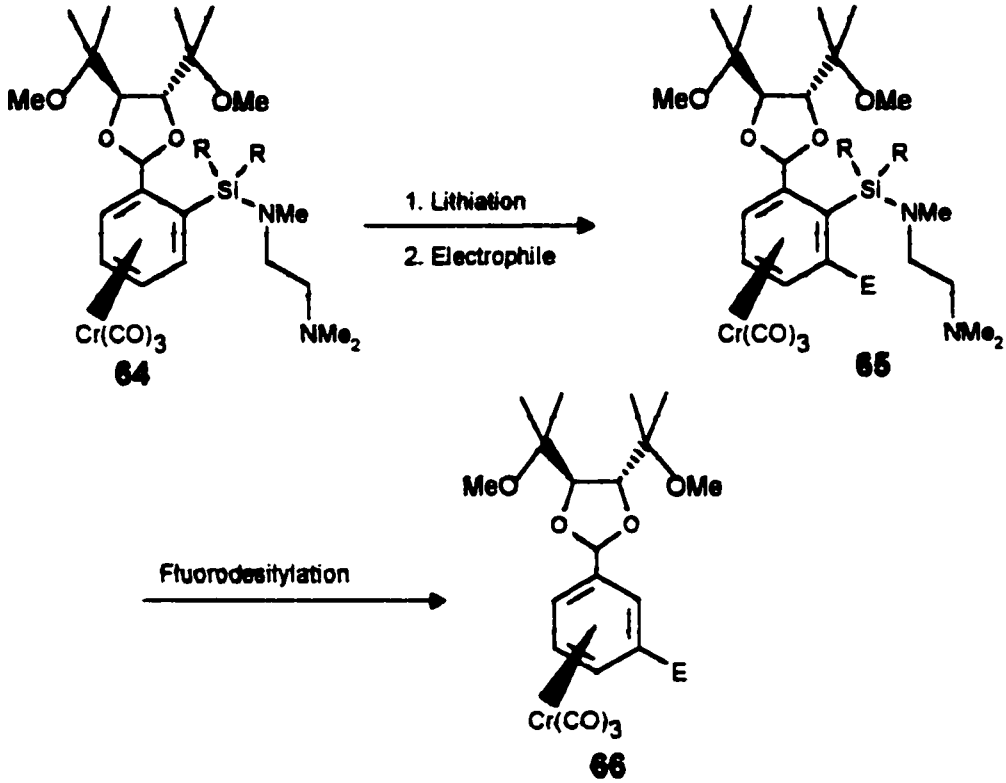
*A=desulfurized complex, B=decomplexed, desulfurized complex

The most successful of the reagents was Raney Nickel. With this reagent, it was possible to remove the phenylthio group. Unfortunately, decomplexation competed with this process; at 80% conversion, a 1:1 ratio of the aryl acetal complex **28** and decomplexed aryl acetal **53** resulted. Nickel boride (prepared *in situ* by the reaction of $NiCl_2$-$6H_2O$ with $NaBH_4$) also caused desulfurization of **45** in competition with

decomplexation to the same extent. The other methods gave either no reaction whatsoever (triethylsilane-Pd/C) or slow decomplexation without desulfurization (molybdenum carbonyl[50], $((PPh_3)_2NiCl_2$- ^tBuMgBr, cobalt boride, and Li naphthalenide).

With the failure of the attempts to cleanly remove the thiophenyl function from **45**, and with limited success of lithiation reactions of **45** and **46**, it was decided that it would not be profitable to attempt the desulfurization of the substituted thiophenyl complexes.

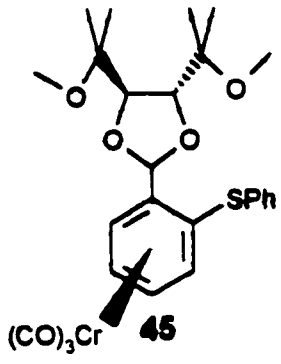
Attempts to further this research would involve the use of a more easily removable directed metallation group *ortho* to the acetal. Possible candidates for this role would silicon-based directing groups. It has been demonstrated that phenylsilanes containing the trimethylethylenediamino group exhibit a strong directing effect for specific ortho lithiation[51]. **(Scheme 29)** Sieburth *et al* have exploited the silanoate group as a metallation-directing group, albeit with considerable deprotonation of the alkyl groups on the silicon atom[52] . This problem should be alleviated somewhat in the case of chromium tricarbonyl complexes due to the greatly enhanced acidity of the ring protons. Silyl groups are readily removed by fluoride ion, including in the presence of (arene)tricarbonylchromium groups[53]. As such, these routes are promising for the synthesis of meta-substituted enantiomerically pure complexes **66**.


MeO
OMe
O
O
R
R
Si
NMe
Cr(CO)3
NMe2
64
1. Lithiation
2. Electrophile
E
65
Fluorodesilylation
66

Scheme 30

2.2 Experimental

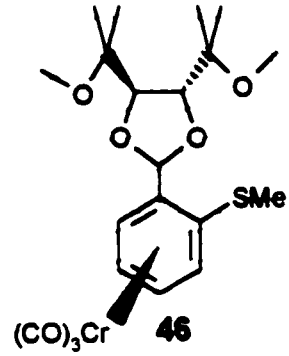
(1'*R*,2'*S*,4*R*,5*R*)-[4,5-Bis(1-methoxy-1-methylethyl)-2-(2'-phenylthio)phenyl)-1,3-dioxolane]tricarbonylchromium(0) (45)



Compound **28** (2.000 g, 4.647 mmol) was placed in an oven dried 250 mL two-necked round-bottom flask fitted with a gas adaptor and a septum. The flask was flushed with nitrogen and 80 mL of freshly distilled diethyl ether was added. The solution was cooled to -30°C and n-BuLi (5.06 mL, 2.21 M, 11.15 mmol, 2.4 equiv) was added over 1.5 h by the use of a syringe pump. The solution was allowed to stir for 3 h at -30°C and 80 mL of freshly distilled THF was added to the flask over 20 minutes. The solution was allowed to stir for 30 minutes and PhSSPh (2.435g, 11.2 mmol, 2.4 equiv) was added as a THF (10 mL) solution. The solution was kept at -30°C for 1 h, and 25 mL of H_2O was added subsequently. A standard aqueous work-up afforded a yellow solid. The solid was

purified by column chromatography on silica gel (eluent 5:1 petroleum ether:ethyl acetate) to provide the product as a yellow solid. Recrystallization from hexane afforded yellow needles (1.823g, 3.392 mmol, 73%) mp140-142°C, (Lit[24]142-143°C).

Preparation of (1'*R*,2'*S*,4*R*,5*R*)-[4,5-Bis(1-methoxy-1-methylethyl)-2-(2'-methylthio)phenyl)-1,3-dioxolane]tricarbonylchromium(0) (46)

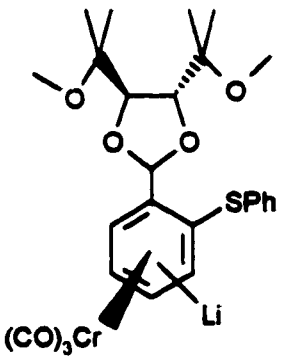


46

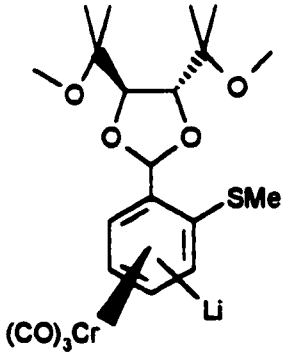
Compound 3 (1.500g, 3.485 mmol) was placed in an oven dried 250 mL two-necked round-bottom flask fitted with a gas adaptor and a septum. The flask was flushed with nitrogen and 50 mL of freshly distilled diethyl ether was added. The solution was cooled to -30°C and n-BuLi (3.78 mL, 2.21 M, 8.364 mmol, 2.4 equiv) was added over 1.5 h by the use of a syringe pump. The solution was allowed to stir for 3 h at -30°C and 80 mL of freshly distilled THF was added to the flask over 20 minutes. The solution was allowed to stir for 30 minutes and MeSSMe (0.614 mL, 0.520g, 8.364 mmol, 2.4 equiv) was added.

The solution was kept at -30°C for 1 h, and 25 mL of H_2O was added subsequently. A standard aqueous work-up afforded a yellow solid. The solid was purified by column chromatography on silica gel (eluent 5:1 petroleum ether:ethyl acetate) to provide the product as a yellow solid. Recrystallization from hexane afforded **46** as yellow needles (1.158g, 2.430 mmol, 69%) mp 104-5 °C (hexanes); IR (NaCl, neat) 3092, 1966, 1890 cm^{-1}; ^1H NMR δ 6.21 (s, 1H), 5.83 (d, 1H, J=6.4), 5.32 (d, 1H, J=3.0), 5.19 (m, 2H), 4.21 (d, 1H, J=2.88), 4.03 (d, 1H, J=2.90) 3.24 (s, 3H), 3.15 (s, 3H), 2.44 (s, 3H), 1.31 (s, 3H), 1.19 (s, 3H) 1.15 (s, 3H) 1.06 (s, 3H), ^{13}C NMR δ 232.2, 107.9, 100.8, 91.8, 90.7, 89.4, 82.9, 77.1, 75.4, 49.3, 22.1, 21.3, 20.7, 19.5, 17.9; MS m/e 476 (M^+); HRMS m/e calcd for $C_{21}H_{28}CrO_7S$ (M+) 476.5049, found 476.0958

Conditions for Lithiation of Thioether Complexes (45,46)



45-Li



46-Li

Method 1

To a solution of **45(or 46)** (0.100-0.120g) in freshly distilled Et_2O (10 mL) at -35°C was added n-BuLi (2.4 equiv) over a period of 1.5 h using a syringe pump. The solution was stirred at -35°C for 3 h. Following the addition of an electrophile (3 equiv) the solution was stirred for 1 h at –35°C and 5 mL of H_2O was added subsequently. A standard aqueous workup resulted in a and the residue diluted with brine and extracted with Et_2O. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure.

Method 2

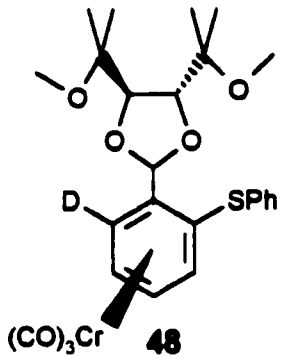
To a solution of **45(or 46)** (0.100-0.120g) in freshly distilled THF (10 mL) at -35°C was added n-BuLi (2.4 equiv) over a period of 1.5 h using a syringe pump. The solution was stirred at -35°C for 3 h. Following the addition of an electrophile (3 equiv) the solution was stirred for 1 h at –35°C and 5 mL of H_2O was added subsequently. A standard aqueous workup resulted in a and the residue diluted with brine and extracted with Et_2O. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure.

Method 3

To a solution of **45(or 46)** (0.100-0.120g) in freshly distilled Et_2O (10 mL) at -35°C was added TMEDA (3 equiv).n-BuLi (2.4 equiv) was added over a period of 1.5 h using a syringe pump. The solution was stirred at -35°C for 3 h. Following the addition of an electrophile (3 equiv) the solution was stirred for 1 h at –35°C and 5 mL of H_2O was added subsequently. A standard aqueous workup resulted in a and the residue diluted

with brine and extracted with Et_2O. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure.

(1'*R*,2'*S*,4*R*,5*R*)-[4,5-Bis(1-methoxy-1-methylethyl)-2-(6'-deuterio 2'-phenylthio)phenyl)-1,3-dioxolane]-tricarbonylchromium(0) (48)

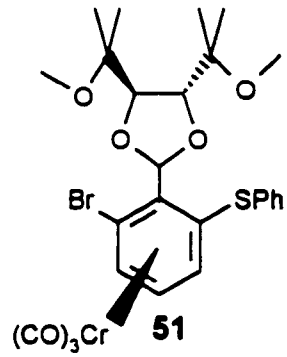


48

Addition of CH_3OD (0.03mL, 0.022g, 0.670 mmol, 3 equiv) to a solution of the lithiated phenylthio compound **45** (0.120g, 0.223 mmol), generated by Method 1, followed by a standard aqueous workup resulted in crude solid. Purification of this solid, by column chromatography (eluent 5:1 petroleum ether:ethyl acetate) followed by recrystallization from hexane afforded **48** yellow needles (0.103g ,0.191mmol, 86%) which was identified as . IR (KBr, neat) ν_{max} 1970, 1905, cm^{-1},1H NMR δ 7.50-7.3 (m, 2H), 7.26-7.37 (m, 3H), 6.43 (s, 1H), 5.19-5.28 (m, 2H), 5.13 (d, 1H, J=6.3), 4.22 (d, 1H, J=3.4), 4.06 (d, 1H, J=3.4), 3.26 (s, 3H), 3.19 (s, 3H), 1.32 (s, 3H), 1.15 (s, 3H),1.14 (s, 3H), 1.09

(s, 3H); ^{13}C NMR d 232.0, 133.6, 132.8, 130.3, 128.3, 108.1, 107.6, 100.8, 95.3, 91.8, 90.3, 89.9, 84.6, 82.9, 77.2, 75.5, 49.4, 22.2, 21.4, 20.9, 19.6; MS *m/e* 539 (M^+)

(1'*R*,2'*S*,4*R*,5*R*)-[4,5-Bis(1-methoxy-1-methylethyl)-2-(6'-bromo- 2'-phenylthio)phenyl)-1,3-dioxolane]-tricarbonylchromium(0) (51)

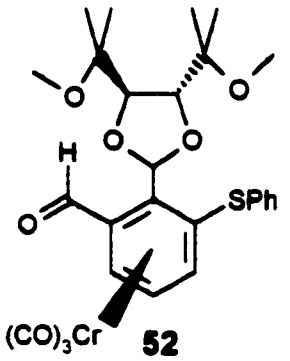


51

Subjecting 0.0324 g of starting material **45** to Method 1, with dibromotetrafluoroethane as the electrophile gave 0.0284 g (77%) of product **51.** $[\alpha]^{24}$ +218 (c 0.0055, Et_2O); IR (KBr, neat) ν_{max} 1975, 1909 cm^{-1} ; ^1H NMR δ 7.58 (m, 2H), 7.35 – 7.45 (m, 3H), 6.39 (s, 1H), 5.32 (d, 1H, J = 6.2,), 5.26 (apparent t, 1H, J = 6.4), 4.59 (d, 1H, J = 6.4,), 4.26 (d, 1H, J = 6.0), 4.05 (d, 1H, J = 6.0), 3.29 (s, 3H), 3.23 (s, 3H), 1.40 (s, 3H), 1.37 (s, 3H),

1.36 (s, 3H), 1.23 (s, 3H); ^{13}C NMR δ 231.0, 135.2, 131.2, 129.8, 129.6, 116.8, 102.3, 102.1, 97.5, 92.8, 91.9, 87.6, 83.1, 83.0, 75.5, 49.4, 49.0, 23.1, 21.9, 21.8, 20.6; MS m/e 618 and 616 (M^+), 534 and 532 (M^+-3CO); HRMS m/e for $C_{26}H_{29}Br^{79}CrO_7S$ calcd (M^+) 616.0222 found 616.0244.

(1'*R*,2'*S*,4*R*,5*R*)-[4,5-Bis(1-methoxy-1-methylethyl)-2-(6'-formyl-2'-phenylthio)phenyl)-1,3-dioxolane]-tricarbonylchromium(0) (52)

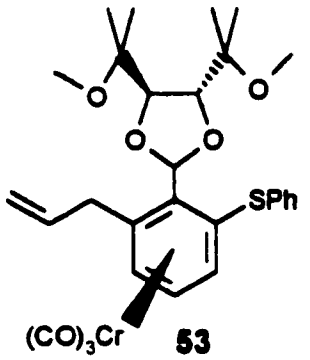


52

Subjecting 0.0302 g of starting material **45** to Method 1, with N-methylformanilide as the electrophile, gave 0.0193 g of product **52** (61%) and 0.0058 g of starting material **45** (19%). $[\alpha]^{23}$ –34 (c 0.0011, Et_2O); IR (KBr, neat) ν_{max} 2872, 2832, 1983, 1920, 1680 cm^{-1}; ^{1}H NMR δ 10.59 (s, 1H), 7.57 (m, 2H), 7.30-7.42 (m, 3H), 6.82 (s, 1H), 5.97 (d, 1H, J = 6.5), 5.41 (dd, 1H, J = 1.1, 6.5,), 5.24 (apparent t, 1H, J = 6.5), 4.22 (d, 1H, J = 4.4), 4.11 (d, 1H, J = 4.4), 3.28 (s, 3H), 3.16 (s, 3H), 1.38 (s, 3H), 1.22 (s, 3H), 1.16 (s, 3H), 1.13 (s, 3H)); ^{13}C NMR δ 229.9, 191.6, 133.4, 133.0, 129.5, 128.7, 107.8, 106.7, 102.9,

96.9, 96.8, 91.3, 89.0, 84.5, 83.2, 74.9, 49.3, 49.0, 22.4, 22.1, 20.8, 20.6; MS *m/e* 566 (M^+), 482 (M^+ - 3CO); HRMS *m/e* for $C_{27}H_{30}CrO_8S$ calcd (M^+) 566.1066, found 566.1069.

(1'*R*,2'*S*,4*R*,5*R*)-[4,5-Bis(1-methoxy-1-methylethyl)-2-(6'-allyl-2'-phenylthio)phenyl)-1,3-dioxolane]-tricarbonylchromium(0) (53)



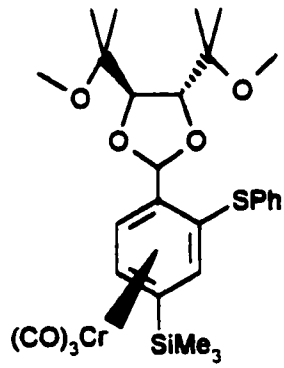
53

Subjecting 0.0336 g of starting material to Method 1, with allyl bromide as the electrophile, gave 0.0114 g of product **53** (32%) and 0.0151 g of recovered starting material **45** (45%).

$[\alpha]^{24}$ +34 (c 0.0021, Et_2O); IR (KBr, neat) ν_{max} 1968, 1898, 1638 cm^{-1}; δ 7.52 (dd, 2H, J = 1.4, 7.9), 7.30-7.40 (m, 3H), 6.56 (s, 1H), 5.96 (m, 1H), 5.32 (apparent t, 1H, J = 6.5), 5.13 (d, 1H, J = 16.9), 5.12 (d, 1H, J = 11), 5.04 (d, 1H, J = 6.0), 4.91 (d, 1H, J = 6.6),

4.18 (d, 1H, J = 5.5), 3.99 (d, 1H, J = 5.5), 3.86 (dd, 1H, J = 6.6, 15.8,), 3.54 (dd, 1H, J = 7.6, 15.8), 3.28 (s, 3H), 3.20 (s, 3H), 1.38 (s, 3H), 1.26 (s, 3H), 1.223 (s, 3H), 1.216 (s, 3H); ^{13}C NMR δ 232.2, 136.7, 133.5, 129.5, 128.7, 117.2, 112.6, 105.3, 103.2, 101.3, 93.1, 91.7, 90.8, 83.8, 82.3, 75.03, 74.95, 49.3, 49.1, 34.8, 22.8, 22.4, 21.4, 20.7.; MS *m/e* 578 (M^+), 494 (M^+ - 3CO); HRMS *m/e* for $C_{29}H_{34}CrO_7S$ calcd (M^+) 578.1430, found 578.1422.

(1'*R*,2'*S*,4*R*,5*R*)-[4,5-Bis(1-methoxy-1-methylethyl)-2-(2'-phenylthio-4'-trimethylsilyl)phenyl)-1,3-dioxolane]-tricarbonylchromium(0) (55)

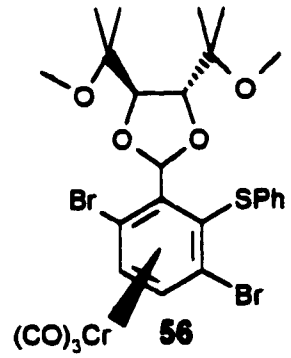


55

Addition of TMSCl (0.071 mL, 0.089g, 0.819 mmol, 3 equiv)to a solution of the lithiated phenylthio compound **45** (0.110g, 0.204 mmol) generated by Method 1, followed by a standard aqueous workup resulted in crude yellow oil. Preparative TLC (eluent 5:1 petroleum ether:ethyl acetate) afforded a yellow oil which contained a mixture of products which proved to be was identified.non-separable. The following

spectral data suggested the presence of the *para* (**55**) isomer. Relevant ^{1}H NMR resonances in the aromatic region include d 5.60 (d, 1H, J=6), 5.41 (d, 1H, J=6), 5.29 (s, 1H).

(1'*R*,2'*S*,4*R*,5*R*)-[4,5-Bis(1-methoxy-1-methylethyl)-2-(3',6'-dibromo 2'-phenylthio)phenyl)-1,3-dioxolane]-tricarbonylchromium(0) (56)



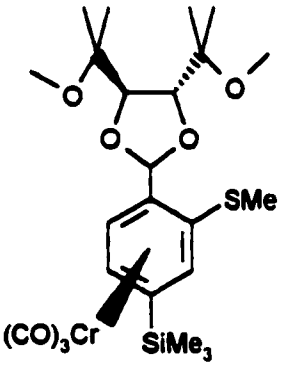
56

Addition of $BrCF_2CF_2Br$ (0.133 mL, 0.290g, 1.116 mmol, 3 equiv)to a solution of the lithiated phenylthio compound **45** generated by method 3 (0.200g, 0.372 mmol) followed by a standard aqueous workup resulted in crude yellow oil. Preparative TLC (eluent 5:1 petroleum ether:ethyl acetate) afforded a yellow oil (0.103g ,0.151 mmol, 41%) which was identified spectroscopically as the dibromo compound **56**. IR (KBr, neat) ν_{max} 1970, 1905, cm^{-1},1H NMR δ 7.34 (d, 2H, J=8.3), 7.25-7.17 (m, 3H), 6.75 (s, 1H), 5.68 (d, 2H, J=6.7), 5.62 (d, 1H, J=6.7), 4.08 (d, 1H, J=3.8), 3.88 (d, 1H, J=3.8), 3.24 (s, 3H), 3.14 (s, 3H), 1.37 (s, 3H), 1.21 (s, 3H),1.15 (s, 3H), 1.12 (s, 3H); MS m/e 610 (M^+-3CO)

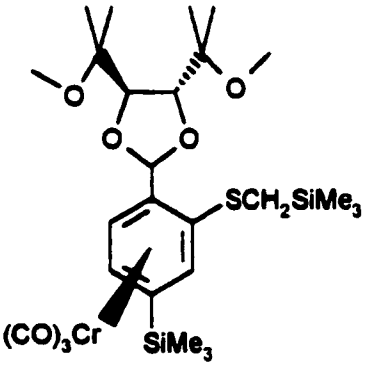
(1'*R*,2'*S*,4*R*,5*R*)-[4,5-Bis(1-methoxy-1-methylethyl)-2-(2'-methylthio-4'-trimethylsilyl)phenyl)-1,3-dioxolane]-tricarbonylchromium(0) (59)

Preparation of (1'*R*,2'*S*,4*R*,5*R*)-[4,5-Bis(1-methoxy-1-methylethyl)-2-(2'-trimethylsilylmethylthio)phenyl)-1,3-dioxolane]tricarbonylchromium(0) (60)

Addition of Me_3SiCl (0.026mL, 0.022g, 0.670 mmol, 3 equiv)to a solution of the lithiated methylthio compound **46** (0.120g, 0.223 mmol) followed by a standard aqueous workup resulted in crude yellow oil.(mixture of p-TMS **59** and methylthiomethyl TMS **60**). The following spectral data suggest the presence of **59**. Relevant 1H NMR peaks in the aromatic region include δ 5.55 (d, 1H, J=6), 5.52 (s, 1H), 5.31 (d, 1H, J=6). Indicative of the presence of **60**, is an AB quartet at δ 2.21 and δ 2.20.



59



60

Desulfurization Trials

Triethylsilane reduction of 45

Phenylthio complex **45** (0.0684g, 0.144mmol) and 5% Pd/C (0.0278g, 7.18×10^{-6} mol, 5 mol %) were weighed into a 50 mL round bottomed flask fitted with a septum and a gas adaptor. The flask was flushed with argon and then 10 mL of freshly distilled CH_2Cl_2 was added to the flask. Et_3SiH was added to the flask and the reaction was allowed to proceed for 12 h. A standard aqueous workup produced a yellow oil which was identified as the starting phenylthio complex **45**. No reduction had taken place.

Molybdenum Carbonyl Reduction of 45

$Mo(CO)_6$ (0.250g, 0.95 mmol) and silica gel (0.057g, 0.95mmol) were placed in a 50 mL round bottomed flask fitted with a gas adaptor and a septum. The flask was flushed with nitrogen and then heated for 90 min at 110-125°C. The flask was allowed to cool to ambient temperature and the phenylthio ether **45** (0.060g, 0.111mmol) was added as a THF solution. The reaction mixture was allowed to stir for 12 h then the reaction mixture was filtered through Celite®. A standard aqueous workup resulted in a yellow oil which was shown to contain primarily starting material **45** and a trace of its decomplexed analogue .

Raney Nickel Reduction of Phenylthio Compound 45

Raney® Nickel (0.400g, 50% suspension in H_2O) was placed in a 50 mL round bottomed flask fitted with a gas adaptor and septum. The flask was flushed with nitrogen and then 8mL of EtOH and was added. The phenylthio ether **45** (0.040g, 0.0743mmol) was added to the flask as an Et_2O solution. The reaction was allowed to proceed for 12 h. The reaction mixture was filtered through Celite® and after a standard aqueous work-up a yellow oil was obtained. ^1H NMR spectrum of the crude product showed 80 % desulfurization of the thioether **45** to yield a 1:1 mixture of the chiral acetal **28** and its decomplexed analogue **53**, which were separated by chromatography on silica gel using petroleum ether: ethyl acetate (5:1) as eluent..

Nickel Boride Reduction of 45

Phenylthio complex **45** (0.057g, 0.11 mmol) and $NiCl_2(H_2O)_6$ (0.176g, 0.738 mmol, 7 equiv) were placed in a round bottomed flask fitted with a septum and a gas adaptor. The flask was flushed with nitrogen and then 10mL of a 3:1 MeOH:THF mixture were added to the flask. The flask was cooled to 0°C and under positive nitrogen pressure, $NaBH_4$ (0.084g, 2.2 mmol, 21 equiv) was added to the flask in four portions. The reaction was allowed to proceed for 12 h at 0°C at which time the contents of the flask were filtered through Celite® and subjected to a standard aqueous workup which gave a viscous yellow oil. This product was examined by ^1H NMR and determined to contain a 1:1 ratio of the

desulfurized chiral acetal **28** and the decomplexed chiral acetal **53**, which were separated by chromatography on silica gel using petroleum ether:ethyl acetate (5:1) as eluent,

Cobalt Boride method of Desulfurization of 45

Phenylthio complex **45** (0.057 g, 0.11 mmol) and $CoCl_2(H_2O)_6$ (0.176 g, 0.739mmol, 7 equiv) were placed in a round bottomed flask fitted with a septum and a gas adaptor. The flask was flushed with nitrogen and then 10mL of a 3:1 MeOH:THF mixture were added to the flask. The flask was cooled to 0°C and under positive nitrogen pressure, $NaBH_4$ (0.084g, 2.2 mmol, 21 equiv) was added to the flask in four portions. The reaction was allowed to proceed for 12 h at 0°C at which time the contents of the flask were filtered through Celite® and subjected to a standard aqueous workup which gave a viscous yellow oil. The oil was identified as **45** by NMR spectroscopy.

$(PPh_3)_2Ni_2Cl_2$ + 2-bromomagnesiobutane mediated Desulfurization of 45

$(Ph_3P)_2NiCl_2$ (0.098 g, 0.150 mmol) was placed in a 2-necked 50mL round bottomed flask fitted with a septum and a reflux condenser. THF (10mL), 2-bromomagnesiobutane (2.34 mL, 0.300 mmol, 2 equiv), and **45** (0.080 g, 0.149 mmol) in THF (2 mL) were added to the flask. The solution was allowed to reflux for 6 h. After filtration, a standard aqueous work-up afforded a yellow residue that was identified as **45** by ^1H NMR spectroscopy.

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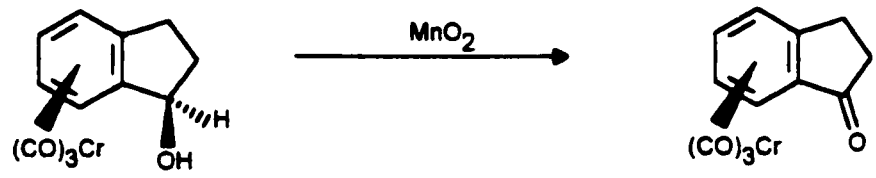
Chapter 3

Oxidation of Benzylic and non-Benzylic Alcohols

3.1 Introduction

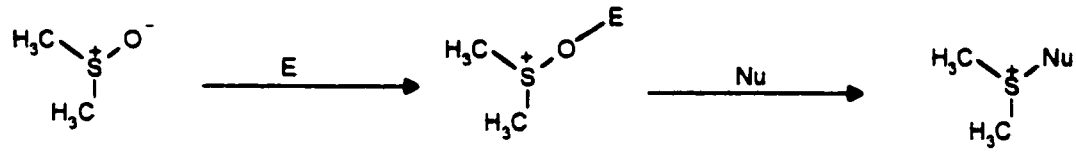
Oxidations of chromium tricarbonyl complexes of non-benzylic alcohols is a synthetic goal that has not yet been achieved. The more reactive benzylic alcohols have been oxidized by MnO_2[1], and by acetic anhydride-DMSO[2] conditions. Jaouen *et al* were able to successfully oxidize the chromium complexes of indanols and tetrolols to the corresponding indanones and tetralones using MnO_2 in good yields (70%) (Scheme 1). An important requirement for these reactions is not only the transformation of the hydroxyl group to the corresponding carbonyl compound, but also to avoid decomplexation.



1 **2**

Scheme 1

Levine *et al* were able to improve the yields of these reactions by using a mixture of acetic anhydride and DMSO. This reagent is a member of the class of reagents referred to as 'activated DMSO' reagents[3]. The nature of this activation stems from the electrophilic attack of the oxygen of the DMSO, which renders subsequent nucleophilic attack on the sulfur atom by an alcohol more facile (**Scheme 2**).

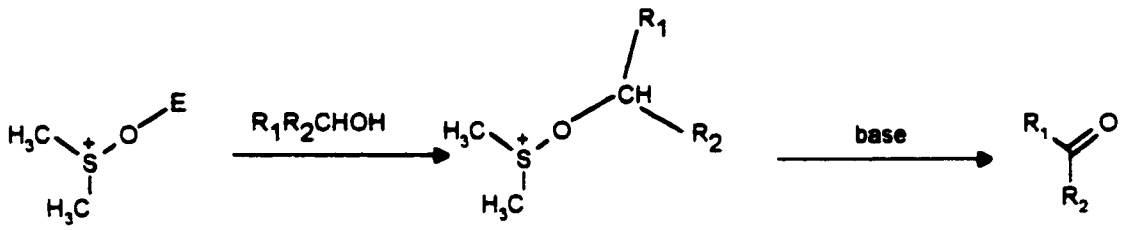


3 **4** **5**

Scheme 2

Reagents which are capable of activating DMSO in this manner include trifluoroacetic anhydride, thionyl chloride, oxalyl chloride, ^{t}butyl hypochlorite, chlorine-

acetic anhydride, acetyl chloride, benzoyl methanesulfonyl and toluenesulfonyl chlorides, carbonochloridates, sulfur trioxide/ pyridine, trifluoromethanesulfonic acid, bromine, ethoxyacetylene and diphenylketen-N-p-tolylimine[3]. Aside from the aforementioned, alcohols, phenols, enols, amines and oxides are possible nucleophiles. A general pathway for the oxidation of an alcohol by activated DMSO reagents is given in **Scheme 3**.

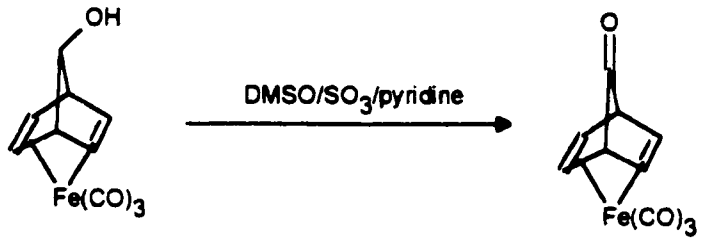


6 **7** **8**

Scheme 3

Typical oxidizing agents such as the Jones reagent ($CrO_3/H_2SO_4/H_2O$/acetone) or the Swern reagent (DMSO/oxalyl chloride/triethylamine) cause removal of the chromium tricarbonyl fragment from the chromium complex; therefore it was deemed useful to develop a technique to oxidize non-benzylic alcohols that would leave the chromium tricarbonyl fragment attached to the aromatic ring. It is thought that the failure of the conventional Swern oxidation conditions is attributable to the presence of chloride ions, either as Bronsted or Lewis acid, which cause rapid decomplexation of (arene)tricarbonylchromium complexes[4].

DMSO/SO_3/pyridine has been used successfully to oxidize tricarbonyl (7-norbornadienol)iron to tricarbonyl (7-norbornadienone)iron without decomplexation. (**Scheme 4**). The success of this reagent indicated that it might also work on other metal carbonyl complexes. Additionally, DMSO/TFAA (trifluoroacetic anhydride) is a halide-free oxidant that has demonstrated effectiveness for many oxidations at low temperatures. Thus, these two reagent systems were chosen for study in the oxidations of (hydroxyarene)tricarbonylchromium complexes.



9 **10**

Scheme 4

3.2 Results and Discussion

In order to examine the effectiveness of the two reagent systems, several non-benzylic (hydroxyarene)tricarbonyl chromium complexes were prepared, as well as a diol which would illustrate the competitive reactivity of the benzylic and non-benzylic sites. Therefore, the alcohols in Figure 1 were prepared in the yields shown. The experiments involved in this project were a collaborative effort between Dr. Jim Green (experiments on chloride ion effects and reagent stoichiometry optimizations), Michael Siwek (compounds **15-18**) and this author (compounds **11-14**), with all of the results presented here. The complexes were prepared in good yields, by the method described in the Experimental section, and were readily purified by column chromatography.

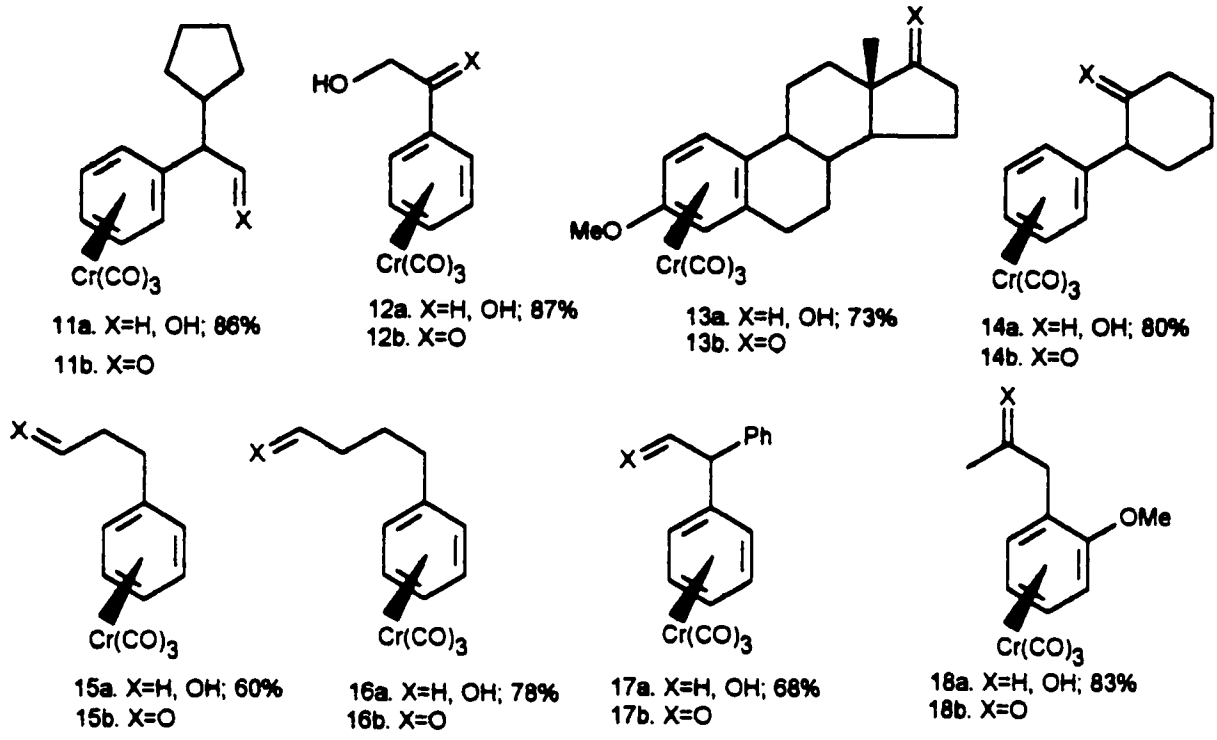


Figure 1: Oxidation Substrates and products

The DMSO/SO_3/pyridine oxidations were performed by adding the substrate to the reagent at 0 °C, followed by warming to room temperature for 30 min. Using these conditions, it was found that 5 equivalents of reagent were necessary to give complete oxidation. The DMSO/TFAA reagent is not stable above -30 °C thus; the preparation of this reagent and the oxidations were performed at -78 °C. With this reagent, 2.5 equivalents gave optimal results for the oxidations while using greater than three equivalents lead to significant decomplexation.

The results for the oxidations of the alcohols **11a-18a**, by both reagents, are given in **Table 1**. In all cases, respectable amounts of the corresponding carbonyl compound, whether ketone or aldehyde, were observed. The efficiency with which the two reagents carried out the oxidations was generally the same, except for the diol **12a**, which was oxidized much more selectively with the SO_3/ pyridine reagent. Both reagents oxidized the benzylic site preferentially to give the corresponding ketone.

There were two side products which accompanied these oxidations, one being the formation of the methythiomethyl ether and the other being the decomplexed arene. The decomplexation occurred in only trace amounts when either reagent was used properly, but became substantial (ca. 20%) with DMSO/TFAA if the stoichiometry of this reagent system was not carefully controlled. The methylthiomethyl ethers accounted for <10% of the crude reaction product in the oxidations of the primary alcohols **11a** and **12a** as indicated by the ^{1}H NMR spectra (singlet at ~4.6 ppm).

Table 1: Oxidation Results

Entry	*Alcohol*	*Product*	*Yield (%) TFAA*	*Yield (%) SO_3/pyridine*
1	**11a**	**11b**	75	72
2	**12a**	**12b**	61	85
3**	**13a**	**13b**	61	61
4	**14a**	**14b**	64	60
5*	**15a**	**15b**	80	75
6*	**16a**	**16b**	73	76
7*	**17a**	**17b**	72	71
8*	**18a**	**18b**	80	81

*Theses entries represent compounds examined by M.J. Siwek
**Joint effort by M.K. M^{c}Kay and M.J. Siwek

In an attempt to illustrate the effect of halide ion on decomplexation, various sources of halide ion (LiI, $ZnCl_2$, $SnCl_2$) were added (equimolar to the oxidizing reagent) to each reagent mixture, prior to the addition of the alcohol **11a**, and the oxidation reactions conducted in the usual manner. For the reactions involving DMSO/SO_3/pyridine, the extent of decomplexation was about one third, while for the reagent DMSO/TFAA, the extent was roughly one half. The extent of the decomplexation was determined by

integration of the complexed and uncomplexed aromatic regions. It is therefore evident that the presence of halide ion is a source of decomplexation, although the exact mechanism has not been elucidated.

Two reagents have been found to successfully oxidize both benzylic and non-benzylic (hydroxyarene)tricarbonylchromium complexes, with structural variety, in respectable yields. Side reactions such as decomplexation or methylthiomethyl ether formation can be kept to a minimal level.

3.3 Experimental

Melting points were measured with a Thomas Hoover capillary melting point apparatus and are uncorrected. ^{1}H HMR spectra and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker AC-300 spectrometer operated at 300 MHz and 75 MHz respectively. *J* values are given in Hertz. Infrared spectra were recorded on Nicolet 5DX FT-IR and Bomem Michelson 100 spectrometers, using neat films on NaCl or KBr plates. Elemental analyses were performed by M-H-W Laboratories, Phoenix AZ. Mass spectra were recorded on a Kratos Profile mass spectrometer.

The experimental results presented here represents only the compounds that were prepared for this thesis.

The general complexation methods for this section are identical to those of Chapter 1.

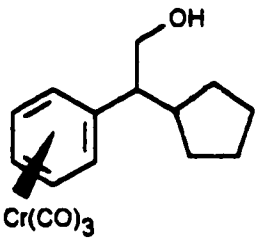
General Procedure DMSO-TFAA Oxidations (Method 1)

To a solution of DMSO (0.14 mL, 3 equiv.) in CH_2Cl_2 at -78°C under nitrogen was added trifluoroacetic anhydride (0.24 mL, 2.5 equiv) over a period of 1 min. The solution was stirred for 5 min. at -78°C and a solution of **11a** (0.221g, 0.677mmol) in CH_2Cl_2 (1mL) was added over a 2 min period. After stirring the reaction for 30 min., NEt_3 (0.5 mL) was added and the solution was allowed to warm to room temperature. Water was added and the mixture was extracted several times with CH_2Cl_2. The combined CH_2Cl_2 layers were dried over $MgSO_4$ and concentrated under reduced pressure. Preparative TLC (1:1 petroleum ether: ethyl acetate) afforded **11b** (0.165g 75% yield).

General Procedure DMSO/SO_3 Oxidations (Method 2)

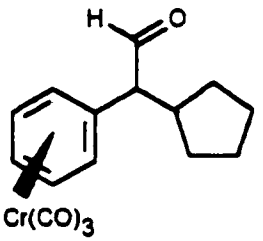
To a vigorously stirred solution of **11a** (0.128g, 0.394mmol) in DMSO (2 mL) and NEt_3 (0.27 ml, 5 equiv) under nitrogen at 0°C was added a solution of SO_3-pyridine (0.314 ml, 5equiv) in DMSO (2mL) over a period of 5 min. The reaction mixture was allowed to stir for 30 min, at which time water was added and the mixture was subjected to a work-up identical to that for the DMSO-TFAA procedure. Preparative TLC (1:1 petroleum ether: ethyl acetate) afforded **11b** (0.096g, 72% yield).

[(1-Cyclopentyl-2-hydroxyethyl)benzene]tricarbonylchromium (0) (11a)



Prepared in 86% yield by standard literature procedure [5]. oil; IR (NaCl) ν_{max} 3415 (br), 1968, 1961, 1881 cm^{-1}; ^1H NMR δ 5.72 (d, 1H, J=6.8), 5.44 (apparent t, 1H, J=6.3), 5.35 (d, 1H, J=6.5), 5.23 (m, 2H), 3.92 (m, 2H), 1.1 - 2.2 (m, 11H); ^{13}C NMR δ 233.5, 115.3, 97.4, 95.0, 94.6, 91.1, 90.6, 66.1, 50.9, 43.4, 31.6, 31.4, 25.0, 24.9; HRMS m/e calculated for $C_{16}H_{18}CrO_4$ (M+) 326.0610, found 326.0603.

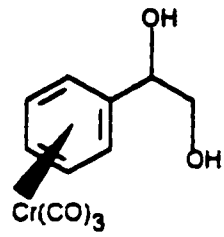
[(1-Cyclopentyl-2-oxoethyl)benzene]tricarbonylchromium (0) (11b)



Prepared from **11a** in 75% yield by Method 1 and 72 % yield by Method 2

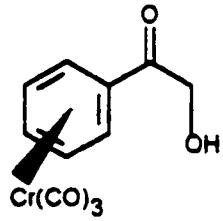
oil; IR (NaCl) ν_{max} 1966, 1877, 1722 cm^{-1}; ^1H NMR δ 9.70 (d, 1H, J=1.7), 5.45 (m, 1H), 5.24 (m, 4H), 3.01 (d, 1H, J=9.8), 2.29 (m, 2H), 1.92 (m, 1H), 1.1-1.7 (m, 6H) ; ^{13}C NMR δ 232.4, 196.8, 102.7, 96.1, 93.9, 93.6, 91.4, 91.0, 60.6, 42.4, 31.2, 30.9, 25.1, 24.7; MS m/e 324 (M^+), 240 (M^+ - 3CO); HRMS m/e calculated for $C_{16}H_{16}CrO_4$ (M^+) 324.0454, found 324.0449.

[(1,2-Dihydroxyethyl)benzene]tricarbonylchromium (0) (12a)



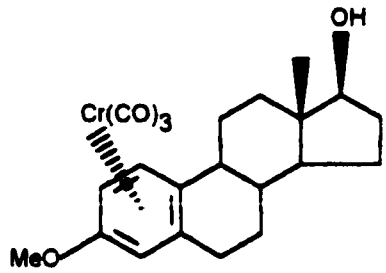
Prepared in 73% yield by the standard literature procedure[5].mp 84-86 °C (hexanes); ^{1}H NMR δ 5.59 (d, 1H, J=6.3), 5.2 - 5.43 (m, 4H), 4.49 (dd, 1H, J=7.0, 3.3), 3.82 (dd, 1H, J=11.3, 3.3), 3.66 (dd, 1H, J = 11.3, 7.0), 2.66 (br s, 1H), 2.28 (br s, 1H), ^{13}C NMR δ 232.6, 111.4, 92.5, 92.4, 92.3, 91.4, 90.1, 72.5, 67.6; MS m/e 274 (M^+); Anal. Calculated for $C_{11}H_{10}CrO_5$: C, 48.19; H, 3.67. Found 48.17; H, 3.67.

[2-Hydroxy-1-oxoethyl)benzene]tricarbonylchromium (0) (12b)



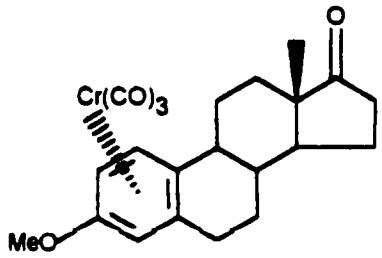
Prepared from **12a** in 61% yield by Method 1 and 85 % yield by Method 2 mp 74 - 76°C (hexanes); IR (NaCl) ν_{max} 3250 (br), 1972, 1890, 1685, cm^{-1}; ^{1}H NMR δ 6.05 (d, 2H, J=6.3), 5.71 (apparent t, 1H, J=6.2), 5.28 (apparent t, 2H, J=6.5), 4.70 (d, 2H J=4.7), 3.26 (t, 1H, J=4.7); ^{13}C NMR δ 229.8, 196.2, 95.7, 93.3, 90.8, 88.7, 64.4; MS m/e 272 (M^+). Anal, Calculated for $C_{11}H_8CrO_5$: C, 48.54; H, 2.96. Found C, 48.29; 3.00.

α-[Estradiol-3-methyl ether]tricarbonylchromium (0) (13a)



Prepared in 48% yield by the standard literature procedure[5]. mp 152-153 °C (hexanes); IR (NaCl) ν_{max} 3307 (br), 1953, 1865 cm^{-1}; ^1H NMR δ 5.79 (d, J=7.1, 1H), 5.13 (dd, 1H, J=7.1, 2.2) 4.99 (d, 1H, J=2.2,), 3.71 (m, obscured, 1H), 3.68 (s, 3H) 2.75 - 3.0 (m, 2H), 2.05 - 2.20 (m, 3H), 1.80 - 2.00 (m, 2H), 1.1 - 1.75 (m, 9H), 0.77 (s, 3H); ^{13}C NMR δ 233.9, 142.5, 111.2, 105.0, 93.5, 81.5, 78.3, 77.2, 55.5, 49.2, 43.1, 43.0, 39.0, 36.3, 30.5, 30.1, 26.5, 25.7, 22.9, 11.0; MS m/e 422 (M^+); HRMS m/e calculated for $C_{22}H_{26}CrO_5$ (M^+) 422.1185 found 422.1177. The assignment of the α- stereochemistry was based on comparison of the ^{13}C NMR chemical shifts with closely related estradiol derivatives[6].

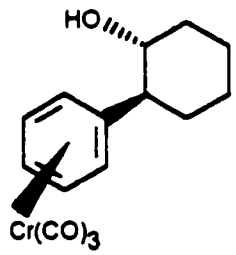
[Estrone-3-methyl ether]tricarbonylchromium (0) (13b)



Prepared from **13a** in 61% yield by Method 1 and 61 % yield by Method 2

mp 159-160 °C (pentane); lit [6] 160 - 1 °C.

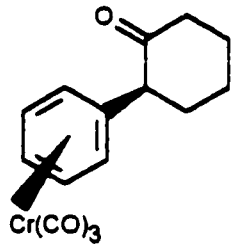
***trans*-[2-Phenyl-1-cyclohexanol]tricarbonylchromium (0) (14a)**



Prepared in 60% yield by the standard literature procedure[5]. oil; IR (NaCl) ν_{max} 3339 (br), 1962, 1883, 1856 cm^{-1}; ^1H NMR δ 5.47 (d, 2H, J=6.9), 5.36 (m, 3H), 3.37 (m, 1H), 1.9 - 2.2 (m, 3H), 1.65-1.9 (m, 3H), 1.2 - 1.45 (m, 4H); ^{13}C NMR δ 233.1, 114.4, 96.9, 93.5,

92.3, 91.3, 90.0, 75.3, 50.1, 35.7, 31.5, 25.7, 24.8; MS m/e 312 (M^+); HRMS m/e calculated for $C_{15}H_{16}CrO_4$ 312.0454, found 312.0447.

[2-Phenyl-1-cyclohexanone]tricarbonylchromium (0) (14b)



Prepared from **14a** in 61% yield by Method 1 and 61 % yield by Method 2

mp 134-136 °C (hexanes-Et_2O); IR (NaCl) ν_{max} 1962, 1857, 1707 cm^{-1}; ^1H NMR δ 5.32 (m, 3H), 5.19 (apparent t, 2H, J=7.3), 3.32 (dd, 1H, J=5.1, 12.3), 2.38 - 2.52 (m, 3H), 2.17 (m, 1H), 2.05 (m, 1H), 1.74 - 1.88 (m, 3H); ^{13}C NMR 233.2, 209.4, 109.1, 96.4, 93.0, 92.2 (2 resonances, incidental overlap), 92.1, 55.6, 42.4, 32.9, 27.9, 25.5; HRMS m/e calculated for $C_{15}H_{14}CrO_4$ (M^+) 310.0297, found 310.0294.

3.4 References

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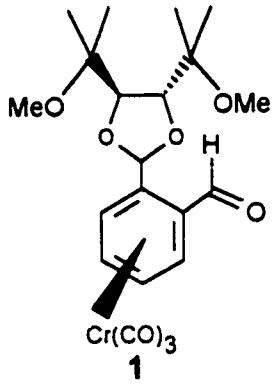
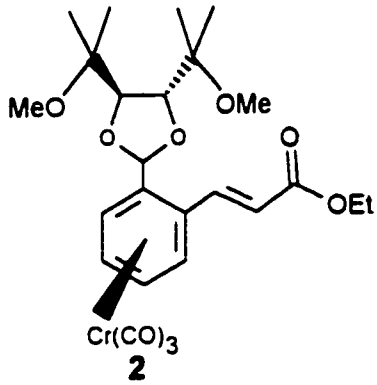
Summary of Results

Chapter 1

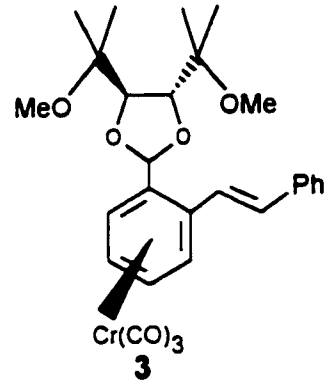
The nucleophilic addition of alkyl and arylmetals to **1** was examined. When the reaction was mediated by $Ti(O^iPr)_4$, diastereomeric excesses ranged from 77% to >94%. X-ray crystallography suggested that the major diastereomer had the absolute configuration of *S*. Conjugate addition of alkylmetal nucleophiles was attempted on **2** and **3** without success.



1



2

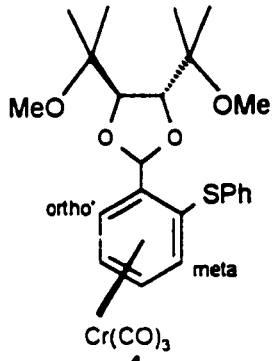


3

Chapter 2

The preparation of meta-disubstituted arenechromium tricarbonyl complexes was attempted. The initial phase of this research involved the directed ortho lithiation of **4**,

with thioether directing groups. In the case of the **4**, carrying out the reaction in Et_2O led to the metallation in the *ortho'* position. In THF lithiation occurred in both the *meta* and *ortho'* position. Desulfurization was attempted on the unsubstituted thiophenyl complex **4**. The use of both Raney Nickel and Nickel Boride led to the formation of the desulfurized complex and its decomplexed analogue in equal proportions.



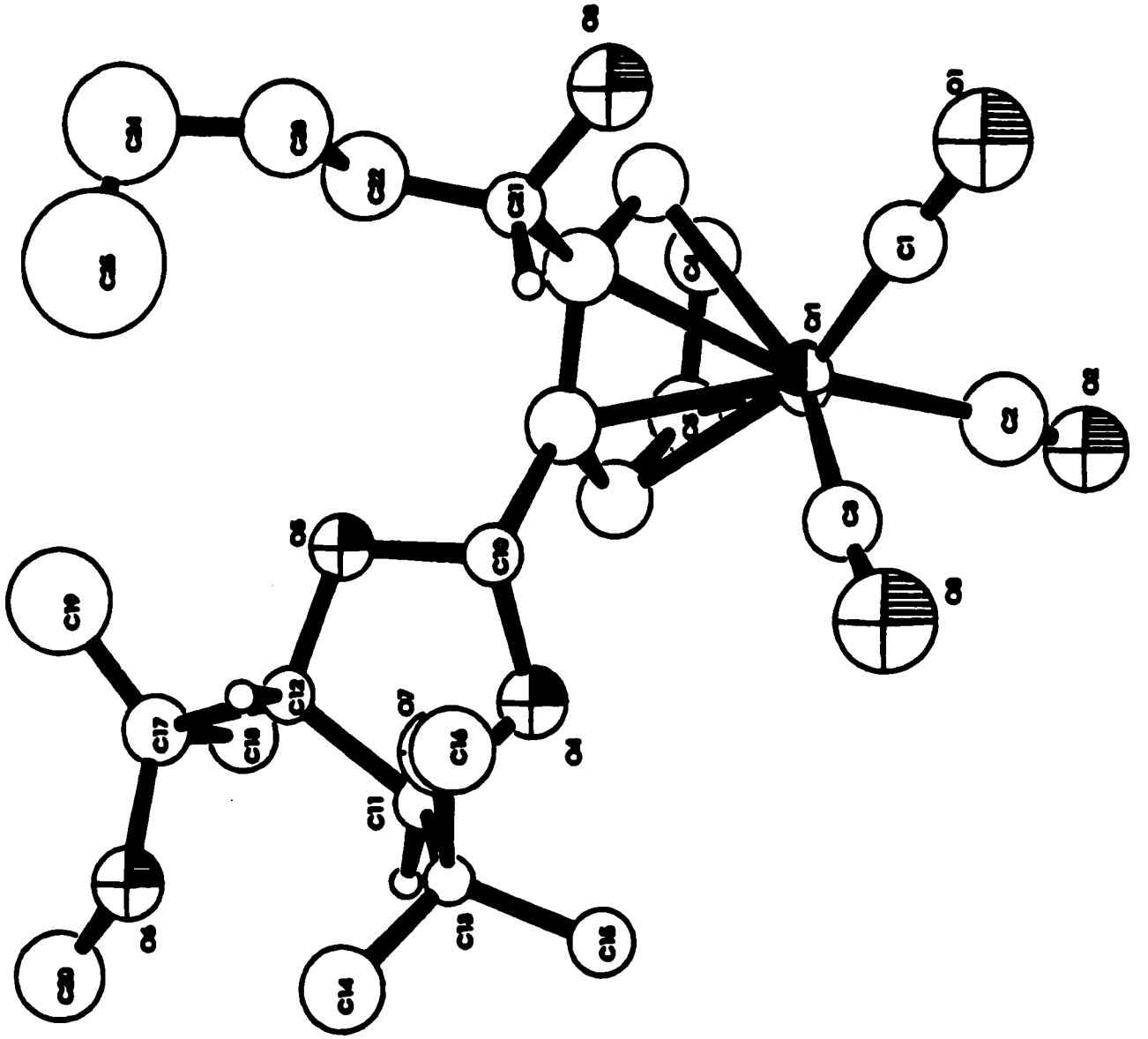
4

Chapter 3

A series of chromium tricarbonyl complexes with benzylic and non-benzylic alcohol functionalities were subjected to DMSO-TFAA and DMSO/SO_3-pyridine. Yields of carbonyl complexes ranged from 61-80% for the DMSO-TFAA oxidation and from 60-81% for the DMSO/SO_3-pyridine oxidation.

APPENDICES

Appendix A: ORTEP of 93a



Appendix B. Relevant X-Ray Parameters Used in Calculating the Structure of **93a**

Crystal Data	
Empirical Formula	$C_{25}H_{36}CrO_8$
Formula Weight	516.55
Crystal Colour, Habit	Yellow plate
Crystal System	Orthorhombic
Lattice Type	primitive
No. of Reflections Used for Unit Cell Determination (2θ)	25 (10.5-22.9°)
ω Scan Peak width @ ½ Height	0.20°
Lattice Parameters	a=11.303(4) Å b=11.295(1) Å c=21.528(2) Å V=2748.4(9) Å^3
Space Group	$P2_12_12_1$ (#19)
Z Value	4

Intensity Measurements	
Diffractometer	Rigaku AFC6S
Radiation	Mo-K α (λ=0.71069 Å)
Take-off Angle	6.0°
Detector Aperture	6.0 mm horizontal 6.0 mm vertical
Crystal to Detector Distance	285 mm
Temperature	23.0 °C
Scan Type	ω-2θ
Scan Width	(0.73 + 0.00 tan θ)°
2θ Max	50.0°
No. of Reflections Measured	Total: 2778
Corrections	Lorentz-polarization Adsorption

Structure Solution and Refinement	
Structure Solution	Direct Methods
Refinement	Full-matrix least-squares
Function Minimized	$\Sigma w(\|F_o\|-\|F_c\|)^2$
p-factor	0.005
Anomalous Dispersion	All non-hydrogen atoms
No. of Observations (I>3.00σI)	681
No. Variables	125
Reflection/Parameter Ratio	5.45
Residuals: R; R_w	0.089; 0.071
Goodness of Fit Indicator	2.30
Max Shift/Error in Final Cycle	0.05
Maximum Peak in Final Difference Map	0.38 $e^-/Å^3$
Minimum Peak in Final Difference Map	-0.38 $e^-/Å^3$

	Positional parameters		
atom	x	y	z
Cr(1)	0.6106(5)	0.2217(4)	0.0460(2)
O(1)	0.790(2)	0.140(2)	0.140(1)
O(2)	0.672(2)	0.008(2)	-0.0272(8)
O(3)	0.427(2)	0.088(2)	0.114(1)
O(4)	0.859(2)	0.425(1)	0.1036(7)
O(5)	0.735(2)	0.585(2)	0.1129(8)
O(6)	0.880(2)	0.499(2)	0.234(1)
O(7)	1.002(2)	0.752(2)	0.0956(9)
O(8)	0.372(2)	0.373(2)	0.1426(9)
C(1)	0.714(3)	0.175(2)	0.104(1)
C(2)	0.643(3)	0.084(3)	0.003(1)
C(3)	0.508(3)	0.139(3)	0.088(1)
C(4)	0.656(2)	0.409(1)	0.0658(7)
C(5)	0.533(2)	0.398(1)	0.0713(6)
C(6)	0.467(1)	0.352(2)	0.022(1)
C(7)	0.523(2)	0.317(1)	-0.0323(7)
C(8)	0.646(2)	0.328(1)	-0.0378(7)
C(9)	0.712(1)	0.374(2)	0.011(1)
C(10)	0.742(3)	0.455(2)	0.117(1)
C(11)	0.932(2)	0.520(3)	0.129(1)
C(12)	0.854(3)	0.627(2)	0.126(1)
C(13)	0.985(3)	0.490(3)	0.196(1)
C(14)	1.038(3)	0.367(3)	0.195(1)
C(15)	1.073(3)	0.582(3)	0.215(1)
C(16)	0.890(5)	0.477(4)	0.299(2)
C(17)	0.890(3)	0.724(3)	0.077(1)
C(18)	0.800(4)	0.823(3)	0.080(1)
C(19)	0.885(3)	0.665(2)	0.013(1)
C(20)	1.069(3)	0.829(3)	0.058(2)
C(21)	0.473(3)	0.441(3)	0.133(1)
C(22)	0.449(3)	0.570(3)	0.126(2)
C(23)	0.403(5)	0.626(4)	0.189(2)
C(24)	0.392(8)	0.764(8)	0.199(4)
C(25)	0.499(8)	0.793(9)	0.202(4)
H(1)	0.3838	0.3447	0.0259
H(2)	0.4786	0.2849	-0.0657
H(3)	0.6846	0.3030	-0.0750
H(4)	0.7957	0.3809	0.0074
H(5)	0.7201	0.4281	0.1568
H(6)	0.9964	0.5328	0.1018
H(7)	0.8537	0.6628	0.1660
H(8)	0.9797	0.3134	0.1798
H(9)	1.1053	0.3661	0.1710

atom	Positional parameters x	y	z
H(10)	1.0559	0.3452	0.2373
H(11)	1.0932	0.5713	0.2577
H(12)	1.1424	0.5743	0.1904
H(13)	1.0405	0.6588	0.2095
H(14)	0.8158	0.4854	0.3182
H(15)	0.9187	0.3982	0.3049
H(16)	0.9451	0.5313	0.3160
H(17)	0.8051	0.8607	0.1198
H(18)	0.8171	0.8796	0.0487
H(19)	0.7228	0.7928	0.0745
H(20)	0.8072	0.6430	0.0034
H(21)	0.9149	0.7187	-0.0171
H(22)	0.9347	0.5959	0.0135
H(23)	1.1443	0.8410	0.0761
H(24)	1.0785	0.7946	0.0178
H(25)	1.0289	0.9024	0.0540
H(26)	0.5299	0.4324	0.1657
H(27)	0.5174	0.6125	0.1144
H(28)	0.3881	0.5812	0.0967
H(29)	0.3265	0.5954	0.1975
H(30)	0.4556	0.5992	0.2218
H(31)	0.3509	0.8027	0.1676
H(32)	0.3547	0.7840	0.2390
H(33)	0.5365	0.7543	0.2349
H(34)	0.5340	0.7684	0.1633
H(35)	0.5059	0.8760	0.2056

Intramolecular Bond Angles Involving the Nonhydrogen Atoms

atom	atom	atom	angle	atom	atom	atom	angle
C(1)	Cr(1)	C(2)	89(1)	C(5)	Cr(1)	C(6)	36.1(7)
C(1)	Cr(1)	C(3)	85(2)	C(5)	Cr(1)	C(7)	65.3(6)
C(1)	Cr(1)	C(4)	90(1)	C(5)	Cr(1)	C(8)	77.7(6)
C(1)	Cr(1)	C(5)	110(1)	C(5)	Cr(1)	C(9)	65.9(7)
C(1)	Cr(1)	C(6)	145(1)	C(6)	Cr(1)	C(7)	36.3(7)
C(1)	Cr(1)	C(7)	164(1)	C(6)	Cr(1)	C(8)	65.7(7)
C(1)	Cr(1)	C(8)	128(1)	C(6)	Cr(1)	C(9)	77.7(6)
C(1)	Cr(1)	C(9)	98(1)	C(7)	Cr(1)	C(8)	36.7(7)
C(2)	Cr(1)	C(3)	87(2)	C(7)	Cr(1)	C(9)	66.2(7)
C(2)	Cr(1)	C(4)	149(1)	C(8)	Cr(1)	C(9)	37.0(7)
C(2)	Cr(1)	C(5)	161(1)	C(10)	O(4)	C(11)	106(2)

C(2)	Cr(1)	C(6)	125(1)
C(2)	Cr(1)	C(7)	96(1)
C(2)	Cr(1)	C(8)	90(1)
C(2)	Cr(1)	C(9)	112(1)
C(3)	Cr(1)	C(4)	124(1)
C(3)	Cr(1)	C(5)	95(1)
C(3)	Cr(1)	C(6)	89(1)
C(3)	Cr(1)	C(7)	111(1)
C(3)	Cr(1)	C(8)	147(1)
C(3)	Cr(1)	C(9)	161(1)
C(4)	Cr(1)	C(5)	36.4(9)
C(4)	Cr(1)	C(6)	65.4(8)
C(4)	Cr(1)	C(7)	77.7(6)
C(4)	Cr(1)	C(8)	66.3(6)
C(4)	Cr(1)	C(9)	36.9(7)
C(10)	O(5)	C(12)	105(2)
C(13)	O(6)	C(16)	118(3)
C(17)	O(7)	C(20)	118(2)
Cr(1)	C(1)	O(1)	174(3)
Cr(1)	C(2)	O(2)	172(3)
Cr(1)	C(3)	O(3)	173(3)
O(4)	C(10)	O(5)	107(2)
O(4)	C(10)	C(4)	112(2)
O(5)	C(10)	C(4)	105(2)
O(4)	C(11)	C(12)	104(2)
O(4)	C(11)	C(13)	114(2)
C(12)	C(11)	C(13)	116(2)
O(5)	C(12)	C(11)	107(2)
O(5)	C(12)	C(17)	110(2)
C(11)	C(12)	C(17)	116(2)

Intramolecular Bond Angles Involving the Nonhydrogen Atoms cont

atom	atom	atom	angle
O(6)	C(13)	C(11)	100(2)
O(6)	C(13)	C(14)	113(2)
O(6)	C(13)	C(15)	111(2)
C(11)	C(13)	C(14)	109(2)
C(11)	C(13)	C(15)	111(2)
C(14)	C(13)	C(15)	112(3)
O(7)	C(17)	C(12)	102(2)
O(7)	C(17)	C(18)	116(3)
O(7)	C(17)	C(19)	113(3)
C(12)	C(17)	C(18)	108(3)
C(12)	C(17)	C(19)	107(2)
C(18)	C(17)	C(19)	110(3)
O(8)	C(21)	C(22)	114(3)
O(8)	C(21)	C(5)	108(2)
C(22)	C(21)	C(5)	108(2)
C(21)	C(22)	C(23)	112(3)
C(22)	C(23)	C(24)	123(4)
C(23)	C(24)	C(25)	101(8)
Cr(1)	C(4)	C(10)	127(1)
Cr(1)	C(4)	C(5)	73(1)
Cr(1)	C(4)	C(9)	71(1)
C(10)	C(4)	C(5)	126(2)
C(10)	C(4)	C(9)	114(2)
C(5)	C(4)	C(9)	120(2)
Cr(1)	C(5)	C(21)	131(2)
Cr(11)	C(5)	C(6)	72(1)
C(21)	C(5)	C(4)	119(2)
C(21)	C(5)	C(6)	121(2)
C(4)	C(5)	C(6)	120(2)
Cr(1)	C(6)	C(5)	72(1)
Cr(1)	C(6)	C(7)	71(1)
C(5)	C(6)	C(7)	120(2)
Cr(1)	C(7)	C(6)	73(1)
Cr(1)	C(7)	C(8)	71(1)
C(6)	C(7)	C(8)	120(2)
Cr(1)	C(8)	C(7)	72.8(9)
Cr(1)	C(8)	C(9)	71(1)
C(7)	C(8)	C(9)	120(1)
Cr(1)	C(9)	C(4)	72(1)
Cr(1)	C(9)	C(8)	72(1)
C(4)	C(9)	C(8)	120(2)
Cr(1)	C(5)	C(4)	71(1)

Intramolecular Distances Involving the Nonhydrogen Atoms

atom	atom	distance	atom	atom	distance
Cr(1)	C(1)	1.80(3)	O(8)	C(21)	1.39(4)
Cr(1)	C(2)	1.85(3)	C(10)	C(4)	1.56(3)
Cr(1)	C(3)	1.74(4)	C(11)	C(12)	1.50(4)
Cr(1)	C(4)	2.22(2)	C(11)	C(13)	1.59(4)
Cr(1)	C(5)	2.25(2)	C(12)	C(17)	1.57(4)
Cr(1)	C(6)	2.25(2)	C(13)	C(14)	1.51(4)
Cr(1)	C(7)	2.23(2)	C(13)	C(15)	1.49(4)
Cr(1)	C(8)	2.20(2)	C(17)	C(18)	1.52(5)
Cr(1)	C(9)	2.20(2)	C(17)	C(19)	1.53(4)
O(1)	C(1)	1.21(4)	C(21)	C(22)	1.48(5)
O(2)	C(2)	1.12(4)	C(21)	C(5)	1.57(4)
O(3)	C(3)	1.23(4)	C(22)	C(23)	1.59(6)
O(4)	C(10)	1.39(4)	C(23)	C(24)	1.6(1)
O(4)	C(11)	1.46(3)	C(24)	C(25)	1.3(1)
O(5)	C(10)	1.47(3)	C(4)	C(5)	1.40(3)
O(5)	C(12)	1.45(4)	C(4)	C(9)	1.40(3)
O(6)	C(13)	1.45(4)	C(5)	C(6)	1.40(3)
O(6)	C(16)	1.43(5)	C(6)	C(7)	1.40(3)
O(7)	C(17)	1.36(4)	C(7)	C(8)	1.40(3)
O(7)	C(20)	1.41(4)	C(8)	C(9)	1.40(3)

VITA AUCTORIS

Name:	Maurice Kevin McKay
DOB:	May 5, 1964 Trenton, Ontario
Education:	B.Sc. (Hons.) Laurentian University Sudbury, Ontario 1990
	Ph.D. (Organic Chemistry) University of Windsor Windsor, Ontario 1999
Publications:	McKay, M.K.; Siwek, M. J.; Green, J.R. *Synthesis*, **1996**, 1203