STEREOSELECTIVE REACTIONS OF ARENE CHROMIUM TRICARBONYL COMPLEXES.

A thesis submitted in partial fulfilment

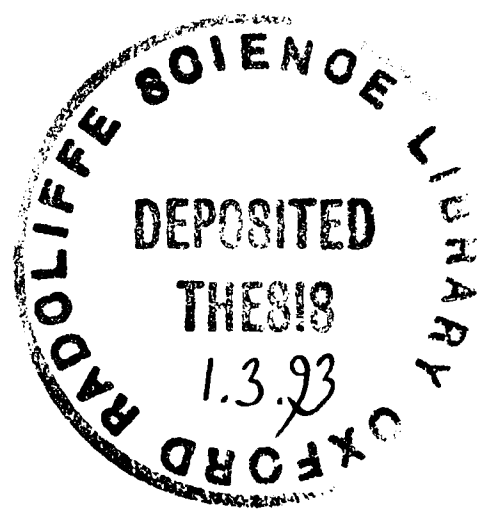
of the requirements for the degree of

Doctor of Philosophy.

by

Craig L. Goodfellow

New College, Oxford



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Stereoselective Reactions of Arene Chromium Tricarbonyl Complexes.

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Abstract

This thesis describes the application of (arene)Cr(CO)3 methodology to the stereoselective and enantioselective synthesis of substituted arenes.

Chapter one reviews the main methods of preparation and decomplexation of (arene)Cr(CO)3 complexes and the electronic and steric influences of the Cr(CO)3 unit on the arene.

Chapter two demonstrates that the benzylic oxygen directing effect in complexation reactions operates *via* a direct oxygen bond to the incoming metal unit. Attachment of bulky π-acceptor groups, such as t-butyldimethylsilyl, to the benzylic oxygen overrides this directing effect.

Chapter three describes the regioselective C1 functionalisation of the cryptopine skeleton. Complexation of dihydrocrytopine gives only a single product, the relative configuration of the product being determined using an X-ray crystal structure analysis. Subsequent alkylation of the O-methyl derivative gives C1 alkylated products.

Chapter four describes the regioselective *ortho* functionalisation of ephedrine and pseudoephedrine derivatives. Treatment of (1S,2R)-(N,O-dimethylpseudo-ephedrine)Cr(CO)3 with *n*-butyllithium leads to exclusive removal of the *pro*-(*R*) *ortho* proton. The observed stereoselectivity arises *via* deprotonation from cyclic bidentate five-membered chelates.

Chapter five describes the regioselective C4 and C5 functionalisation of (hydrocotarnine)Cr(CO)3. Complexation of 1-methylhydrocotarnine occurs to give exclusively the *exo*-1-methyl derivative. Further functionalisation to give the 1,5- and 4,5-dimethyl products is also described

Chapter six describes the synthesis of *ortho* substituted (benzaldehyde)Cr(CO)3 complexes. Chiral material is available *via* preferential kinetic hydrolysis of, or classical separation of, the L-valinol derived imines.

Chapter seven describes the stereoselective addition of nucleophiles to (*o*-anis-aldehyde)Cr(CO)3 and (*o*-trialkylsilylbenzaldehyde)Cr(CO)3. With (*o*-anisaldehyde)-Cr(CO)3 the additions are completely stereoselective giving the (*RR*,*SS*) diastereoisomer. With (*o*-trialkylsilylbenzaldehyde)Cr(CO)3 the ratio of products is influenced by the nature of Lewis acidic species present.

Chapter eight describes the stereoselective benzylic elaboration of (*o*-methoxybenzyl methyl ether)Cr(CO)3 achieved *via* selective removal of the *exo* benzylic proton from transition states with the methoxy groups *anti* to each other.

To Mum, Dad and Tricia

Acknowledgements

I would like to thank Dr Stephen Davies for his considerable advice and encouragement over the last three years. I would also like to thank members of T3, both past and present and especially Mario, Rob and Louie for making life different.

I am grateful to Mrs E.V. McGuinness for running n.m.r. spectra and to Dr R.T. Aplin for numerous mass spectra. My thanks also go to Dr Kevin Sutton, Steve Coote and Lindsay Bromley for obtaining the X-ray crystal structure data presented in this thesis. I am also indebted to Mrs V. Lamburn for running elemental microanalyses efficiently.

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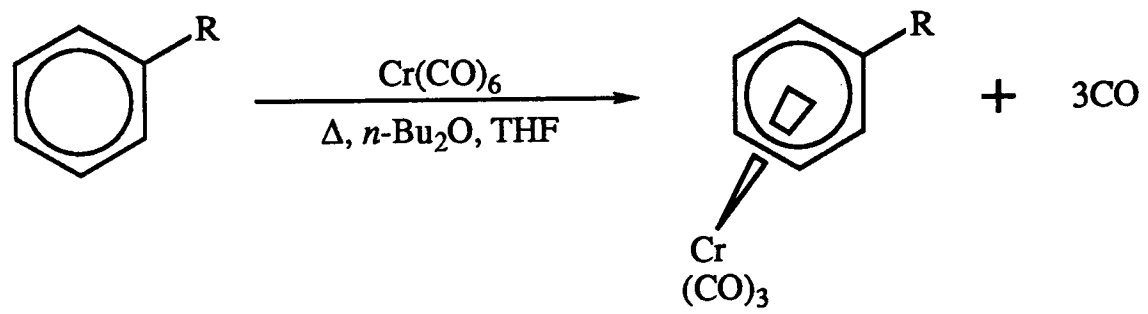
Abbreviations

Me	methyl
Et	ethyl
i-Pr	*i*-propyl
n-Bu	*n*-butyl
t-Bu	*t*-butyl
Ph	phenyl
Ac	acetyl
Ar	aryl radical
R	organic radical
M	metal species
Nu^-	nucleophile
E^+	electrophile
X	halogen atom
Z	electron withdrawing group
L	ligand
Ts	*p*-toluenesulphonyl
TBDMS	*t*-butyldimethylsilyl
TMS	trimethylsilyl
TBAF	tetra-*n*-butylammonium fluoride
DMF	N,N-dimethylformamide
py	pyridine
Red-Al	sodium *bis*(2-methoxyethoxy)aluminium hydride
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMEDA	N,N,N^1,N^1-tetramethylethylenediamine
o	*ortho*
m	*meta*
p	*para*
n.m.r.	nuclear magnetic resonance
n.O.e	nuclear Overhauser enhancement
ORD	optical rotatory dispersion
CD	circular dichroism
s	singlet
d	doublet
t	triplet
q	quartet
m	multiplet
br	broad
m/z	molecular ion
ee	enantiomeric excess
de	diastereoisomeric excess
hν	sunlight
[O]	oxidising agent

Chapter 1. Arene Chromium Tricarbonyl Complexes.

a. *Preparation of* (η^6-*Arene*)$Cr(CO)_3$ *Complexes.*

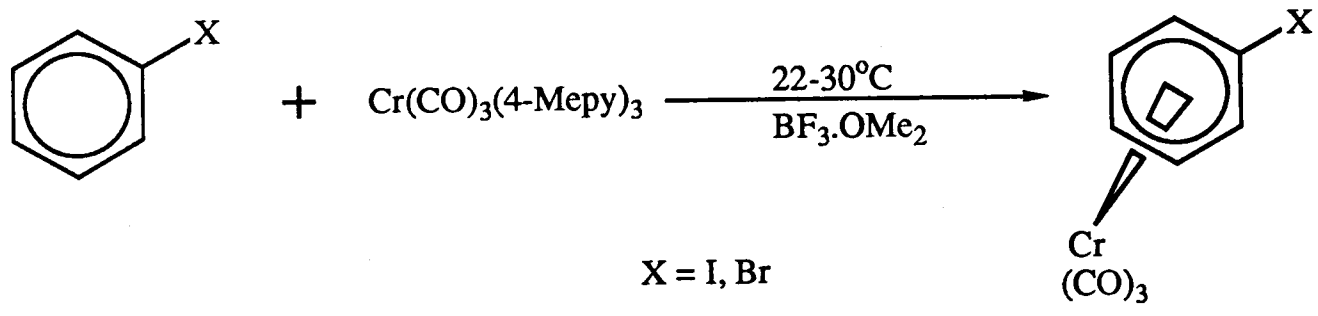
(η^6-Arene)$Cr(CO)_3$* complexes may be prepared in a variety of ways *via* a ligand exchange reaction with reagents of the type $Cr(CO)_3L_3$. The most convenient method is thermolysis of $Cr(CO)_6$ (L=CO) with the arene typically for 24-48h in a refluxing 10:1 mixture of *n*-Bu_2O:THF under an inert atmosphere.[1] The addition of coordinating solvents such as THF to the refluxing mixture shortens reaction times and improves yields.



This method is widely applicable to arenes possessing a variety of functional groups. In general electron-donating groups enhance the rate of complexation, whilst the converse applies to electron-withdrawing groups.[2]

Arenes possessing nitro, terminal acetylene, nitrile or aldehyde substituents (R = NO_2, C≡CH, CN or CHO) have not been successfully complexed, although in the case of the latter, formation of the corresponding acetal, complexation of the protected arene and acid catalysed liberation of the free aldehyde circumvents this problem.[3]

High temperatures and prolonged reaction times may be avoided using reagents of the type $Cr(CO)_3L_3$ (L = NH_3,[4] CH_3CN,[5] pyridine,[6] *etc.*), where the nitrogen-bound ligands have increased lability compared to CO. Indeed some otherwise inaccessible complexes have been synthesised by this method.[7]



Other mild methods of arene complexation include ligand exchange with commercially available (naphthalene)$Cr(CO)_3$ **1**. For example, (styrene)$Cr(CO)_3$ **2** was prepared in good yield by refluxing a Et_2O:THF solution of styrene with complex **1** for 19h.[8]

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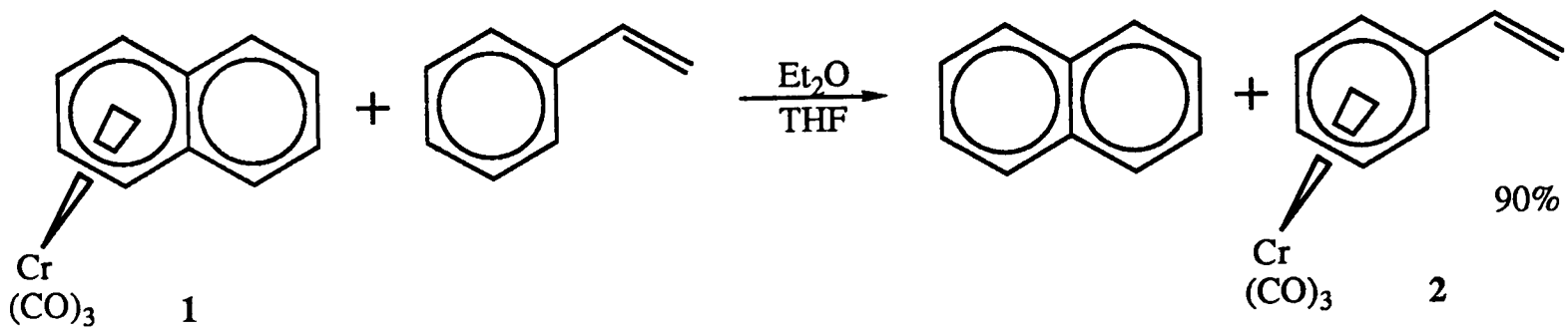
* η^N: N is the number of carbon atoms of a ligand bonded to the metal centre. For clarity the descriptor η^6 will be omitted in simple (arene)$Cr(CO)_3$ complexes.

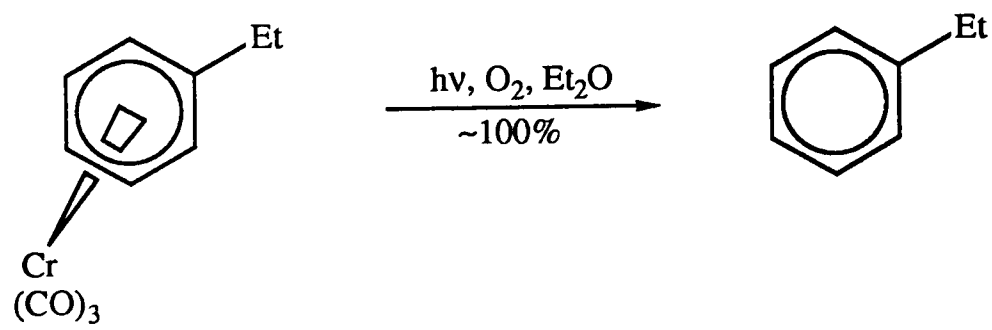


b. *Decomplexation of (Arene)Cr(CO)3 Complexes.*

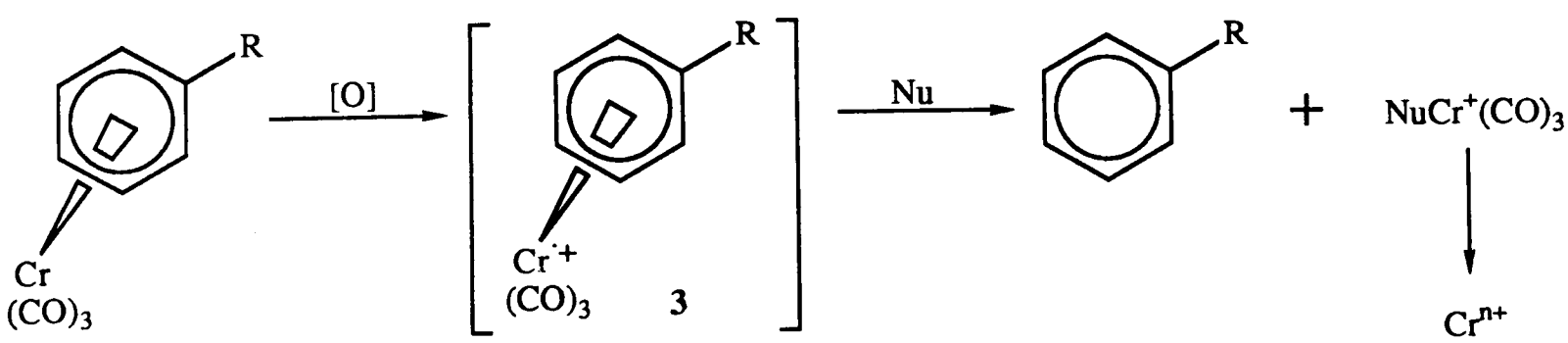
Decomplexation may be effected either oxidatively or *via* a ligand exchange reaction.

i. *Oxidative Decomplexation.*

The most convenient and widely applicable method of decomplexation involves atmospheric oxidation of the complex in the presence of sunlight. Typically the complex is dissolved in Et_2O and allowed to stand in air and sunlight for 24-48h until a colourless solution with a green or brown precipitate results. Filtration removes the insoluble oxidised chromium salts and evaporation of the filtrate quantitatively yields essentially pure arene.[9]



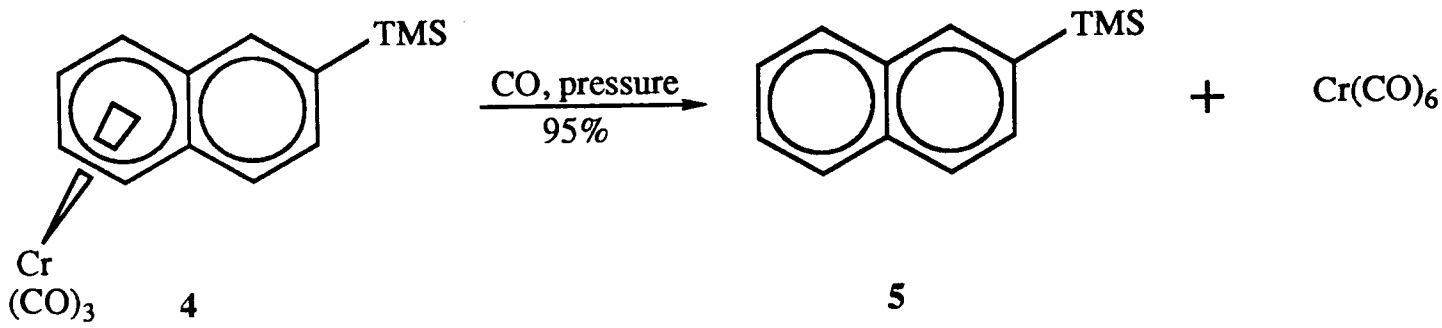
The mechanism of this reaction involves initial oxidation of the complex to the chromium radical cation **3** followed by rapid nucleophilic attack of solvent impurities such as water and cleavage of the arene-chromium bond. The chromium species are further oxidised to give Cr^{II} and Cr^{III} salts.[10]



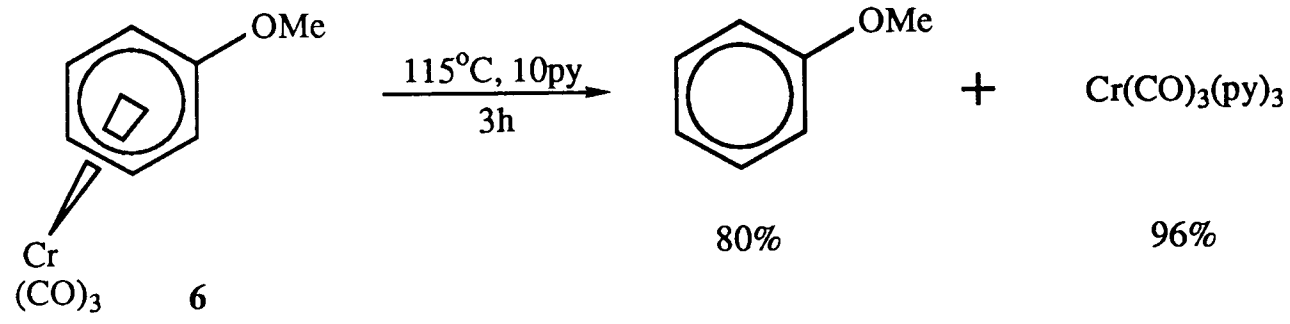
Rapid decomplexation may be achieved using mild oxidising agents such as I_2, $NaIO_4$ or Ce^{IV}.

ii. *Ligand Displacement Decomplexations.*

These methods are used preferentially when recovery of a Cr^0 species is desirable. Treatment of (2-trimethylsilylnaphthalene)$Cr(CO)_3$ **4** with CO under high pressure gave the free naphthalene derivative **5** and regenerated $Cr(CO)_6$.[11]

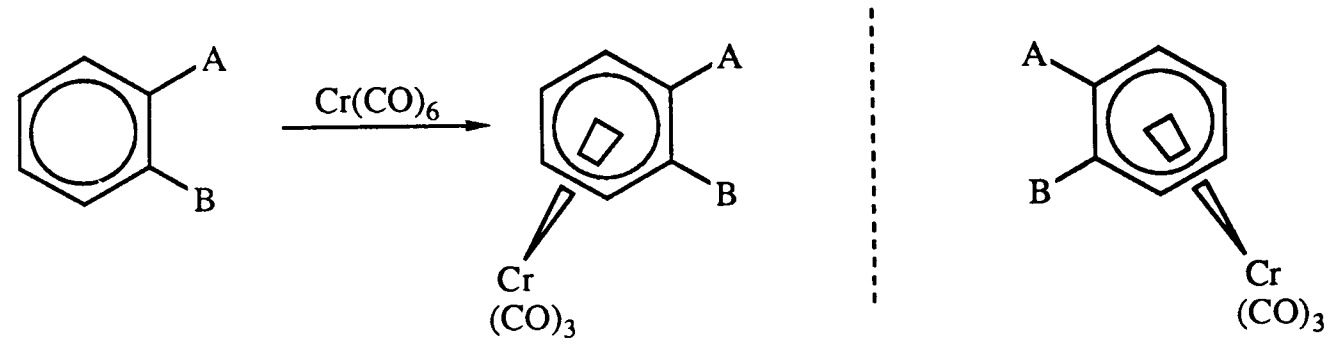


Other donor ligands, such as pyridine or PPh_3, have been used to release the arene and generate the corresponding $Cr(CO)_3L_3$ species (L = py, PPh_3). Thus, (anisole)$Cr(CO)_3$ **6** can be decomplexed with excess pyridine at 115°C.[12]

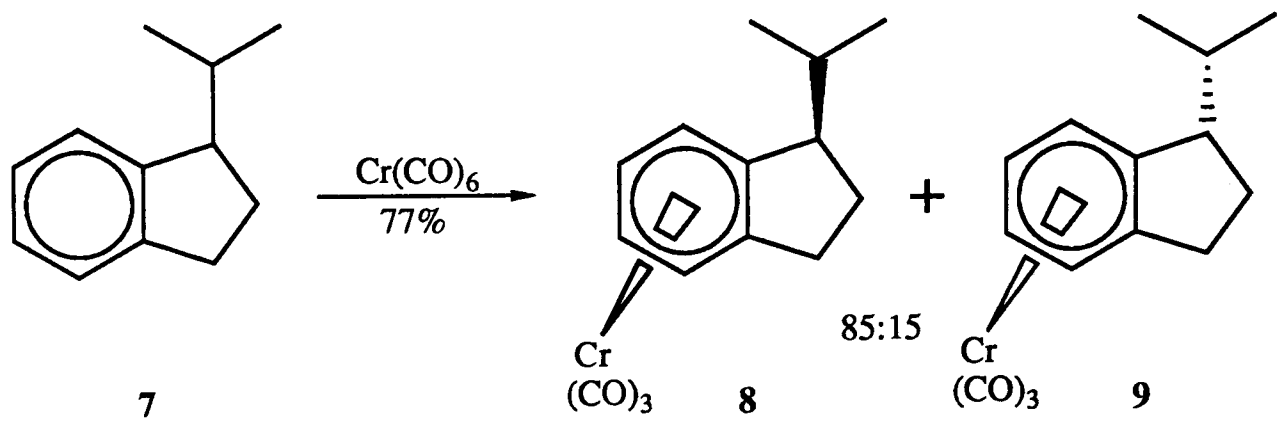


c. *Chiral Properties of (Arene)$Cr(CO)_3$ Complexes.*

Unsymmetrically *ortho* or *meta* disubstituted arenes are prochiral and possess enantiotopic faces. Thus, complexation of such arenes to the $Cr(CO)_3$ unit gives a racemic mixture.



If either of the substituents contains a chiral centre the two faces of the arene are rendered diastereotopic. Consequently, complexation of such arenes can give rise to a mixture of diastereoisomers. The ratio of products may be governed by steric, electronic or chelating effects. For example, thermolysis of $Cr(CO)_6$ with 1-*i*-propylindane **7** in refluxing decalin gave a 85:15 mixture of the *exo* and *endo* complexes **8** and **9**, the chromium unit preferentially approaching the arene from the least hindered face.[13]

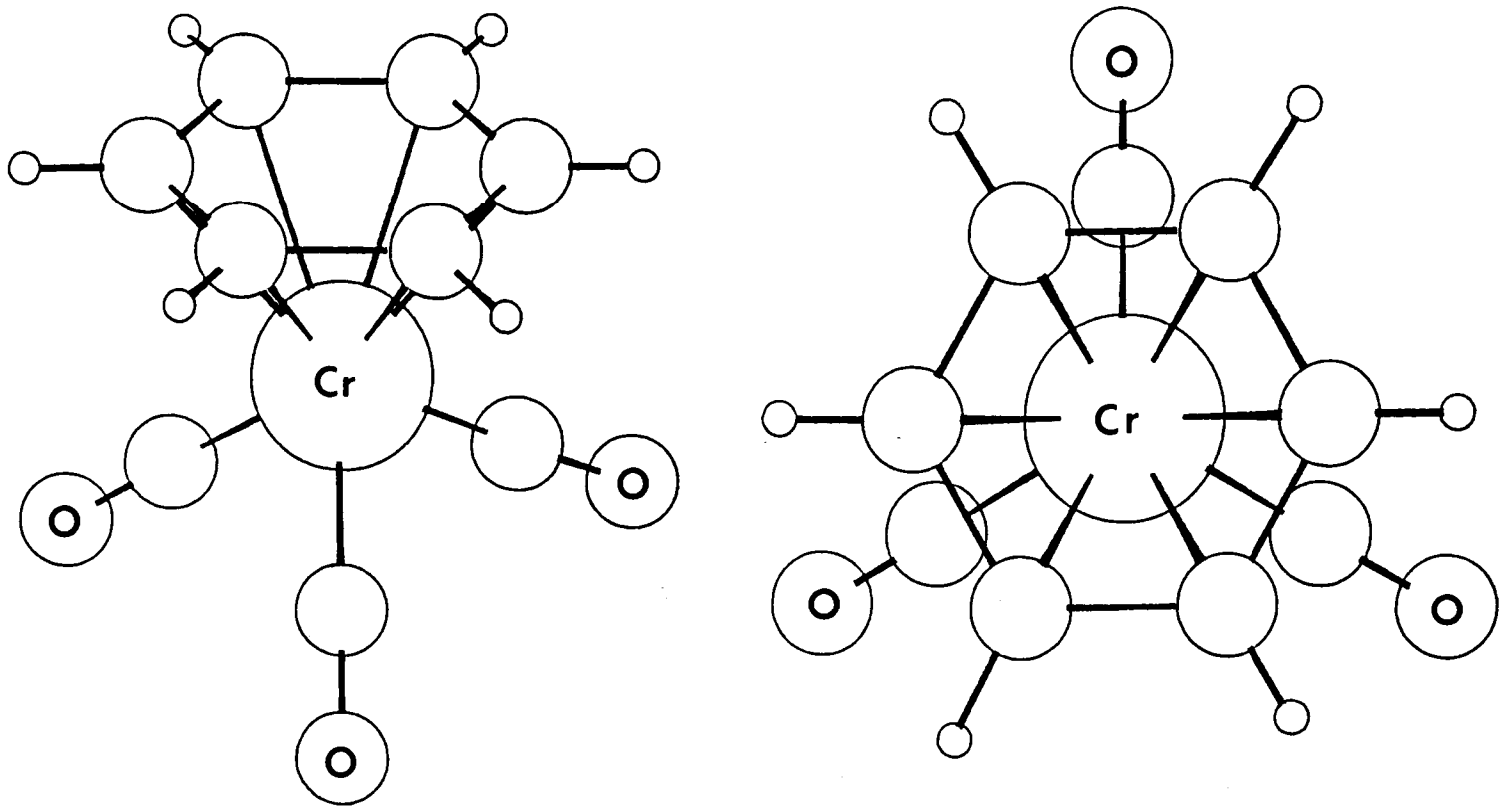


7 **8** **9**

d. *General Features of (Arene)Cr(CO)3 complexes.*

(Arene)Cr(CO)3 complexes are bright yellow to red diamagnetic solids or oils. In solution they are moderately air-sensitive and reactions are generally performed under an inert atmosphere, but as solids they may be handled in air. Complexation of an arene to the Cr(CO)3 unit generally results in an upfield shift of the aromatic proton signals of about 2ppm in the ^1H n.m.r spectrum relative to the free arene. The solution infrared spectrum displays two characteristic carbonyl absorption bands (*A* and *E*) between 1800 and 2000cm^{-1}.[14]

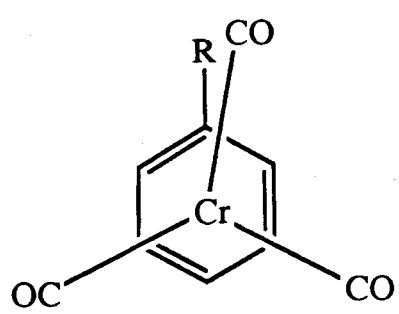
(Arene)Cr(CO)3 complexes adopt a "piano-stool" type structure, with the arene occupying three sites of the pseudo-octahedrally coordinated metal. The X-ray crystal structure of (benzene)Cr(CO)3 **10** is shown in Figure I.[15] The benzene ring is essentially planar, (although some perturbation from planarity occurs when strongly electron-donating or sterically bulky substituents are present on the ring), with the chromium lying under one face equidistant from all six carbons. The chromium-arene carbon bond lengths are 2.23$\overset{0}{A}$ and the metal sits 1.73$\overset{0}{A}$ below the centroid of the benzene ring.



a) b)

Figure I. X-Ray crystal structure of (benzene)$Cr(CO)_3$ **10**, a) side view, b) Newman projection from the benzene centroid to the chromium.

In solution the Cr(CO)3 unit is free to rotate about the chromium to ring centroid axis, thus effectively sweeping out a "forbidden" volume below the bonded face of the arene. However, in the solid state the Cr(CO)3 unit prefers to adopt primarily one conformation. Thus, for electron-donating substituents the substituent eclipsed conformation **11** is favoured, whilst the substituent staggered conformation **12** is preferred with electron-withdrawing groups. The preference of the Cr(CO)3 unit to adopt essentially one conformation in the solid state may be reinforced by crystal packing requirements.



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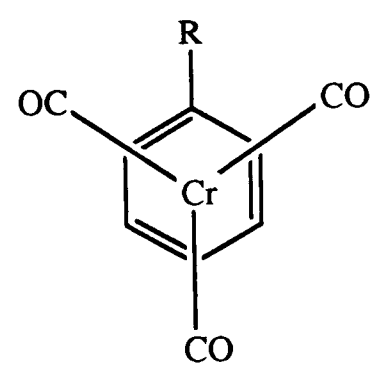


12

It has been reported that the preferred conformation adopted by the $Cr(CO)_3$ unit has a profound influence on the regioselectivity of metallation, and nucleophilic and electrophilic attack on the ring.[16] Since the preferred orientation of the carbonyl ligands is a direct consequence of the electronic and steric properties of the substituent, the regioselectivity of any reaction may be due to the directing influences of the ring substituent and not the carbonyl ligands.

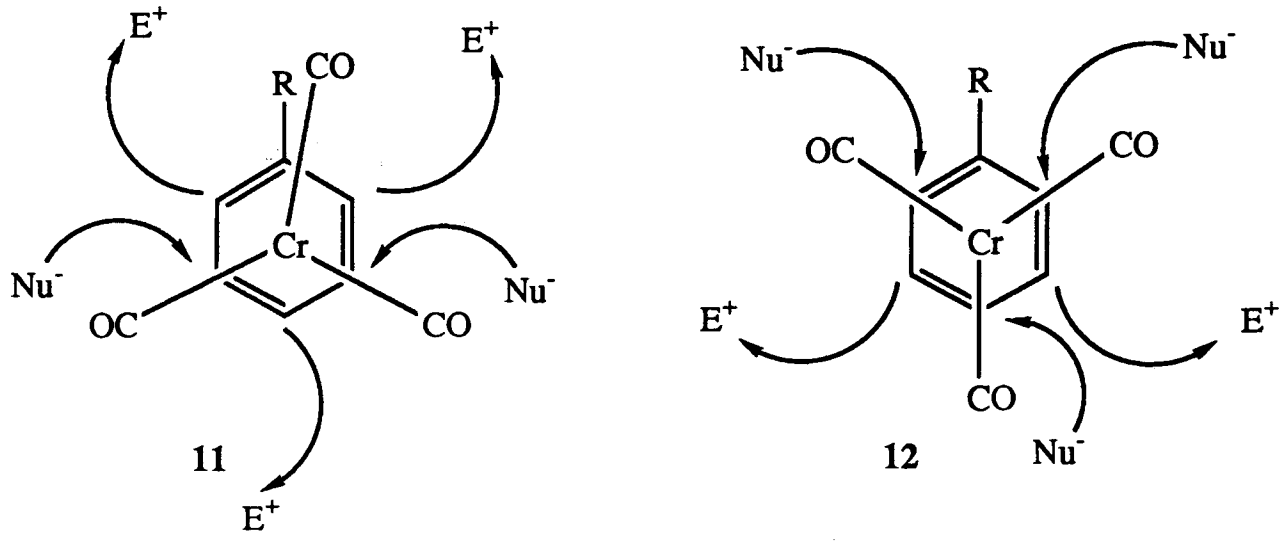


Figure II demonstrates the steric and electronic effects imparted to an arene upon coordination to the $Cr(CO)_3$ unit.

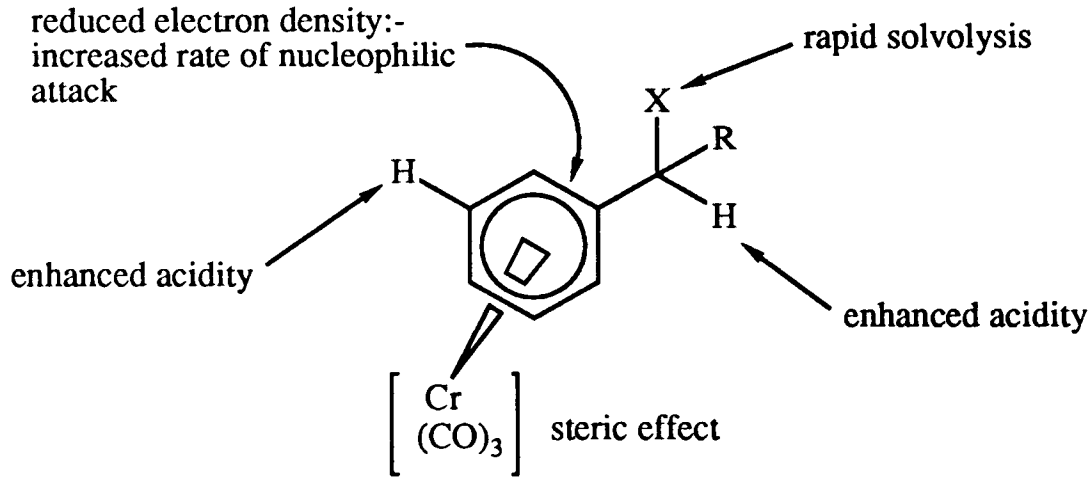
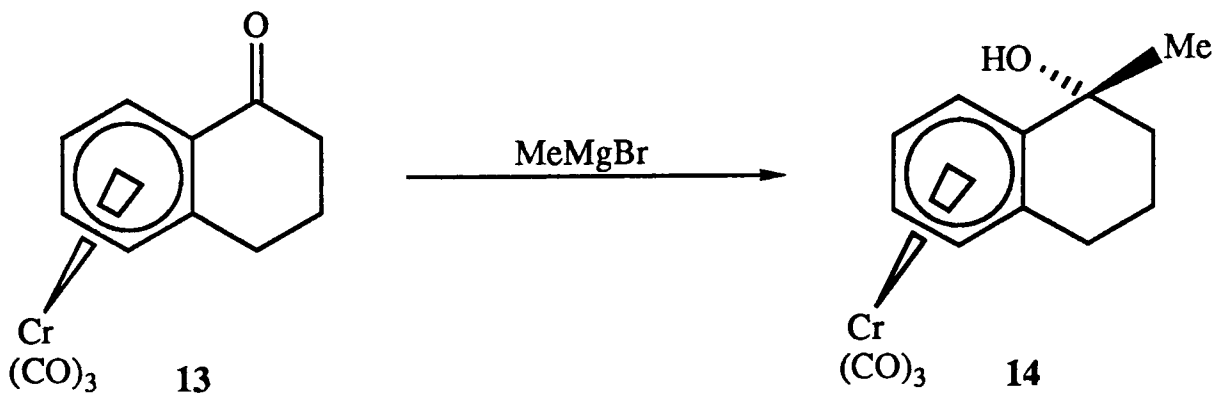


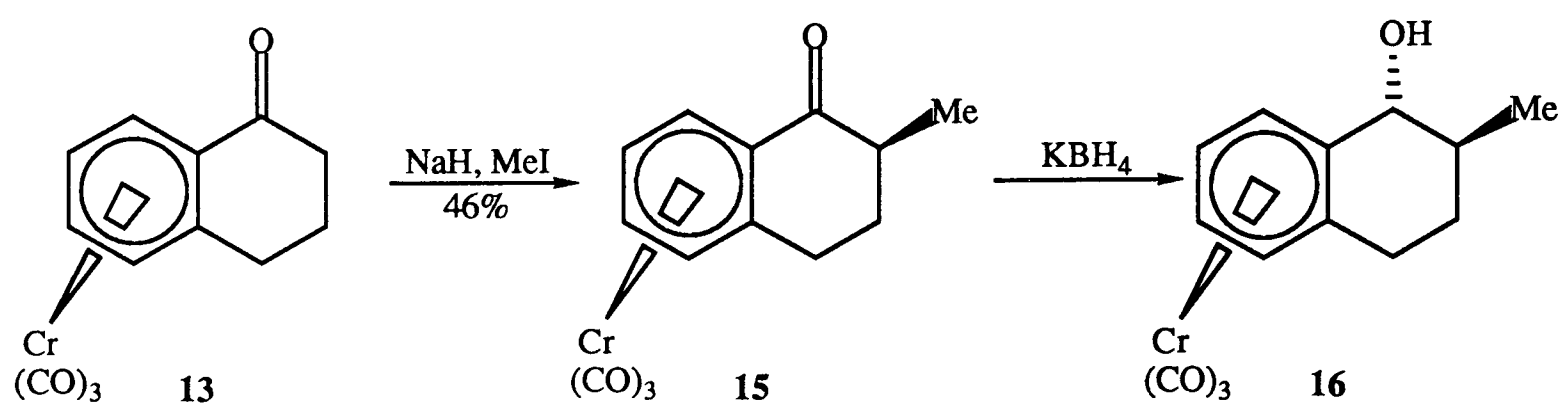
Figure II. General steric and electronic features of (arene)$Cr(CO)_3$ complexes.

i. *General Steric Effects.*

Since the $Cr(CO)_3$ unit is free to rotate about the chromium to ring centroid axis in solution, the swept out "forbidden" volume below the bonded face of the arene precludes the approach of reagents from this face. Consequently, all reagents approach only from the *exo* face away from the metal unit. For example, addition of MeMgBr to (1-tetralone)-$Cr(CO)_3$ **13** occurs exclusively from the *exo* face to give *endo*-(1-methyl-1-tetralol)$Cr(CO)_3$ **14**.[17]

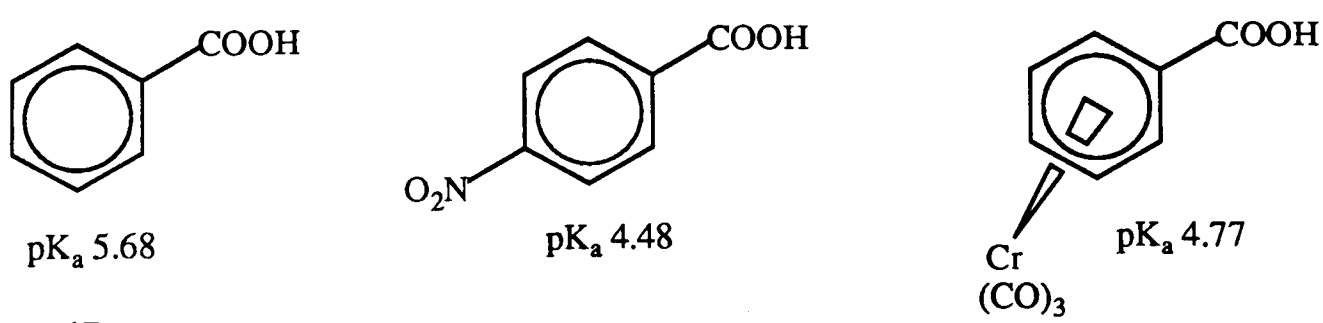


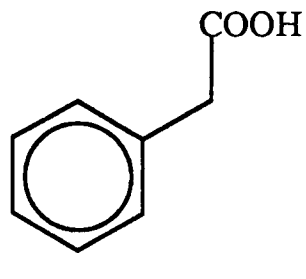
Similarly, the enolate derived from complex **13** was stereoselectively methylated from the *exo* face to give *exo*-(2-methyl-1-tetralone)Cr(CO)3 **15**. Subsequent reduction also occurred from the least hindered face to give *endo*-(*trans*-2-methyl-1-tetralol)Cr(CO)3 **16**.[18]



ii. *General Electronic Effects.*

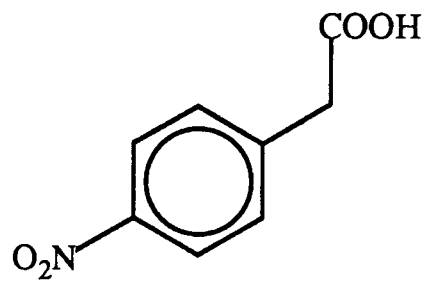
The Cr(CO)3 group acts as a powerful inductive electron withdrawing group due to the strongly π-acidic nature of the CO ligands. Consequently, there is an inductive reduction of electron density in the aromatic ring of a complexed arene, by an amount comparable to that of the introduction of a *p*-nitro group in the free arene. Thus, the acidity of benzoic and phenylacetic acids **17** and **18** is significantly increased upon coordination.[2]



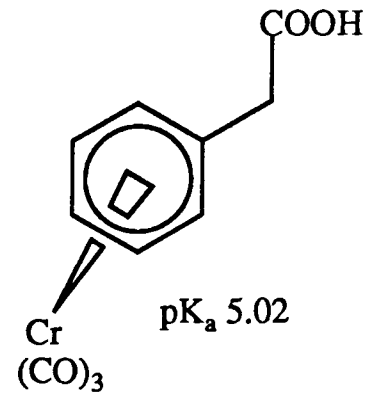


pK_a 5.64

18

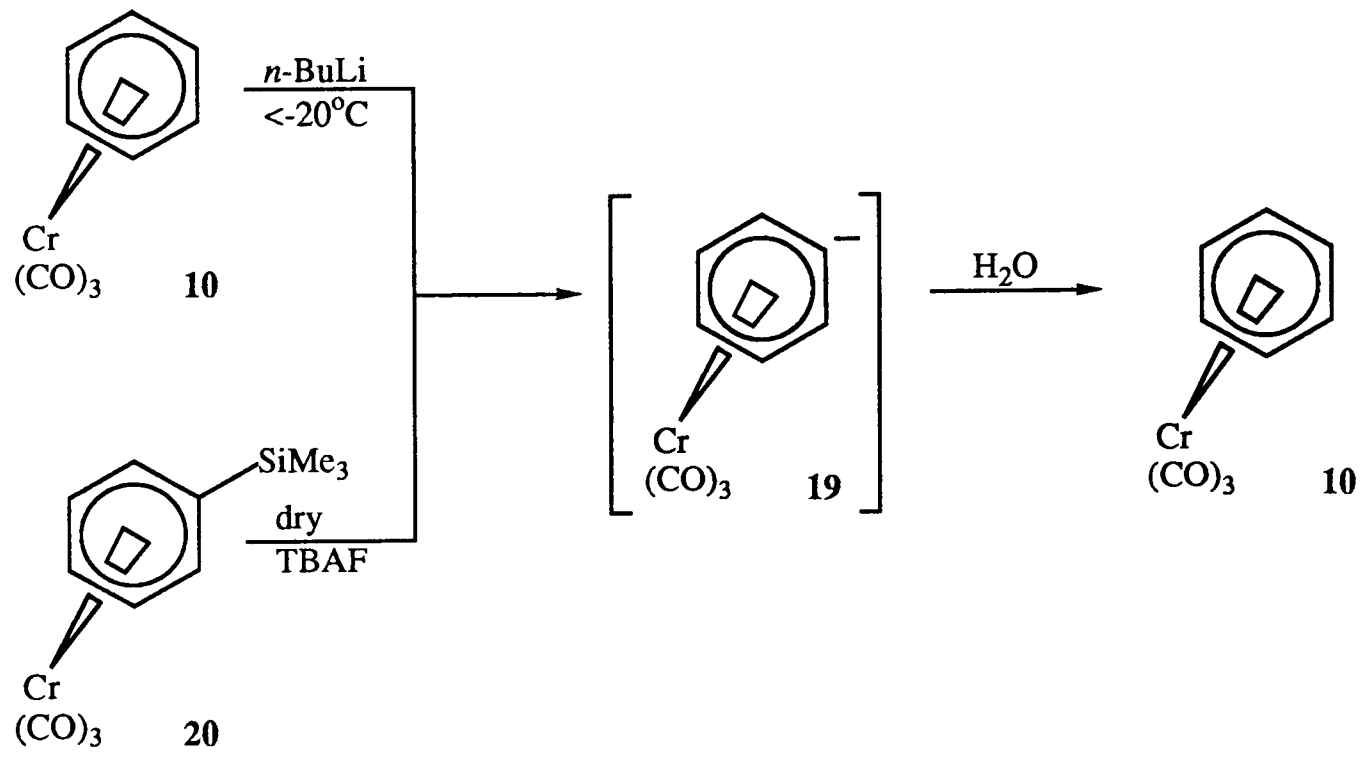


pK_a 5.01

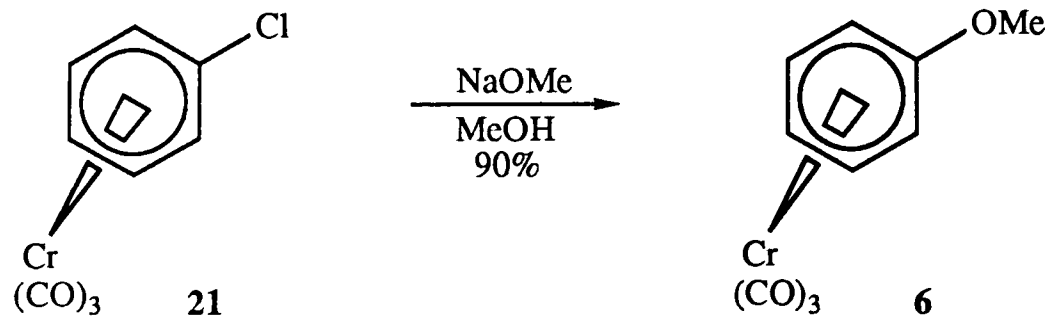


pK_a 5.02

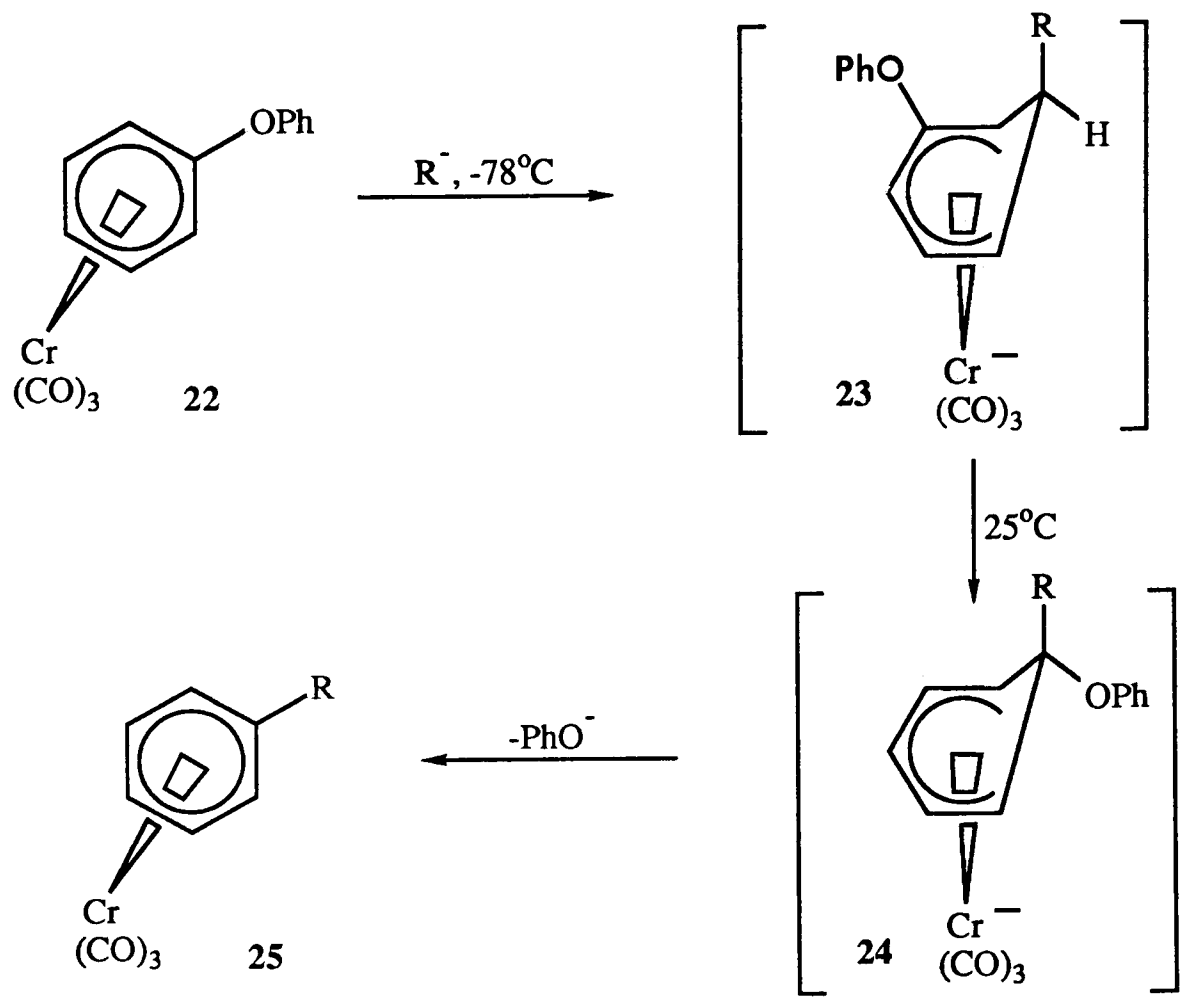
The inductively reduced ring electron density in (arene)Cr(CO)3 complexes also accounts for the increase in acidity of the aromatic protons *via* stabilisation of the corresponding aryl anion. For example, treatment of (benzene)Cr(CO)3 **10** with *n*-BuLi:TMEDA generated the corresponding aryl anion **19**.[19] The carbanion **19** could also be generated by fluoride-mediated desilylation of (phenyltrimethylsilane)Cr(CO)3 **20** under conditions where phenyltrimethylsilane was inert.[20]



The inductive electron-withdrawing nature of the Cr(CO)3 group also increases the rate of nucleophilic aromatic attack on coordinated arenes. Thus, (chloro-benzene)Cr(CO)3 **21** reacted with sodium methoxide in methanol to give (anisole)Cr(CO)3 **6** under relatively mild conditions.[2]



A mechanistic study has investigated the origins of the regioselectivity of nucleophilic addition to (diaryl ether)Cr(CO)3 complexes such as compound **22.** Nucleophiles were found to initially attack the ring *meta* to the substituent at low temperature. When the intermediate η^5-anion **23** was allowed to warm, isomerisation occurred to give the *ipso* substituted anion **24.** Subsequent loss of phenoxide generated the monosubstituted complex **25.**[21]



In the absence of a suitable leaving group on the arene, initial nucleophilic attack of a carbanion proceeds to give an intermediate *exo*-alkylated η^5-anion. In one case the intermediate **26** resulting from addition of 2-lithio-1,3-dithiane to complex **10** was isolated. A single crystal X-ray structure analysis revealed a planar pentadienyl fragment with the sixth ring carbon above the plane and away from the chromium and the dithiane group in an *exo* disposition relative to the chromium, Figure III.[22]

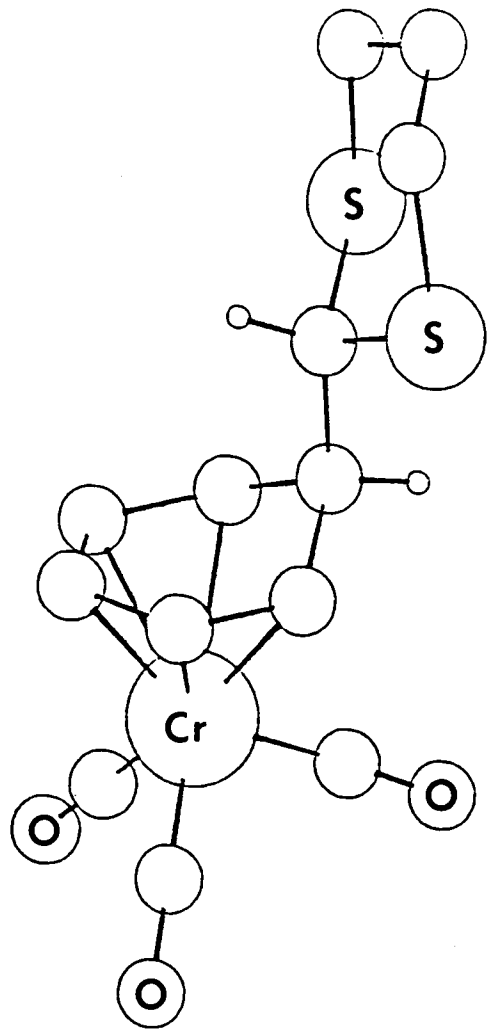
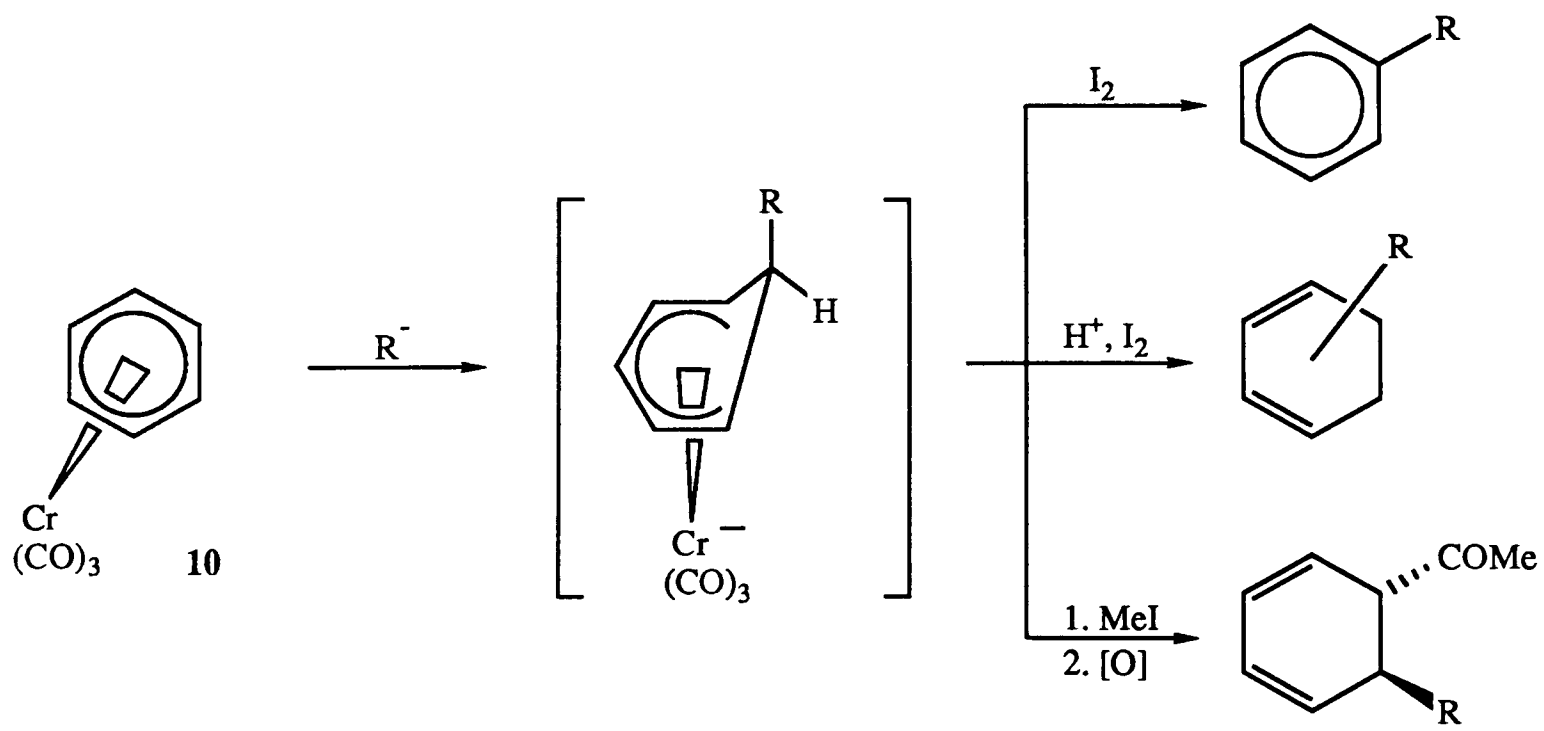
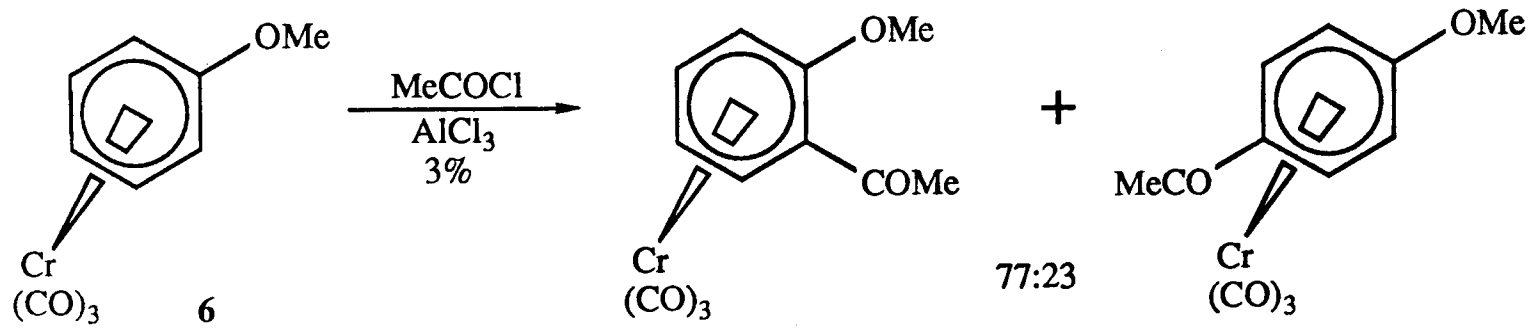


Figure III. X-Ray crystal structure of the lithium salt of [η^5-6-(1,3-dithian-2-yl)cyclohexadienyl]Cr(CO)$_3$ **26**.

Intermediate η^5-chromium stabilised anions resulting from nucleophilic attack at the aromatic ring can react further in a number of ways. For example, mild oxidation with iodine gives the free arene corresponding to overall substitution for hydrogen. Addition of acid and subsequent oxidation with iodine gives a mixture of substituted cyclohexadienes,[23] whilst treatment with MeI and subsequent oxidation gives a *trans* acetyl substituted cyclohexadiene.[24]

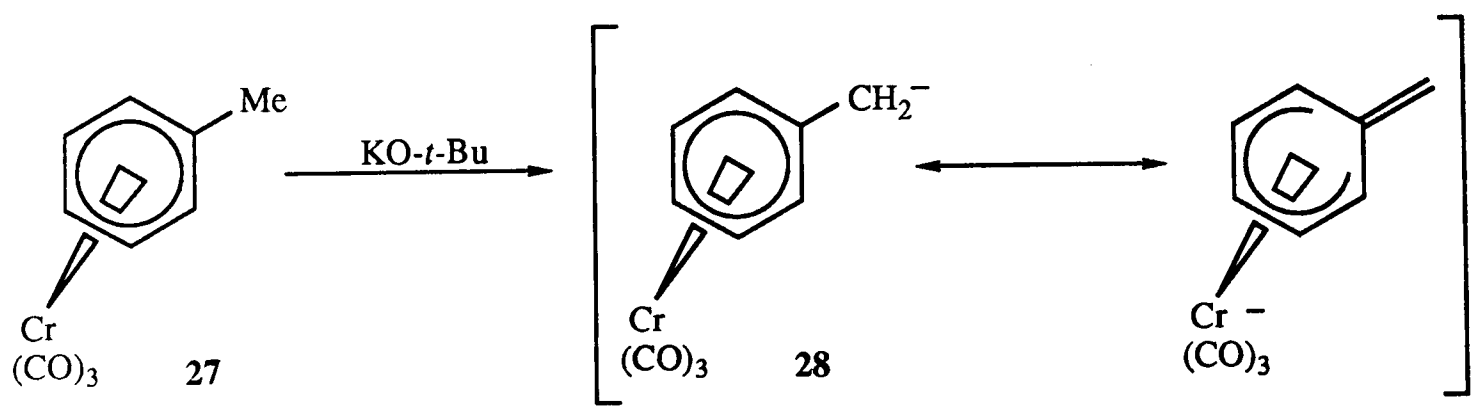


Direct electrophilic attack on the ring of (arene)$Cr(CO)_3$ complexes has been observed despite the reduced ring electron density.[25] Acylation of (anisole)$Cr(CO)_3$ **6** proceeds only in very low yield to give a 77:23 mixture of the *ortho*:*para* isomers.[26]

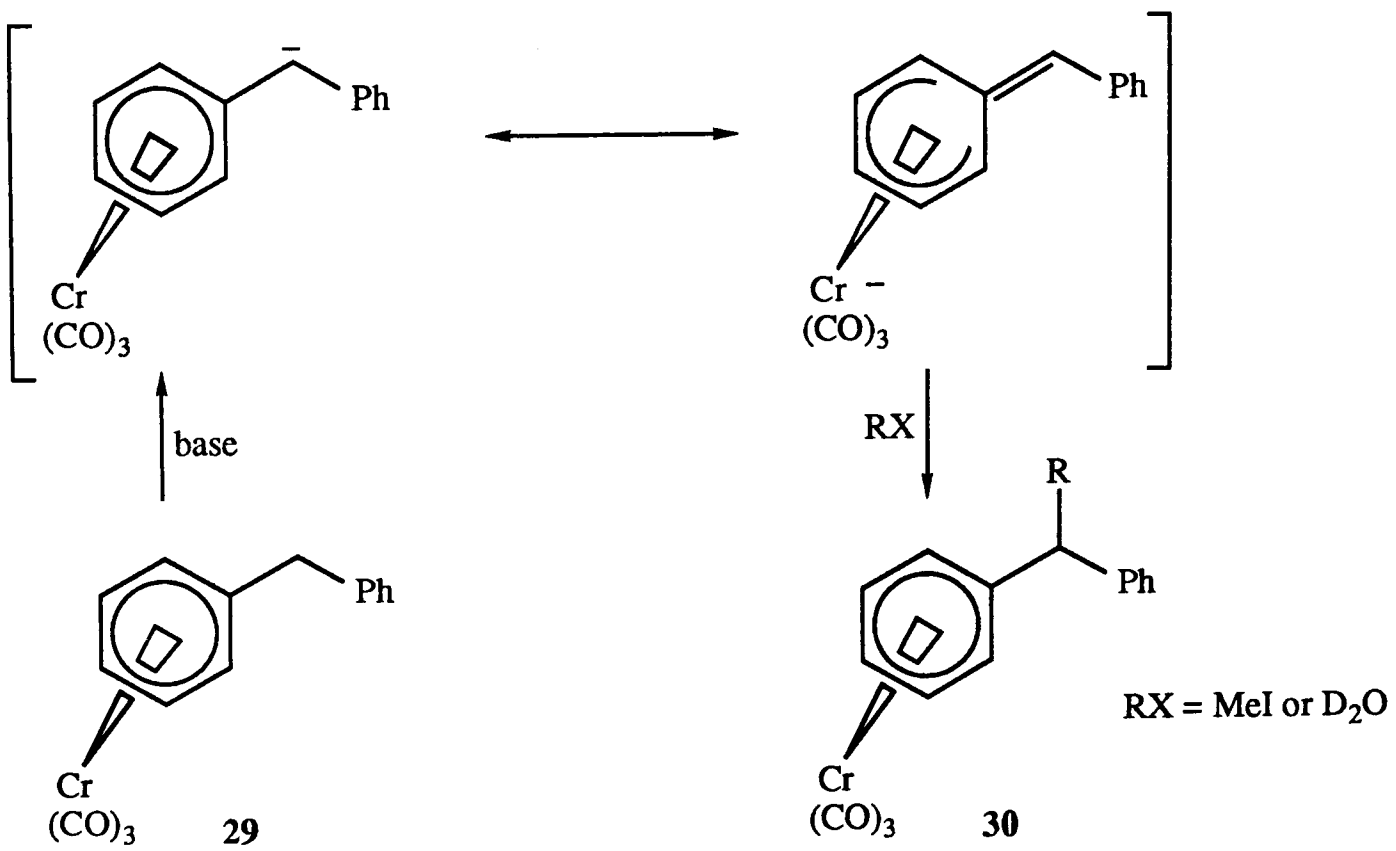


The resonance effect of the chromium unit in (arene)$Cr(CO)_3$ complexes can be electron-withdrawing or electron-donating. The electron-withdrawing effect results in a marked increase in the acidity of phenols upon complexation, *via* resonance stabilisation of the conjugate phenoxide ion.[27]

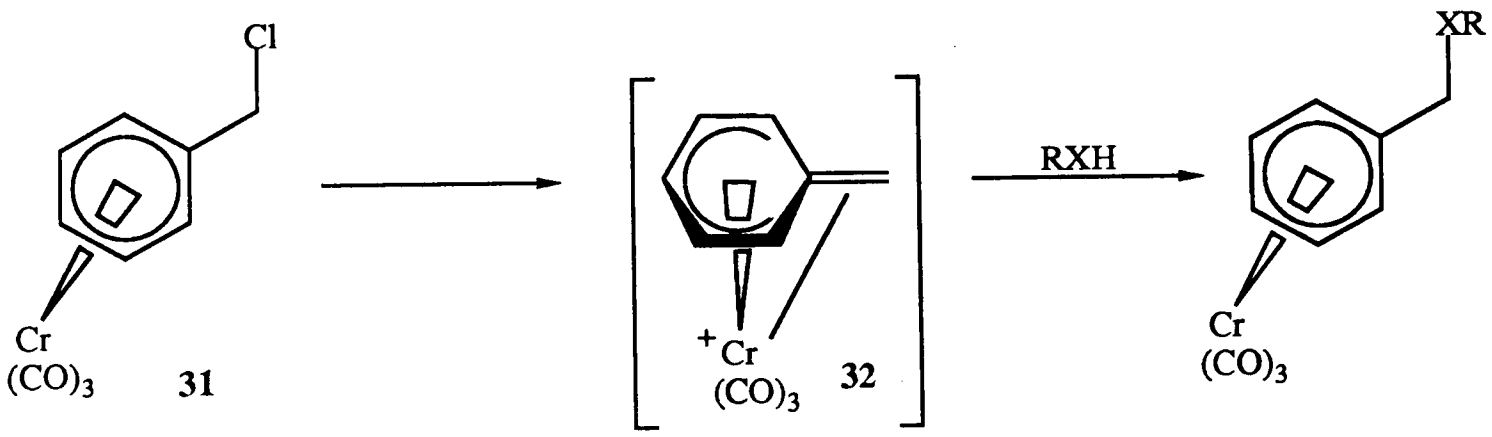
The electron-withdrawing effect also gives rise to the increase in acidity of benzylic protons *via* stabilisation of the conjugate benzylic carbanion. For example, treatment of (toluene)$Cr(CO)_3$ **27** with KO-*t*-Bu generated the corresponding carbanion **28**.[28] This is best represented as possessing significant exocyclic double bond character with the arene bound in η^5-fashion to the $Cr(CO)_3$ unit to give an 18-electron species.



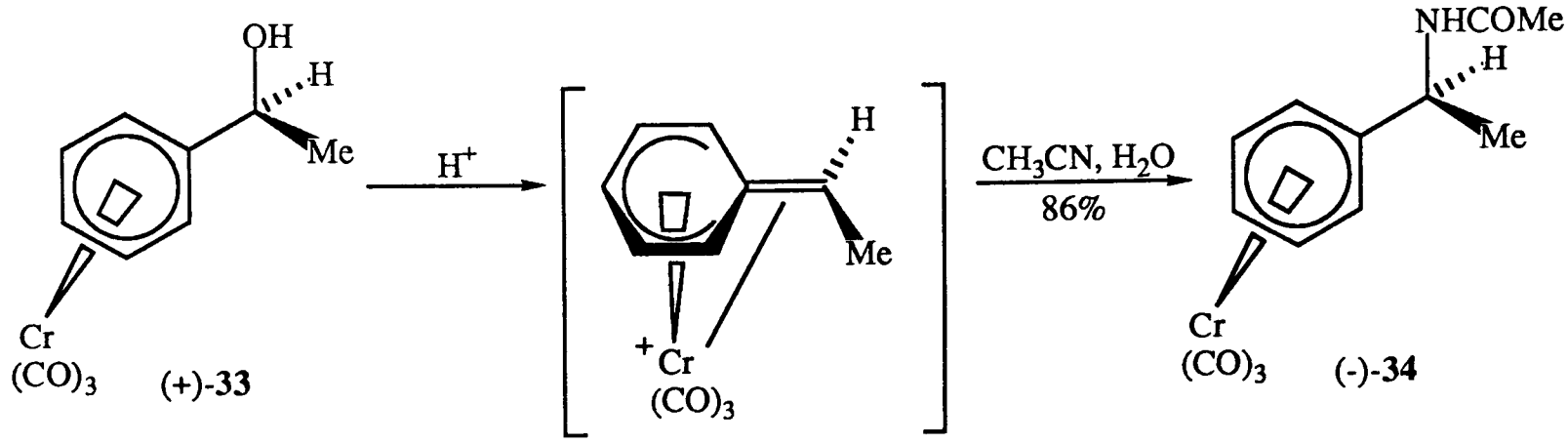
An n.m.r. spectroscopic analysis of benzylic carbanions generated from complexes such as **29** has shown that the *ortho* hydrogens and carbons are magnetically inequivalent. This is consistent with significant *exocyclic* double bond character in the carbanion and restricted rotation about the $C\alpha$-C_{ipso} bond. Such benzylic carbanions can be quenched with a variety of electrophiles to give the benzylically substituted derivatives **30**.[29]



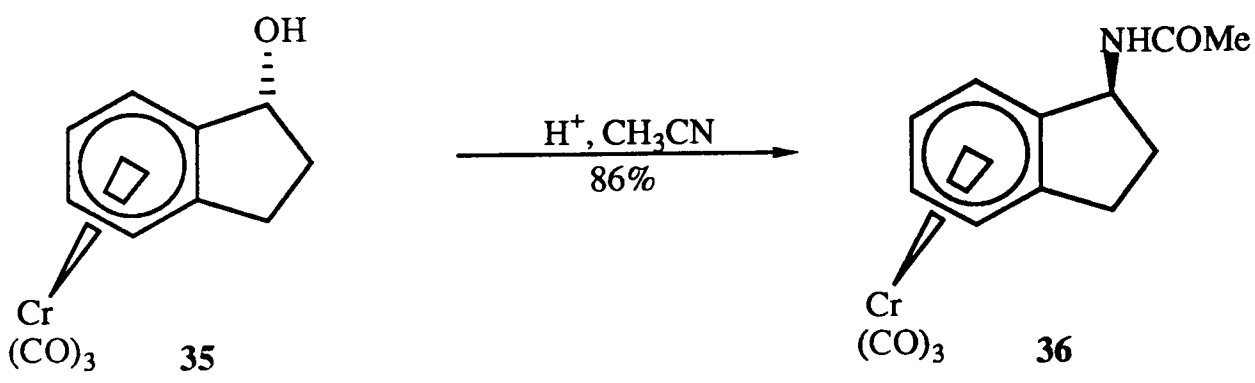
The electron-donating resonance effect results in a stabilisation of benzylic carbonium ions. Thus, neighbouring group participation by an electron pair in a chromium d-orbital increases the rate of S_N1 solvolysis of benzylic leaving groups. For example, the rate of (benzyl chloride)Cr(CO)3 **31** solvolysis is 10^5 times greater than that of the free arene.[30] The intermediate cation is best represented as an 18-electron η^7 species **32** possessing significant *exocyclic* double bond character, again with restricted rotation about the $C\alpha$-C_{ipso} bond.[2]



With acyclic substituents, for maximum orbital overlap the benzylic leaving group and chromium lone pair must attain an *antiperiplanar* relationship. Thus, *antiperiplanar* departure of the leaving group from the *exo* face is strongly preferred. Attacking nucleophiles must approach from the *exo* face *antiperiplanar* to the metal unit. Consequently, an overall retention of configuration occurs in substrates with a chiral centre at the benzylic position. For example, treatment of (*S*)-(1-phenethanol)Cr(CO)3 (+)-**33** with acetonitrile and acid under Ritter reaction conditions gave the corresponding (*S*)-amide complex (-)-**34** with essentially complete retention of configuration.[31]



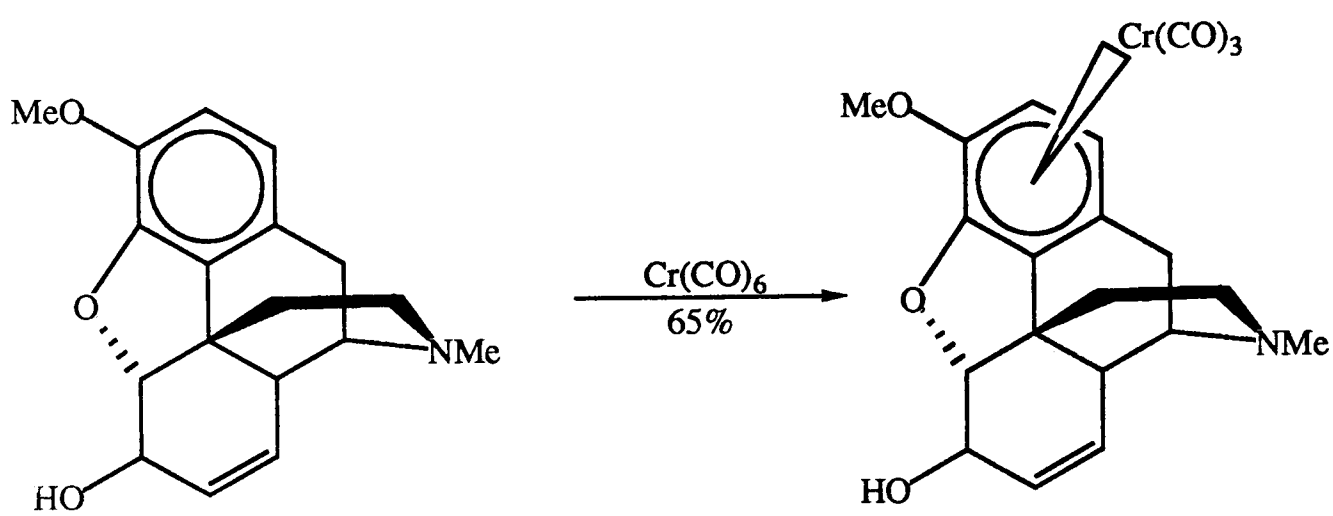
When the side-chain leaving group is geometrically restrained and can only lie *endo*, for example in the *endo*-1-indanol complex **35**, initial departure of the benzylic substituent occurs in a *synperiplanar* mode. Subsequent *exo* attack of nucleophile can occur to give overall inversion of configuration. For example, treatment of *endo*-(1-indanol)Cr(CO)3 **35** with acetonitrile and acid gave exclusively the *exo*-amide complex **36** with total inversion at the benzylic position.[31]



Chapter 2. Origins of the Benzylic Oxygen Directing Effect in Complexation Reactions.

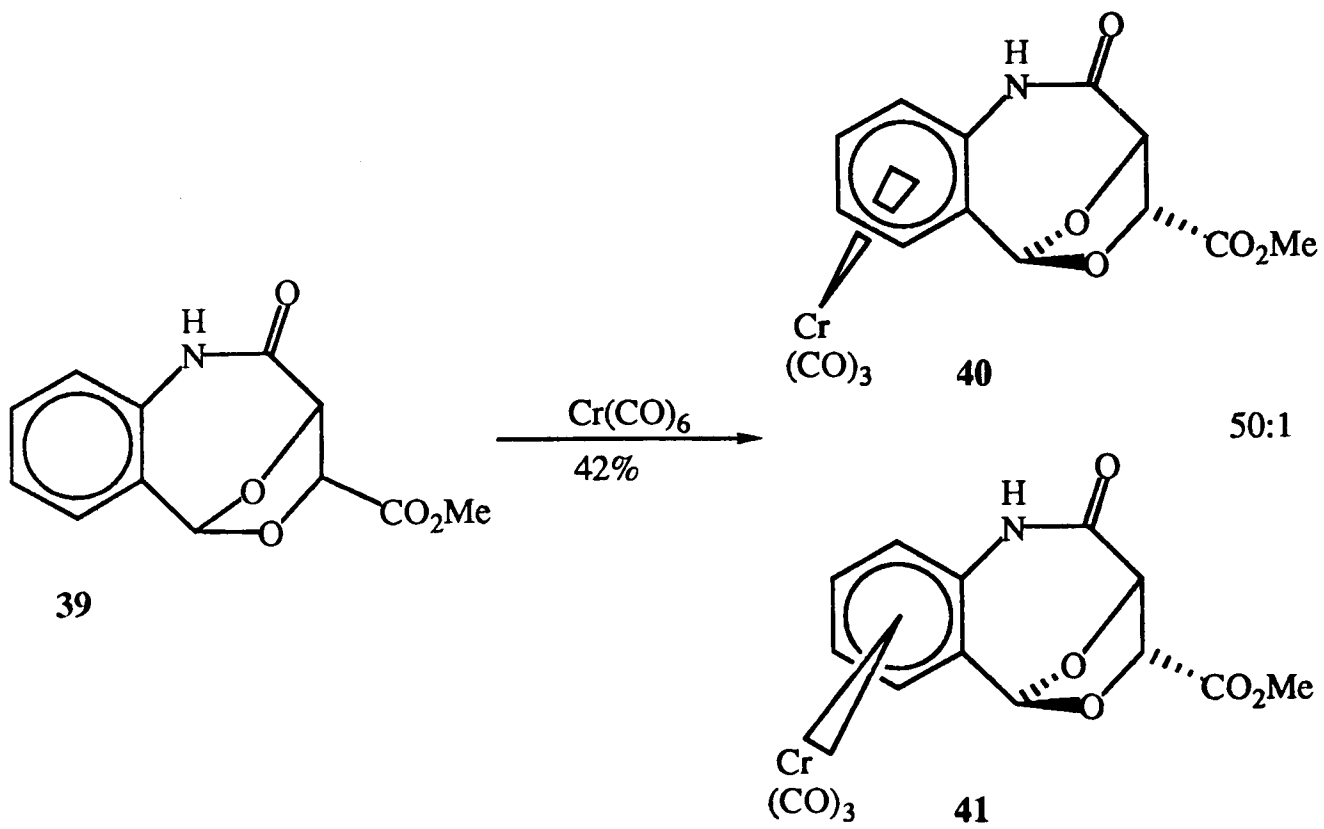
a. *Introduction.*

Unsymmetrically *ortho* and *meta* disubstituted arenes possess enantiotopic faces and complexation to the $Cr(CO)_3$ unit generates racemates. When one of the substituents contains a chiral centre, the faces are rendered diastereotopic. Consequently, complexation of such arenes can give a mixture of diastereoisomers. The face selectivity may be influenced by steric, electronic or chelating effects. The steric effect is exemplified in the complexation of codeine **37** to the $Cr(CO)_3$ unit. The reaction is completely stereoselective, with the metal unit coordinating to the more accessible face of the arene, *syn* to the alkyl bridge, to give complex **38**.[32]

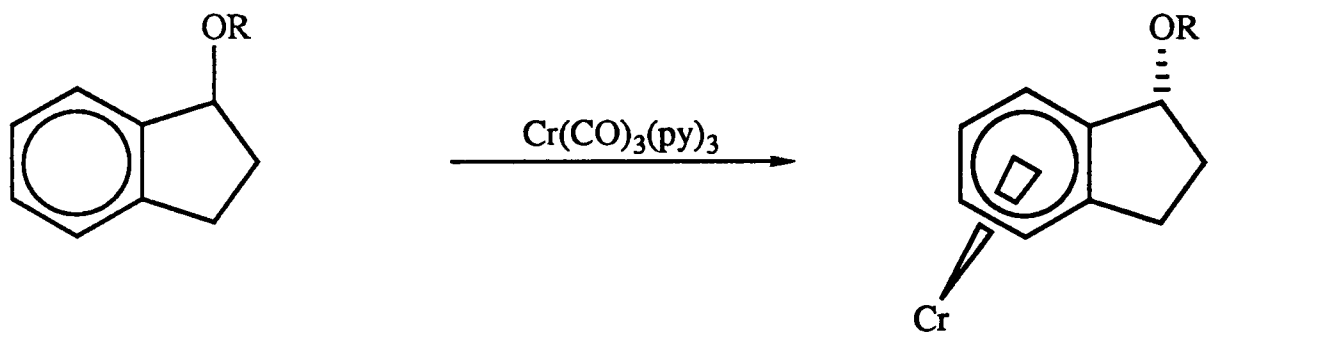


37 **38**

Similarly, complexation of the benzoxazocine **39** to the $Cr(CO)_3$ unit gave a 50:1 mixture of diastereosisomers **40** and **41**. The structure of the major product **40** was determined by an X-ray crystal structure analysis and was consistent with coordination of the metal unit to the least hindered face of the arene.[33]



Benzylic oxygen functions can direct complexation of the $Cr(CO)_3$ unit to the proximate face of an aromatic ring. For example, 1-indanol **42** or the corresponding methyl ether **43** react with $Cr(CO)_3(py)_3$ to give exclusively the *endo*-$Cr(CO)_3$ complexes **35** and **44**.[6]



42 R = H
43 R = Me

35 R = H 18%
44 R = Me 69%

A mechanism involving initial chelation of the incoming chromium unit to an oxygen lone pair, followed by delivery to the proximate face has been invoked for these reactions.[6,34] We wished to investigate the extension of this methodology to the complexation of 1-tetralol **45** and its derivatives **46** and **47** and were particularly interested in the balance between opposing steric and chelate directing effects in compound **47**.

b. *Origins of the Benzylic Oxygen Directing Effect for 1-Tetralol Derivatives.*[35]

Thermolysis of $Cr(CO)_6$ with 1-tetralone **48** in a 10:1 mixture of di-*n*-butyl ether and THF followed by work up and column chromatography* gave bright red crystals of (1-tetralone)$Cr(CO)_3$ **13**. The ^1H n.m.r. spectrum of complex **13** contained four upfield aromatic protons (δ6.16-5.14) characteristic of a complexed arene, and two infrared carbonyl absorption bands (1971, 1900cm^{-1}) characteristic of the $Cr(CO)_3$ group. A molecular ion *m/z* 282 (M^+) in the mass spectrum was consistent with the assignment of complex **13**.

Reduction of complex **13** with $NaBH_4$ in MeOH:THF occurred exclusively from the face *exo* to the metal unit to give the *endo* diastereoisomer of (1-tetralol)$Cr(CO)_3$ **49** as a yellow solid. The ^1H n.m.r. spectrum of complex **49** contained a one proton multiplet (δ4.52) characteristic of the new *exo* benzylic proton. The assignment of complex **49** as the *endo* isomer was in accord with the literature precedent.[18] Complexation of 1-tetralol **45** under standard conditions also gave *endo*-(1-tetralol)$Cr(CO)_3$ **49** as a single diastereoisomer (>200:1), identical in every respect to the previously prepared sample. This stereoselective complexation was consistent with either an oxygen chelated or hydrogen bond directed delivery of the incoming metal unit to the proximate face of the arene.

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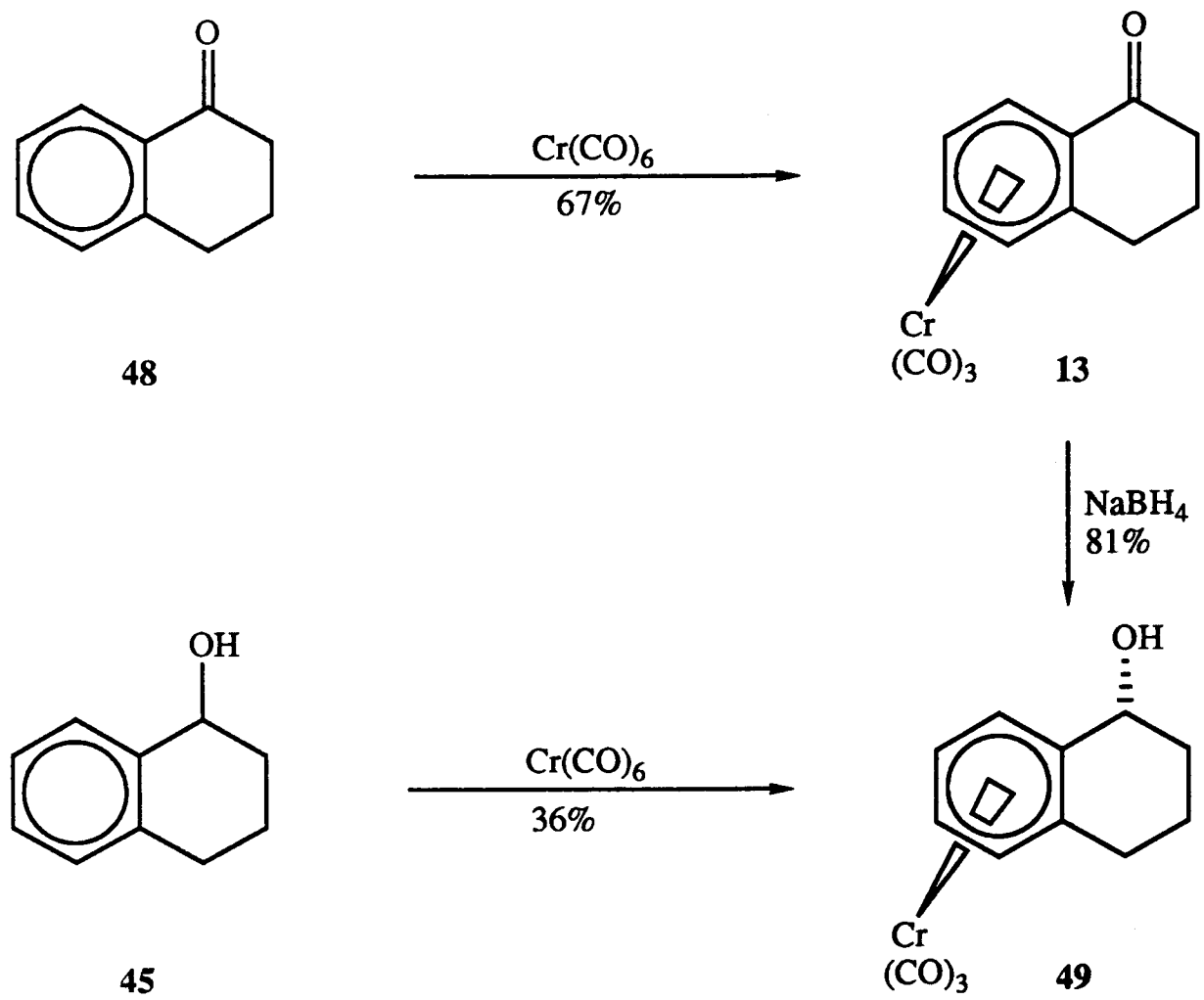
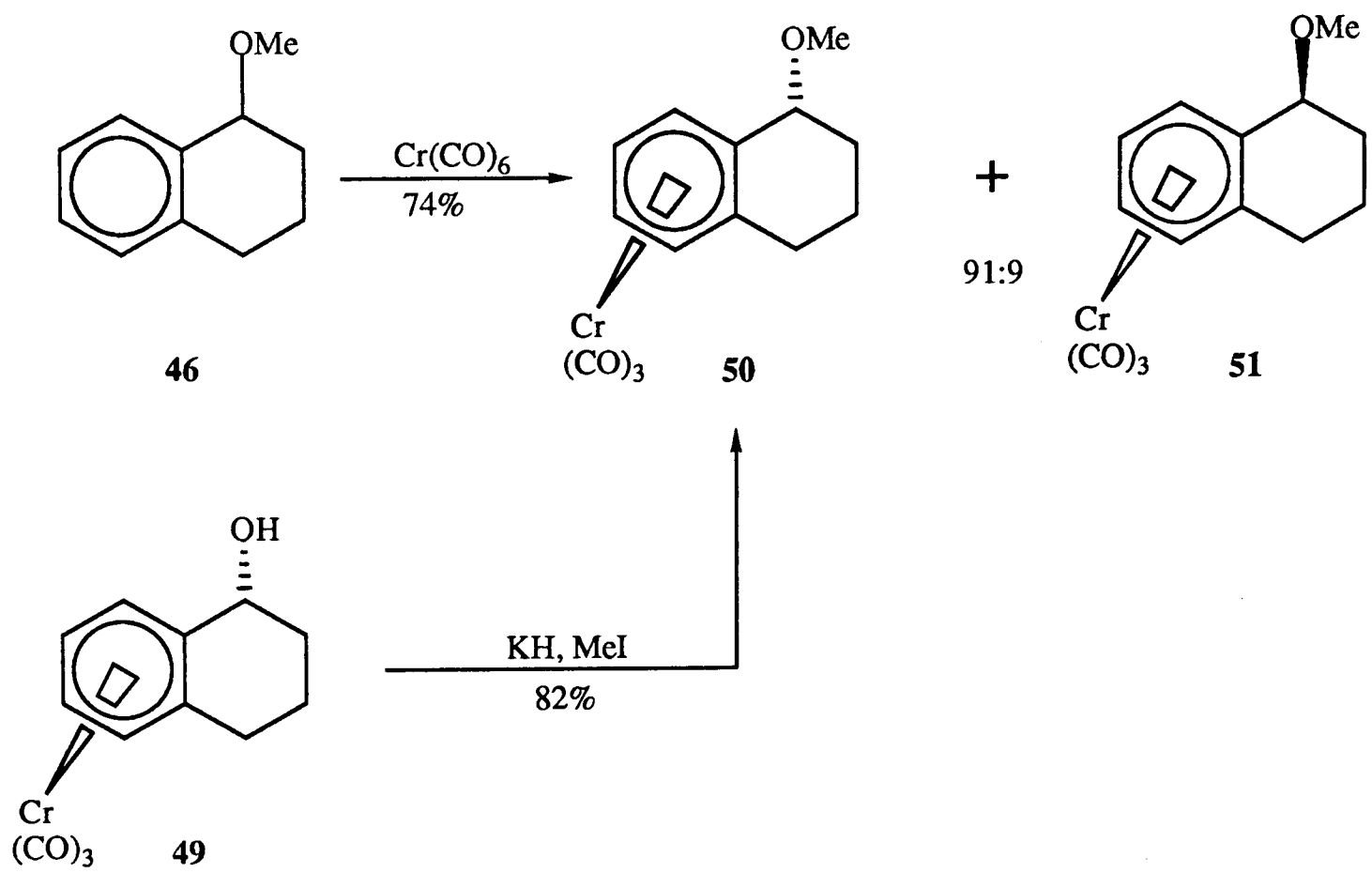
* Henceforth referred to as standard complexation procedure.



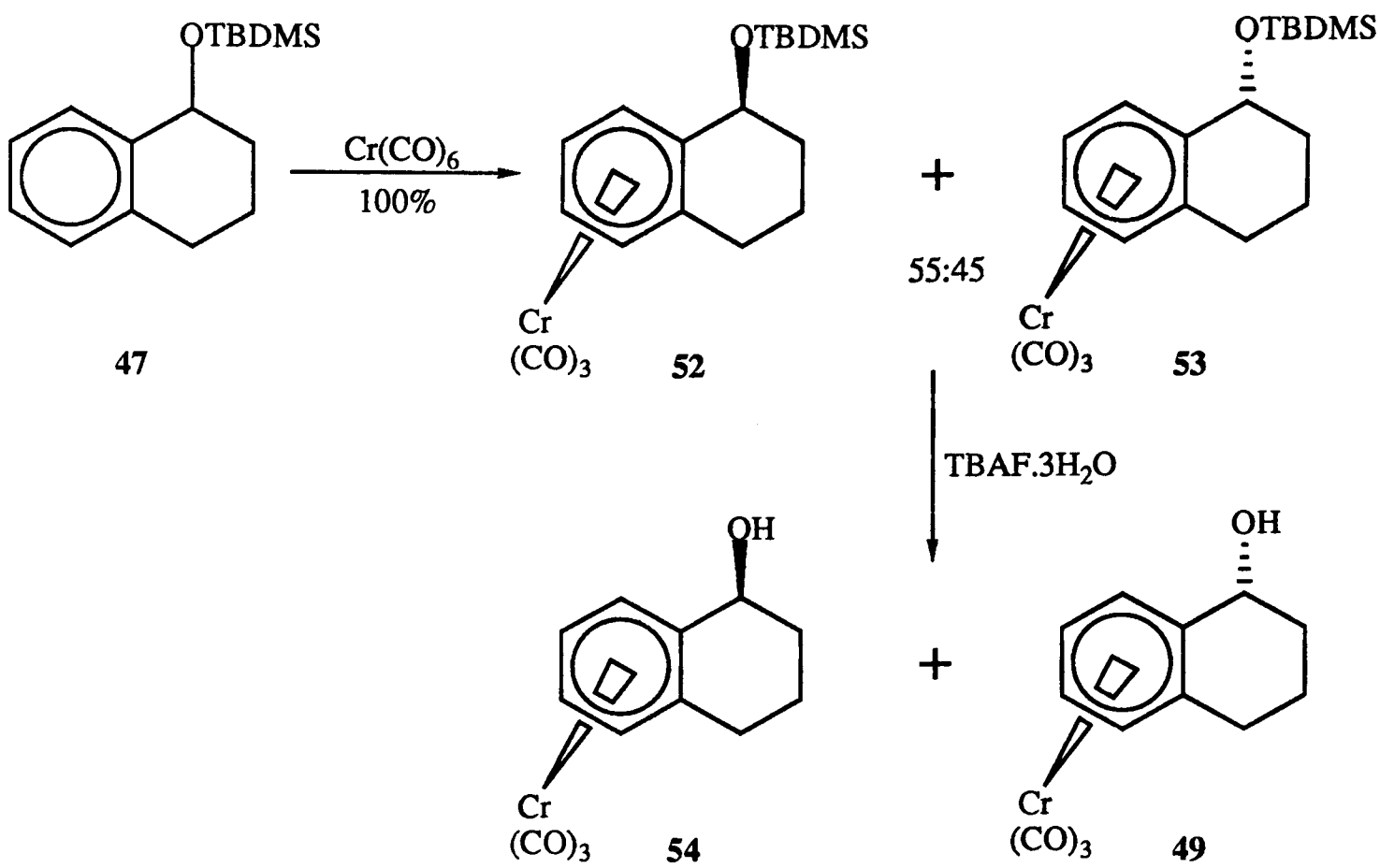
Thermolysis of $Cr(CO)_6$ with 1-methoxytetralin **46**, gave a 91:9 mixture of two products, the *endo* and *exo* complexes **50** and **51**. O-Methylation of *endo*-(1-tetralol)Cr(CO)3 **49**, achieved by sequential treatment of complex **49** with KH and MeI, gave only compound **50**, spectroscopically identical to the major product from the above complexation reaction. This confirmed the assignment of the major isomer from the complexation reaction as *endo*-(1-methoxytetralin)Cr(CO)3 **50**. Since both 1-tetralol **45** and 1-methoxytetralin **46** underwent preferential coordination of Cr(CO)3 to the *endo* face, the possibility of the stereoselective complexation of 1-tetralol **45** being hydrogen bond directed is unlikely. Consequently, a direct oxygen-chromium chelate is presumably formed in the complexation rection. The formation of a small quantity of the *exo* isomer **51** in the complexation of 1-methoxytetralin **46** can be attributed to the increase in steric bulk around the coordinating oxygen disfavouring chelation to some extent when compared with 1-tetralol **45**.

When π-acceptor atoms are attached to oxygen, the Lewis basicity of the heteroatom is decreased.[36] Consequently, complexation of *t*-butyldimethylsilyl (TBDMS) protected 1-tetralol, arene **47** should result in decreased *endo* selectivity, since the steric bulk of the silyl group and the reduced Lewis basicity of the oxygen lone pairs would presumably favour a non-chelated mechanism. Indeed the steric bulk of the silyl group will probably promote coordination of the metal unit to the least hindered *exo* face.



O-*t*-Butyldimethylsilyl-1-tetralol **47** was prepared by treating 1-tetralol **45** with imidazole and chloro-*t*-butyldimethylsilane in anhydrous DMF. The ^{1}H n.m.r. spectrum of the product contained the characteristic nine proton singlet (δ0.99) and two three proton singlets (δ0.21, 0.20) of an O-*t*-butyldimethylsilyl group. Thermolysis of $Cr(CO)_6$ with arene **47** gave a mixture of products **52** and **53** in 55:45 ratio, determined by relative integration of the *t*-butyl proton peaks (**52**, δ0.93; **53**, δ0.99) in the ^{1}H n.m.r. spectrum. The relative assignments of products **52** and **53** were unknown at this stage. Partial desilylation of the mixture with tetra-*n*-butylammonium fluoride trihydrate ($TBAF.3H_2O$) gave, following chromatography, three fractions. The first contained a 1:5 mixture of complexes **52** and **53**. The remaining two fractions were identified as the *endo*- and *exo*-1-tetralol complexes **49** and **54** in 13% and 39% yields respectively. Recrystallisation of the 1:5 mixture of complexes **52** and **53** gave pure *endo*-(O-*t*-butyl-dimethylsilyl-1-tetralol)$Cr(CO)_3$ **53**. The ^{1}H n.m.r. spectrum (C_6D_6) of complex **53** contained a nine proton *t*-butyl singlet (δ1.05) and two three proton methyl singlets (δ0.06, 0.05). Complex **53** gave a molecular ion *m/z* 398 (M^+) in the mass spectrum and a correct elemental microanalysis. The ^{1}H n.m.r. spectrum (C_6D_6) of *exo*-(1-tetralol)$Cr(CO)_3$ **54** contained two aromatic proton doublets (δ5.11-5.08, 4.29-4.27) and two aromatic proton triplets (δ4.47-4.43, 4.41-4.37). Complex **54** gave a correct high resolution mass spectrum. The depletion of complex **52** relative to **53** and the preponderance of complex **54** over **49**, identify complex **52** unambiguously as the *exo* isomer. In the complexation of **47** to $Cr(CO)_3$ the steric effect of the silyl group outweighs any remaining oxygen chelate effect giving rise to a slight predominance of the *exo* isomer **52** formed by a non-chelated coordination of $Cr(CO)_3$ to the least hindered face. Isomer **52** is presumably desilylated more rapidly that its epimer **53** due to

the increased steric bulk around the silicon in **53**, because of its proximate disposition relative to the $Cr(CO)_3$ group.



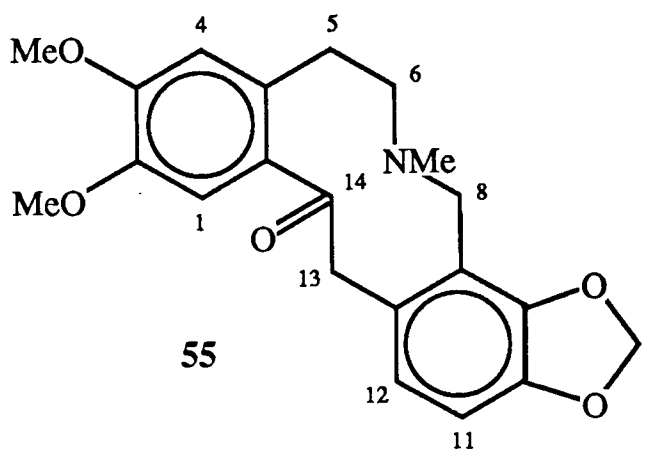
c. *Conclusion.*

This work shows unambiguously that the benzylic oxygen directing effect in the complexation of suitably functionalised arenes can be attributed to a direct oxygen-chromium chelate and that delivery of the metal unit is to the proximate face of the arene. The attachment of bulky π-acceptor groups such as *t*-butyldimethylsilyl to the benzylic heteroatom results in a drastic decrease in *endo* selectivity in 1-tetralol derivatives due to a reduction in Lewis basicity of the lone pairs and an increase in the steric bulk around the heteroatom.

Chapter 3. Regioselective Functionalisation of Protopine Alkaloids.

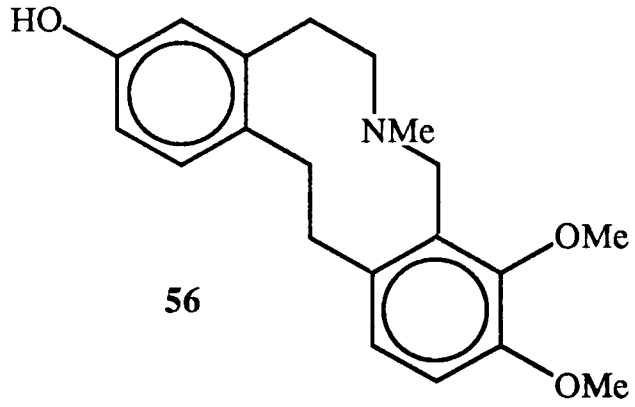
a. *Introduction.*

A wide range of naturally occurring protopine alkaloids have been isolated from a variety of sources. These compounds differ primarily in the nature of oxygen substituents on the two aromatic rings. For example, cryptopine **55** has been found in a number of species, *e.g. B. cordata, C. pallida* and *P. commutatum* and is present in opium.[37]



55

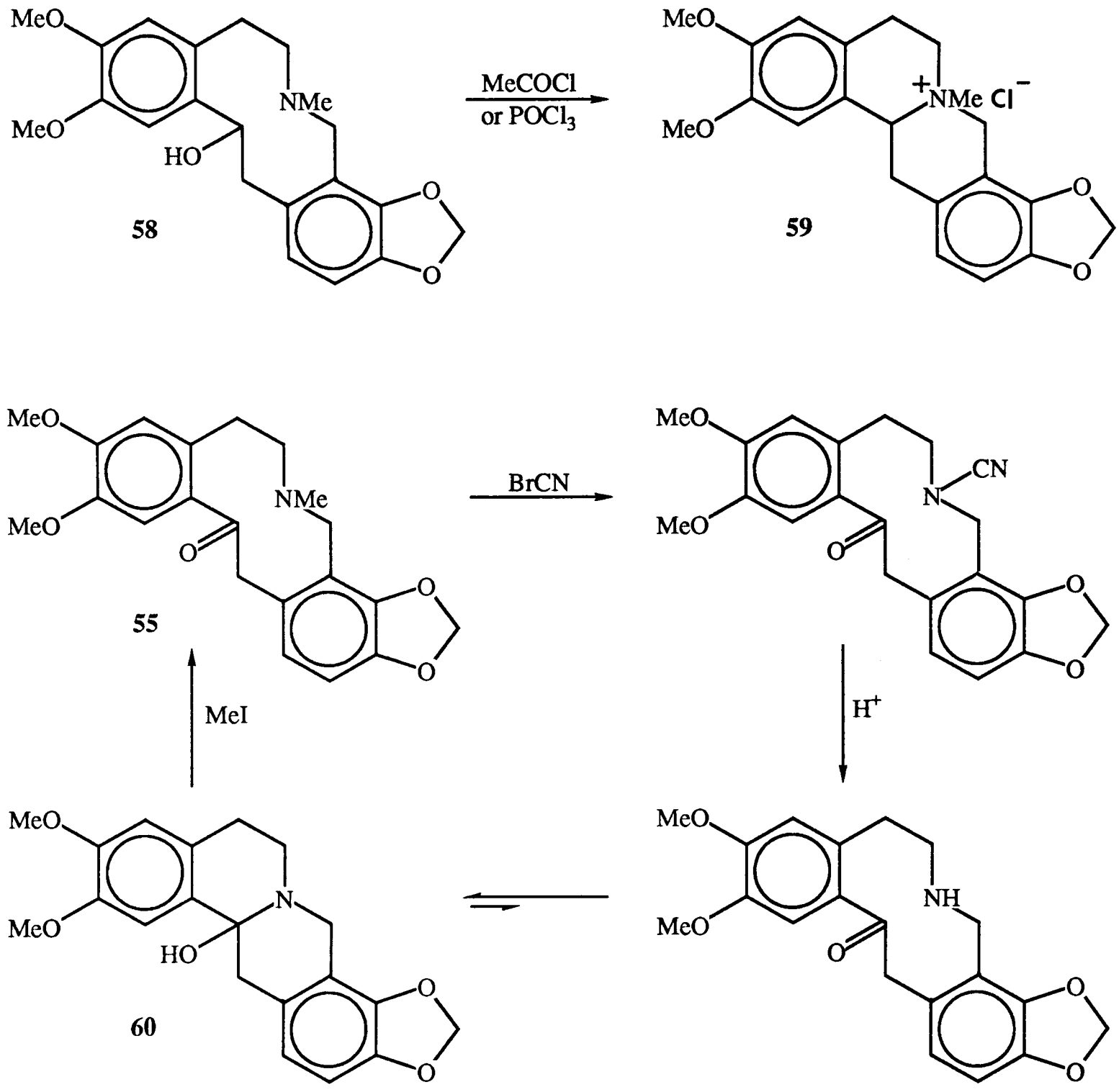
Many protopine alkaloids have important pharmacological effects. Cryptopine **55** is an active coronary vessel dilator and in dogs causes hypotension, inhibition of cardiac activity and stimulation of respiration. In rabbits cryptopine **55** causes a relaxation of skeletal muscles[38] and in humans, excised strips of pregnant uterus contract violently.[39] The deoxygenated protopine alkaloid **56** has non-narcotic analgesic properties.[40]



56

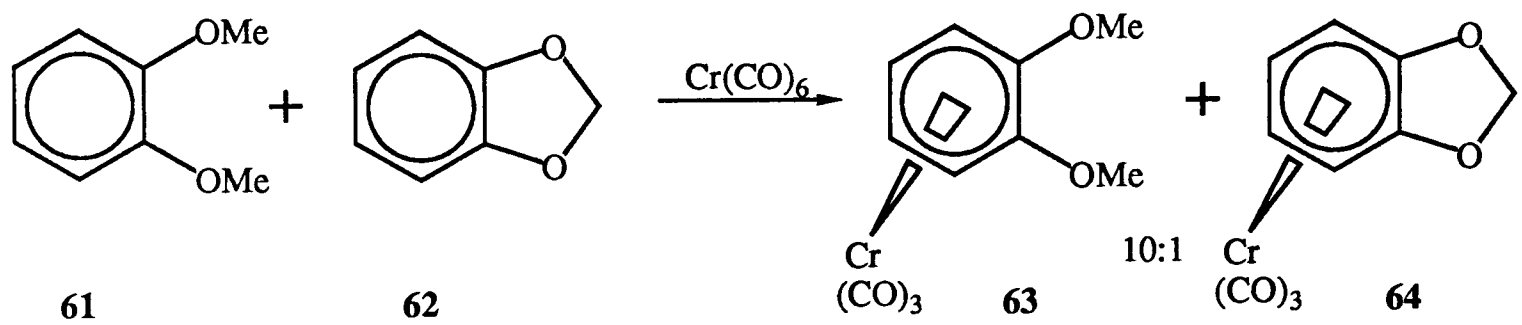
Protopine alkaloids containing a C14 oxo substitutent have strong N-C=O transannular interactions, their infrared spectra typically showing displacement of the carbonyl absorption bands to lower wavenumbers.[37,41,42] In protopine **57** and cryptopine **55** the nature of the intramolecular N-C=O interaction has been determined by X-ray crystallography.[43] The short distance between the carbon atom of the carbonyl group and the nitrogen atom across the ten-membered ring is 2.58$\overset{0}{A}$ in cryptopine **55** and 2.55$\overset{0}{A}$ in protopine **57**. In both structures the nitrogen atom is tetrahedrally surrounded by four carbons and the C14 oxo group lies well off the plane of the dimethoxy substituted aromatic ring. The C=O bond length in cryptopine **55** is 1.21$\overset{0}{A}$, whilst in protopine **57** it is 1.22$\overset{0}{A}$.

Protopine alkaloids can be readily converted into protoberberines. Thus, treatment of dihydrocryptopine **58** with acetyl chloride or phosphorus oxychloride gave isodihydrocryptopine chloride **59**.[44] Similarly, sequential addition of BrCN and a proton to cryptopine **55** led to N-demethylation and generation of 14-hydroxyepiberberine **60**. Addition of MeI to **60** readily regenerated cryptopine **55**.[45]



There is interest in the synthesis of a wide range of derivatives of protopine and protoberberine alkaloids, because of their pharmacological activity and ready interconversion. Selective complexation of one of the two protopine aromatic rings to the $Cr(CO)_3$ unit would increase the acidities of the protons on that ring. Subsequent chelation controlled deprotonation directed by a benzylic oxygen substitutent, followed by electrophilic quench and decomplexation would give rise to a regioselectively substituted protopine skeleton.

It has been found that treatment of an equimolar mixture of 1,2-dimethoxybenzene **61** and 1,3-benzodioxole **62** with $Cr(CO)_6$ under standard conditions gave a 10:1 mixture of complexes **63** and **64** respectively.[46]

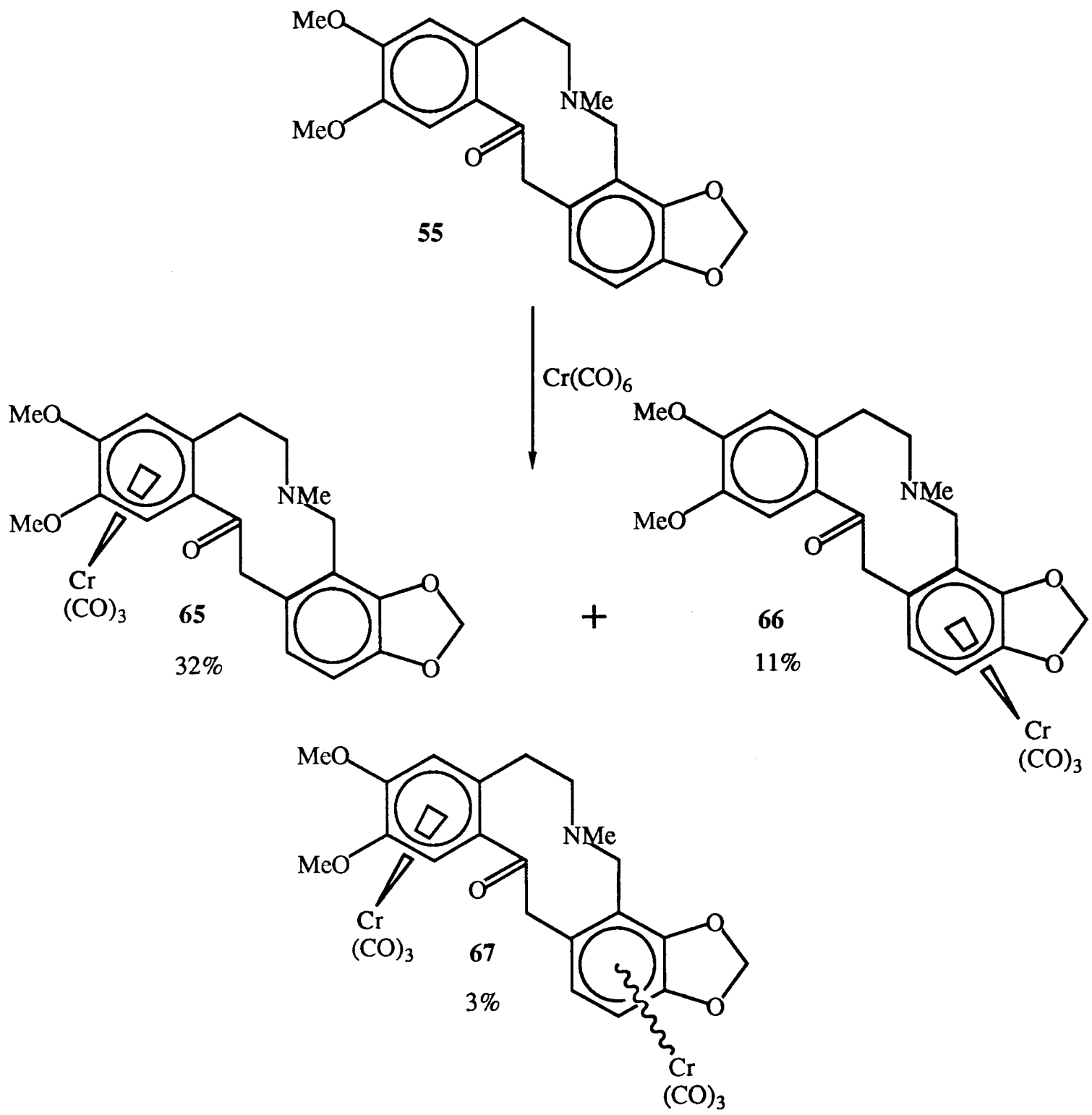


61 **62** **63** **64**

The preferential complexation of the metal unit to arene **61** implies a greater electron density in this ring. In arene **61** there are two mesomeric electron-donations into the ring by *trans-antiperiplanar* lone pairs of electrons on the oxygen atoms. In arene **62**, however, the constraints of the methylenedioxy bridge prevent simultaneous electron-donation by both oxygen *antiperiplanar* lone pairs of electrons and thus the mesomeric electron-donation is reduced. Thus, of the two possible $Cr(CO)_3$ coordinated regioisomers of cryptopine **65** and **66**, the metal unit is expected, in the absence of other effects, to complex preferentially to the dimethoxy substituted ring. The presence of the C14 oxo group, albeit with its reduced carbonyl character (*vide supra*), may somewhat counteract the extra electron density in the dimethoxy ring and thus lower the regioselectivity of complexation compared with that observed in canadine.[46]

b. *Diastereoselective Complexation of Dihydrocryptopine.*

Complexation of cryptopine **55** under standard conditions gave, on work up, a yellow powder consisting of three compounds. Column chromatography gave two fractions, the major one of which contained two products identified by ^1H n.m.r. spectroscopy as the two $Cr(CO)_3$ regioisomers **65** and **66**. Recrystallisation of the mixture from CH_2Cl_2:light petroleum gave exclusively complex **65**, with the metal unit coordinated to the dimethoxy ring. The ^1H n.m.r. spectrum of complex **65** contained two upfield aromatic proton singlets (δ5.73, 4.97) characteristic of a coordinated tetrasubstituted arene with a *para* disposition of the two protons. The other chromatographic fraction was identified as the *bis*-$Cr(CO)_3$ complex **67** on the basis of the ^1H n.m.r. spectrum which contained four upfield shifted aromatic proton peaks as two singlets and an AB system (δ5.67, 4.94 and AB system δ5.52, 4.99, J_{AB} = 6.37Hz).

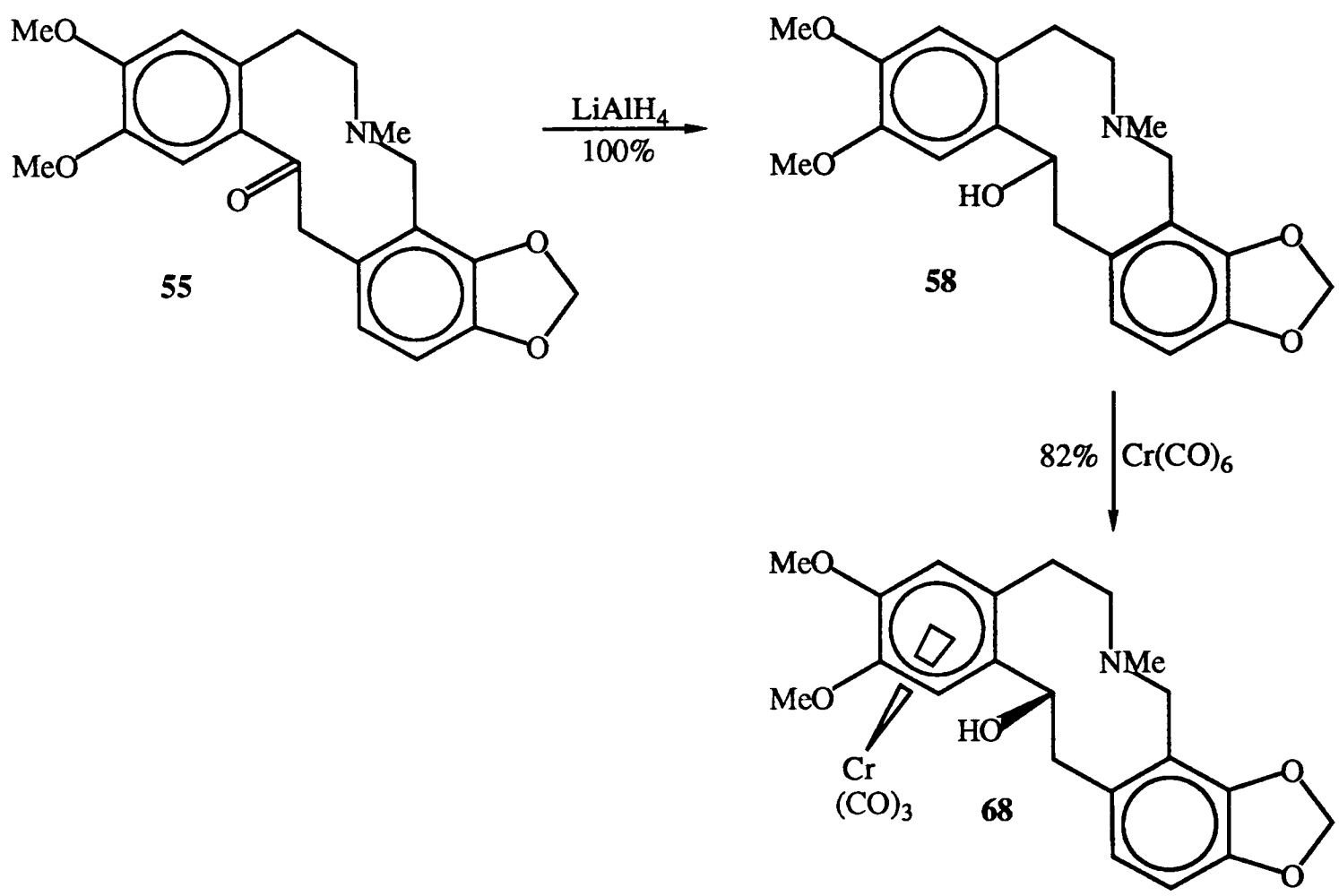


The poor regioselectivity encountered in this reaction demonstrates the similarity in electron density in both arene rings of cryptopine **55**. The electron-withdrawing C14 oxo group essentially counteracts the extra electron density[46] provided by the two methoxy functions in the dimethoxy ring.

Reduction of cryptopine **55** to dihydrocryptopine **58** was envisaged as a means of activating the dimethoxy ring to complexation, by removing the electron-withdrawing effect of the carbonyl group. The presence of a new chiral centre at the benzylic position would render the faces of both aromatic rings diastereotopic and consequently, four possible *mono*-Cr(CO)3 complexed products could result. However, whilst overall regioselective complexation to the dimethoxy ring is predicted, the face selectivity will presumably be influenced by the benzylic oxygen substituent, such that the major product

diastereoisomer would result from coordination of the metal unit to the arene face proximate to the C14 substituent.

Treatment of cryptopine **55** with $LiAlH_4$ in THF gave a quantitative yield of dihydrocryptopine **58**. Complexation of arene **58** under standard conditions gave a single diastereoisomeric product **68** and therefore the reaction is both regio- and stereoselective.



The arene proton peaks in the ^1H n.m.r. spectrum of complex **68** consisted of a two proton AB system (δ6.68, 6.65, J_{AB} = 7.9Hz) and two upfield one proton singlets (δ5.76, 5.10). The upfield shift of the two singlet peaks is consistent with the metal unit coordinated exclusively to the dimethoxy ring of dihydrocryptopine **58**. Complex **68** gave a molecular ion *m/z* 507 (M^+) in the mass spectrum and a correct elemental microanalysis. The regioselectivity of complexation is the same as that observed in the complexation of canadine, where the metal unit also preferentially complexes to the dimethoxy ring due to the greater electron density in this ring.[46] However, the observed regioselectivity may also be due to the benzylic oxygen function directing complexation to the proximate ring.

The relative configurations of the C14 hydroxyl and metal moiety were determined by an X-ray crystal structure analysis. The *exo* disposition of the hydroxyl relative to the chromium within complex **68** is clearly shown in Figure IV. Final atomic coordinates, selected bond lengths, angles and torsional angles are presented in Appendix I.

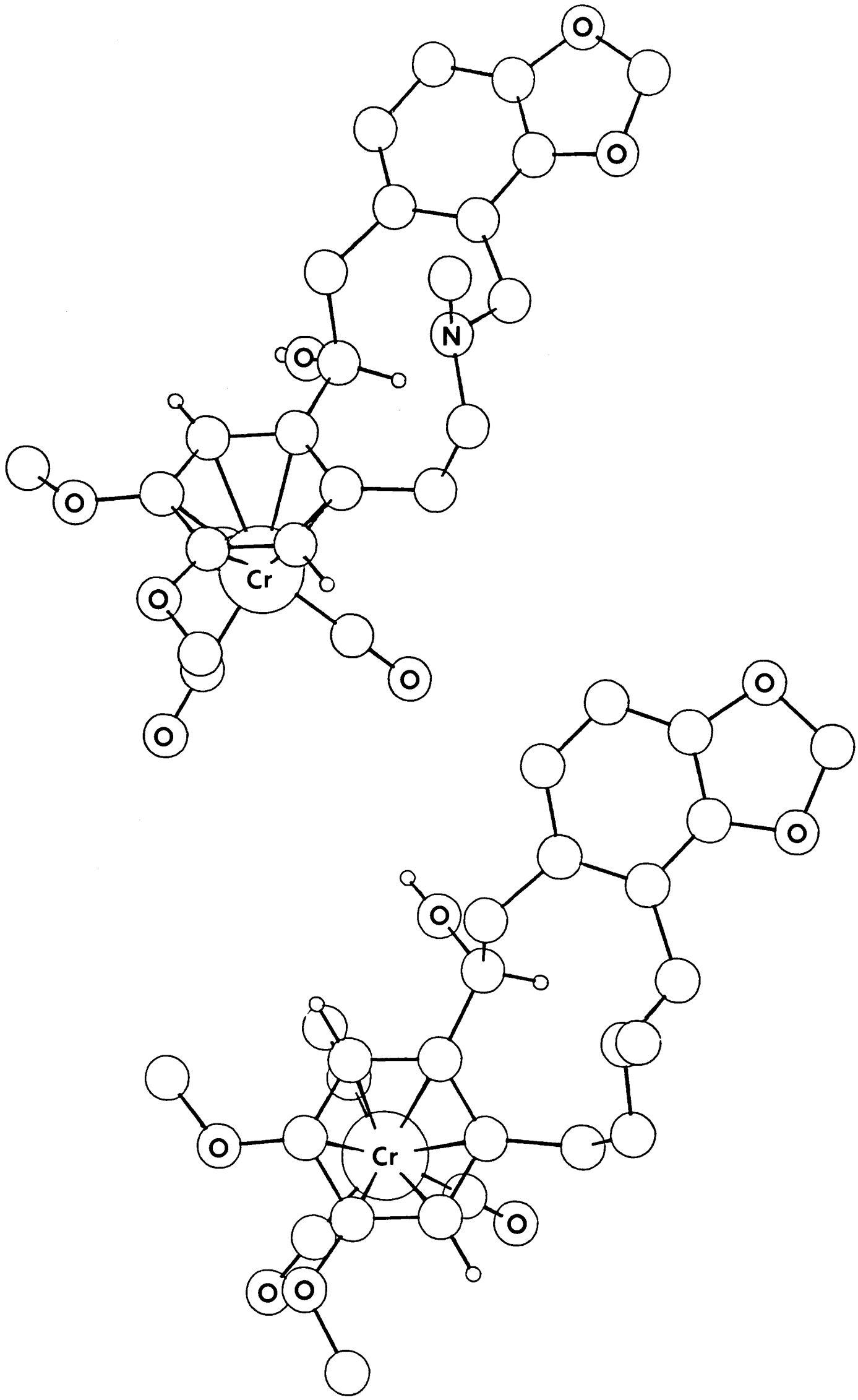


Figure IV. X-Ray crystal structure of *exo*-(dihydrocryptopine)$Cr(CO)_3$ **68**.

The diastereoselective complexation of $Cr(CO)_3$ to dihydrocyptopine **58** to give exclusively the *exo* complex **68**, can be rationalised on the basis of the benzylic oxygen directing effect. Presumably due to the inherent flexibility within the central ten-membered ring, the benzylic hydroxyl function can achieve preferred conformations which place it proximate to the one face of the dimethoxy substituted aromatic ring giving, on complexation, the *exo* isomer **68**.

An attempt was made to reduce the ketone function of complex **65**, the major isomer isolated from the complexation of cryptopine **55**, to provide another route through to *exo*-(dihydrocryptopine)$Cr(CO)_3$ **68** or its *endo* epimer. Treatment of compound **65** in THF solution with $NaBH_4$ or $LiEt_3BH$ gave no reaction. $LiAlH_4$ reacted with complex **65** to give a low yield of an uncharacterisable mixture of both complexed and decomplexed products. Treatment of complex **65** with Red-Al in THF gave an inseparable mixture of several products containing some *exo*-(dihydro-cryptopine)$Cr(CO)_3$ **68** identified by ^1H n.m.r. spectroscopy. The decreased reactivity of ketone **65** towards hydride donors and lack of diastereoselectivity can be attributed to the presence of a strong transannular N-C=O interaction which drastically reduces the double bond character of the C14 oxo group. Assuming that the conformations of the central ten-membered ring of non-complexed and complexed cryptopine **55** and **65** are similar, the benzylic carbonyl group also lies well out of plane with the aromatic ring. These two features are responsible for the colour of complex **65**, which is yellow. $Cr(CO)_3$ complexes of arenes possessing a benzylic oxo group are generally orange to red due to the conjugation of the carbonyl with the (arene)$Cr(CO)_3$ group.

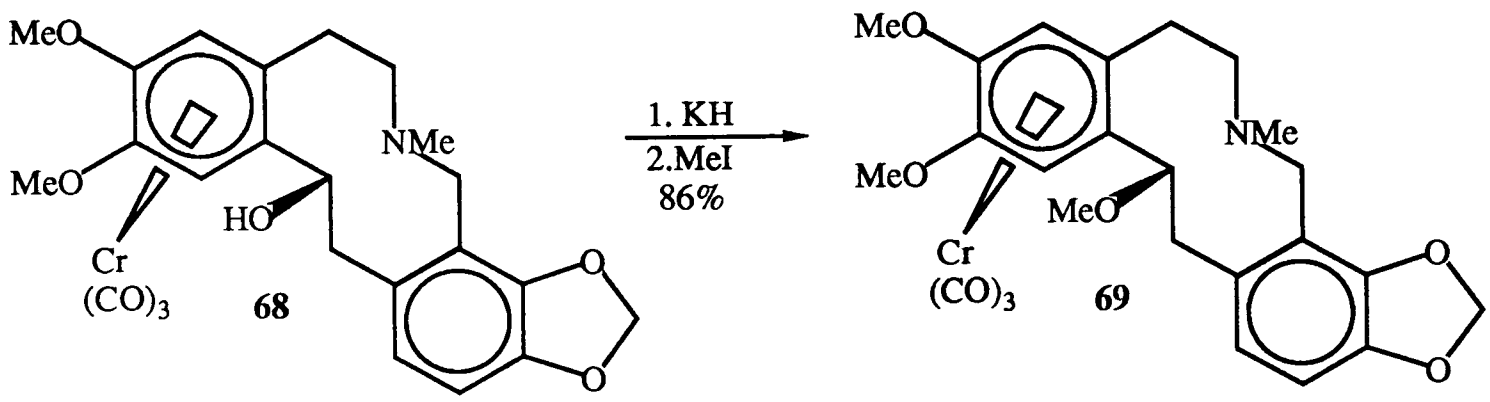
c. *Regioselective C1 Functionalisation of exo-(O-Methyldihydrocryptopine)$Cr(CO)_3$.*

exo-(Dihydrocryptopine)$Cr(CO)_3$ **68** proved to be unreactive to methylation with MeI in the presence of *n*- or *t*-BuLi. Although presumably C14 hydroxyl deprotonation was occurring, O-Li salts do not readily undergo alkylation when treated with alkyl halides. Treatment of **68** with both trifluoroacetic acid (TFA) or $HBF_4.OMe_2$ in the presence of either H_2O or MeOH gave only starting materials, the resistance of the C14-O bond to ionisation presumably demonstrating the inability of the complex **68** to achieve a conformation with the hydroxyl group *antiperiplanar* to the $Cr(CO)_3$ unit.

The C14 hydroxyl was protected by O-methylation, performed by sequential treatment of KH and MeI on complex **68**, to give complex **69**. The ^1H n.m.r. spectrum of complex **69** was similar to that of **68** but with the incorporation of a three proton singlet (δ3.41) characteristic of a methoxy group. The two aromatic proton signals for the complexed ring (δ5.73, 4.98) were notably different with one peak being deshielded by about 0.8ppm. Inspection of the X-ray crystal structure of complex **68** shows the C1-H bond almost *synperiplanar* to the C14-O bond. Assuming that complex **69** adopts a

similar conformation in the solution phase there will be a van der Waals effect due to the steric interaction between the methoxy and C1 aromatic proton.[47] Consequently, the proton attached to C1 will be deshielded, by typically 1ppm. Complex **69** contained a molecular ion peak *m/z* 522 (*M*+1) in the mass spectrum and gave a correct elemental microanalysis.

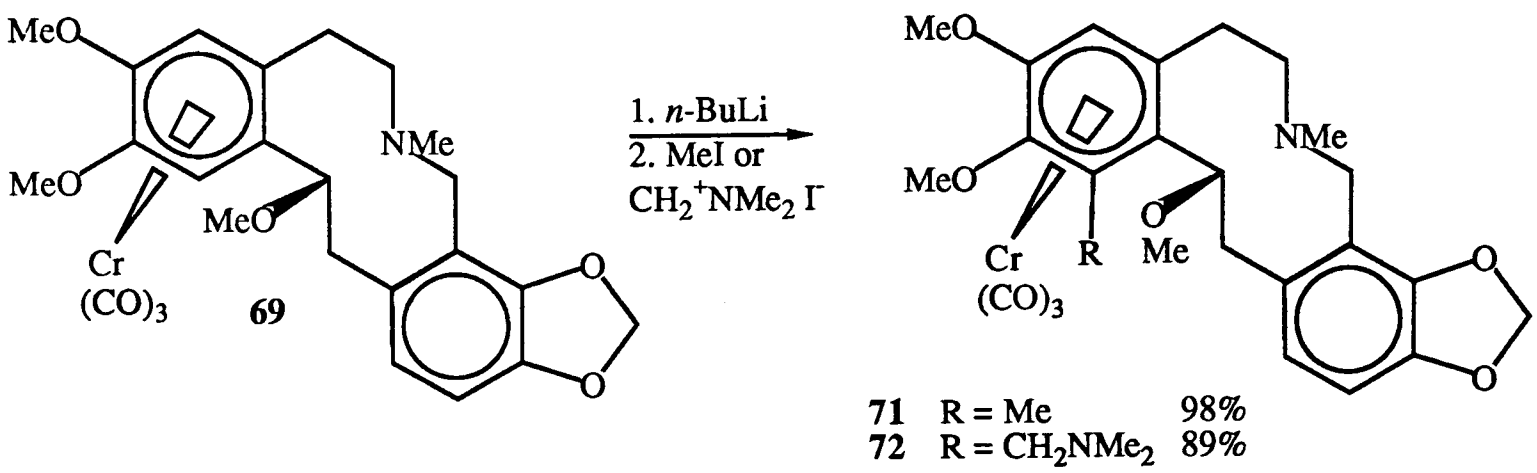
A second route to compound **69** was also envisaged involving the O-methylation of dihydrocryptopine **58** followed by a chelation controlled diastereoselective complexation. Dihydrocryptopine **58** was treated with KH in boiling THF followed by MeI. Work up gave an excellent yield of a white powder identified as O-methyldihydrocryptopine **70** by the presence of a new three proton singlet (δ3.10) in the ^{1}H n.m.r. spectrum, a molecular ion *m/z* 386 (*M*+1) in the mass spectrum and a correct elemental microanalysis. Complexation of **70** under standard conditions gave after work up, a single yellow compound spectroscopically identical to complex **69**.



The regioselective complexation of the metal unit to the dimethoxy ring of **70** can be attributed to the greater electron density in this ring (*vide supra*), whilst the diastereofacial selectivity is due to the directing influence of the C14 oxygen function which is presumably held in such a conformation that it is proximate to the *exo* face of the dimethoxy arene ring.

Treatment of non-complexed O-methyldihydrocryptopine **70** with *n*- or *t*-BuLi under a variety of conditions, followed by MeI quench gave only recovered starting material. However, complex **69** could be efficiently metallated at C1 by *n*-BuLi in THF at -40°C.

The metallated species was quenched with MeI or Eschenmoser's salt ($CH_2N^+Me_2\ I^-$) to give the corresponding 1-functionalised compounds **71** and **72**.

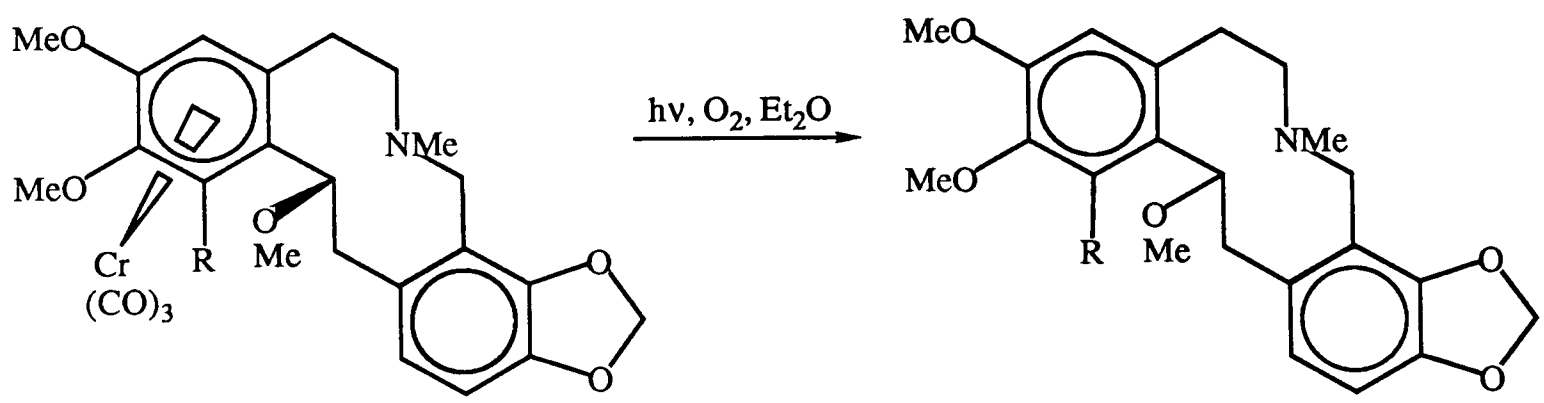


69

71 R = Me 98%
72 R = CH_2NMe_2 89%

The position of metallation and subsequent alkylation was confirmed by ^1H n.m.r. spectroscopy. The spectrum of complex **69** contained two aryl proton singlets for the complexed ring, (δ5.73, *H1*, δ4.98, *H4*), assigned on the basis of the extra deshielding of the H1 proton due to the van der Waals interaction with the C14 substituent (*vide supra*). The ^1H n.m.r. spectra of the alkylated complexes **71** and **72** both demonstrated loss of the lower field aromatic proton singlet (δ5.73) with retention of the upfield singlet (**71**, δ4.73; **72**, δ4.84). This is consistent with exclusive removal of the C1 aryl proton *via* chelation of *n*-BuLi to the benzylic methoxy group, followed by alkylation.[48] Note that both C1 and C4 aryl protons are activated to deprotonation by the aromatic methoxy groups. Presumably, therefore, the C1 directing effect of the benzylic and 2-methoxy substitutents outweighs that of the 3-methoxy group. Both complexes **71** and **72** gave correct elemental microanalyses.

Complexes **71** and **72** were decomplexed by exposing CH_2Cl_2:Et_2O solutions to air and sunlight for several days, giving the free arenes **73** and **74**, after filtration and evaporation of the solvent.



71 R = Me
72 R = CH_2NMe_2

73 R = Me 75%
74 R = CH_2NMe_2 66%

d. *Conclusion.*

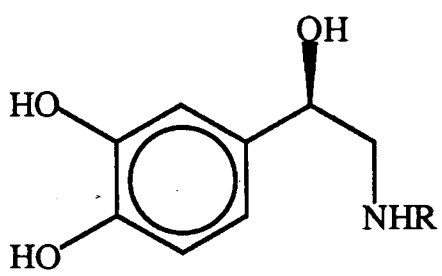
Regioselective complexation of the dimethoxy ring of dihydrocryptopine **58** to $Cr(CO)_3$ has been achieved. The reaction also proved to be face-selective, the metal unit complexing to the arene face *exo* to the benzylic hydroxyl group. A similar diastereoselective complexation reaction was observed for the O-methyl derivative **70**. These stereoselectivities can presumably be attributed to the preferred conformations of the central ten-membered ring, which place the C14 oxygen substituent proximate to the *exo* face of the dimethoxy arene ring.

Regioselective metallation at C1 of complex **69** was achieved *via* a chelation controlled deprotonation, under conditions where the corresponding non-complexed analogue is unreactive. Oxidative decomplexation of the C1 functionalised derivatives released the free arenes **73** and **74**.

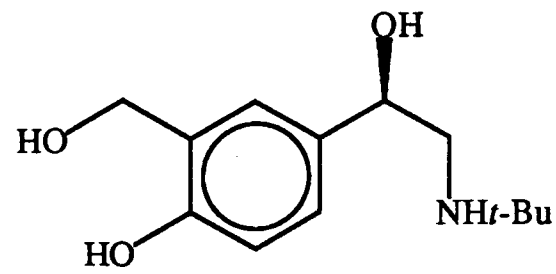
Chapter 4. Regioselective Functionalisation of Phenethanolamines.

a. *Introduction.*

Many phenethanolamines, for example, adrenaline **75** and noradrenaline **76** possess α- or β-adrenergic activity.[49] Salbutamol **77** is a potent β-agonist used in the treatment of asthma.[50]

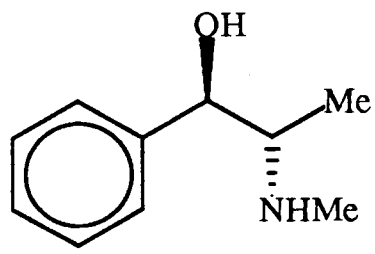


75 R = Me
76 R = H

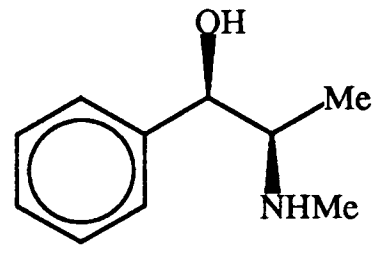


77

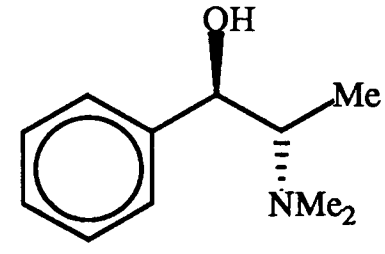
The ephedra bases isolated from the herb *Ma Huang* and typefied by (1*R*,2*S*)-ephedrine **78** and (1*R*,2*R*)-pseudoephedrine **79**, have important physiological effects.[51] (1*R*,2*S*)-Ephedrine **78** is a sympathomimetic drug and in mammals raises the blood pressure, increases cardiac activity, dilates the pupils and raises blood sugar level, whilst its epimer **79** shows similar effects but with a decrease in potency. The N-methyl derivatives of **78** and **79** are also naturally occurring. (1*R*,2*S*)-N-Methylephedrine **80** is an analeptic in humans.[52]



78

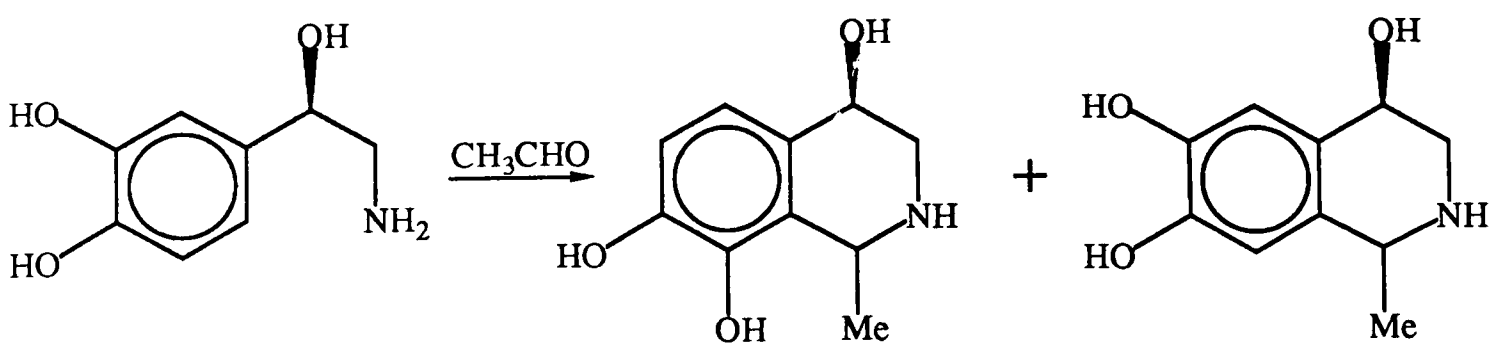


79



80

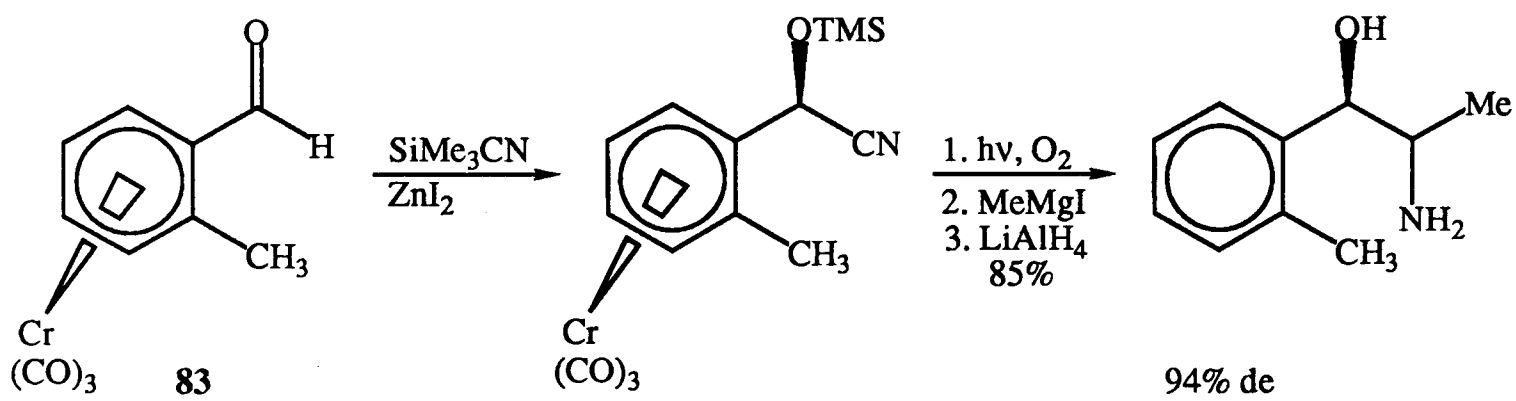
In vivo, phenethanolamines are biological precursors for an important class of 1,4-disubstituted 1,2,3,4-tetrahydroisoquinolines.* Thus, an important pathway in the metabolism of alcohol and a cause of alcoholism is the reaction of noradrenaline **76** with acetaldehyde to give the 4-hydroxytetrahydroisoquinolines **81** and **82**.[53]



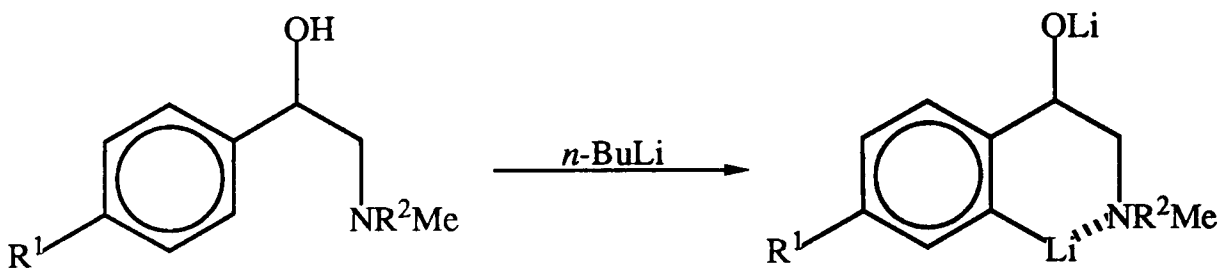
76 **81** **82**

* Henceforth the descriptor 1,2,3,4 applied to tetrahydroisoquinolines will be omitted for clarity.

There is a great deal of interest in the synthesis of unnaturally functionalised phenethanolamines because of their important pharmacological effects. Indeed two recent reports of syntheses of β-amino alcohols of the ephedrine type have used the $Cr(CO)_3$ group to induce diastereoselective addition of trimethylsilyl cyanide, or nitromethane anion to the *o*-tolualdehyde complex **83**.[54,55]



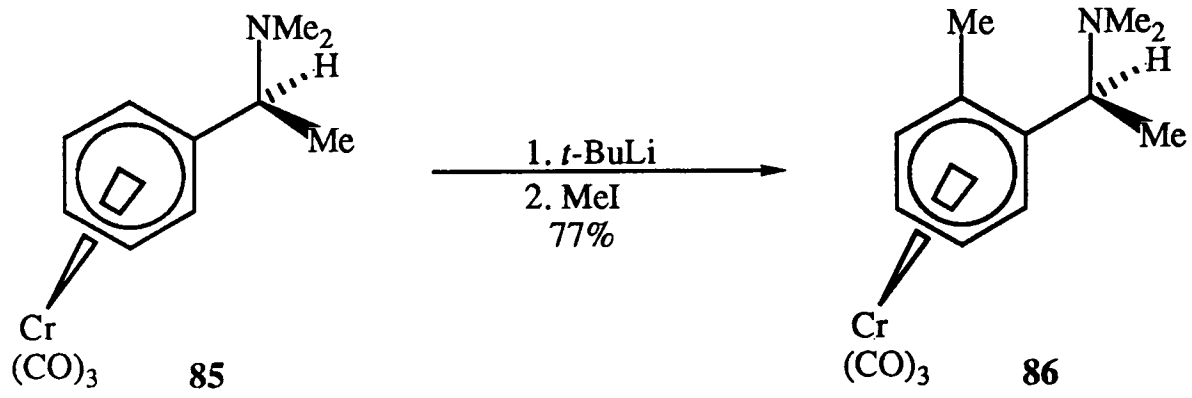
Racemic halostachine **84** and two other phenethanolamine systems undergo regioselective *ortho* metallation with *n*-BuLi *via* coordination of the base to the β-amino function.[56] Attempts to repeat these reactions on (1*R*,2*S*)-N-methylephedrine **80** failed.



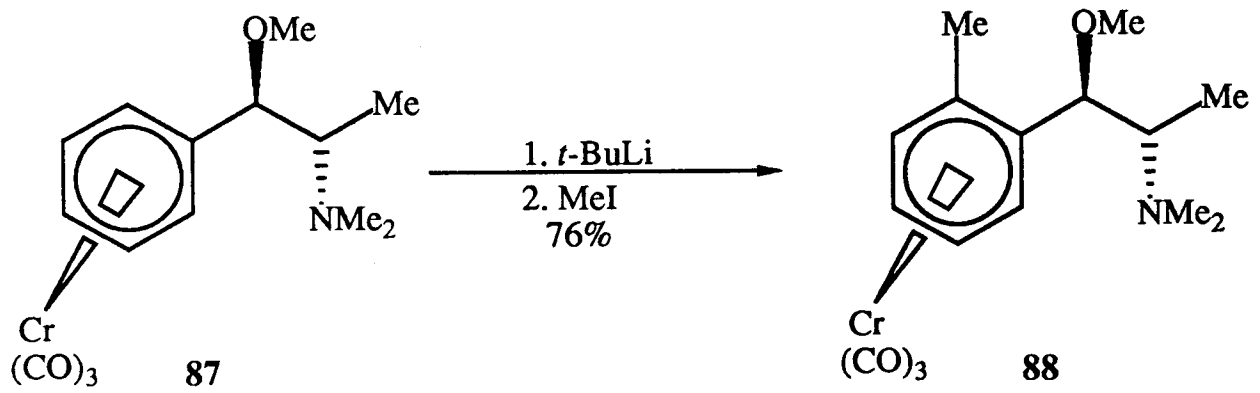
84 $R^1 = H$, $R^2 = H$; $R^1 = H$, $R^2 = Me$; $R^1 = OMe$, $R^2 = Me$

$R^1 = H$, $R^2 = Li$; $R^1 = H$, $R^2 = Me$; $R^1 = OMe$, $R^2 = Me$

Coordination of ephedrine and pseudoephedrine derivatives to the $Cr(CO)_3$ unit renders the two *ortho* protons diastereotopic. The increased acidities of these protons may allow regioselective *ortho* metallation, giving two possible diastereoisomers. Indeed treatment of (*S*)-(N,N,α-trimethylbenzylamine)$Cr(CO)_3$ **85** with *t*-BuLi followed by MeI gave a single *ortho* methylated product **86**, the relative configuration of which was assigned by a single crystal X-ray structure analysis. Only the *pro*-(*R*)[57] *ortho* hydrogen of complex **85** had been removed to give (*RS*)-(N,N,α,*o*-tetramethylbenzyl-amine)$Cr(CO)_3$ **86**.[58]



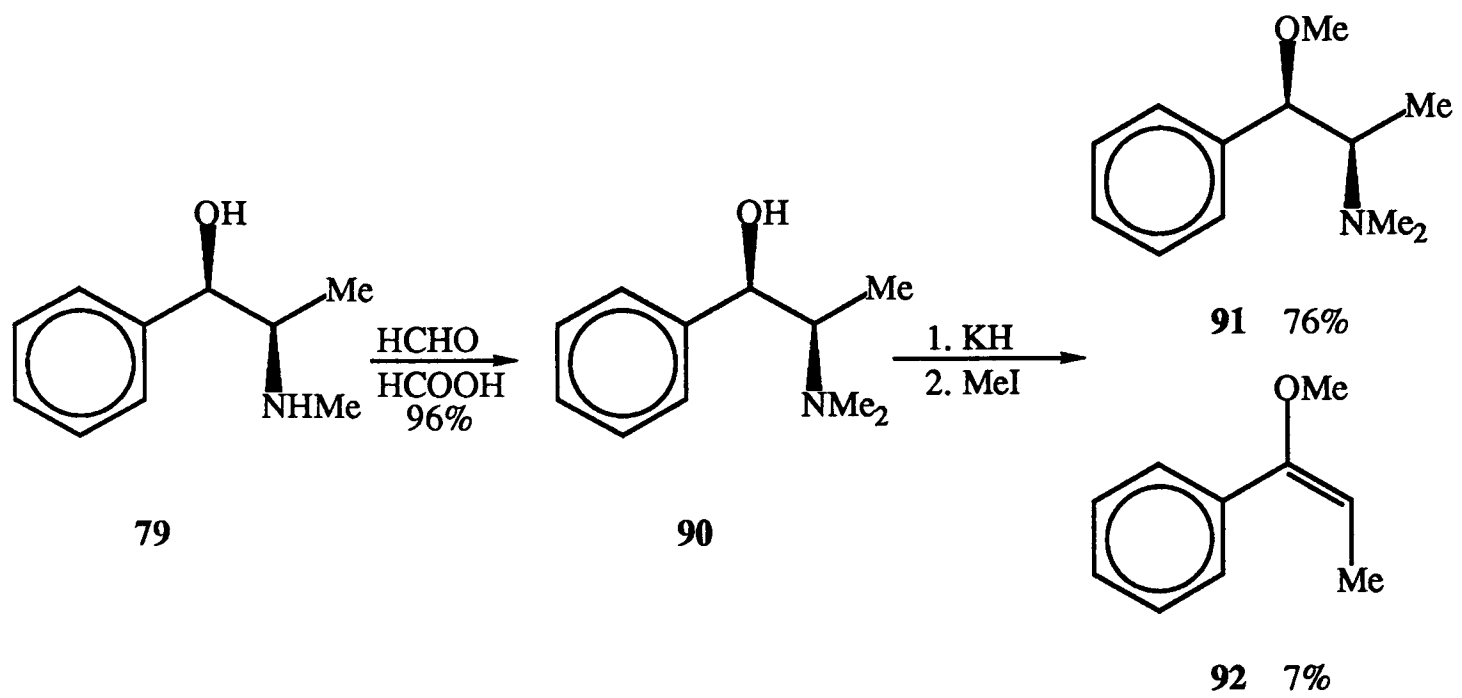
In a previous study[59] (1*S*,2*S*)-(N,O-dimethylephedrine)Cr(CO)$_3$ **87** was diastereoselectively metallated with *t*-BuLi in one of the *ortho* positions and subsequently methylated to give complex **88**. A single crystal X-ray structure analysis of complex **88** revealed that the *pro*-(*R*) *ortho* proton of compound **87** had been exclusively removed. However, an attempt to extend this methodology to the epimeric complex (1*S*,2*R*)-(N,O-dimethylpseudoephedrine)Cr(CO)3 **89** failed under identical reaction conditions and gave rise to a mixture of products. It was hoped that adjusting the conditions or metallating reagent used might increase the diastereoselection in this reaction.



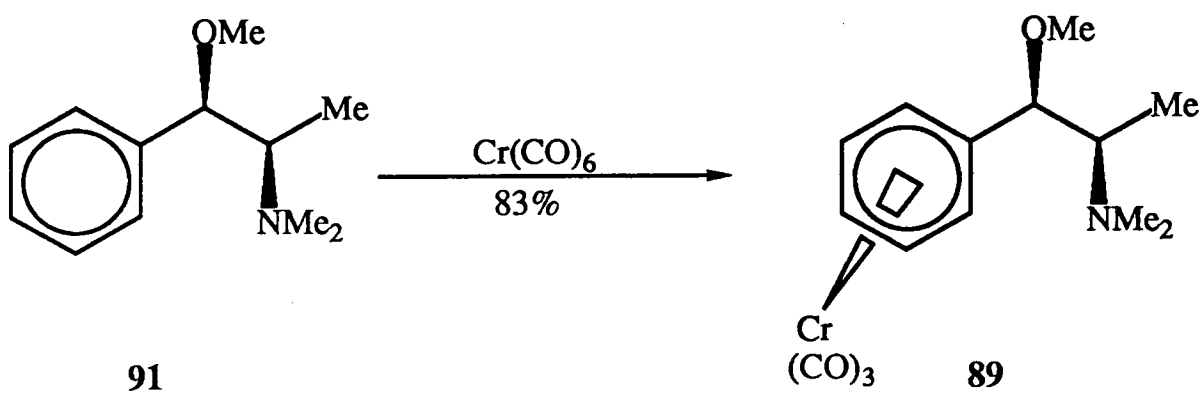
b. *Diastereoselective Functionalisation of (1S,2R)-(N,O-Dimethylpseudo-ephedrine)Cr(CO)3.*

(1*R*,2*R*)-Pseudoephedrine **79** was N-methylated upon treatment with HCHO:HCOOH and the product distilled to give (1*R*,2*R*)-N-methylpseudoephedrine **90**.[59] The ^{1}H n.m.r. spectrum of arene **90** contained a six proton singlet (δ2.31) assigned to the N-methyl groups. An absorption at 2788cm^{-1} in the infrared spectrum was also consistent with the presence of the N-methyl groups. Treatment of a THF solution of **90** with KH and MeI gave, on work up, two compounds **91** and **92**. The major compound was assigned as (1*R*,2*R*)-N,O-dimethylpseudoephedrine **91**, whilst the minor compound was spectroscopically consistent with the *E*-β-methylstyrene derivative **92**. The ^{1}H n.m.r. spectrum of the major product **91** contained a new three proton methoxy singlet (δ3.15), an N-methyl six proton singlet (δ2.36) and a three proton β-methyl doublet (δ0.61, J = 6.81Hz). A molecular ion *m/z* 194 (*M*$^+$+1) in the mass spectrum and a correct elemental

microanalysis confirmed the identity of arene **91**. A nuclear Overhauser enhancement (n.O.e.) experiment on arene **92** confirmed *E* geometry about the double bond. Irradiation of the methoxy singlet (δ3.56) gave enhancements of the aromatic proton multiplet (δ7.47-7.24, 5.20%) and the alkene proton quartet (δ5.40, 4.83%).



Complexation of the methylated pseudoephedrine derivative **91** under standard conditions gave, following work up, yellow cubic crystals of (1*S*,2*R*)-(N,O-dimethyl-pseudoephedrine)Cr(CO)3 **89**. The ^{1}H n.m.r. spectrum of complex **89** was similar to that of arene **91** but the five aromatic proton multiplet had shifted upfield (from δ7.36-7.27 to δ5.63-5.23). Singlets (3H, δ3.58; 6H, δ2.27) were assigned to the methoxy and N-methyl groups, whilst two carbonyl absorption bands in the infrared spectrum (1967, 1883br cm^{-1}) and a correct elemental microanalysis confirmed that complexation had occurred.



Treatment of a THF solution of (1*S*,2*R*)-(N,O-dimethylpseudoephedrine)Cr(CO)3 **89** with *n*-BuLi (-78°C, 2h) followed by addition of MeI (-78°C, 2h)* gave, after work up and recrystallisation, a single compound **93** {$[\alpha]_D^{22}$ = -60° (c 0.7 CHCl3)} as yellow needles in essentially quantitative yield. The ^{1}H n.m.r. spectrum of compound **93** was

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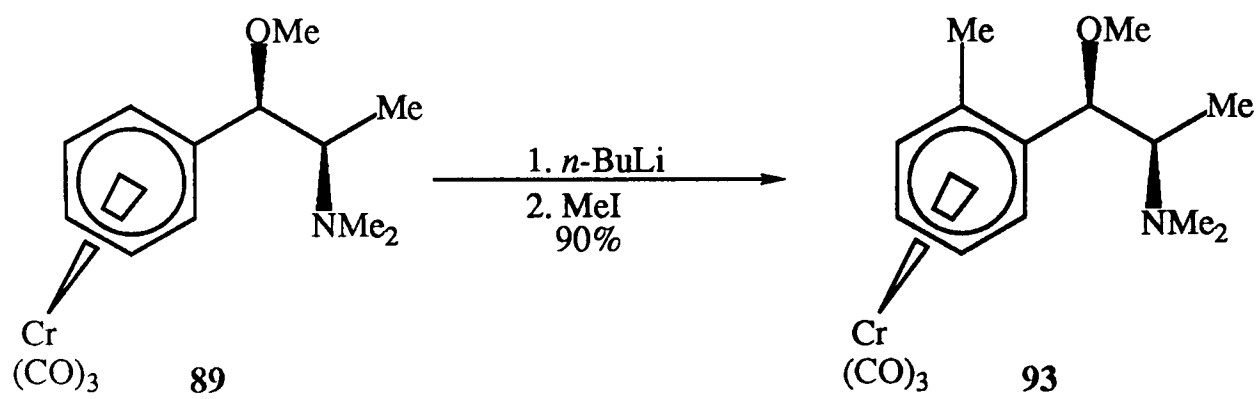
* Henceforth referred to as standard alkylation procedure.

similar to that of starting material **89** but contained two aromatic proton multiplets integrating to four protons (δ5.57-5.53, 5.04-4.98) and a three proton singlet (δ2.33) characteristic of an aromatic methyl group. The aromatic multiplet splitting pattern was characteristic of four contiguous protons, indicating that exclusive *ortho* methylation had occurred. Complex **93** was thus identified as a single diastereoisomer of (1*S*,2*R*)-(N,O,*o*-trimethylpseudoephedrine)Cr(CO)3 and gave a correct elemental microanalysis.



The configuration of the (arene)Cr(CO)3 fragment relative to the side-chain in complex **93** was determined by a single crystal X-ray structure analysis. A perspective diagram of the structure is shown in Figure V below. Final atomic coordinates, selected bond lengths, angles and torsional angles are presented in Appendix II. Since the absolute configuration at the α-position is (*S*) and that at the β-position (*R*) it follows that the *pro*-(*R*) *ortho* proton of complex **89** has been exclusively removed.

c. *Further Functionalisation of (R,1S,2S)-(N,O,o-Trimethylephedrine)Cr(CO)3 and (R,1S,2R)-(N,O,o-Trimethylpseudoephedrine)Cr(CO)3.*

With the preferred site of metallation in these ephedrine and pseudoephedrine derivatives blocked, the possibilities of further diastereoselective functionalisation are worthy of investigation. Indeed metallation can proceed at any of several sites; the two benzylic positions, the remaining *ortho* position or any of the other unsubstituted ring positions. Since complexes **88** and **93** are epimeric at the β-centre, further functionalisation may be highly dependent upon chelation of base with this centre and so a difference in reactivity of complexes **88** and **93** is possible.

Treatment of a THF solution of (*R*,1*S*,2*S*)-(N,O,*o*-trimethylephedrine)Cr(CO)3 **88** with *n*- or *t*-BuLi followed by addition of MeI under standard conditions gave, after work up, an inseparable mixture as a yellow oil. ^{1}H n.m.r. spectral analysis showed the oil to consist of three different compounds, the major one of which possessed two multiplets integrating to three protons (δ2.87-2.72, 2.46-2.39) and a three proton triplet, (δ1.25, J = 7.4Hz) characteristic of an ethyl group. The other two products gave two three proton singlets (δ3.30, 3.39) characteristic of O-methyl groups and a total of four three proton singlets (δ2.28, 2.23, 2.21, 2.13) characteristic of aryl methyl groups. The mixture was

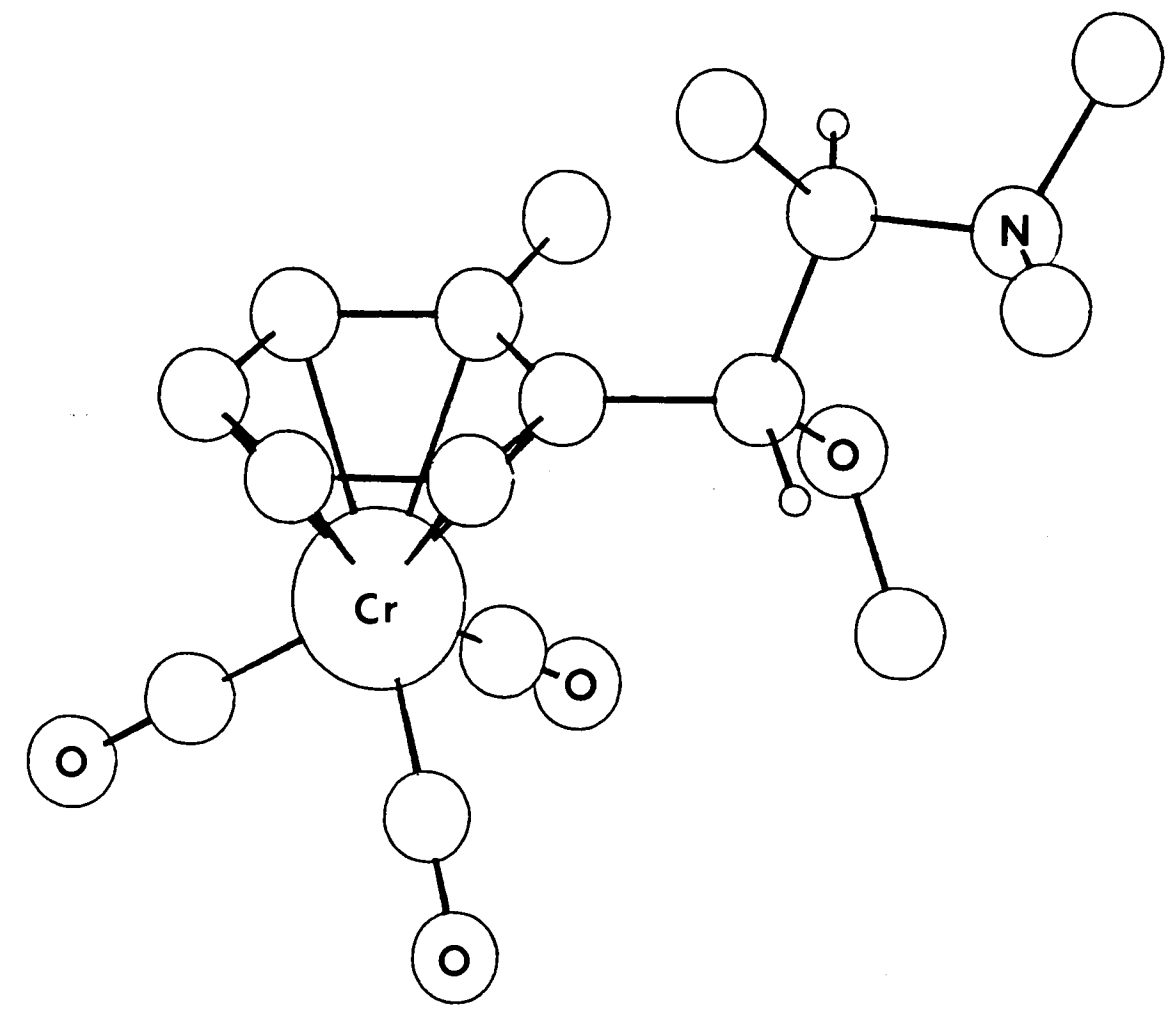
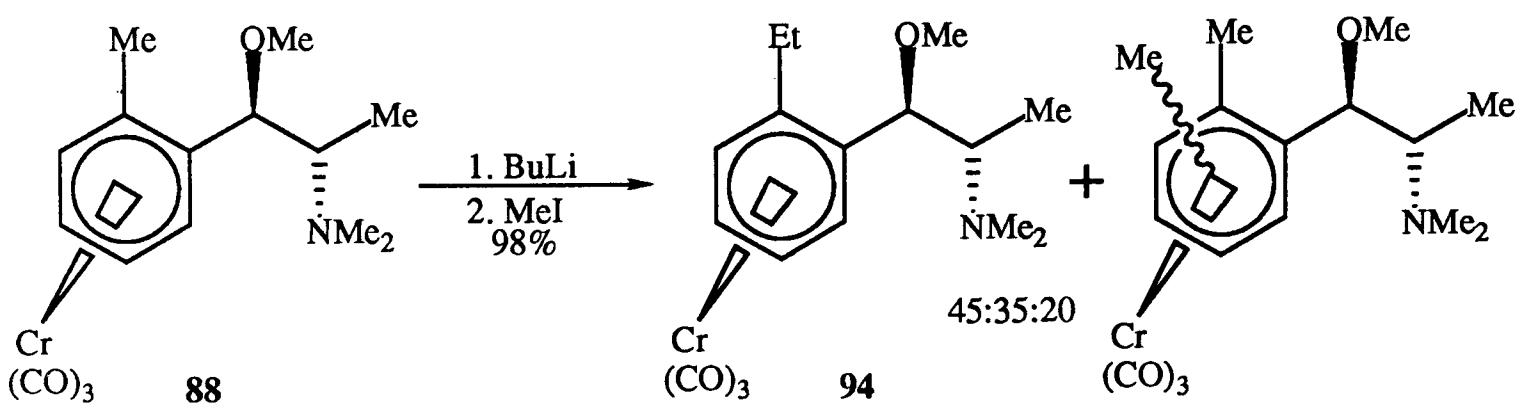
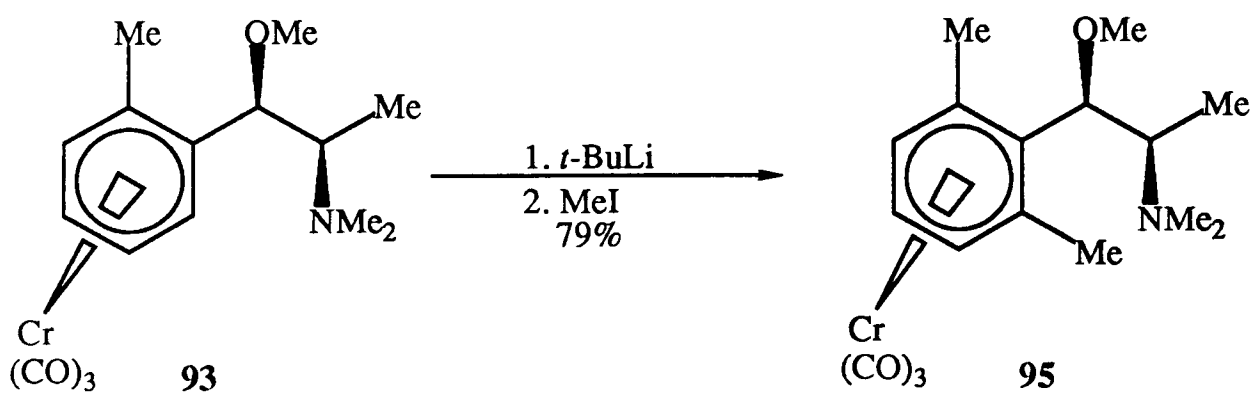


Figure V. X-Ray crystal structure of (*R*,1*S*,2*R*)-(N,O,*o*-trimethyl-pseudoephedrine)$Cr(CO)_3$ **93**.

assigned as (*R*,1*S*,2*S*)-(N,O-dimethyl-*o*-ethylephedrine)Cr(CO)$_3$ **94** and two ring methylated isomers in ratio 45:35:20. Attempts to prepare an authentic sample of complex **94**, *via* deprotonation of (1*S*,2*S*)-(N,O-dimethylephedrine)Cr(CO)3 **87** with *n*- or *t*-BuLi and quenching with a variety of ethylating agents, (EtI, EtOTs and Et3O+BF4-), under standard conditions gave only recovered starting material. Presumably the intermediate *ortho* lithiated species is somewhat basic and abstracts a proton from the ethylating agent in preference to nucleophilic attack.[60]



Metallation of (*R*,1*S*,2*R*)-(N,O,*o*-trimethylpseudoephedrine)Cr(CO)3 **93** with *t*-BuLi under standard conditions proceeded smoothly to give, following MeI quench, a single compound **95** {$[\alpha]_D^{21}$ = +18o (c 1 CHCl3)} as a yellow solid in good yield. Complex **95** was assigned as (1*S*,2*R*)-(N,O,*o*,*o*-tetramethylpseudoephedrine)Cr(CO)3 on the basis of the ^{1}H n.m.r. spectrum which contained the aromatic proton multiplets of three contiguous protons (δ5.58-5.54, 4.89-4.87, 4.86-4.84) and two aryl methyl proton singlets (δ2.42, 2.28). Compound **95** also gave a molecular ion *m/z* 357 (M^+) in the mass spectrum and a correct elemental microanalysis.



The origins of these regioselective reactions can be rationalised in terms of chelation control. Presumably the selectivity observed in these methylations arises in the metallation step. Treatment of (1*S*,2*S*)-(N,O-dimethylephedrine)Cr(CO)3 **87** or (1*S*,2*R*)-(N,O-dimethylpseudoephedrine)Cr(CO)3 **89** with BuLi results in formation of bidentate chelates **96** and **97** respectively. Removal of either *pro*-(*R*) or *pro*-(*S*) *ortho* protons from these chelates can proceed through six-membered intramolecular transition states. Conformations leading to removal of *pro*-(*R*) or *pro*-(*S*) *ortho* protons from both

complexes are shown in Figure VI. In the case of the ephedrine chelate **96**, the required conformations **B** for removal of the *pro*-(*S*) *ortho* proton place not only the α-dimethylaminoethyl side-chain *syn* to the bulky metal unit, but also the β-methyl group in an eclipsing *cis*-1,2 arrangement with the (arene)Cr(CO)3 fragment and proximate to the Cr(CO)3 group. Thus, deprotonations from these conformations are highly disfavoured. However, the required conformations **A** for removal of the *pro*-(*R*) *ortho* proton have only a weak eclipsing *cis*-1,2 interaction of the β-methyl group and (arene)Cr(CO)3 fragment, with the chromium on the distal face of the arene. Similarly, in the case of the pseudoephedrine chelate **97**, the required conformations **D** for removal of the *pro*-(*S*) *ortho* proton place the α-dimethylaminoethyl side-chain *syn* to the Cr(CO)3 unit, thus disfavouring deprotonation. The required conformations **C** for deprotonation at the *pro*-(*R*) *ortho* site, however, have no such bad interaction. Consequently, both ephedrine and pseudoephedrine derivatives **87** and **89** metallate at the *pro*-(*R*) *ortho* site.

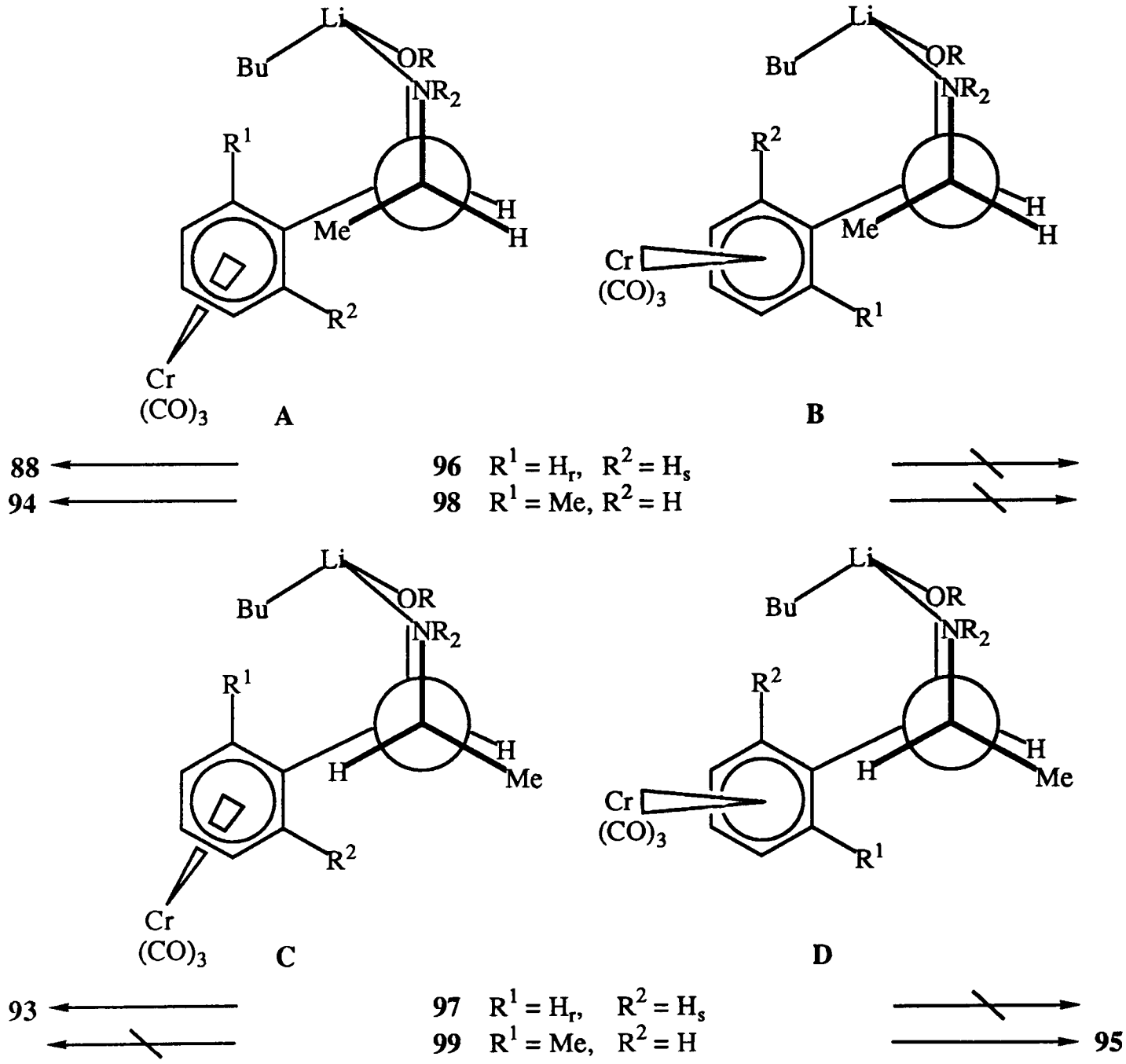
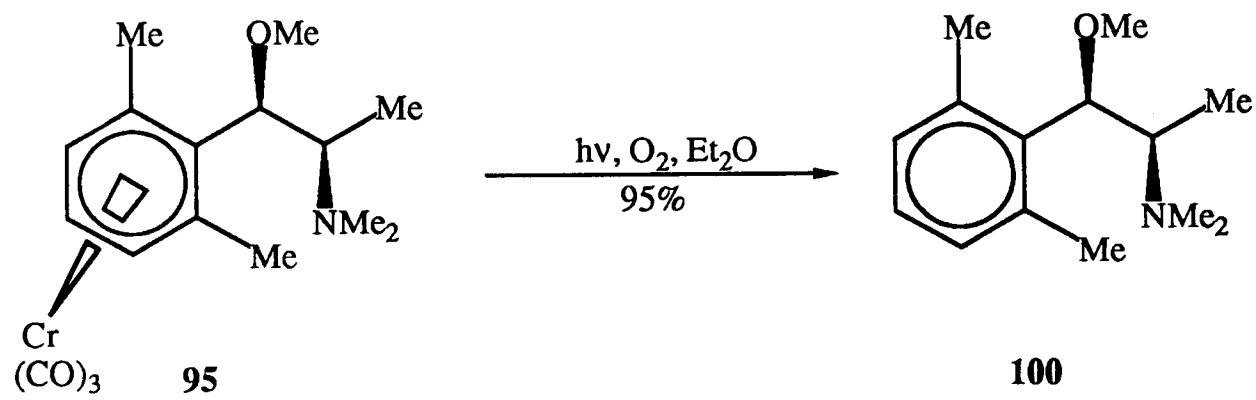


Figure VI. Newman projections along the C1-C2 bond showing the required conformations for *ortho* deprotonation within chelates **96** and **97**.

The regioselectivity of further methylation of complexes **88** and **93** can also be rationalised on a similar basis. Treatment of complexes **88** and **93** with BuLi results in formation of the bidentate chelates **98** and **99** respectively. In the case of the ephedrine derivative **98**, the required conformation for removal of the *ortho* proton is high in energy due to bad steric interactions of the β-methyl group and α-dimethylaminoethyl side-chain with the metal unit. Thus, only a slow metallation at the *ortho* methyl site is observed *via* a seven-membered transition state. The slow rate of metallation at this site accounts for the formation of ring methylated by-products presumably produced *via* a non-chelation controlled deprotonation with free base. In the case of the pseudoephedrine derivative **99**, conformations leading to removal of the *ortho* proton have only one high energy interaction between the α-dimethylaminoethyl side-chain and metal unit. Presumably this interaction in transition states leading to removal of the *ortho* proton is not as disfavoured as the formation of a seven-membered cyclic transition state, required in the deprotonation of the other available site, the *ortho* methyl goup, and consequently only metallation and subsequent methylation is observed at the free *ortho* position.

A Et_2O solution of complex **95** was placed in air and sunlight until a colourless suspension resulted.* Filtration, followed by evaporation of the filtrate gave the free arene **100** in excellent yield. The ^1H n.m.r. spectrum of arene **100** contained two three proton singlets (δ2.47, 2.39) characteristic of the two aryl methyl groups. Two signals were observed since the steric bulk of both *ortho* methyl groups and the size of the heteroatom bearing side-chain increases the barrier to rotation about the ethanolamine-C_{ipso} bond, so that at room temperature the rotation of this group on the n.m.r. timescale is slow and thus the two aromatic methyl groups have different chemical environments.



95 **100**

d. *Conclusion.*

The diastereoselective *ortho* functionalisation of (1*S*,2*S*)-(N,O-dimethyl-ephedrine)Cr(CO)3 **87** has been extended to (1*S*,2*R*)-(N,O-dimethylpseudo-ephedrine)Cr(CO)3 **89** by a change in metallating reagent from *t*-BuLi to *n*-BuLi. The

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* Henceforth referred to as standard decomplexation procedure.

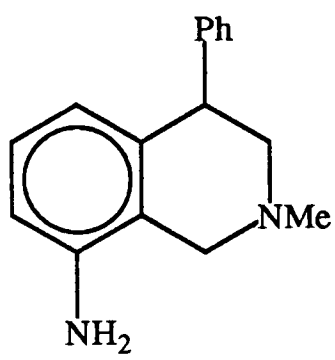
mechanism of this reaction presumably involves formation of a bidentate chelate with BuLi and leads to exclusive removal of the *pro*-(*R*) *ortho* proton.

Further selective functionalisation has proved possible in the case of complex **93** *via* a bidentate chelate directing metallation to the remaining site *ortho* to the ethanolamine side-chain. In the case of the epimeric complex **88**, transition states leading to *ortho* deprotonation *via* a bidentate chelate are unfavourable due to an adverse steric interaction between the metal unit and β-methyl group. Consequently, slow metallation occurs predominantly at the aromatic methyl group presumably *via* a seven-membered chelated transition state.

Chapter 5. The Synthesis of Functionalised 1,2,3,4-Tetrahydo-isoquinolines.

a. *Introduction.*

An extensive range of natural products is based upon the tetrahydoisoquinoline framework. Many of these compounds have important pharmacological activity. For example, nomifensine **101** and the pyrroletetrahydroisoquinoline **102** both demonstrate important antidepressant activity.[61]



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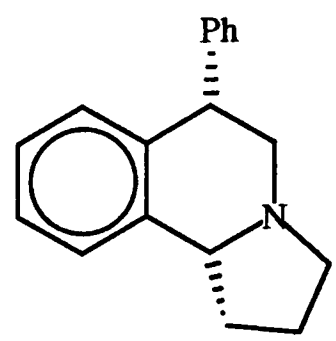
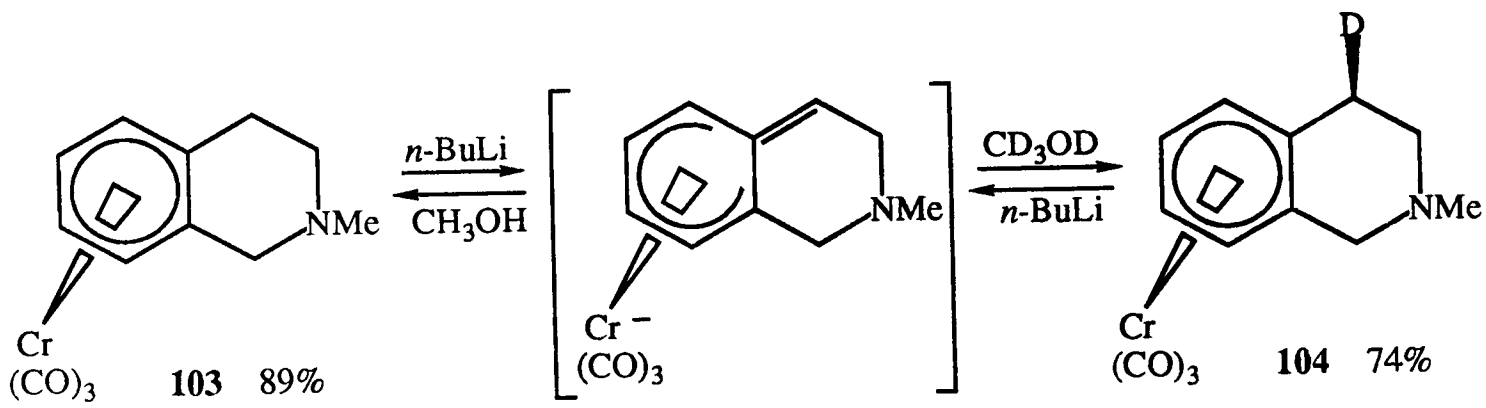
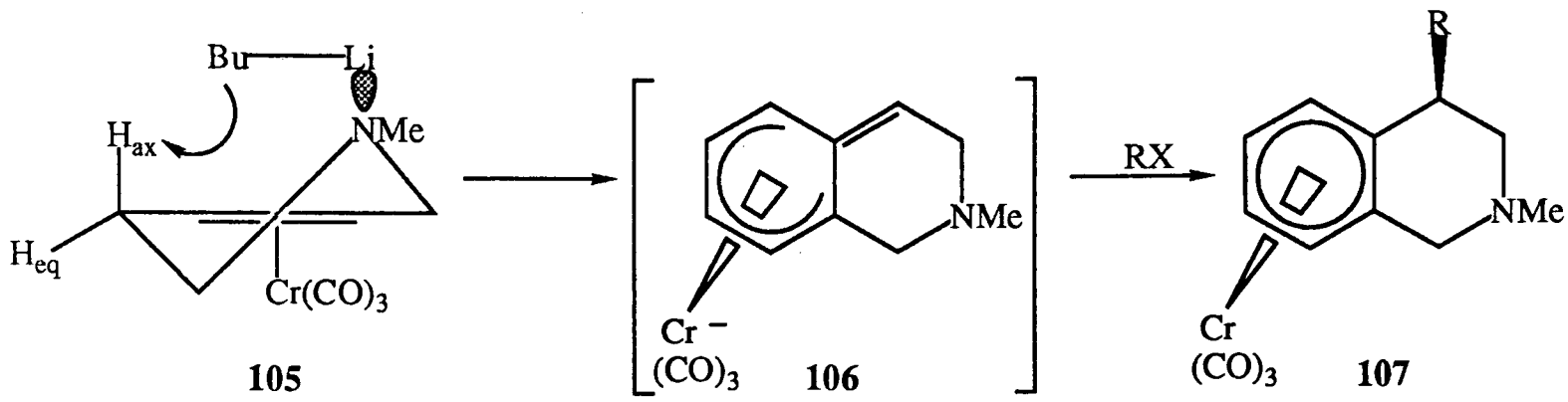


102

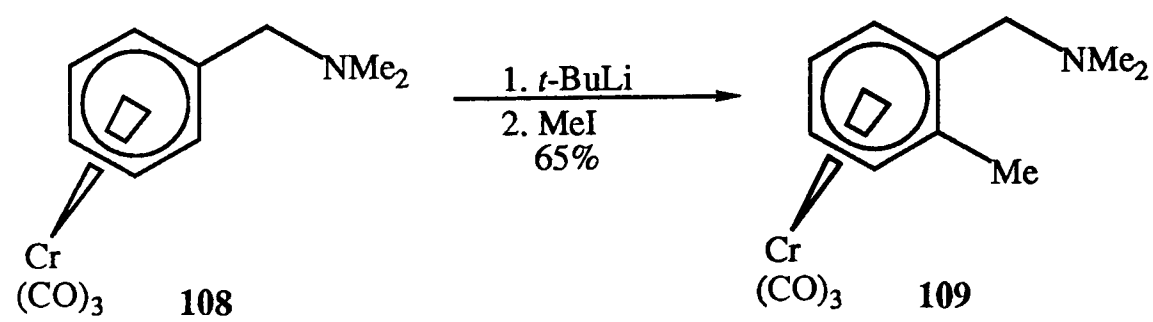
There is a great deal of interest in the preparation of a wide range of biologically active functionalised tetrahydroisoquinolines. There have been many recent studies directed towards stereoselective functionalisation of tetrahydroisoquinolines. Indeed the $Cr(CO)_3$ unit has been used in a variety of ways to induce activity at different positions. Thus, the parent complex **103** underwent exclusive 4-lithiation upon treatment with *n*-BuLi. Addition of d^4-methanol gave only the *exo*-4-deuteriated complex **104**. Selective removal of the deuterium occurred upon treatment of complex **104** with *n*-BuLi and addition of methanol regenerated (N-methyltetrahydroisoquinoline)$Cr(CO)_3$ **103**.[62,63]



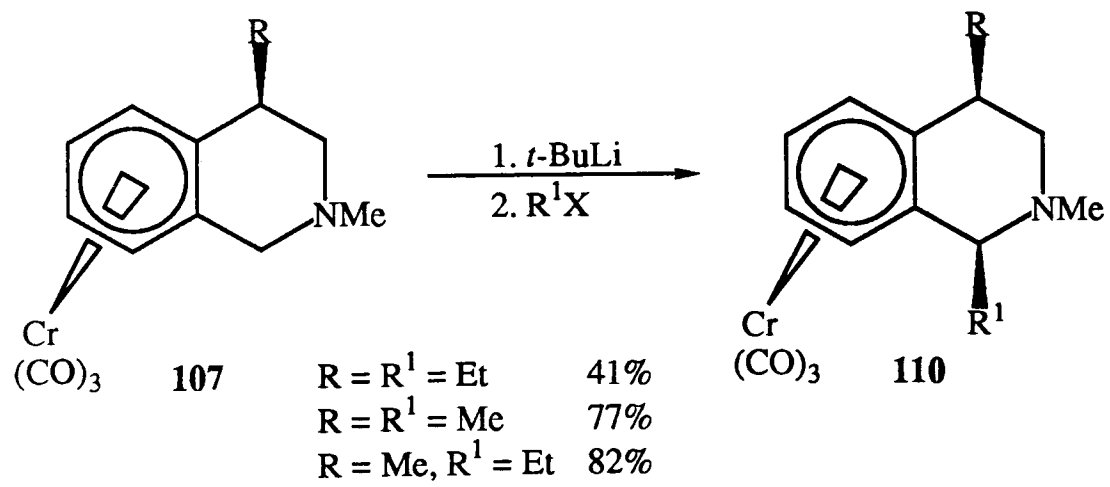
The regio- and stereoselectivity of this reaction has been ascribed to the formation of a six-membered cyclic transition state **105** involving a direct N-Li chelate. Subsequent removal of the axial C4 proton *antiperiplanar* to the metal gives the chromium stabilised carbanion **106**, which can only be quenched from the *exo* face with a variety of electrophiles to generate complex **107**.



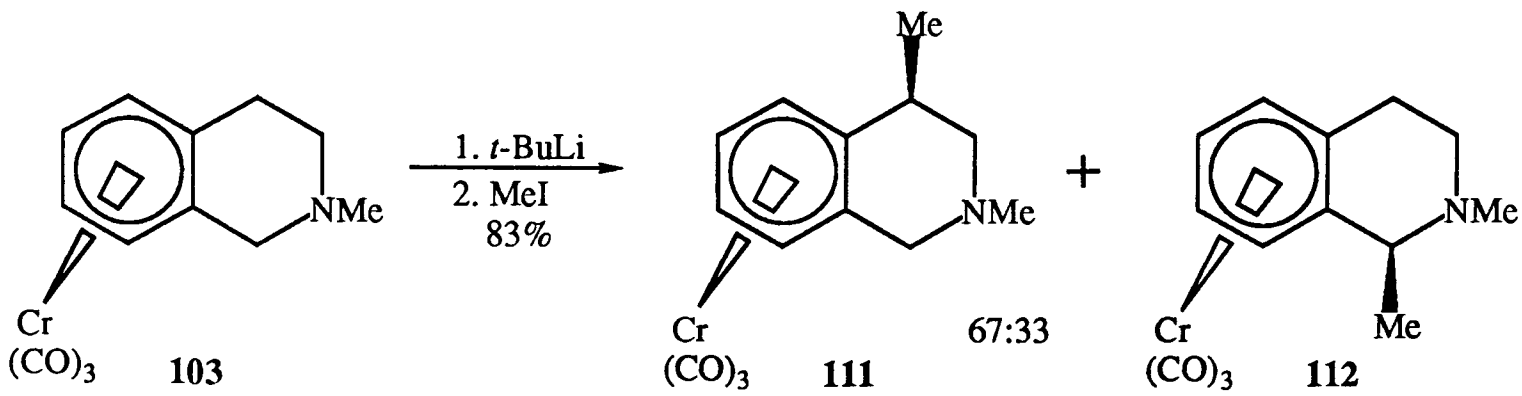
Note that in this reaction no aromatic deprotonation occurs. The nature of the heterocycle means that chelated alkyllithium base cannot approach sufficiently close to the C8 proton on the ring. This contrasts with the acyclic compound **108** which undergoes selective *ortho* alkylation with *t*-BuLi under standard conditions to give complex **109**.[59]



Complexes such as **107** can be further alkylated upon treatment with *t*-BuLi and an electrophile to give the *cis*-1,4-disubstituted derivatives **110**.[64] In these cases, since the C4 axial proton *antiperiplanar* to the chromium has already been replaced, the base removes the C1 proton. This can occur either by a fast kinetic deprotonation in conformations which place the C1 proton axial to the $Cr(CO)_3$ unit, or *via* a six-membered chelate involving more than one molecule of base.



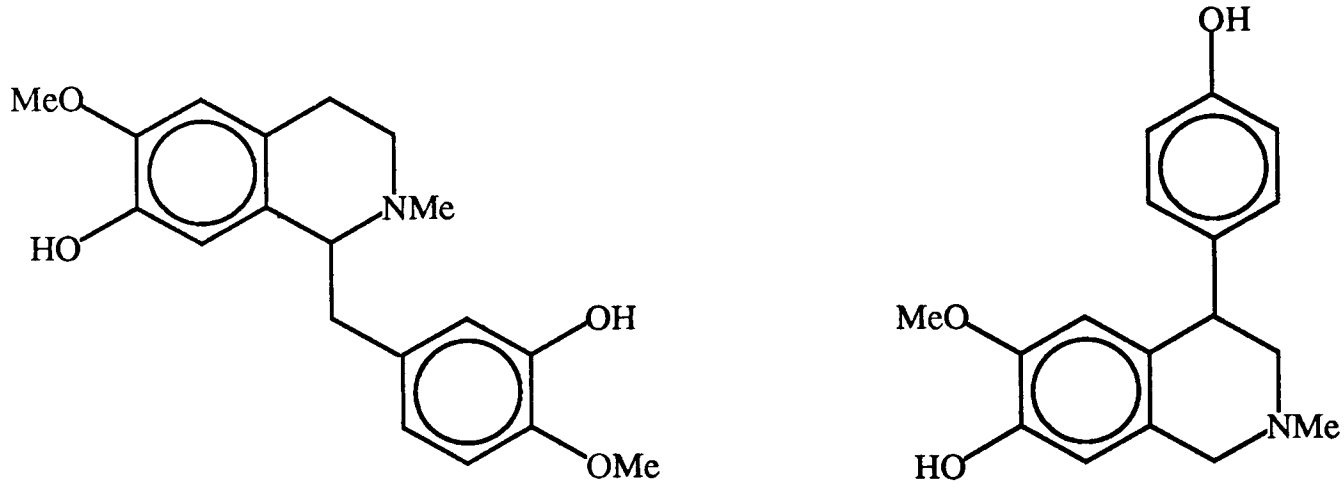
Treatment of the parent complex **103** with *t*-BuLi and MeI, however, gave a 2:1 mixture of the *exo*-4- and *exo*-1-methylated complexes **111** and **112**.[64]



103 111 112

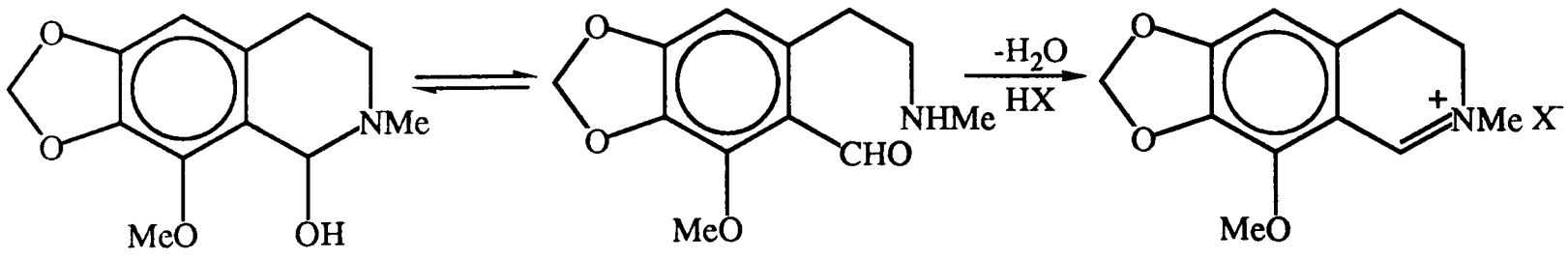
Two mechanisms are operative in this reaction; chelation controlled *exo*-4-lithiation and a fast kinetic *exo*-1-lithiation. Steric constraints within the molecule do not favour a chelation controlled C1 deprotonation over a chelation controlled C4 deprotonation since there are no sufficiently low energy chelated transition states with the *exo*-1-proton *antiperiplanar* to the metal unit and the nitrogen lone pair in such an orientation as to allow the alkyllithium to lie proximal to this proton.

Many naturally occurring tetrahydroisoquinolines contain oxygen substituents in the 6-, 7- and 8-positions.[65,66] Reticuline **113** is an intermediate in the biosynthetic pathway to apomorphine, morphine and protoberberine families of alkaloids.[67] Cherylline **114** is a 4-phenylated derivative and has been the focus of some synthetic activity.[68]



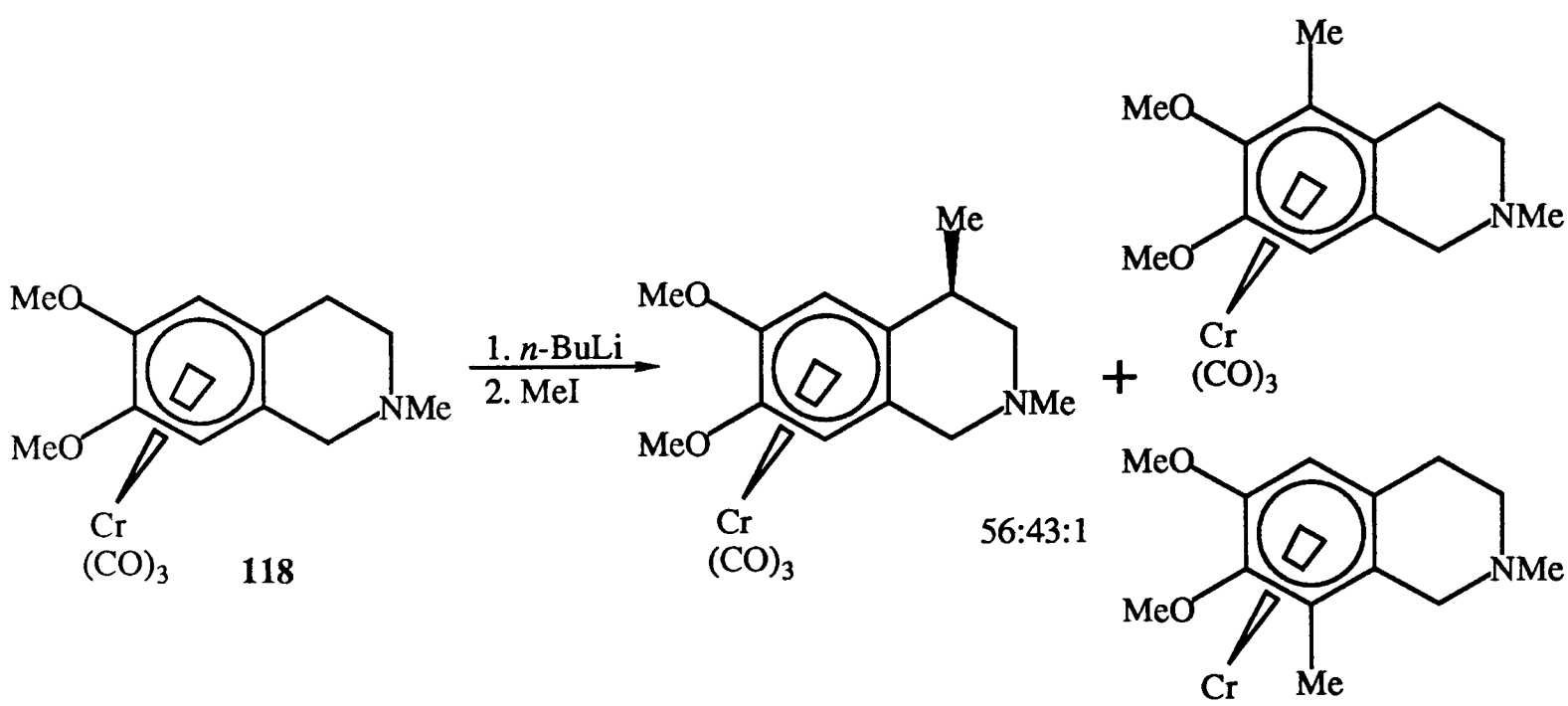
113 **114**

Cotarnine is a 6,7,8-trioxygenated naturally occurring alkaloid and in its hydrated form consists of a mixture of two isomers **115** and **116**. Ready dehydration under suitable conditions can also occur to give the quaternary ammonium salt **117**.[69]

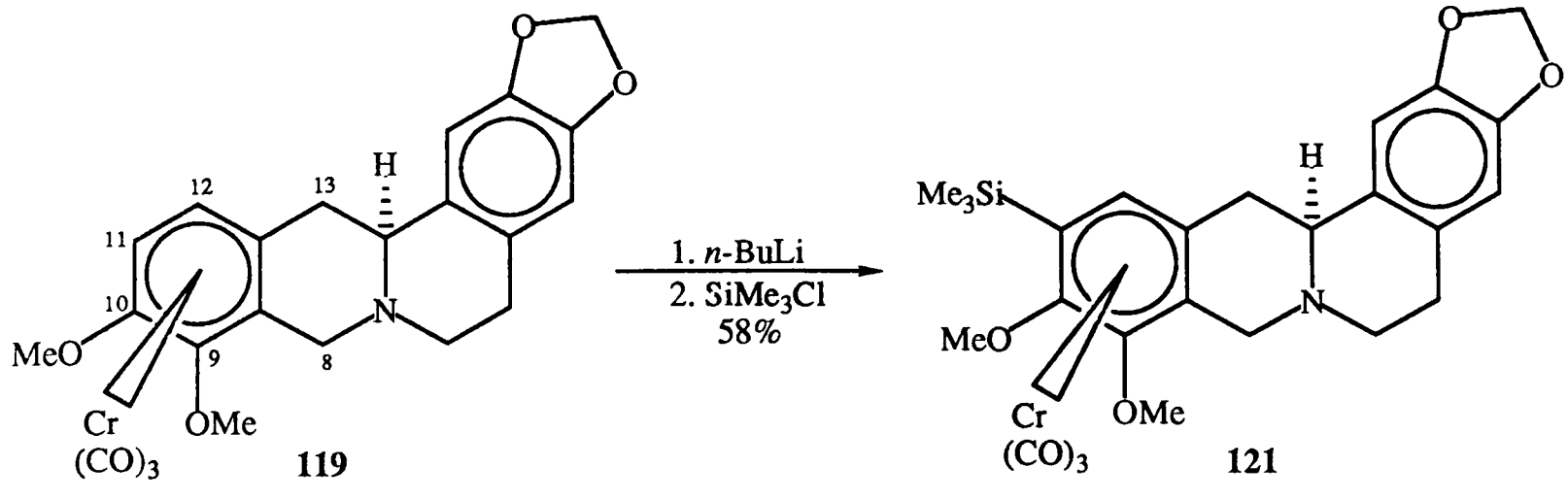


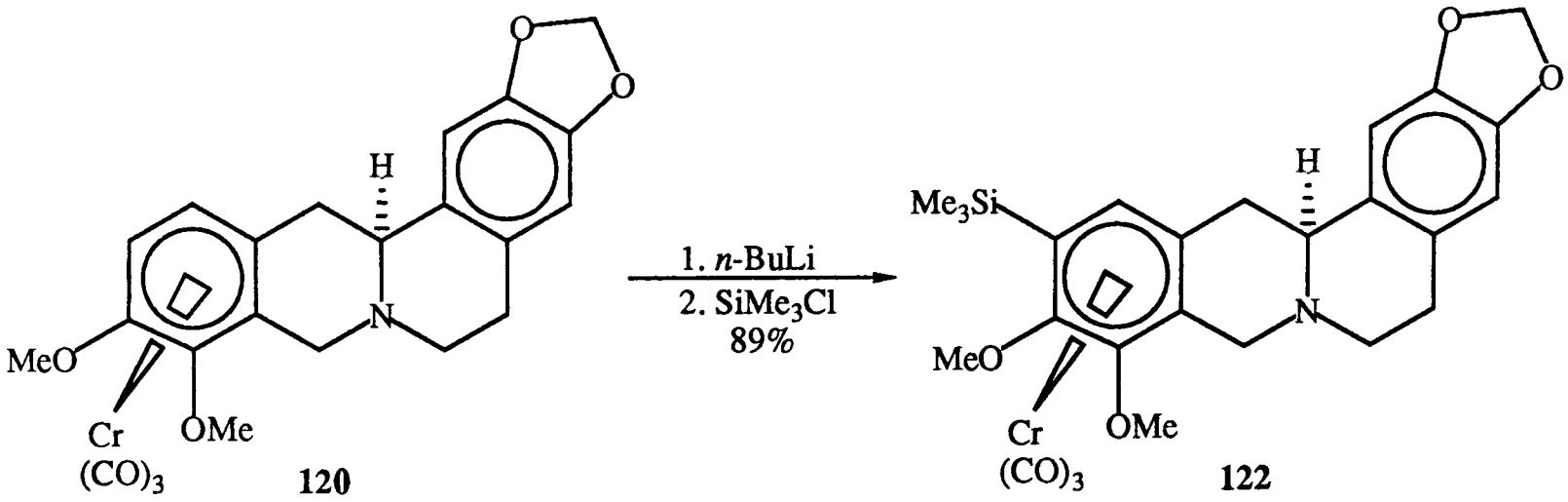
115 **116** **117**

Recent work on (2-methylheliamine)$Cr(CO)_3$ **118** demonstrated that the presence of the 6- and 7-methoxy groups can redirect the site of alkylation with *n*-BuLi and MeI such that a mixture of *exo*-4-, 5- and 8-methylated isomers is produced. The latter two products may arise from a chelation of base to either of the aromatic methoxy substituents, followed by *ortho* deprotonation. Note that the acidities of the two aromatic protons of complex **118** are increased due to the inductive electron-withdrawing effect of the 6- and 7-methoxy groups, whilst the benzylic protons are rendered less acidic, due to their mesomeric electron-donating effect. Thus, the aromatic protons are activated towards deprotonation relative to the benzylic protons.[70]

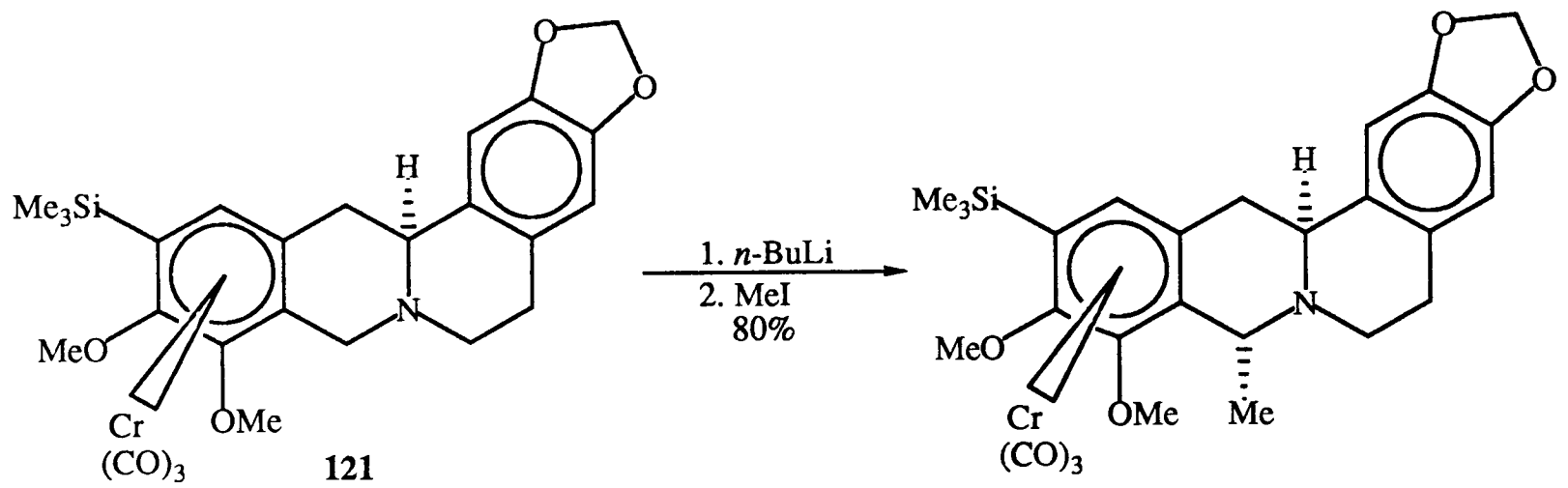


n-BuLi treatment of complexes **119** and **120** the *exo*- and *endo*-$Cr(CO)_3$ complexes of (-)-canadine, (a tetrahydroisoquinoline protoberberine alkaloid), with the chromium attached to the dimethoxy arene ring, gave only metallation at the C11 position *ortho* to the 10-methoxy substituent. Subsequent silylation with chlorotrimethylsilane gave only the C11 silylated products **121** and **122**. Presumably the regioselectivity of the reaction arises by chelation of the base to the C10 methoxy group, giving rise to selective removal of the proximal C11 hydrogen to give the corresponding inductively stabilised anion.

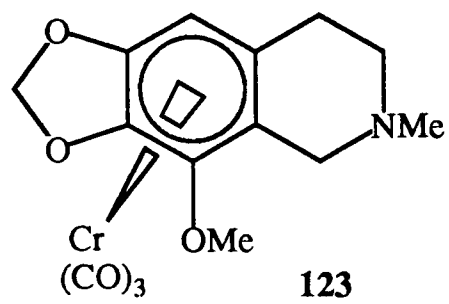




Treatment of, for example, the *exo* complex **121** with *n*-BuLi gave only C8 methylation *exo* to the metal unit on quenching with MeI, no C13 functionalisation was observed. In this reaction the regioselectivity of metallation is presumably directed by the C11 trimethylsilyl function. Transition states leading to deprotonation at the C8 position are mesomerically stabilised by the trimethylsilyl group, whereas those leading to C13 deprotonation are not due to the relative *meta* relationship between the silyl function and C13 alkyl group.[46]



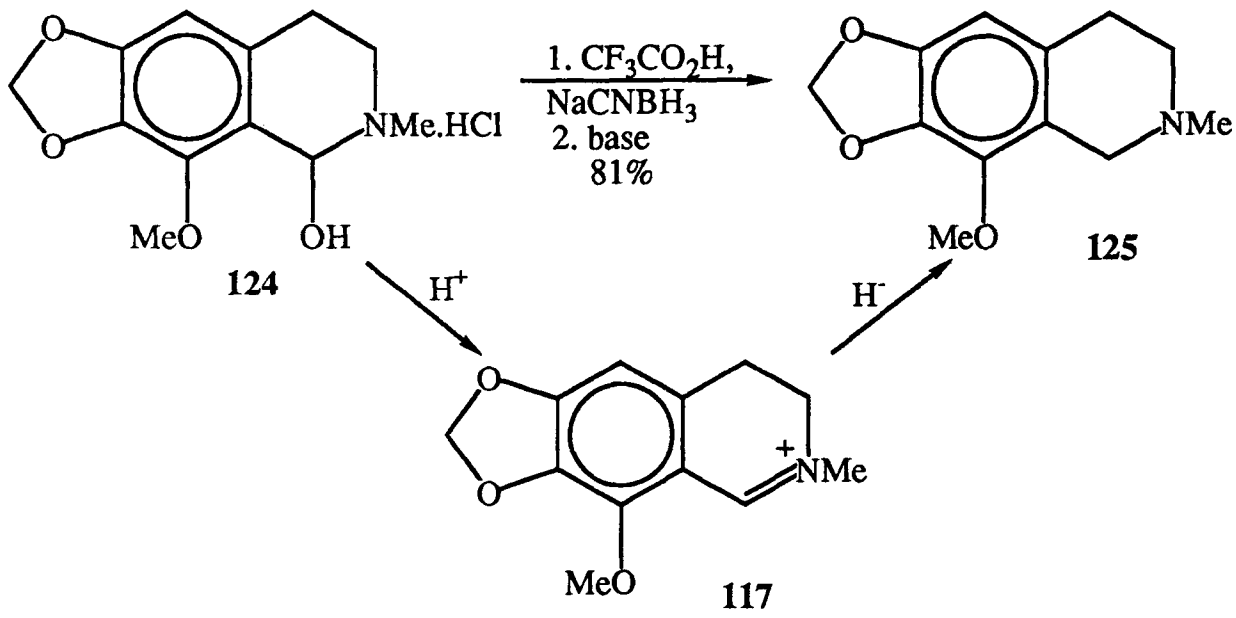
In principle alkylation of the coordinated cotarnine derivative **123** could occur at the 1-, 4- or 5-positions and an attempt was made to selectively synthesise each of these derivatives.



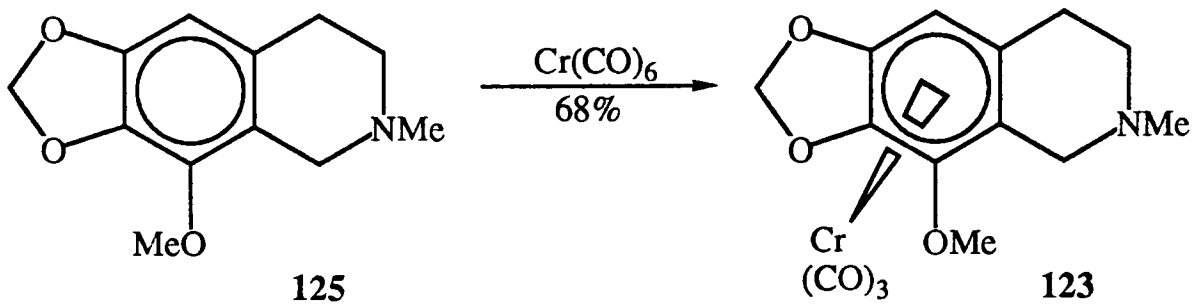
123

b. *Preparation of (Hydrocotarnine)Cr(CO)$_3$ and exo-(1-Methylhydrocotarnine)Cr(CO)$_3$.*

To prevent the ready ring opening of cotarnine **115**, the 1-hydroxyl group was reduced to the dihydro derivative. Addition of TFA to a CH_2Cl_2 suspension of cotarnine hydrochloride **124** gave a clear yellow solution. Sodium cyanoborohydride was added and the solution stirred for 1.5h. Work up gave a clear, colourless oil **125** in good yield. The ^{1}H n.m.r. spectrum of compound **125** contained an aromatic proton singlet (δ6.34), a three proton methoxy singlet (δ4.00) and a two proton singlet (δ3.46) characteristic of an uncoupled benzylic methylene group. A molecular ion *m/z* 221 (*M*+) in the mass spectrum confirmed the assignment of **125** as hydrocotarnine. Presumably this reaction proceeds through formation of the intermediate immonium cation **117** which is generated on acid mediated loss of water from arene **124**. Addition of a mild hydride source then smoothly reduces the immonium function to give the product in good yield.

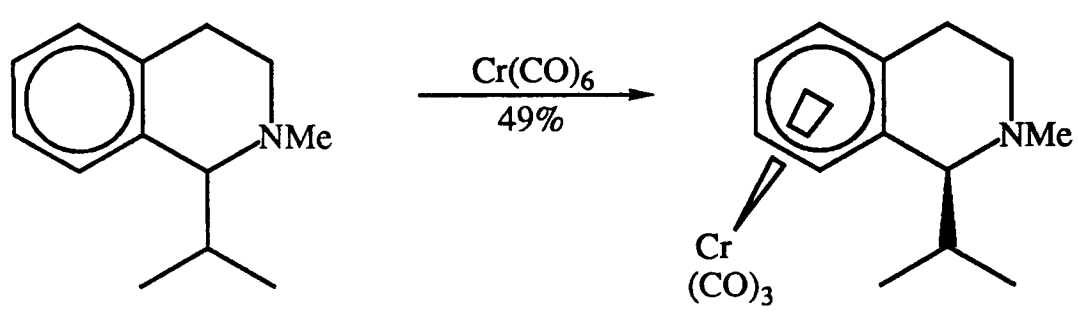


Thermolysis of $Cr(CO)_6$ with compound **125** under standard conditions gave a good yield of the corresponding $Cr(CO)_3$ complex **123** as yellow needles. The ^{1}H n.m.r. spectrum of complex **123** was similar to that of the starting material but with the C5 aromatic proton singlet shifted upfield (δ5.04). The two C1 benzylic protons now appeared as an AB system (δ3.73, 3.15, J_{AB} = 15.63Hz) due to their different *endo* and *exo* dispositions relative to the chromium unit. Complex **123** gave a molecular ion *m/z* 357 (*M*+) in the mass spectrum, infrared carbonyl absorption bands (1955, 1868br cm^{-1}) and a correct elemental microanalysis, confirming that coordination of the metal unit to the arene had occurred.



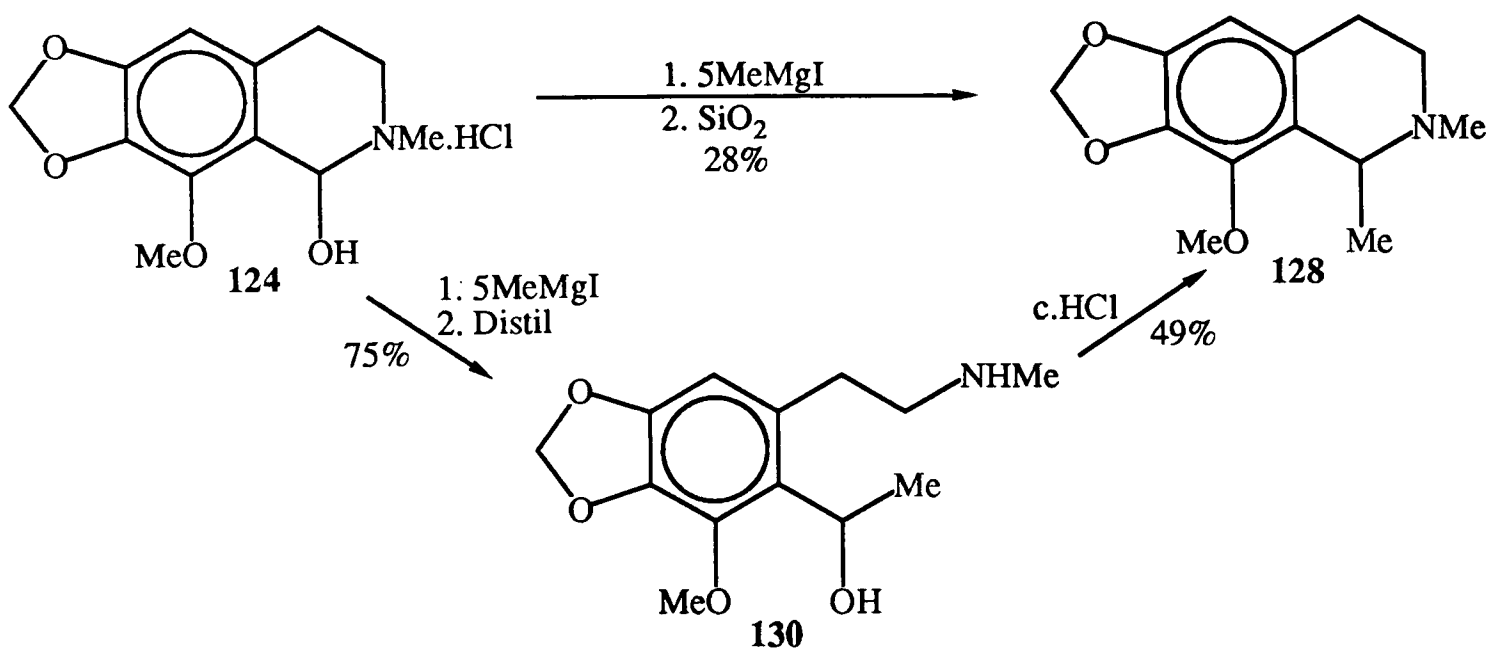
125 **123**

Complexation of 1-substituted tetrahydroisoquinolines, in the absence of heteroatomic directing effects, see Chapter 2, occurs preferentially to the less sterically hindered face *anti* to the 1-substituent. Thus, 1-*i*-propyl-N-methyltetrahydroisoquinoline **126** underwent complexation to give a single diastereoisomer **127** with the $Cr(CO)_3$ unit *anti* to the bulky *i*-propyl group.[64] It was hoped to extend this methodology to 1-methylhydrocotarnine **128** to generate *exo*-(1-methylhydrocotarnine)$Cr(CO)_3$ **129**.

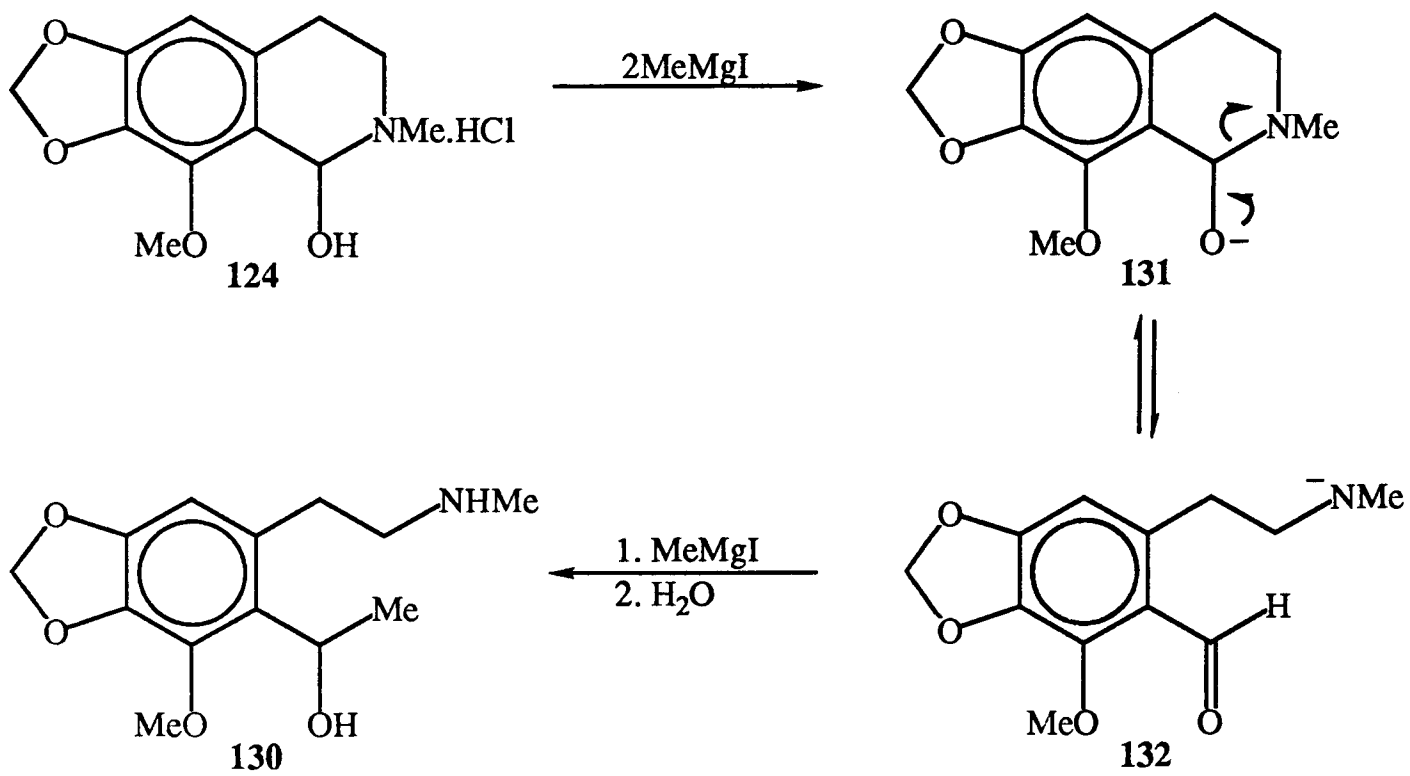


126 **127**

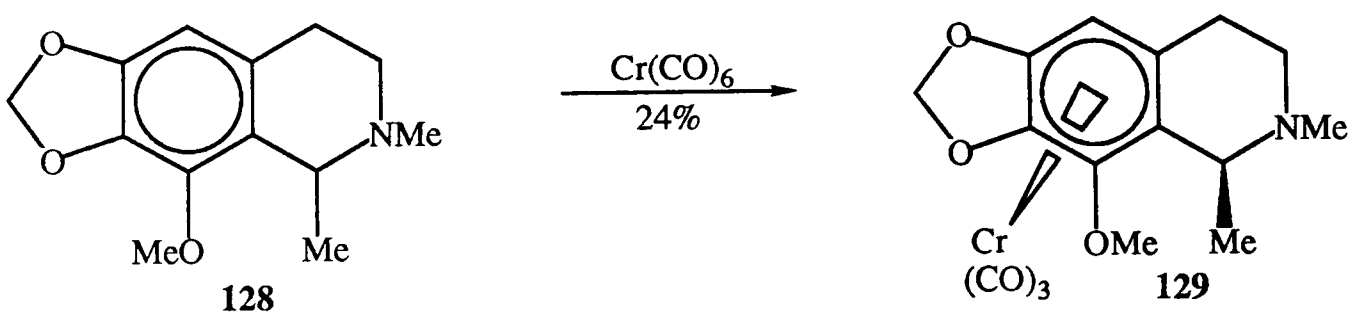
Addition of excess MeMgI to cotarnine hydrochloride **124** gave, on work up, a pink oil. Distillation of this crude oil gave the open chain phenethanol derivative **130**, which upon treatment with c.HCl gave cyclised 1-methylhydrocotarnine **128**. Alternatively, chromatography (SiO_2) of the crude oil gave the cyclised product **128** directly as a clear, colourless oil. Arene **128** was identified by the ^1H n.m.r. spectrum which contained an aromatic proton singlet (δ6.32), a one proton quartet (δ3.93, J = 6.57Hz) and a three proton doublet (δ1.25, J = 6.45Hz) characteristic of a C1 methyl substituent. A molecular ion m/z 236 (*M*+1) in the mass spectrum confirmed that overall methylation and loss of the C1 hydroxyl had occurred.



Presumably the first step in the Grignard addition reaction is removal of all acidic protons of compound **124**, thus producing the intermediate oxygen anion **131**. This undergoes rapid reversible opening, to give the aldehyde **132,** which reacts with excess Grignard reagent to produce, on work up, compound **130**. Subsequent acid catalysed intramolecular elimination of water then irreversibly generates the cyclised arene **128**.[71]



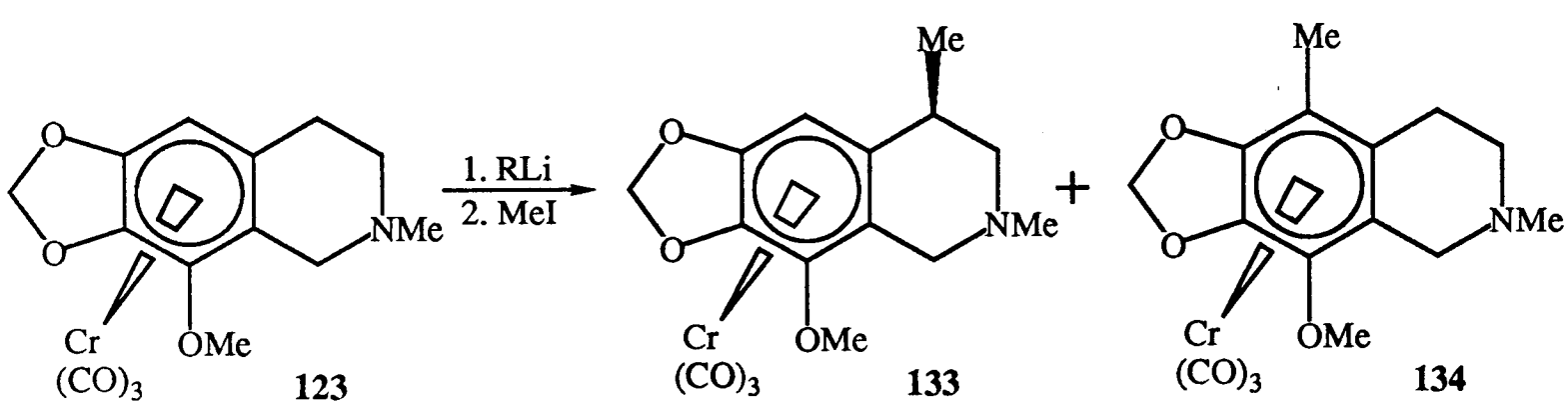
Coordination of the methylated tetrahydroisoquinoline **128** to the $Cr(CO)_3$ unit under standard complexation conditions gave complex **129** as a single diastereoisomer. The presence of an upfield aromatic proton singlet (δ4.00), a one proton quartet (δ3.57, J = 6.35Hz) and three proton doublet (δ1.32, J = 6.32Hz) in the ^1H n.m.r. spectrum (C_6D_6) and a molecular ion *m/z* 371 (M^+) in the mass spectrum, confirmed the identity of **129** as the assigned compound. Complex **129** also gave a correct elemental microanalysis. The relative configuration of the 1-methyl substituent and metal unit was tentatively assigned by analogy to the literature precedent, with the chromium presumably attached to the less hindered face *anti* to the 1-methyl substitutuent.[64]



c. *C4 and C5 Functionalisation of (Hydrocotarnine)Cr(CO)$_3$.*

In principle complex **123** can undergo metallation at 1-, 4- or 5-positions. Whilst C4 deprotonation *via* a N-Li chelate is usually preferred to C1 deprotonation, with very strong bases kinetic C1 metallation can occur (*vide supra*). However, little was known about the relative acidity of the aromatic proton, though presumably the presence of three inductively electron-withdrawing oxygen substituents would decrease the pK$_a$ of this proton, whilst mesomerically increasing those of the benzylic C1 and C4 protons. Thus, use of a range of bases could feasibly give access to any of these derivatives.

Treatment of the tetrahydroisoquinoline complex **123** with a variety of bases followed by addition of MeI under standard alkylation conditions gave only *exo*-4- and 5-alkylated products **133** and **134**, but in differing ratios, Table I.



123 **133** **134**

Entry	Base	Conditions	Ratio of products (% yield)	
			133	**134**
1	*t*-BuLi	-78°C, 2h then MeI, -78°C, 2h	58 (42%)	42 (30%)
2	*n*-BuLi	-78°C, 2h then MeI, -78°C, 2h	21 (15%)	79 (56%)
3	LDA	-78°C, 2h then MeI, -78°C, 2h	——	100 (64%)

Table I. Effect of metallating agent on the regioselectivity of alkylation of complex **123**.

Products **133** and **134** were easily separable by column chromatography (Al_2O_3) and assigned on the basis of their ^{1}H n.m.r. spectra. That of complex **133** contained a new three proton doublet (δ1.36, J = 7.15Hz), but with the characteristic C1 two proton AB system intact (δ3.66, 3.12, J_{AB} = 15.62Hz), thus confirming that C4 and not C1

methylation had occurred. The spectrum of complex **134** contained no aromatic proton peaks and a new three proton singlet due to an aromatic methyl group (δ2.14). The aliphatic proton signals were similar to those of complex **123** with a two proton AB system (δ3.70, 3.24, J_{AB} = 15.44Hz) characteristic of the C1 protons and two multiplets integrating to four protons (δ2.86-2.73, 2.59-2.51) characteristic of the C3 and C4 hydrogens. Complex **133** gave a correct high resolution mass spectrum and complex **134** a correct elemental microanalysis.

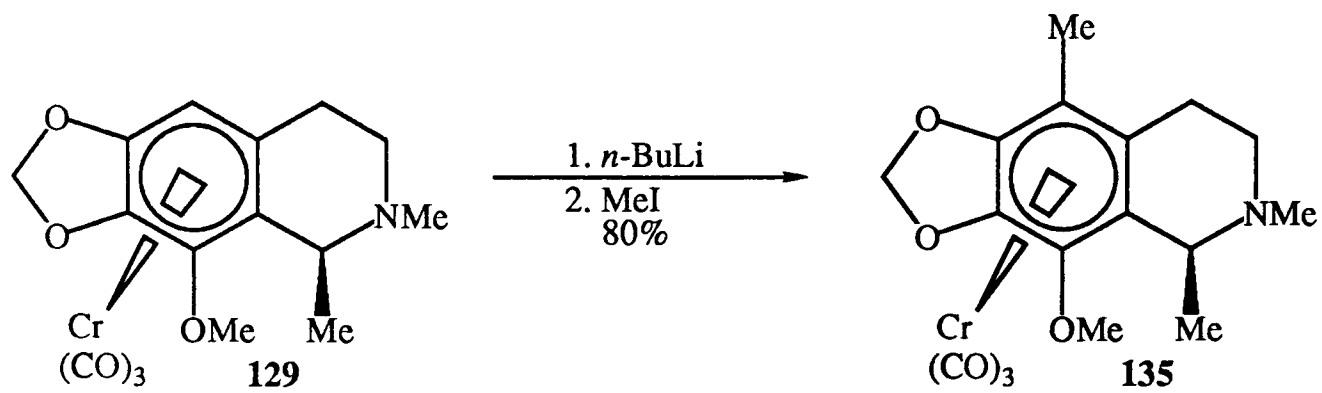
The basicity of the metallating reagents increases LDA < *n*-BuLi < *t*-BuLi with LDA being a reversible base and therefore, kinetic deprotonation is more likely to occur with *t*-BuLi and reversible thermodynamic deprotonation with LDA. The exclusive production of complex **134** in the reaction with LDA indicates that 5-lithiation is, as expected, thermodynamically preferred. Changing base to *t*-BuLi gives essentially random C4 and C5 deprotonation. This presumably occurs *via* a non-chelated kinetic pathway. Deprotonation with *n*-BuLi probably proceeds *via* two different pathways, a direct chelate with the nitrogen, promoting *exo*-C4 lithiation *via* a cyclic six-membered transition state and a non-chelated kinetic pathway resulting in approximately equivalent amounts of C4 and C5 lithiation. Thus overall, *n*-BuLi mediated metallation results in a predominance of C4 alkylation. Note that C1 alkylation is not observed. This is because the 8-methoxy substituent sufficiently blocks the attack of base to allow faster deprotonation elsewhere in the molecule. Also the transition states leading to deprotonation will have some carbanionic character at the C1 carbon. This would be electronically disfavoured since there are two mesomerically electron-donating oxygen substituents at the 6- and 8-positions. Note that C4 lithiation proceeds through a transition state with only one such mesomeric interaction with the C7 oxygen substituent.

d. *Further Functionalisation of the Tetrahydroisoquinoline Skeleton.*

Further alkylation of the *exo*-1-, *exo*-4- and 5-methylated derivatives of complex **123**, compounds **129**, **133** and **134** respectively, could conceivably occur at any of the remaining sites. In the case of complex **134** a new benzylic position on the aryl methyl group had been formed and deprotonation at this site could also occur.

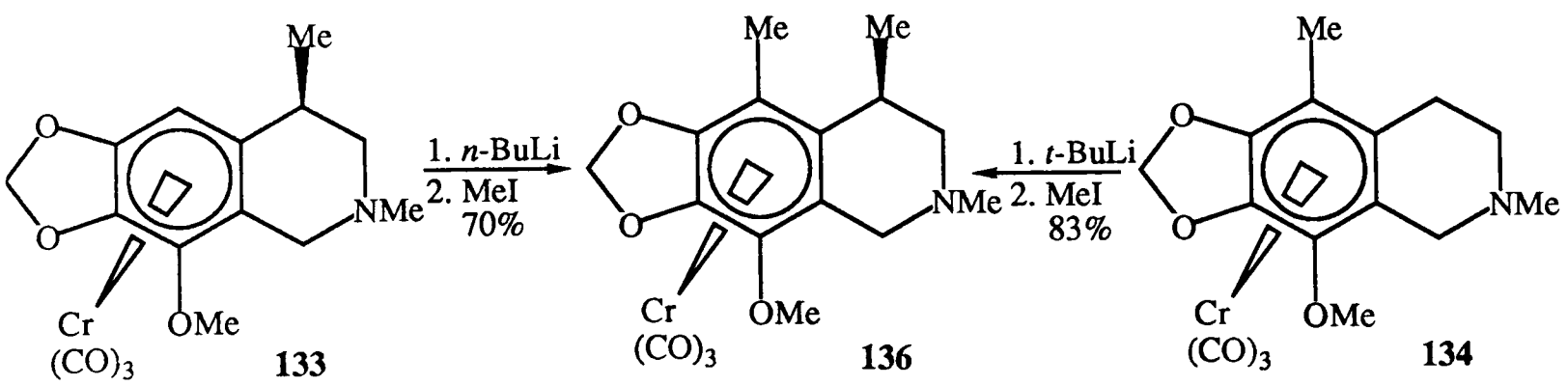
Methylation of *exo*-(1-methylhydrocotarnine)$Cr(CO)_3$ **129** with *n*-BuLi and MeI under standard conditions occurred regiospecifically to give the 1,5-dimethylated product **135** in good yield. The ^1H n.m.r. spectrum of complex **135** contained a new three proton singlet, characteristic of an aryl methyl group (δ2.09) and no aromatic proton signals, whilst the aliphatic proton signals were similar to those of complex **129** with three multiplets integrating to four protons (δ3.12-3.06, 2.84-2.75, 2.62-2.51) charactersitic of the C3 and C4 hydrogens and a one proton C1 benzylic quartet (δ3.82, J = 5.95Hz). A correct high resolution mass spectrum confirmed the assignment of the product. No

exo-4-methylation was observed, since presumably the presence of the *exo*-1-methyl group sterically hinders coordination of the base to the nitrogen lone pair.

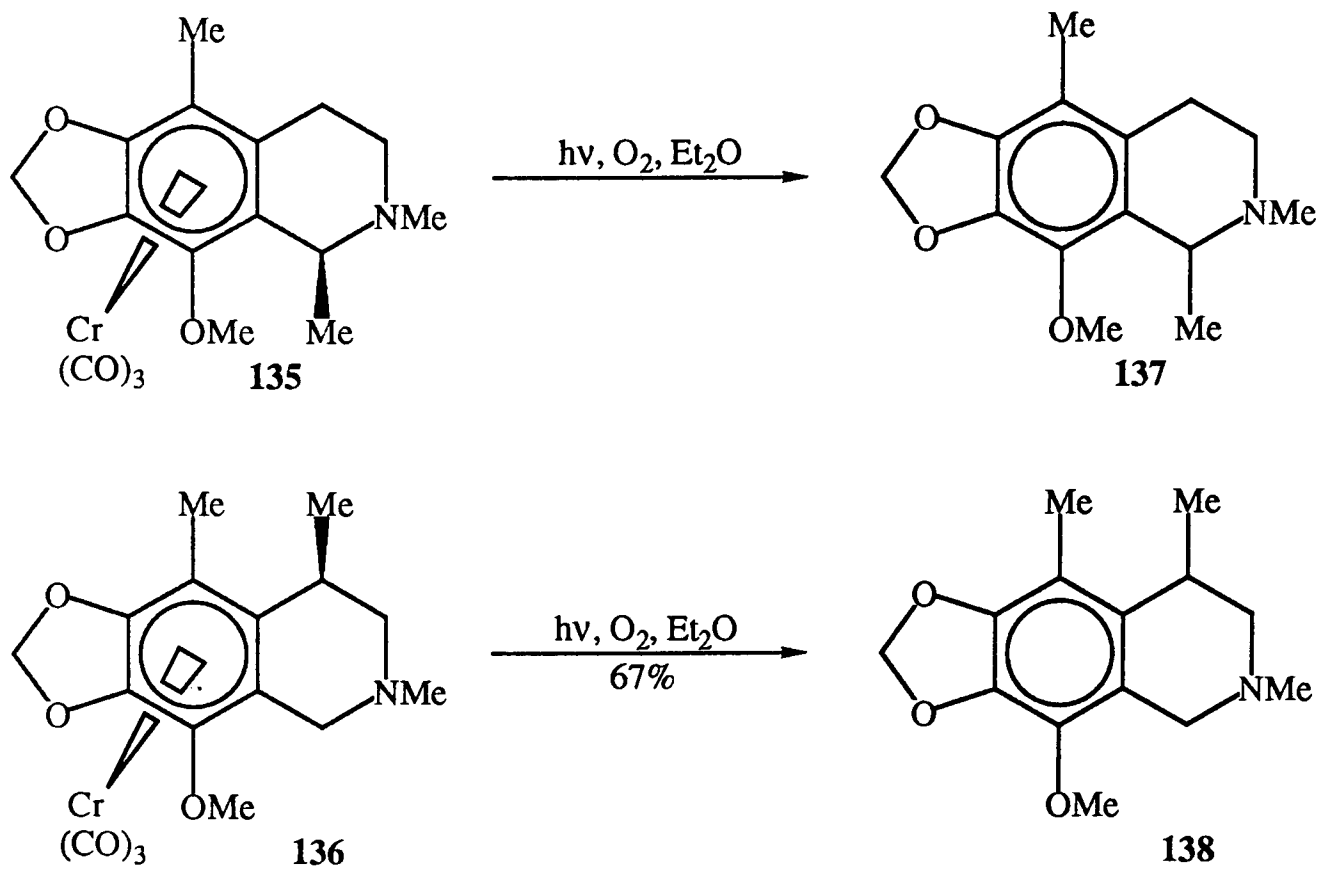


Treatment of the *exo*-4-methyl complex **133** under standard conditions with *n*-BuLi and MeI gave, on work up, a yellow solid **136** in good yield, identified as the *exo*-4,5-dimethylated complex on the basis of the ^{1}H n.m.r. spectrum which contained a three proton aromatic methyl singlet (δ2.21) and no aromatic proton signals. Complex **136** gave a molecular ion *m/z* 385 (*M*+) in the mass spectrum and a correct elemental microanalysis, confirming its identity. Complex **136** was also produced in good yield *via* standard alkylation of the 5-methyl complex **134** with *t*-BuLi and MeI. The two samples of complex **136** were spectroscopically identical in every respect.

In complex **133** the most acidic proton is the aromatic proton, since the conjugate base, the aryl anion, is inductively stabilised by the C6-oxygen atom. Consequently, only methylation at the 5-position is observed, C1 lithiation being sterically and electronically disfavoured (*vide supra*). In complex **134**, however, there are three different benzylic positions. C1 and C5 methyl metallation are electronically disfavoured, with C1 metallation also being sterically disfavoured. C4 lithiation, however, has only one mesomeric interaction with the C7 oxygen substituent. Thus, metallation at this site will be preferred.



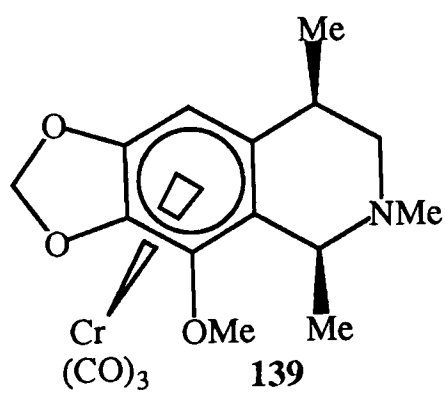
Complexes **135** and **136** were decomplexed under standard conditions to give the free 1,5-dimethyl and 4,5-dimethyl derivatives **137** and **138** respectively, as clear, colourless oils. Both complexes gave molecular ion *m/z* 250 (*M*++*1*) in their mass spectra, confirming that decomplexation had occurred.



e. *Conclusion.*

The synthesis of the *exo*-1-methyl derivative **129** of (hydrocotarnine)Cr(CO)3 **123** has been achieved *via* a diastereofacial complexation of arene **125**. The *exo*-4- and 5-methyl derivatives, **133** and **134** were prepared by deprotonation of complex **123** with various bases, mixtures of complexes **133** and **134** being separable by column chromatography.

Further functionalisation of the *exo*-1-methyl complex **129** or *exo*-4-methyl complex **133** at the 5-position occurred *via* standard alkylation to give complexes **135** and **136** respectively, whilst similar treatment of complex **134** led to *exo*-4-alkylation giving complex **136**. Production of the *cis*-4,5-dimethyl derivative **139** proved elusive.



139

Chapter 6. Resolution of *Ortho* Substituted Benzaldehyde Chromium Tricarbonyl Complexes.

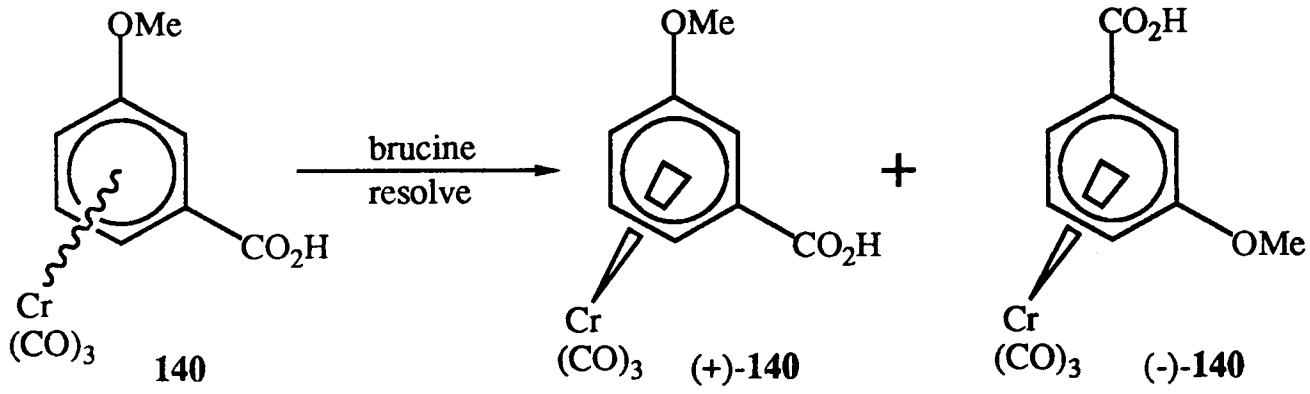
a. *Introduction.*

Di- or polysubstituted arenes possessing only one plane of symmetry, the plane of the ring, and no centre of inversion, have enantiotopic faces and therefore complexation of these arenes to the $Cr(CO)_3$ group gives a racemic mixture. When a chiral centre is present in one of the side-chains, the faces of the arene are rendered diastereotopic and so complexation can give rise to two possible diastereoisomers.

Relatively few chiral disubstituted (arene)$Cr(CO)_3$ complexes have been successfully resolved with elucidation of their absolute configuration and consequently the asymmetric synthesis of homochiral arenes *via* elaboration of chiral (arene)$Cr(CO)_3$ complexes has been limited.

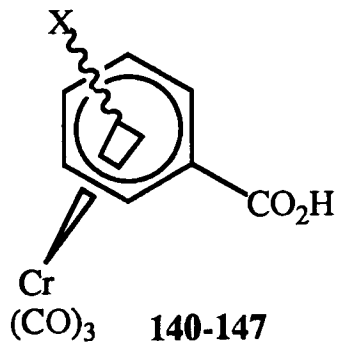
i. *Benzoic Acid Derivatives.*

(*m*-Methoxybenzoic acid)$Cr(CO)_3$ **140** was the first resolved chiral disubstituted (arene)$Cr(CO)_3$ complex. Complex **140** was treated with brucine and the diastereoisomeric salts fractionally recrystallised. The free chiral acid **140** was released by standard acid-base manipulations.[72]



140 (+)-**140** (-)-**140**

Brucine, cinchonidine, quinine and quinidine have been similarly used to resolve other racemic *ortho* and *meta* substituted benzoic acid complexes **140-147** *via* separation of the corresponding diastereoisomeric salts, Table II. The optical rotations of each enantiomer were found to be equal and opposite.[73-75]

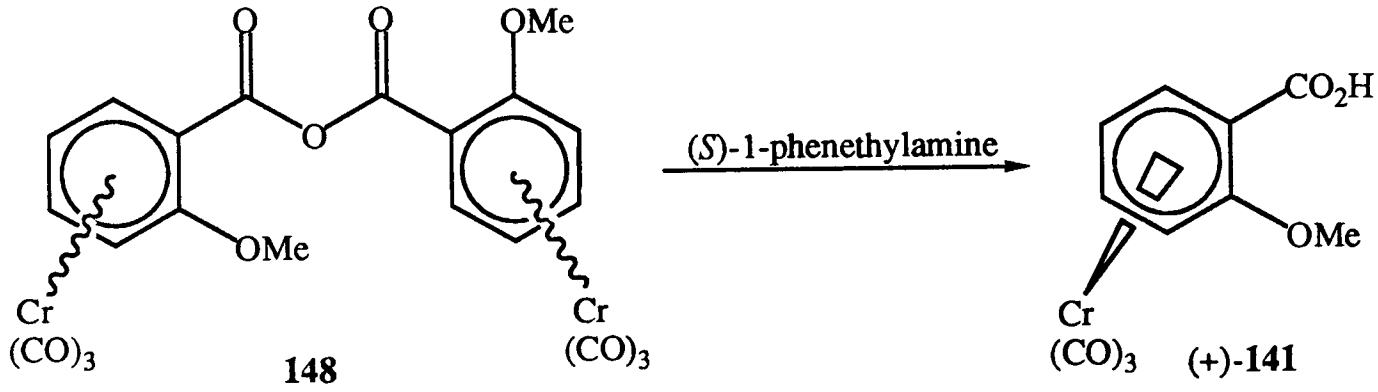


140-147

Entry	X =	No.	(-)-enantiomer	(+)-enantiomer
1	*o*-OCH_3	**141**	brucine	brucine[73]
2	*m*-OCH_3	**140**	brucine	quinidine[74]
3	*o*-CH_3	**142**	cinchonidine	brucine[74]
4	*m*-CH_3	**143**	brucine	cinchonidine[74]
5	*o*-NH_2	**144**	quinine	quinidine[74]
6	*m*-NH_2	**145**	quinine[74]	—
7	*o*-F	**146**	quinine	quinidine[75]
8	*m*-F	**147**	quinine[75]	—

Table II. Resolution of substituted (benzoic acid)$Cr(CO)_3$ complexes **140-147.**

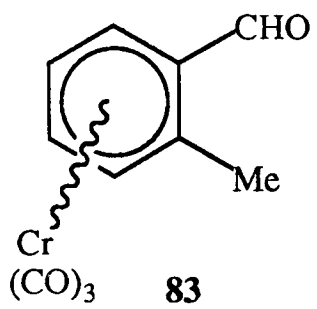
Another method of resolution of (*o*-methoxybenzoic acid)Cr(CO)3 **141** has been to kinetically resolve the anhydride with (*S*)-α-phenethylamine. Addition of chiral amine to the anhydride **148** resulted in liberation of the (+)-acid (+)-**141** in 9% ee.[76]



148 (+)-**141**

ii. *Benzaldehyde Derivatives.*

The substituted benzaldehyde derivatives **83** and **149-151** have been successfully resolved *via* chromatographic separation of the diastereoisomeric semioxamazones derived from (*S*)-5-(1–phenethyl)semioxamazide **152**.[3] Subsequent acid catalysed hydrolysis released the homochiral Cr(CO)3 complexes **83** and **149-151.**



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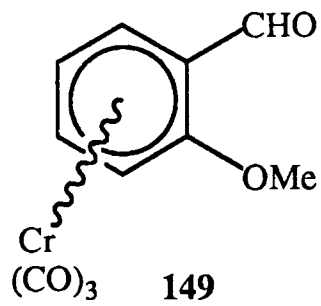

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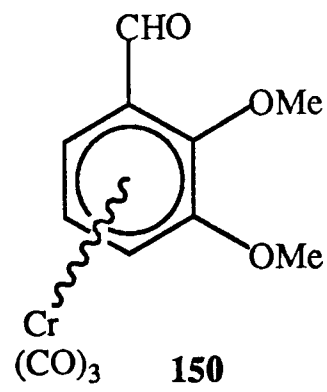

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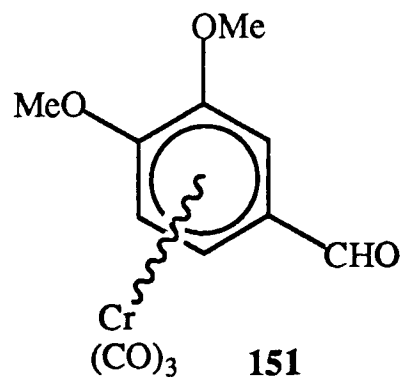

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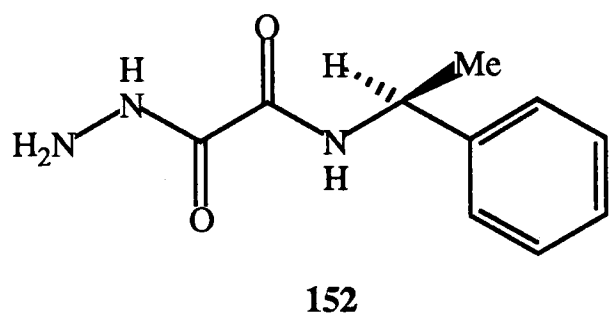
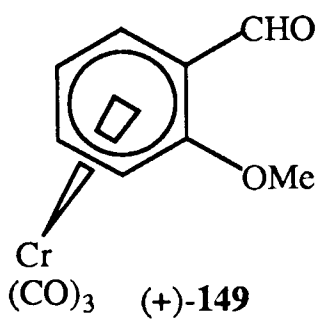


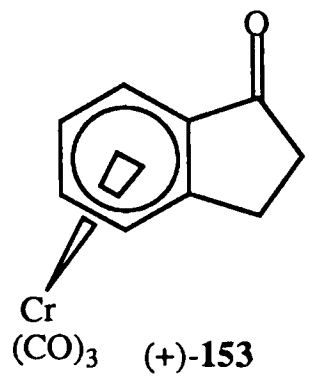
152

iii. *Miscellaneous Compounds.*

(1-Tetralone)Cr(CO)3 **13** has been partially resolved using an acetylated cellulose chiral column.[75] (*o*-Anisaldehyde)Cr(CO)3 **149** and (1-indanone)Cr(CO)3 **153** have been kinetically resolved using baker's yeast. Addition of yeast to racemic mixtures of complexes **149** and **153** resulted in preferential reduction of the (-)-enantiomers in both cases and recovered starting material was found to be enriched in the (+)-enantiomers, [81% ee for (+)-**149** and 25% ee for (+)-**153**].[77]

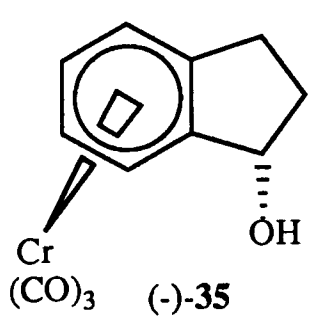


(+)-**149**

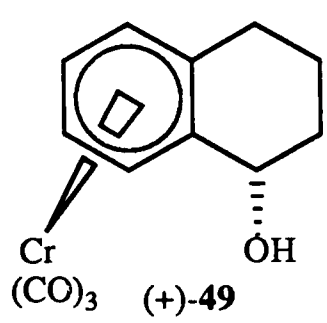


(+)-**153**

endo-(1-Indanol)Cr(CO)3 **35** and *endo*-(1-tetralol)Cr(CO)3 **49** have been resolved *via* fractional crystallisation of the cinchonidine salts of their acid succinates, followed by hydrolysis.[18]



(-)-**35**

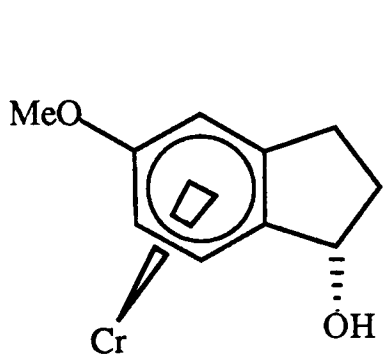


(+)-**49**

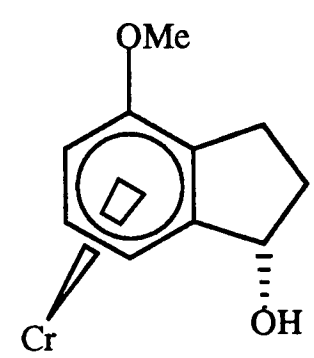
iv. *Determination of Absolute Configuration.*

One of the earliest X-ray crystal structure analyses performed on a chiral disubstituted (arene)Cr(CO)3 complex was that on the (*S*)-α-phenethylamine salts of *o*- and *m*-toluic acid complexes (+)-**142** and (-)-**143**.[78] Chemical correlation of these compounds with a range of other chiral *ortho* or *meta* disubstituted complexes has revealed their absolute configurations.[79]

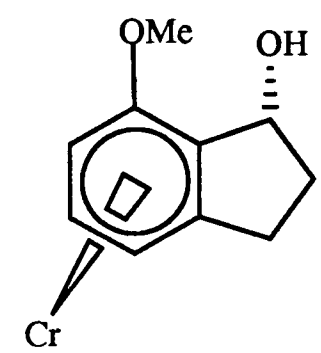
Horeau's method[80] has been applied to (-)-*endo*-(1-tetralol)Cr(CO)3 (-)-**49**[81] and the 1-indanol derivatives **154-156**.[82]



(-)-**154**

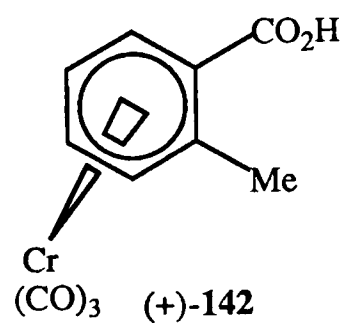


(+)-**155**

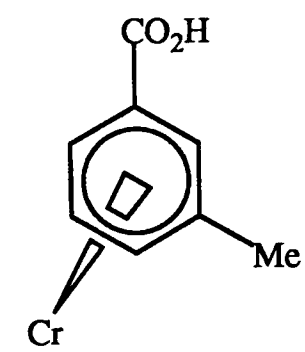


(+)-**156**

Measurement of ORD and CD curves sometimes gives an indication of the absolute configuration of a chiral disubstituted arene complex.[79,83] However, the method should be used with caution since erroneous results have been reported. For example, the ORD curves of *o*- and *m*-toluic acid complexes (+)-**142** and (-)-**143** are similar but bear a mirror image relationship to each other. The electronic spectra of complexes **142** and **143** and (benzoic acid)Cr(CO)3 **157** are also similar and so opposite absolute configurations for (+)-**142** and (-)-**143** were assigned.[79] Since the absolute configuration within the (arene)Cr(CO)3 unit of (+)-**142** is (*S*),[78] it was predicted that that of complex (-)-**143** is (*R*). However, the unambiguous assignment of the absolute configuration within complex (-)-**143** was made using an X-ray crystal structure analysis (*vide supra*) and found to be (*S*).[78]



(+)-**142**

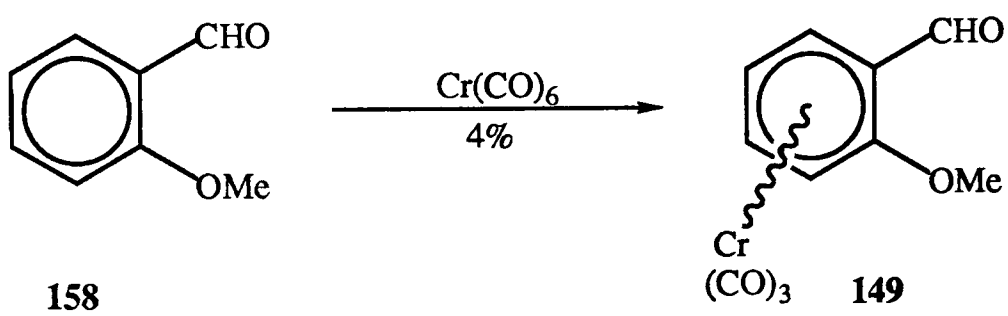


(-)-**143**

We were interested in extending the techniques available for resolution of a range of *ortho* substituted (benzaldehyde)Cr(CO)3 complexes so as to facilitate easy access to large quantities of homochiral starting materials suitable for further elaboration. We also wished to confirm or assign absolute configurations to the resolved enantiomers.

b. *Preparation of Ortho Substituted (Benzaldehyde)Cr(CO)$_3$ Complexes.*

In general, arenes possessing an aldehyde function cannot be complexed in good yield. An attempt to complex *o*-anisaldehyde **158** under standard conditions and thus avoid two steps of the literature preparation of (*o*-anisaldehyde)Cr(CO)3 **149**, gave a green solution. Work up gave the required Cr(CO)3 complex **149** in very low yield, as a red solid. The ^{1}H n.m.r. spectrum of complex **149** contained an aldehyde proton singlet (δ10.05), two aromatic proton doublets (δ6.25-6.23, 5.07-5.05) and two aromatic proton triplets (δ5.87-5.82, 5.02-4.98) characteristic of four contiguous protons. The spectroscopic data of complex **149** were identical with those in the literature.[3]

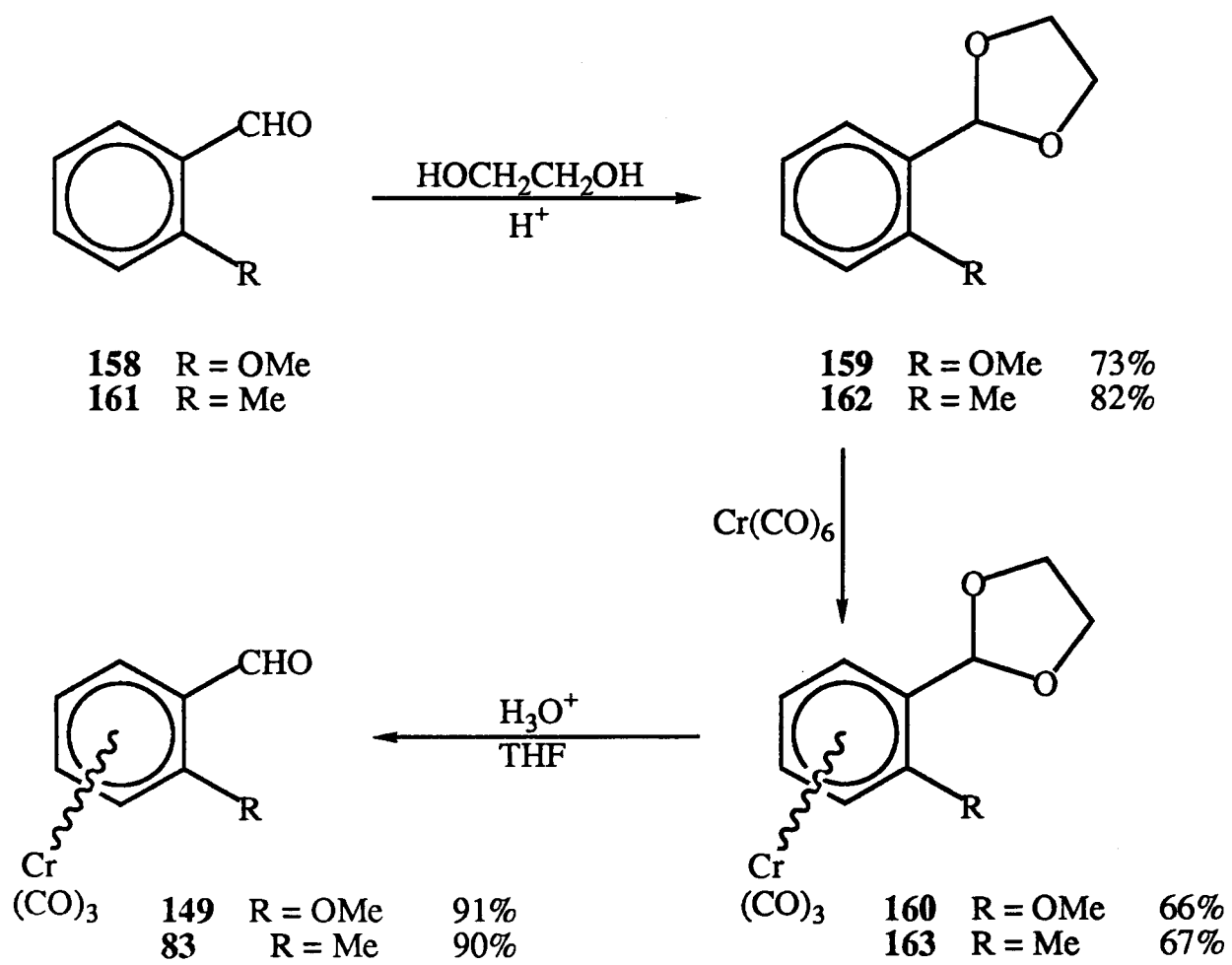


158 **149**

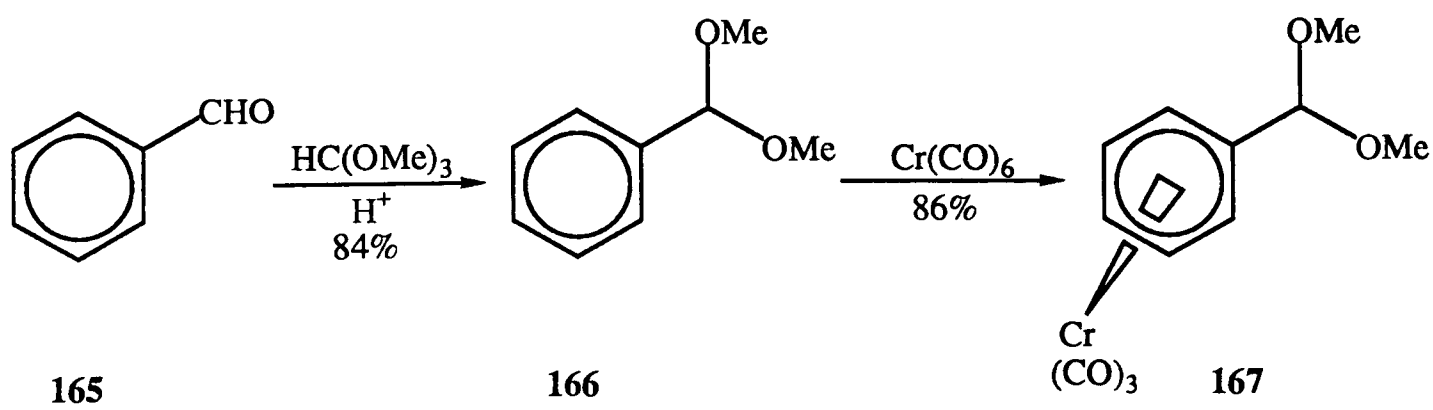
Repetition of the literature method overcame the low yield.[3] *o*-Anisaldehyde **158** was treated with ethane-1,2-diol and a catalytic quantity of *p*-TsOH, and refluxed with benzene in a Dean-Stark trap (4h). Work up and distillation gave the corresponding acetal **159** in good yield. The ^{1}H n.m.r. spectrum of acetal **159** contained two multiplets (δ4.03-3.98, 3.91-3.87) characteristic of the dioxolane ring protons. Complexation of the protected aldehyde **159** under standard conditions gave the corresponding Cr(CO)3 complex **160**, again in good yield. The ^{1}H n.m.r. spectrum of complex **160** contained two aromatic proton doublets (δ5.95-5.92, 5.04-5.02) and two aromatic proton triplets (δ5.59-5.55, 4.90-4.86). The dioxolane ring protons appeared shifted downfield somewhat (δ4.20-4.03). A molecular ion *m/z* 316 (M^+) in the mass spectrum confirmed the product as the required acetal complex. Treatment of complex **160** with *p*-TsOH in aqueous THF gave, after stirring (4.5h) and work up, large red needles of the required racemic complex **149** in excellent yield, spectroscopically identical to the sample previously prepared.

Repetition of the above procedure with *o*-tolualdehyde **161** gave initially the acetal **162**. The ^{1}H n.m.r. spectrum of acetal **162** contained two two proton multiplets (δ4.19-4.14, 4.08-4.02) characteristic of the dioxolane ring protons. Thermolysis of Cr(CO)6 with acetal **162** under standard conditions gave complex **163**. The ^{1}H n.m.r. spectrum of complex **163** was similar to that of acetal **162** except with the aromatic proton peaks shifted upfield (from δ7.58-7.56 and 7.31-7.19 to δ5.83-5.81, 5.11-5.09, 5.45-5.40 and 5.17-5.13). Treatment of complex **163** with acidic aqueous THF followed by work up and recrystallisation gave (*o*-tolualdehyde)Cr(CO)3 **83** as red blocks.[3] The ^{1}H n.m.r. spectrum of complex **83** contained a downfield aldehyde proton singlet (δ9.81), two

aromatic proton doublets (δ6.07-6.04, 5.05-5.03) and two aromatic proton triplets (δ5.75-5.70, 5.25-5.21) characteristic of four contiguous protons.



The preparation of (*o*-trimethylsilylbenzaldehyde)Cr(CO)3 **164**, a previously unknown complex, was by a different method. Benzaldehyde **165** was reacted with trimethylorthoformate in the presence of a catalytic quantity of c.H_2SO_4. The solution was stirred (24h) and quenched with base. Distillation gave the corresponding dimethoxy acetal derivative **166** in good yield.[84] The ^1H n.m.r. spectrum of acetal **166** contained two equivalent three proton methoxy singlets (δ3.35). Standard complexation of arene **166** gave, following recrystallisation, complex **167** as yellow granules in good yield. The ^1H n.m.r. spectrum of complex **167** contained the upfield proton multiplets of five contiguous aromatic protons (δ5.54-5.52, 5.38-5.34, 5.31-5.29) and a six proton singlet (δ3.39) characteristic of the dimethoxy acetal group. A molecular ion *m/z* 288 (M^+) in the mass spectrum confirmed that the product was (α,α-dimethoxytoluene)$Cr(CO)_3$ **167**.

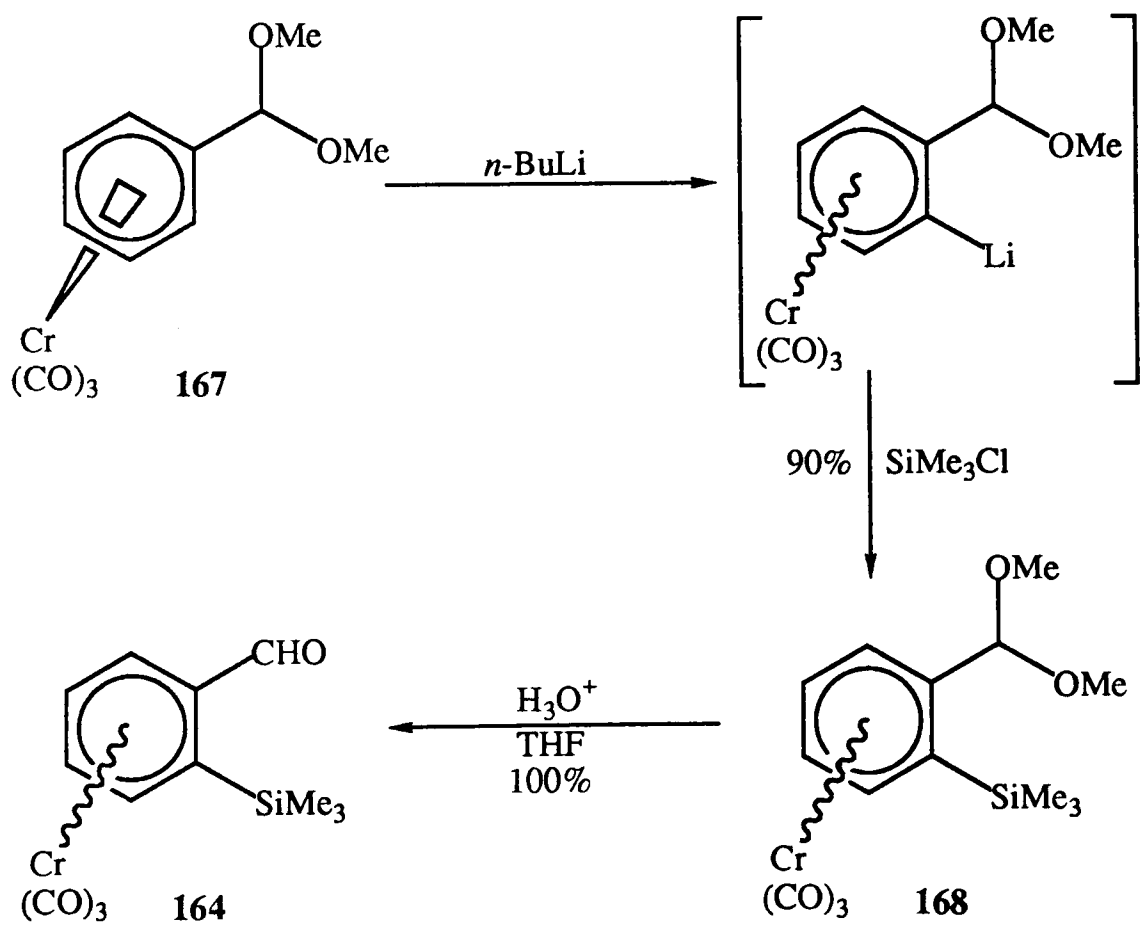


165 **166** **167**

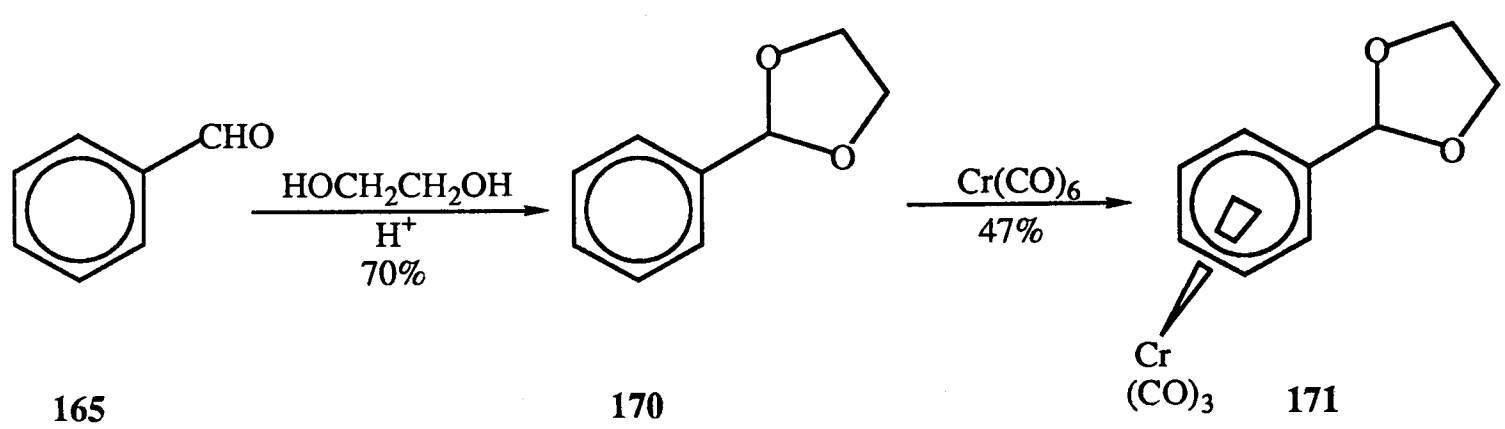
Benzaldehyde acetals undergo chelation controlled lithiated regiospecifically *ortho* to the acetal group in moderate yields.[85] Increasing the acidity of the aromatic protons

via coordination of the arene to the $Cr(CO)_3$ group should enhance the yield of this reaction.[48] Thus, addition of *n*-BuLi followed by chlorotrimethylsilane to complex **167** under standard alkylation conditions gave on work up and recrystallisation, yellow needles in good yield. The product was identified on the basis of the ^1H n.m.r. spectrum, which contained three aromatic proton multiplets consistent with four contiguous protons (δ5.61-5.59, 5.47-5.45, 5.20-5.15) and a nine proton singlet (δ0.37) characteristic of a trimethylsilyl group. A molecular ion *m/z* 360 (*M*+) in the mass spectrum and a correct elemental microanalysis confirmed the identity of the product as the *o*-trimethylsilyl acetal **168**.

Subsequent prolonged (72h) treatment of complex **168** with acidic aqueous THF released (*o*-trimethylsilylbenzaldehyde)$Cr(CO)_3$ **164** as a low melting point red solid in essentially quantitative yield. The ^1H n.m.r. spectrum of complex **164** was similar to that of **168** but with the loss of the two three proton methoxy singlets (δ3.53, 3.15) and a downfield shift of the benzylic proton (from δ5.32 to δ9.73). Presumably, the rate of hydrolysis of this acetal was slow due to the destabilising effect of the *o*-trimethylsilyl group on α-carbonium ions. One of the intermediates in the hydrolysis of the acetal has a resonance contributor with such a carbonium ion and transition states leading to this intermediate will be high in energy. Alternatively, since the loss of the benzylic methoxy groups occurs preferentially from conformations which place the leaving group *antiperiplanar* to the $Cr(CO)_3$, then hydrolysis may proceed at a relatively fast rate to the hemiacetal stage, but subsequent loss of the remaining methoxy group will presumably be slow due to the inability of the molecule to achieve conformations which place this group *antiperiplanar* to the $Cr(CO)_3$ group. Such conformations are inaccessible due to an adverse steric interaction between the benzylic hydroxyl group and the *o*-silyl function.

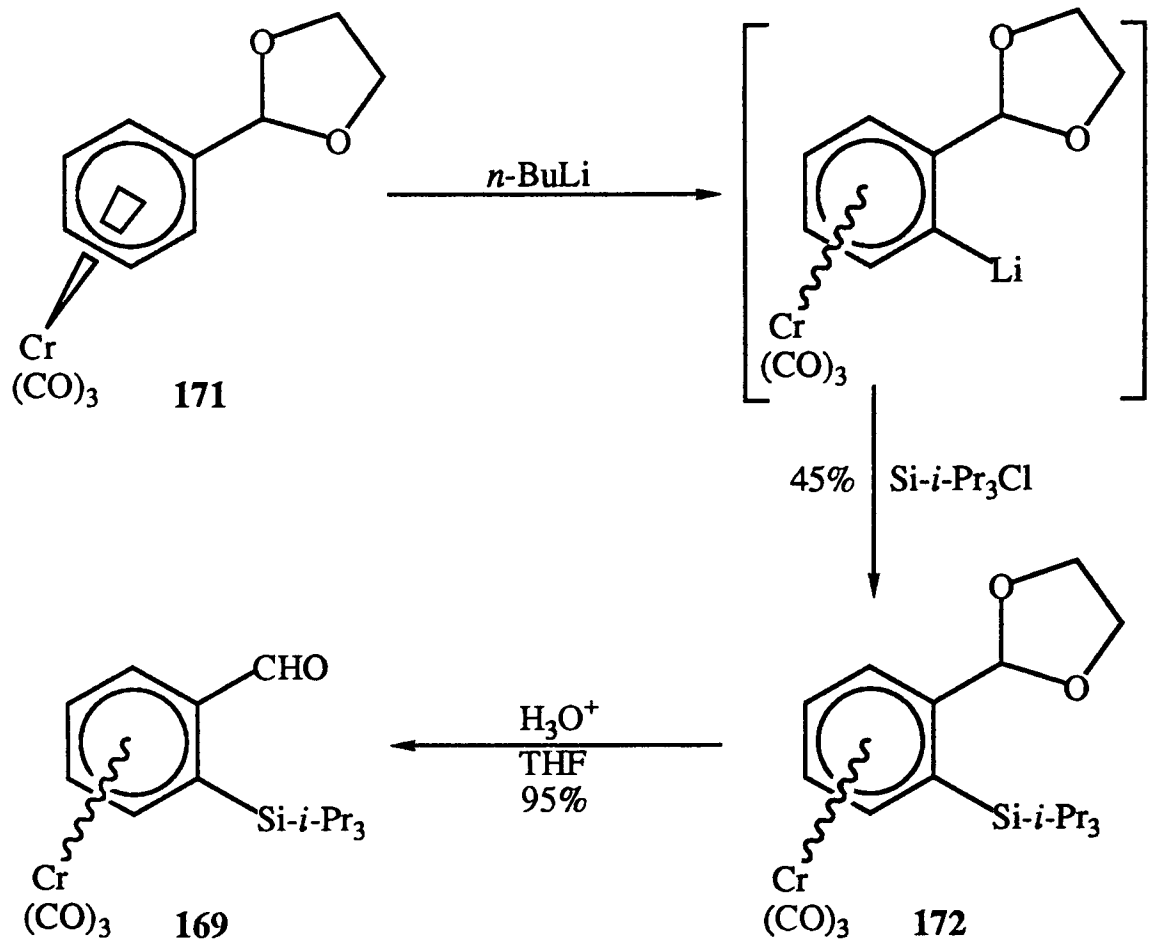


Preparation of (*o*-tri-*i*-propylsilylbenzaldehyde)$Cr(CO)_3$ **169** followed a similar route, but using the ethane-1,2-diol derived acetal of benzaldehyde **170**, since it was found that quenching the *o*-lithiated acetal from complex **167** with chlorotri-*i*-propyl-silane proceeded in only very low yield. Benzaldehyde **165** was reacted with ethane-1,2-diol and acid and heated in a Dean-Stark apparatus at reflux with benzene solvent. Distillation gave the required acetal **170** in good yield. The ^1H n.m.r. spectrum of the product **170** contained a benzylic proton singlet (δ5.85) and a four proton multiplet (δ4.21-4.02) characteristic of the dioxolane ring protons. Complexation of acetal **170** under standard conditions gave, on work up and recrystallisation, yellow plates in moderate yield, identified as (2-phenyl-1,3-dioxolane)$Cr(CO)_3$ **171** on the basis of the upfield shifted aromatic proton signals in the ^1H n.m.r. spectrum (from δ7.55-7.39 to δ5.58-5.54 and 5.37-5.29).



165 **170** **171**

Regioselective silylation of complex **171**, *via* a chelation controlled deprotonation *ortho* to the acetal substituent, was observed on treatment with *n*-BuLi followed by chlorotri-*i*-propylsilane under standard alkylation conditions. The product was identified as the *o*-tri-*i*-propylsilylated compound **172** by ^1H n.m.r. spectroscopy. The silyl group signals consisted of a three proton multiplet (δ1.50-1.32) assigned as the protons alpha to silicon and two nine proton doublets (δ1.23, J = 7.07Hz, δ1.18, J = 7.07Hz) characteristic of the diastereotopic methyl protons of the *i*-propyl groups. The two aromatic proton triplets (δ5.72-5.66, 5.18-5.12) and two aromatic proton doublets (δ5.54-5.51, 5.44-5.41) were characteristic of four contiguous protons, consistent with *ortho* functionalisation having occurred. Hydrolysis of complex **172** was achieved on treatment with acidic aqueous THF for 6 days. Again the slow rate of liberation of free aldehyde **169** can be ascribed to the presence of the *o*-silyl group (*vide supra*). (*o*-Tri-*i*-propylsilyl-benzaldehyde)$Cr(CO)_3$ **169** was isolated as red needles in excellent yield. The ^1H n.m.r. spectrum of the product was similar to that of the acetal complex **172**, but with the benzylic proton signal shifted downfield (from δ5.56 to δ9.80) and loss of the dioxolane ring proton multiplet. A molecular ion *m/z* 398 (M^+) in the mass spectrum and a correct elemental microanalysis confirmed the identity of complex **169**.



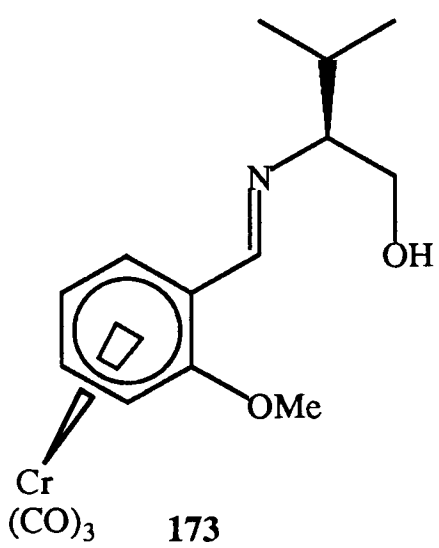
c. *Kinetic Resolution of Ortho Substituted (Benzaldehyde)Cr(CO)3 Complexes.*

i. *(o-Anisaldehyde)Cr(CO)3.*

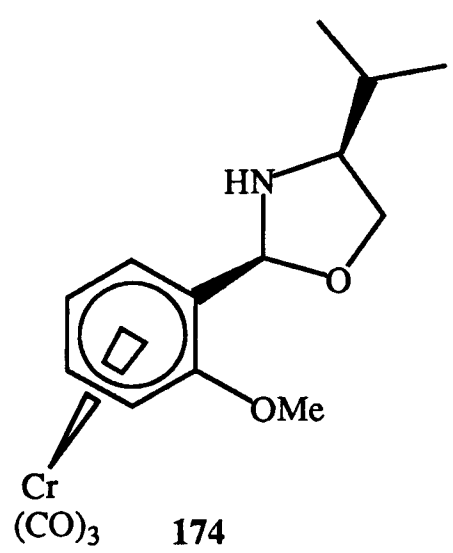
Treatment of a red Et2O solution of racemic (*o*-anisaldehyde)Cr(CO)3 **149** with one equivalent of L-valinol, (prepared from L-valine by LiAlH4 reduction), gave an orange solution. Absorption of this solution onto a column of deactivated alumina (Grade V) followed by slow elution with Et2O, gave a red and a yellow band. The first fraction (Et2O) gave a red solid on evaporation of the solvent. The yellow second fraction (CH_2Cl_2:MeOH 10:1) was evaporated to a red oil. Both fractions were briefly stirred in acidic aqueous THF, the colour initially darkening and slowly turning crimson. Work up gave both products as red solids. The ^1H n.m.r. spectra of the compounds were identical with that of racemic starting material. The optical rotation of fraction one clearly indicated the (-)-enantiomer (-)-**149** {$[\alpha]_D^{23}$ = -1015o (c 0.06 CHCl3), Lit.[3] $[\alpha]_D$ = -1020o (c 0.09 CHCl3)}, whilst that of fraction two indicated the (+)-enantiomer (+)-**149** {$[\alpha]_D^{23}$ = +1016o (c 0.06 CHCl3), Lit.[3] $[\alpha]_D$ = +1015o (c 0.06 CHCl3)}. The production of homochiral (*o*-anisaldehyde)Cr(CO)3 **149** confirms that the sample of L-valinol used was also homochiral and thus the reduction of L-valine with LiAlH4 proceeds with no racemisation at the α-centre. This is in contrast to the reduction of L-valine esters to L-valinol, which under similar conditions gives partially racemised product.[86]

Treatment of a Et2O solution of complex (+)-**149** with one equivalent of L-valinol gave a colour change from red to orange. The ^1H n.m.r. spectrum of an aliquot of the

solution, contained only one set of peaks consistent with either the imine **173** or oxazolidine **174**. The main features of the ^1H n.m.r. spectrum (C_6D_6) were a benzylic proton singlet (δ8.34), two aromatic proton doublets (δ6.34-6.31, 3.95-3.93) and two aromatic proton triplets (δ4.76-4.71, 4.11-4.06). The orange colour of the product initially suggested the formation of the imine **173**. (Arene)$Cr(CO)_3$ complexes, such as complex **173**, possessing double bonds in a side-chain conjugated with the ring are generally orange to red, whilst non-conjugated complexes such as the oxazolidine **174** are generally yellow in colour.

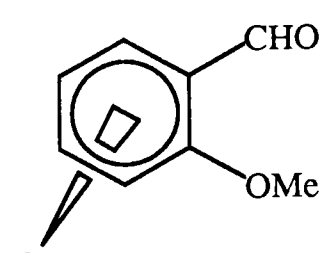


173

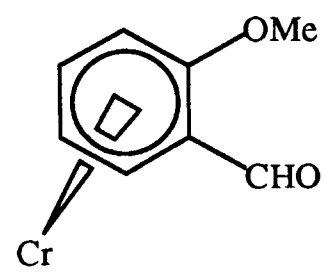


174

Evaporation of the remainder of the solution and crystallisation of the residue from Et_2O:light petroleum gave large orange blocks. The solution infrared spectrum of the complex (CH_2Cl_2) contained an absorption at 1633cm^{-1} characteristic of a C=N stretch. This clearly indicated, in conjunction with the ^1H n.m.r. spectral data which showed only a single compound, that the complex was the imine **173** and not oxazolidine **174.** Complex **173** gave a correct elemental microanalysis. A single crystal X-ray structure analysis unambiguously confirmed the product as the imine **173**, Figure VII. Final atomic coordinates, selected bond lengths, angles and torsional angles are presented in Appendix III. Note the coplanar arrangement of the C=N bond, aromatic ring and methoxy substituent. Since the absolute configuration of the L-valinol is known, (as it is derived from L-valine),[87] the X-ray crystal structure analysis clearly establishes the absolute configuration of the (arene)$Cr(CO)_3$ fragment to be (*S*) and thus the absolute configuration of complex (+)-**149** must also be (*S*), as shown below.



(+)-**149**



(-)-**149**

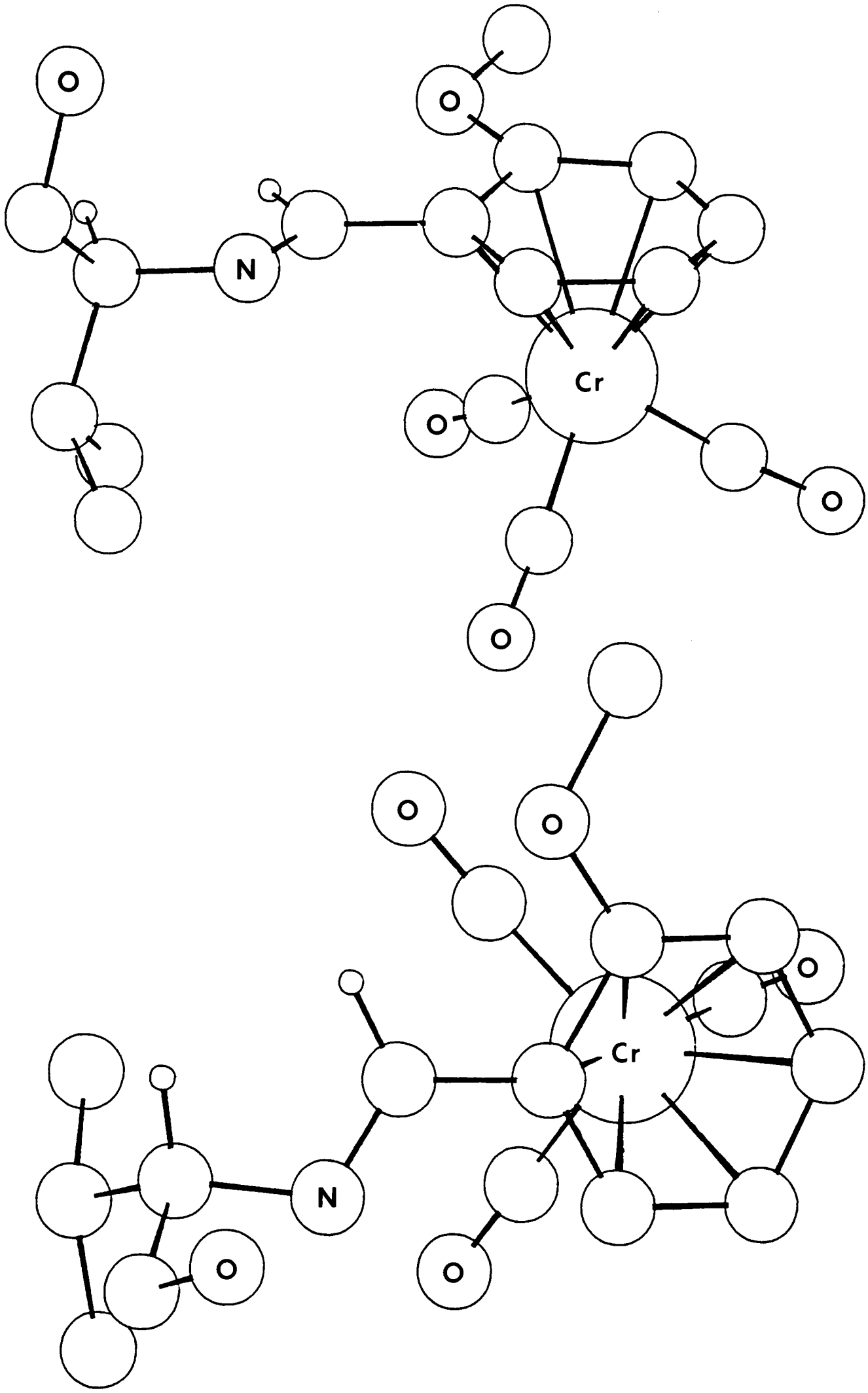
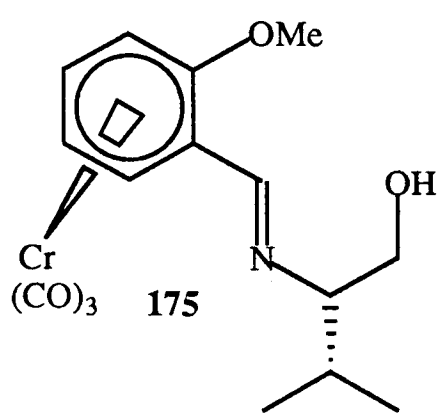
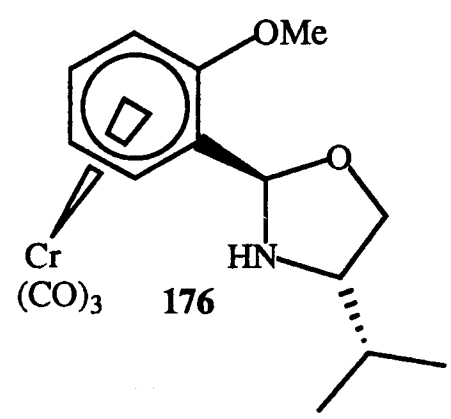


Figure VII. X-Ray crystal structure of the L-valinol derived imine of (+)-(*o*-anisaldehyde)Cr(CO)3 (+)-**149**, complex **173**.

Treatment of complex (-)-**149** with one equivalent of L-valinol gave a pale orange solution. An aliquot of the solution was evaporated to an orange oil and shown to contain only one compound either the imine **175** or oxazolidine **176** by ^{1}H n.m.r. spectroscopy. The main features of the ^{1}H n.m.r. spectrum (C_6D_6) were a benzylic proton singlet (δ8.28), two aromatic proton doublets (δ6.26-6.22, 4.06-4.02) and two aromatic proton triplets (δ4.75-4.69, 4.17-4.11). Recrystallisation of the product from Et_2O:hexane failed, but the solution infrared spectrum (CH_2Cl_2) of the product contained an absorption at 1631cm^{-1} characteristic of an imine. Consequently, since the ^{1}H n.m.r. spectrum demonstrated only a single compound in solution and the infrared spectrum contained an imine absorption peak it follows that the product can again be identified as the imine **175** and not oxazolidine **176**.



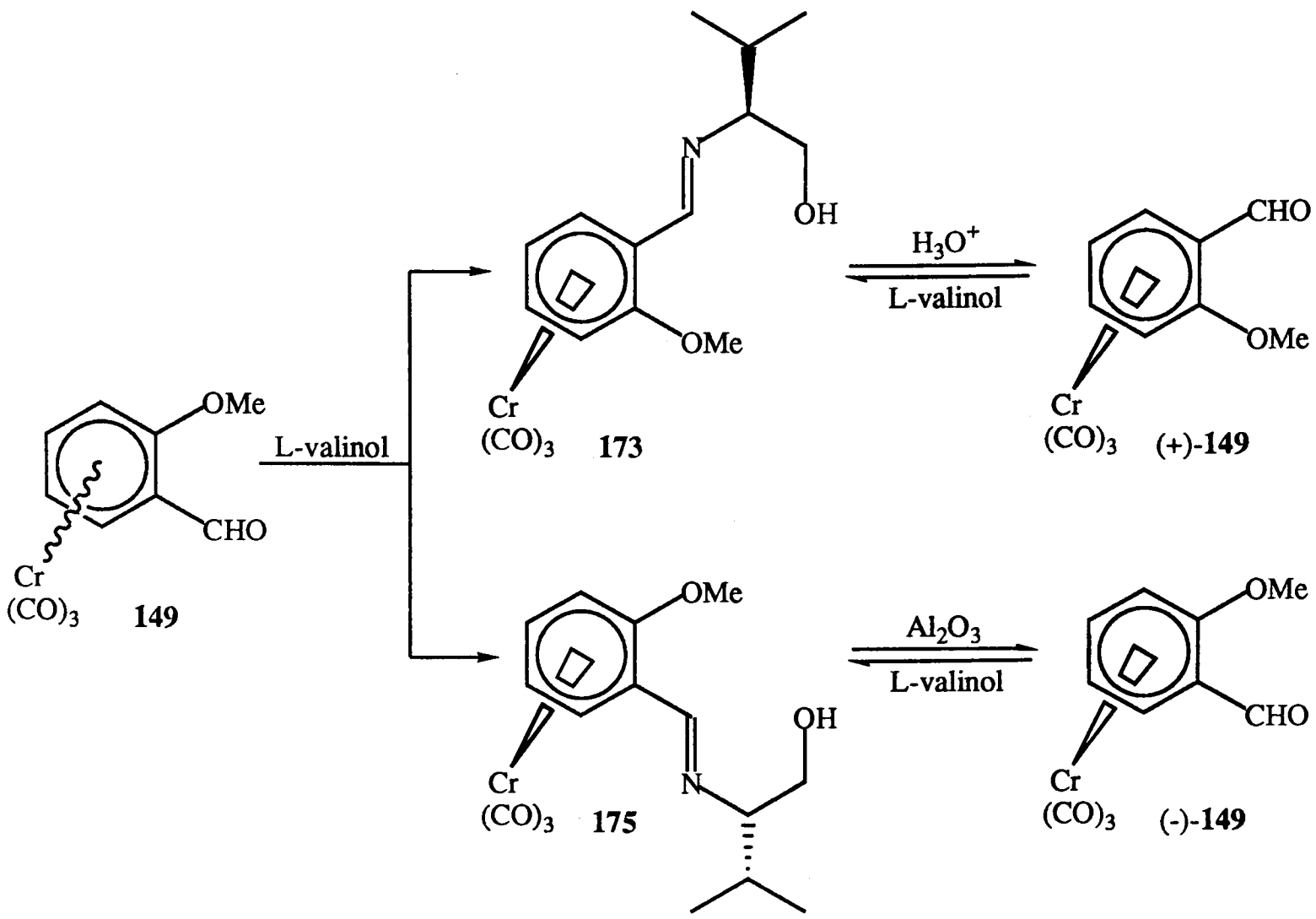
175



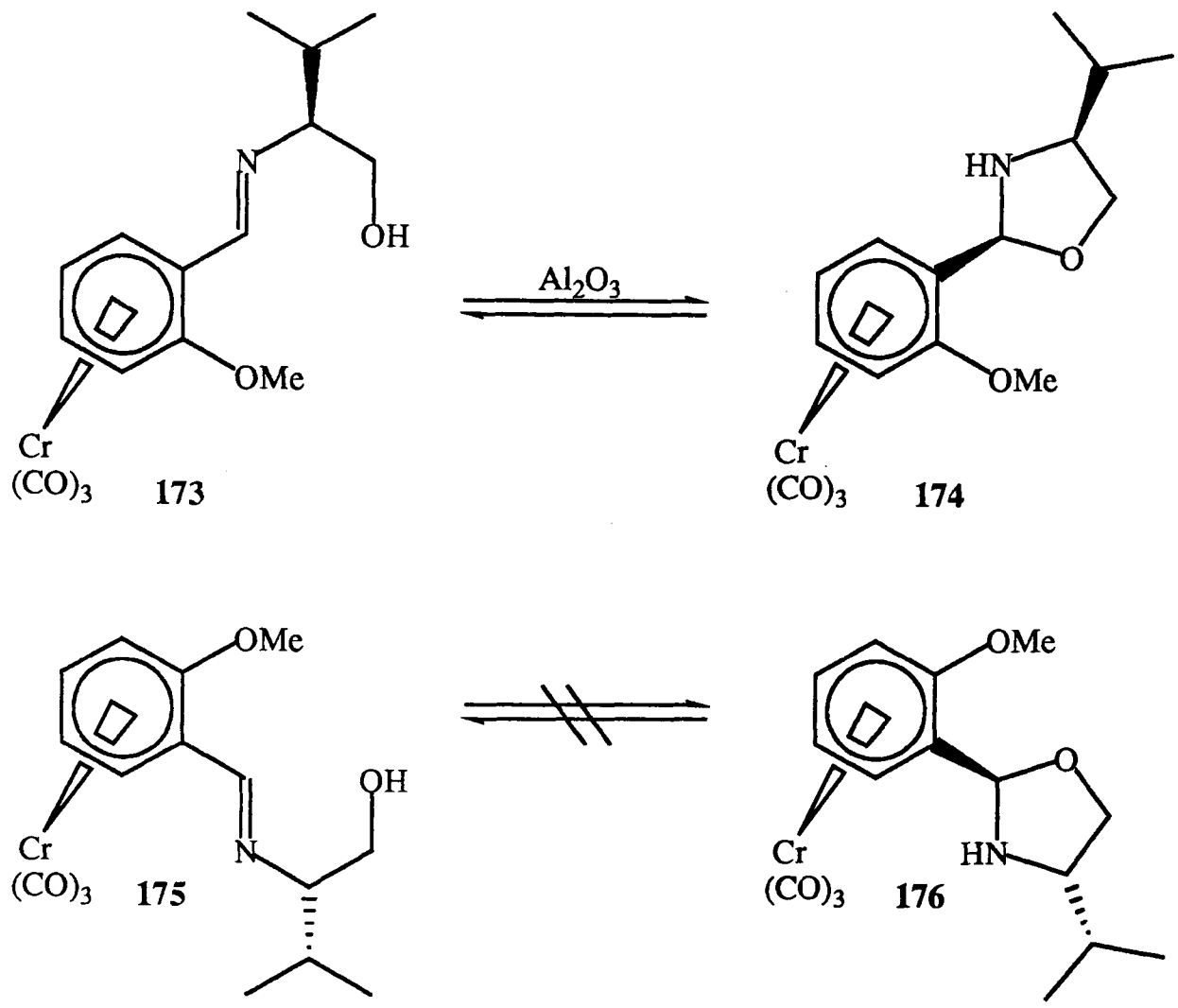
176

The presence of only imine products and no oxazolidines in the above reactions is consistent with a literature report on the effect of arene substituents on the position of the ring-chain tautomerism of these compounds.[88] Placing electron-donating substituents on the ring of the (arene)Cr(CO)3 complex will favour the imine over oxazolidine, whilst the reverse is true for electron-withdrawing substituents. Thus, in the case of an arene possessing an *o*-methoxy group, the presence of only the imine tautomer is consistent with the above trend.

The exclusive production of a single diastereoisomeric compound upon treatment of resolved (+)-**149** or (-)-**149** with L-valinol clearly indicates that both samples of aldehyde were homochiral. Acid hydrolysis of complex **173** regenerated homochiral (+)-**149** showing that no racemisation occurs on formation or hydrolysis of the imine.



The above methodology represents a kinetic resolution procedure for the preparation of homochiral (*o*-anisaldehyde)Cr(CO)3 **149**. The method is based on the selective hydrolysis of imine **175** by deactivated alumina, associated with the large difference in R_f values between the aldehyde and imine complexes on deactivated alumina. Presumably the imine group prefers to lie coplanar with the aromatic ring allowing maximum conjugation. The orientation with respect to the *o*-methoxy group is *anti* for both electronic dipole and steric reasons. Examination of molecular models indicates that closure of imine **173** by intramolecular *exo* attack of the hydroxyl gives rise to the *cis*-1,3-disubstituted oxazolidine **174**, whilst closure of imine **175** by a similar mechanism gives the *trans*-1,3-disubstituted oxazolidine **176**. *cis*-1,3-Disubstituted oxazolidines have greater stability and are more easily formed that the corresponding *trans* isomers.[89] In the presence of deactivated alumina imine **173** can undergo rapid reversible oxazolidine formation, thus protecting it from hydrolysis. Under the same conditions imine **175**, however, can only undergo hydrolysis to give (-)-**149**.



Preparation of the diastereoisomeric mixture of imines **173** and **175** from **149** prior to column chromatography proved unnecessary for resolution. Thus, a deactivated alumina column was doped with one equivalent of L-valinol in both top and middle portions. One equivalent of racemic aldehyde **149** in Et_2O solution was absorbed onto the column and allowed to stand. Elution with Et_2O gave a red solution which was evaporated to a red solid. The remaining yellow coloured bands were removed with Et_2O:MeOH 5:1 and evaporated to give an orange oil, Figure VIII. Both fractions were separately treated with acidic aqueous THF until no further colour change was observed and then isolated as red solids. ^1H n.m.r. spectroscopy identified both compounds as (*o*-anisaldehyde)$Cr(CO)_3$ **149** whilst optical rotation measurements identified the first band as (-)-**149** {$[\alpha]_D^{25}$ = -1006° (c 0.06 $CHCl_3$)} and the second band as (+)-**149** {$[\alpha]_D^{24}$ = +1020° (c 0.06 $CHCl_3$)}. Treatment of the first fraction with acidic aqueous THF was necessary as a purification step. Presumably a small quantity of L-valinol elutes through the column with the first fraction. Once removed from alumina the amine may then recondense with the aldehyde to regenerate a small quantity of imine **175**. Subsequent evaporation of the solvent gives (-)-(*o*-anisaldehyde)$Cr(CO)_3$ **149** containing some imine impurity.

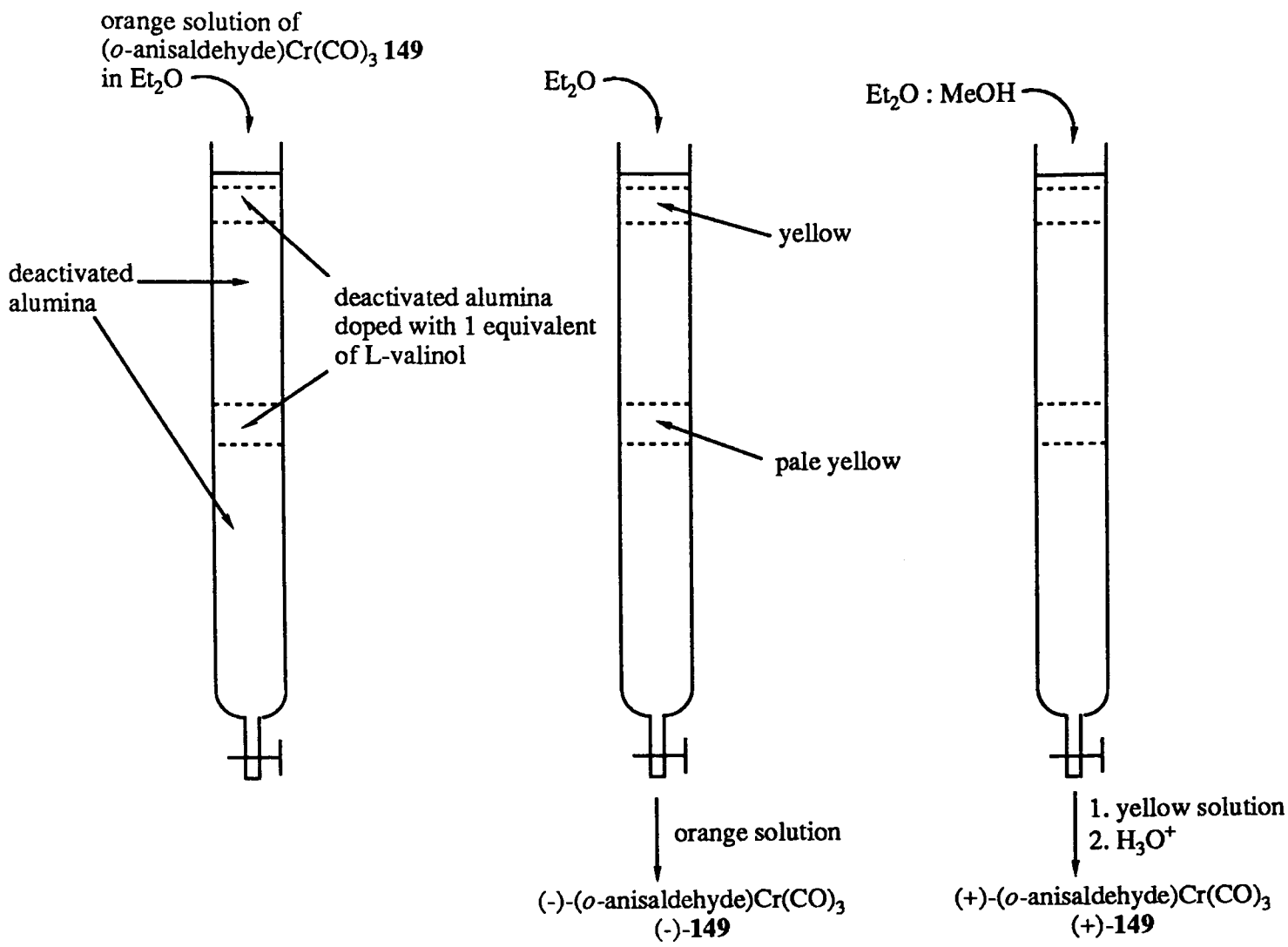


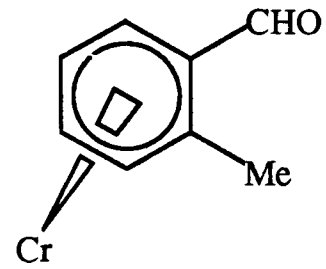
Figure VIII. Resolution of (*o*-anisaldehyde)$Cr(CO)_3$ **149** using an L-valinol doped deactivated alumina column.

The use of two L-valinol doped bands of alumina proved necessary to produce essentially homochiral products. Presumably quantitative production of imine **173** does not occur in the top doped band and any unreacted (+)-**149** complex is trapped out selectively by the second band. This is consistent with the observation that the second doped band turns pale yellow as the first fraction elutes through, presumably due to formation of the L-valinol adduct with any remaining complex (+)-**149**.

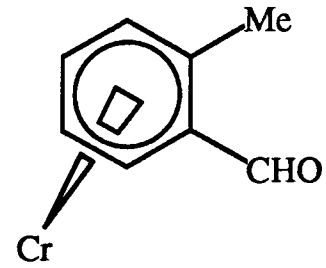
ii. *Other Ortho Substituted (Benzaldehyde)Cr(CO)3 Complexes.*

The above methodology was extended to (*o*-tolualdehyde)Cr(CO)3 **83** and (*o*-trimethylsilylbenzaldehyde)Cr(CO)3 **164**. Thus, treatment of (*o*-tolualdehyde)Cr(CO)3 **83** with one equivalent of L-valinol in Et2O (4h) gave an orange solution. Column chromatography on deactivated alumina (Grade V) gave two fractions as before. Brief acidic aqueous THF hydrolysis and work up gave both products as red solids, with 1H n.m.r. spectra identical to that of starting aldehyde complex. The first fraction was identified as (-)-**83** {$[\alpha]_D^{22}$ = -542o (c 0.3 CHCl3) 82% ee, Lit.[3] $[\alpha]_D$ = -664o (c 0.3

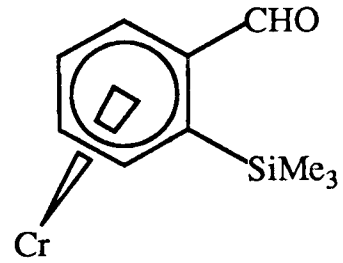
$CHCl_3$)} and the second fraction as (+)-**83** {$[\alpha]_D^{22}$ = +619o (c 0.2 CHCl3) 93% ee, Lit.[3] $[\alpha]_D$ = +665o (c 0.2 CHCl3)}. The preferential hydrolysis of the imine derived from (-)-**83** implies that the absolute stereochemistries of (-)-**83** and (-)-**149** are the same. This is in agreement with the literature assignment.[78,79]



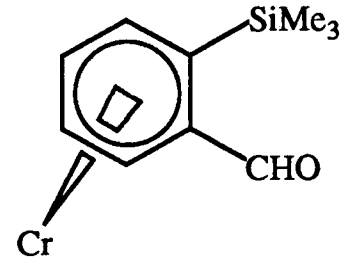
(+)-**83**



(-)-**83**



(+)-**164**



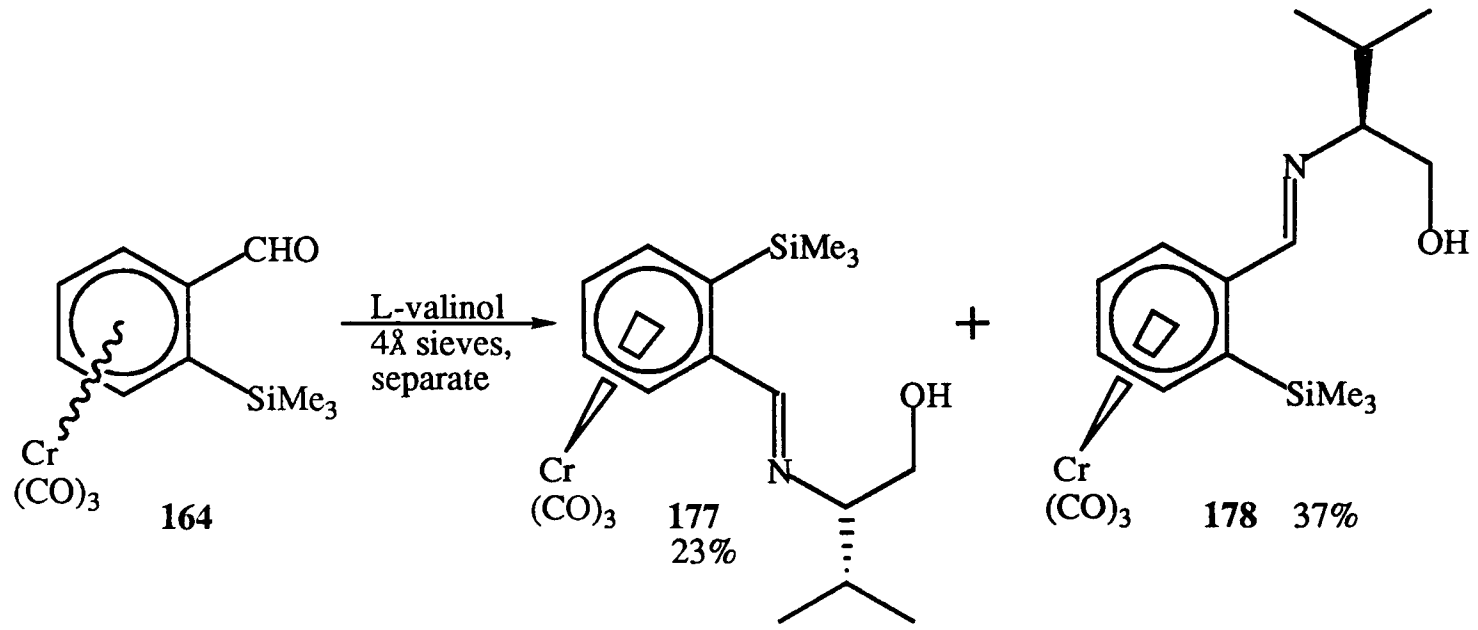
(-)-**164**

In the cases of compounds **83** and **164** because neither the methyl nor trimethylsilyl substituents are strong electron-donors, the position of the oxazolidine-imine ring-chain tautomerism may not lie completely on the imine side.[88] This may account for the production of only optically enriched and not homochiral material.

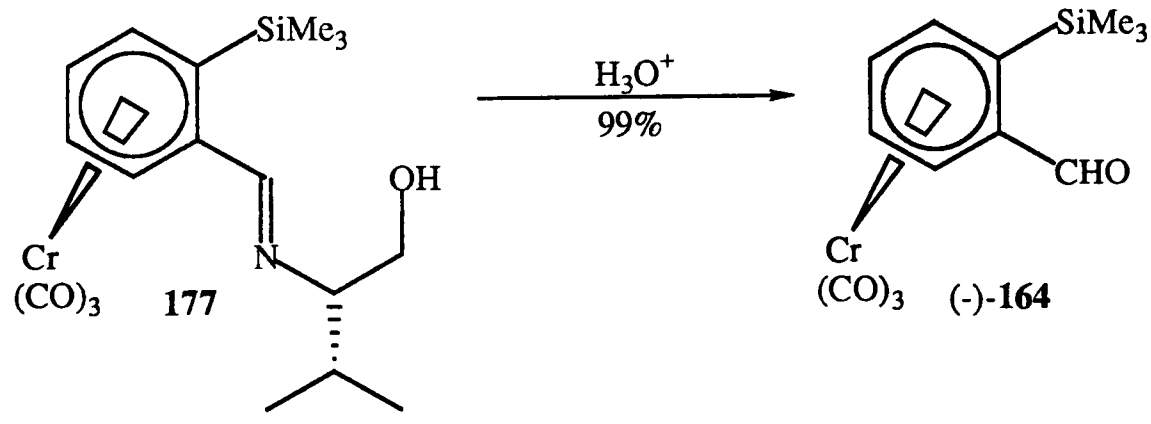
d. *Resolution of (o-Trimethylsilylbenzaldehyde)Cr(CO)3 and (o-Tri-i-propylsilyl-benzaldehyde)Cr(CO)3.*

Treatment of (*o*-trimethylsilylbenzaldehyde)Cr(CO)3 **164** with L-valinol in Et_2O containing 4^0_A molecular sieves, gave an orange solution. Filtration through celite and evaporation of the solvent left an orange oil which crystallised on addition of hexane. ^1H n.m.r. spectroscopy showed the solid to be a 50:50 mixture of the two imines **177** and **178** or their corresponding oxazolidines, with characteristic benzylic proton singlets

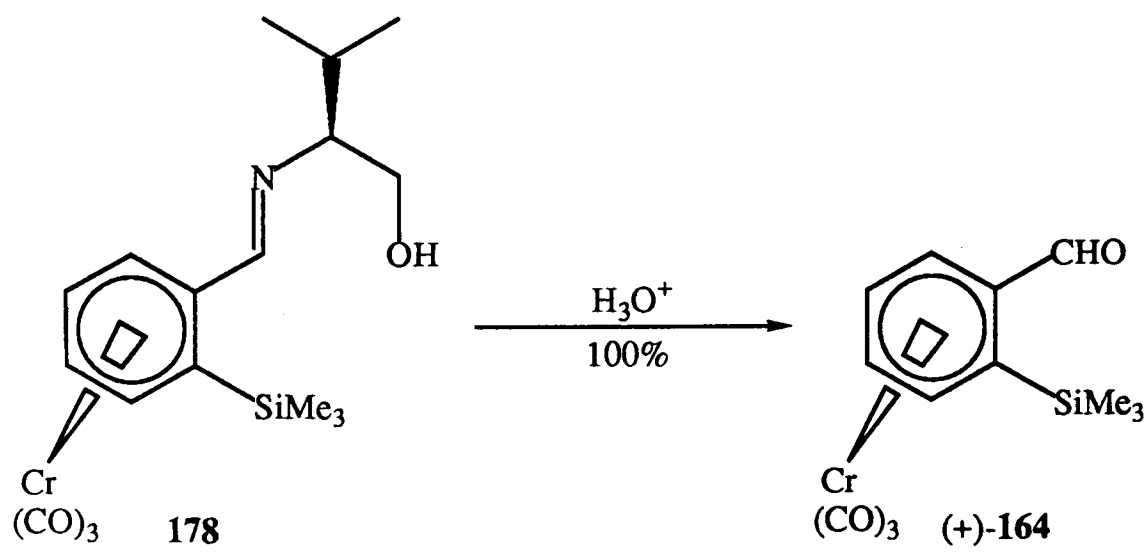
(δ8.24, 8.22). Column chromatography (SiO_2) with Et_2O:Et_3N 10:1 as a basic eluant gave two fractions, which were separately evaporated and recrystallised from hexane to give orange needles. The ^1H n.m.r. spectrum of fraction one contained a benzylic proton singlet (δ8.24), two aromatic proton doublets (δ6.10-6.07, 5.54-5.50), two aromatic proton triplets (δ5.70-5.63, 5.31-5.25) and a nine proton silyl singlet (δ0.44). The ^1H n.m.r. spectrum of fraction two contained a benzylic proton singlet (δ8.22), two aromatic proton doublets (δ5.98-5.95, 5.48-5.31), two aromatic proton triplets (δ5.66-5.59, 5.31-5.24) and a nine proton silyl singlet (δ0.43). Both products gave molecular ions *m/z* 399 (*M*+) in their mass spectra and correct elemental microanalyses. The two fractions were identified as imines **177** and **178** and not oxazolidines on the basis of their solution (CH_2Cl_2) infrared C=N stretches at 1632cm^{-1} for fraction one and 1640cm^{-1} for fraction two.



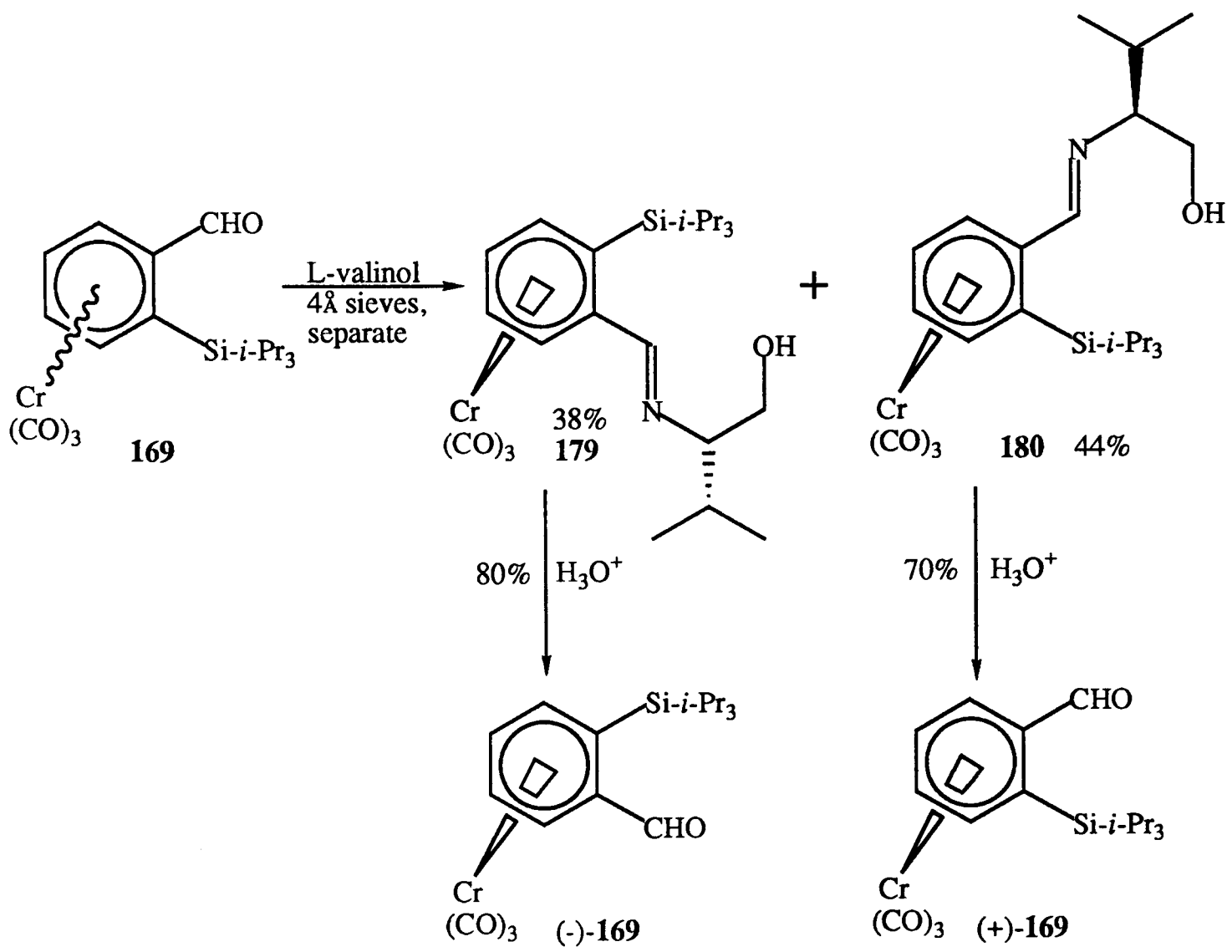
Hydrolysis of the first fraction in acidic aqueous THF gave a red oil, with a ^1H n.m.r. spectrum identical to that of the racemic starting material **164**. Optical rotation {$[\alpha]_D^{18}$ = -154o (c 1 CHCl3)}, identified the product as (-)-(*o*-trimethylsilyl-benzaldehyde)Cr(CO)3 (-)-**164**. The presence of only a single compound, as detected by ^1H n.m.r. spectroscopy, in fraction one prior to hydrolysis confirmed that the sample of (-)-**164** must be homochiral. Since the absolute configuration of (-)-**164** is (*R*) (*vide supra*) and that of L-valinol is (*S*),[87] it follows that complex **177** is the (*RS*) diastereoisomer and complex **178** the (*SS*).



Similarly hydrolysis of the (*SS*) diastereoisomer **178** gave complex (+)-**164** {$[\alpha]_D^{20}$ = +146o (c 0.1 $CHCl_3$)}. Again the presence of only a single compound as detected by ^1H n.m.r. spectroscopy in fraction two prior to hydrolysis, confirmed that the sample of (+)-**164** must be homochiral.



The above methodology was extended to the resolution of (*o*-tri-*i*-propylsilyl-benzaldehyde)$Cr(CO)_3$ **169**. Thus, treatment of racemic complex **169** with L-valinol in Et_2O containing 4^0_A molecular sieves, gave an orange solution. Column chromatography (SiO_2) with Et_2O:hexane:Et_3N 10:10:1 gave three bands. The first fraction was identified as starting material (-)-**169** {$[\alpha]_D^{19}$ = -384o (c 0.8 $CHCl_3$)} by ^1H n.m.r. spectroscopy. The optical activity of this fraction indicated that partial kinetic resolution had occurred, L-valinol reacting with (+)-**169** at a greater rate than with (-)-**169**. The remaining two fractions were isolated separately and identified as the imines **179** and **180** and not oxazolidines by analogy with above. The ^1H n.m.r. spectrum (C_6D_6) of the second fraction contained a benzylic proton singlet (δ8.17), two aromatic proton doublets (δ5.84-5.80, 5.13-5.10) and two aromatic proton triplets (δ4.84-4.78, 4.34-4.28). The ^1H n.m.r. spectrum (C_6D_6) of the third fraction contained a benzylic proton singlet (δ8.21), two aromatic proton doublets (δ5.82-5.78, 5.11-5.08) and two aromatic proton triplets (δ4.86-4.80, 4.35-4.29). Acidic aqueous THF hydrolysis of the second fraction gave compound (-)-**169** as a red solid, {$[\alpha]_D^{19}$ = -485o (c 0.1 $CHCl_3$)}, which must be homochiral due to the presence of only a single compound at the imine stage prior to hydrolysis. Similarly, fraction three gave homochiral (+)-**169** as a red solid, {$[\alpha]_D^{21}$ = +515o (c 0.1 $CHCl_3$)}. The absolute configuration of (-)-**169** and (+)-**169** and the relative assignments of **179** and **180** were unknown at this stage, but a later study, see Chapter 7, confirmed them as those shown below. Thus, imine **179** gave, on hydrolysis, the (*R*) enantiomer of the aldehyde (-)-**169**. Since the absolute configuration of L-valinol is (*S*)[87] it follows that imine **179** can be identified as the (*RS*) diastereoisomer and imine **180** the (*SS*).



e. *Conclusion.*

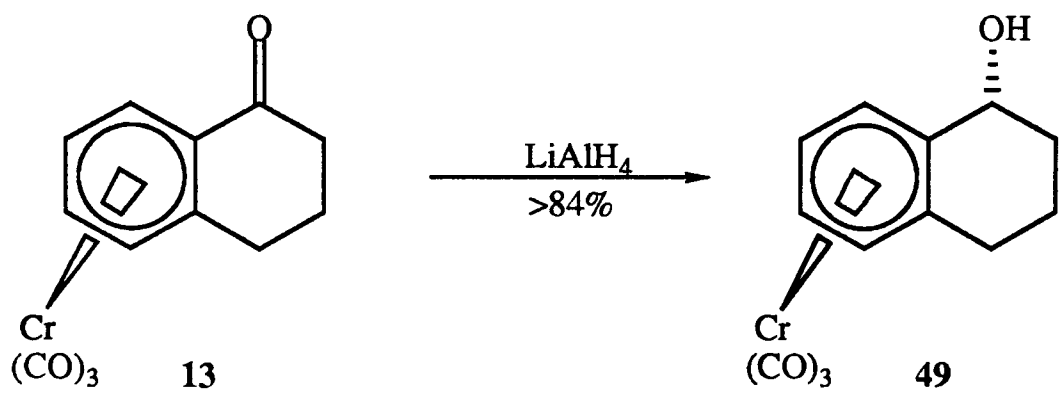
(*o*-Anisaldehyde)Cr(CO)3 **149** has been kinetically resolved by a preferential hydrolysis of one of the L-valinol derived imines in the presence of deactivated alumina. Formation of the imines and their selective hydrolysis can be accomplished entirely on an L-valinol doped alumina column. This methodology has been extended to (*o*-tolualdehyde)Cr(CO)3 **83** and (*o*-trimethylsilylbenzaldehyde)Cr(CO)3 **164** with limited success, presumably reflecting the necessity for strong electron-donating groups on the arene to entirely displace the oxazolidine-imine ring-chain equilibrium to the imine side.

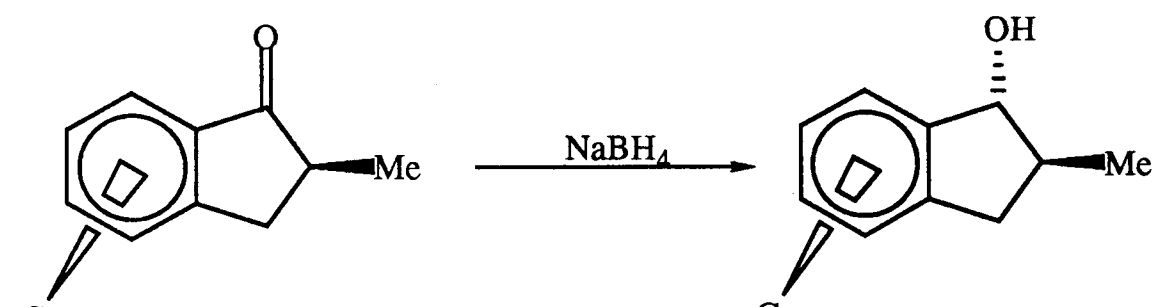
The *o*-silylated derivatives **164** and **169** have been resolved by a classical separation of diastereoisomers. The L-valinol derived imines were separated by chromatography (SiO_2) using an eluant containing Et3N. Each fraction was hydrolysed to give single enantiomers of the aldehyde complexes **164** and **169**.

Chapter 7. Addition of Nucleophiles to *Ortho* Substituted Benzaldehyde Chromium Tricarbonyl Complexes.

a. *Introduction.*

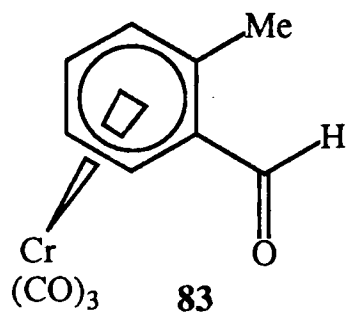
In cyclic systems bearing a benzylic ketone function, such as (1-tetralone)Cr(CO)3 **13** or *exo*-(2-methyl-1-indanone)Cr(CO)3 **181**, the conformational restraints of the aliphatic ring restrict the orientation of the carbonyl group. Since conformations possessing a high degree of conjugation of the ketone with the aromatic ring are most energetically favourable, the C1 oxo group will prefer to lie coplanar with the aromatic ring. Attack of nucleophiles *exo* to the Cr(CO)3 unit will give rise to *endo* alcohols.[90,91]



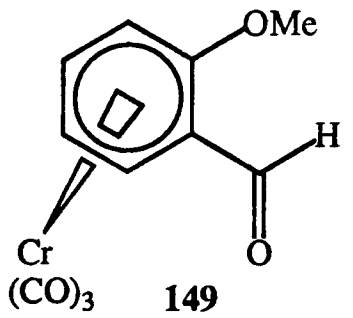


(Benzaldehyde)Cr(CO)3 **182** can lie in one of two favoured conformations with the carbonyl group conjugated to the aromatic system and in the absence of other ring substituents these conformations are enantiotopic. The two *ortho* and indeed the two *meta* protons of complex **182** are also enantiotopic.

Introduction of an *ortho* substituent influences the conformer population markedly since the two conformers with a conjugated aldehyde group coplanar with the aromatic ring are diastereotopic. Thus, (*o*-tolualdehyde)Cr(CO)3 **83** and (*o*-anisaldehyde)Cr(CO)3 **149** both adopt the same preferred conformations.[92]



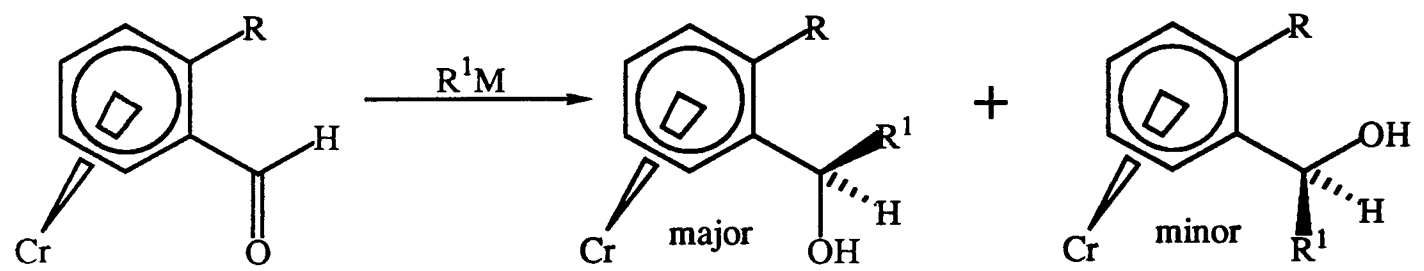
83



149

In the case of complex **83** this is purely a steric feature whereby the smallest atom on the aldehyde function, the hydrogen, lies *syn* to the *ortho* substituent. In the case of (*o*-anisaldehyde)Cr(CO)3 **149** this effect is reinforced by a high energy dipolar interaction between the lone pairs of electrons on both oxygen substituents disfavouring the conformations placing the two oxygens *syn*.

Treatment of both complexes **83** or **149** with a suitable nucleophile would be expected to give predominantly one diastereoisomer **183** or **184** resulting from *exo* attack of the nucleophile away from the bulky Cr(CO)3 unit.

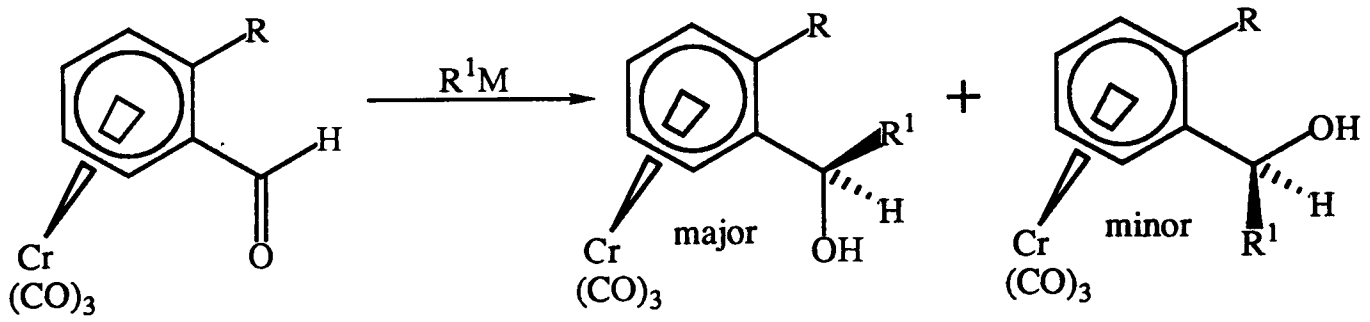


83 R = Me
149 R = OMe

183 R = Me
184 R = OMe

R = Me
R = OMe

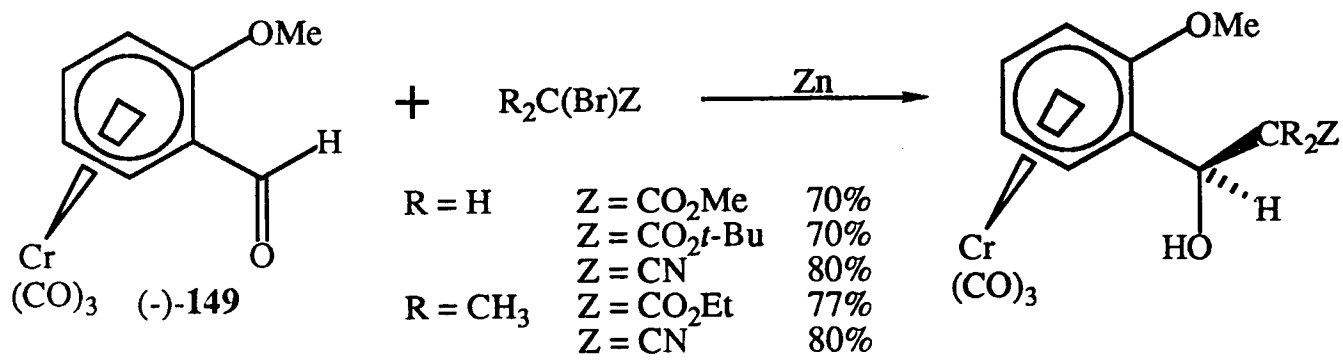
Thus, the addition of a range of carbanions to *ortho* substituted (benzaldehyde)Cr(CO)3 complexes **83**, **149** and **185-187** gave predominantly one diastereoisomer, Table III.[55,93] The major isomer formed in each case was assigned as the (*RR*,*SS*) diastereoisomer, which is consistent with the above prediction.



Entry	R =	No.	R^1M	major:minor
1	*o*-CH_3	**83**	MeMgI	93:7
2	*o*-OCH_3	**149**	MeMgI	95:5
3	*o*-OC_2H_5	**185**	MeMgI	95:5
4	*o*-Cl	**186**	MeMgI	97:3
5	*o*-CH_3	**83**	PhMgBr	95:5
6	*m*-OCH_3	**187**	PhMgBr	97:3
7	*o*-OC_2H_5	**185**	PhMgBr	96:4
8	*o*-CH_3	**83**	$^-CH_2NO_2$, 20°C	64:36
9	*o*-CH_3	**83**	$^-CH_2NO_2$, -20°C	92:8
10	*o*-CH_3	**83**	$^-CH_2NO_2$, -40°C	97:3

Table III. Addition of Grignard reagents to substituted (benzaldehyde)Cr(CO)3 complexes.

The variable temperature experiments show that addition of these carbanions is kinetically controlled and greater selectivity is achieved at lower temperature. 100% asymmetric induction was achieved on the addition of 2-bromoesters or 2-bromonitriles, under Reformatsky conditions, to (-)-(*o*-anisaldehyde)Cr(CO)3 (-)-**149**.[94]

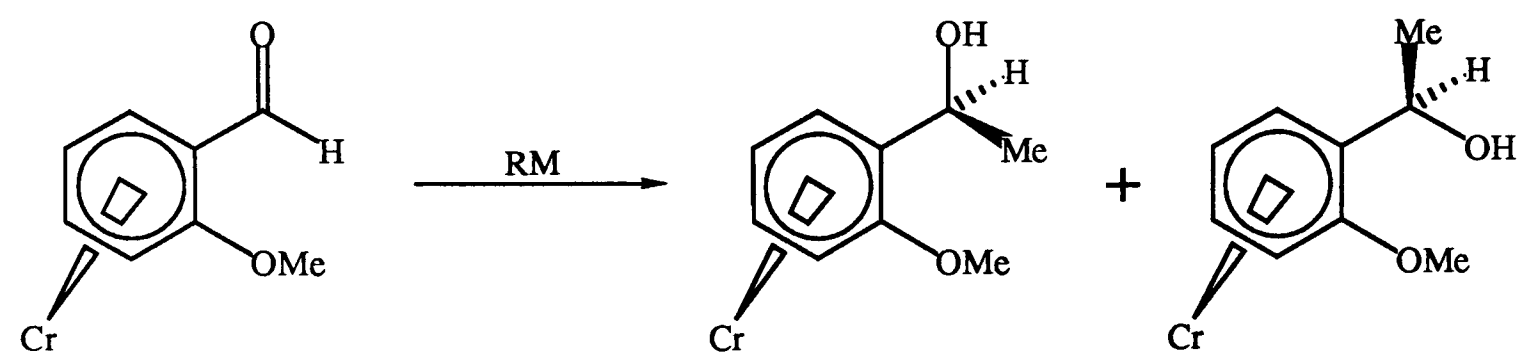


We were interested in extending this methodology to improve the previously observed stereoselectivities in the case of (*o*-anisaldehyde)Cr(CO)3 **149** and to study the addition of nucleophiles to *o*-silylated benzaldehyde derivatives, where the *o*-silyl group could later be removed *via* a fluoride mediated desilylation.

b. *Addition of Carbanions to (o-Anisaldehyde)Cr(CO)3.*

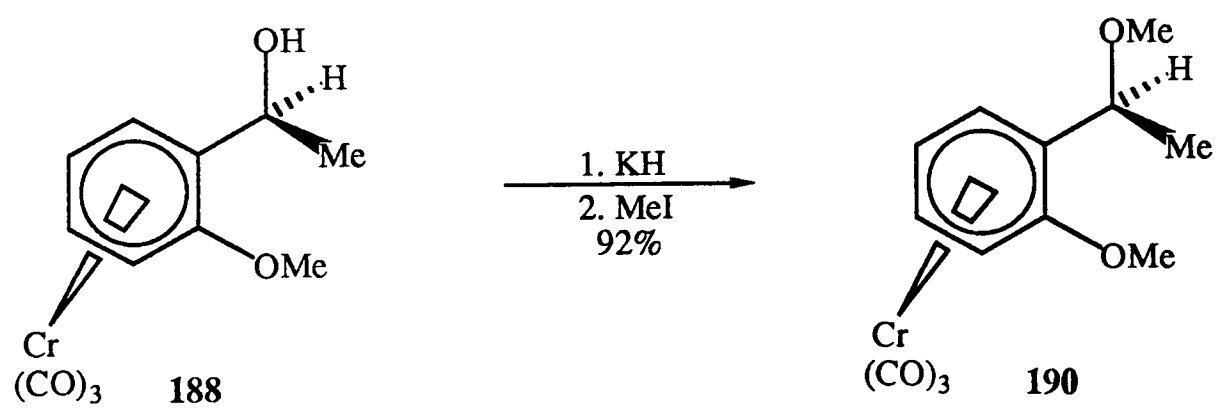
Addition of excess MeMgI to (+)-(*o*-anisaldehyde)Cr(CO)3 (+)-**149** in THF at -78°C gave an immediate colour change from red to yellow. After work up, a yellow solid was

isolated in essentially quantitative yield. ^{1}H n.m.r. spectroscopy (C_6D_6) showed only a single set of peaks with a benzylic proton doublet of quartet (δ4.70, J_d = 3.99Hz, J_q = 6.35Hz) and three proton methyl doublet (δ1.15, J = 6.37Hz). The product was assigned as a single diastereoisomer of the 1-phenethanol derivative (-)-**188**. A molecular ion *m/z* 288 (*M*+) in the mass spectrum confirmed the identity of the product. Repeating the reaction under similar conditions but using MeLi as the carbanion source, similarly gave a yellow solid in quantitative yield. However, ^{1}H n.m.r. spectroscopy clearly indicated a mixture of products in a ratio of 94:6. The major isomer was identical to complex **188** and the minor isomer was assigned as the other diastereoisomer **189** by analogy with the previous literature report.[55,93]



(+)-**149** RM = MeMgI 99% (-)-**188** 100:0 **189**
149 RM = MeLi 100% **188** 94:6

The unambiguous assignment of the relative configuration within complex **188** and hence absolute configuration within complex (-)-**188**, was achieved by O-methylation of a racemic sample of complex **188** and comparison with an authentic sample of (*RR*,*SS*) complex **190**. A THF solution of complex **188** was treated with KH and stirred. MeI was added and the orange solution turned yellow. Work up and chromatography gave, after recrystallisation, complex **190**. The ^{1}H n.m.r. spectrum of complex **190** contained two aromatic proton doublets (δ5.87-5.84, 5.04-5.01), two aromatic proton triplets (δ5.51-5.46, 4.97-4.93), a benzylic proton quartet (δ4.41, J = 6.40Hz) and two three proton methoxy singlets (δ3.74, 3.57). Complex **190** was spectroscopically identical to an authentic sample of (*RR*,*SS*) complex **190**, the relative configuration within which was confirmed by an X-ray crystal structure analysis, see Chapter 8 and Appendix IV.



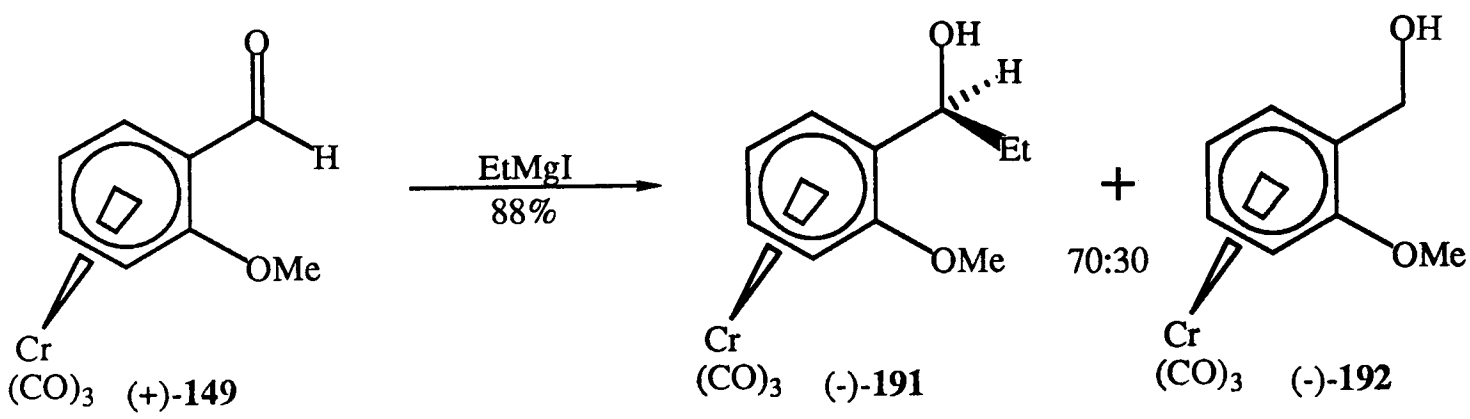
188 **190**

The difference in observed stereoselectivities between the MeMgI and MeLi additions may arise as a result of the nature of the Lewis acidic species present in

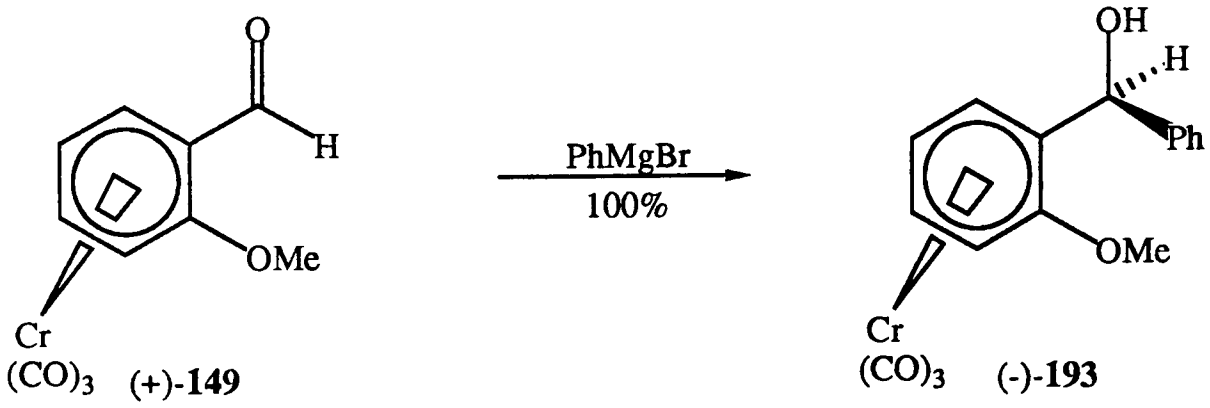
solution; Mg^{2+} is a stronger Lewis acid than Li^{+} due to its greater charge density. Thus in the case of the Grignard addition, the first step is presumably coordination of Mg^{2+} to the carbonyl oxygen atom. This increases the effective bulk of the group and consequently only conformations with the coordinated carbonyl group lying *anti* to the *o*-methoxy group and coplanar with the ring will be appreciably populated. Thus, a strict *exo* attack of nucleophile gives only a single diastereoisomer. Presumably in the case of the alkyllithium, *exo* addition of the carbanion may occur on some non-coordinated aldehyde. Whilst the preferred conformation of the free aldehyde is also *anti* to the *o*-methoxy group and coplanar with the ring (*vide supra*), there may be a small but significant population of the *syn* conformer. Thus, the overall ratio of major:minor diastereoisomer may reflect these conformer populations.

Similar treatment of complex (+)-**149** with EtMgI gave three products separable by column chromatography. The major fraction, isolated as a yellow solid was identified as a single diastereoisomer of the addition product (-)-**191** {$[\alpha]_D^{21}$ = -201o (c 1 CHCl3)}. The ^{1}H n.m.r. spectrum clearly indicated the presence of an ethyl group with a two proton multiplet (δ1.79-1.59) and three proton triplet (δ1.01, J = 7.40Hz). Also present were two aromatic proton doublets (δ5.90-5.88, 5.06-5.04), two aromatic proton triplets (δ5.56-5.51, 4.98-4.94) and a methoxy singlet (δ3.74).

The remaining two fractions had ^{1}H n.m.r. spectra consistent with starting material (+)-**149** and the reduced complex (-)-**192** {$[\alpha]_D^{21}$ = -216o (c 1 CHCl3)}. Presumably the latter complex was produced by the Grignard reagent donating a β-hydride to the aldehyde function. The ^{1}H n.m.r. spectrum of (-)-**192** contained a characteristic two proton benzylic AB system (δ4.64, 4.38, J_{AB} = 13.12Hz) and a broad one proton hydroxyl singlet (δ1.96).

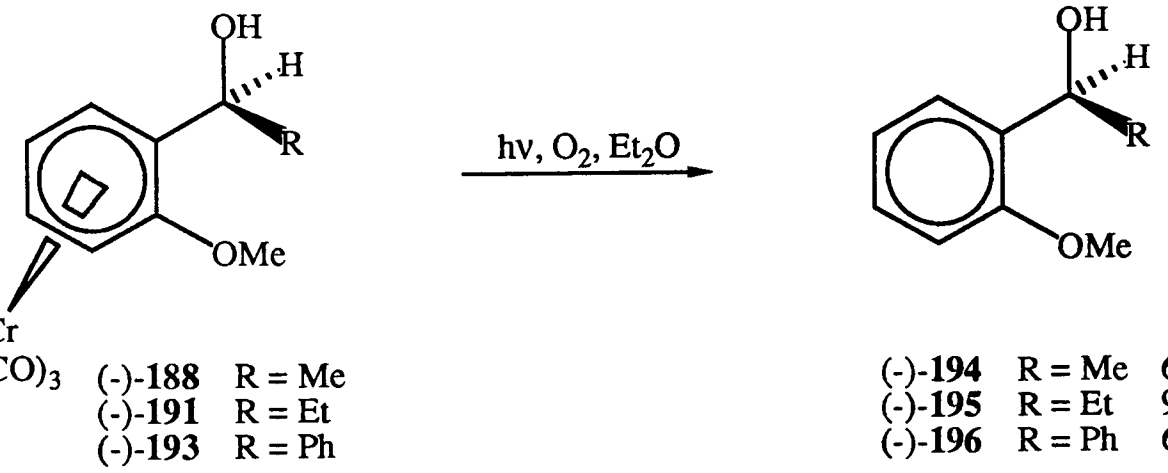


Addition of PhMgBr to complex (+)-**149**, in THF solution at -78oC, gave on work up a yellow solid (-)-**193** {$[\alpha]_D^{24}$ = -178o (c 1 CHCl3)}. The ^{1}H n.m.r. spectrum contained a single set of peaks with two downfield aromatic proton multiplets characteristic of a non-complexed ring (δ7.48-7.44, 7.40-7.29). A molecular ion *m/z* 350 (M^+) in the mass spectrum and a correct elemental microanalysis confirmed the identity of (-)-**193** as a single diastereoisomer of the addition product.



(+)-**149** (-)-**193**

The homochiral complexes (-)-**188**, (-)-**191** and (-)-**193** were decomplexed under standard conditions to give the free arenes (-)-**194** {$[\alpha]_D^{20}$ = -59o (c 1 toluene)}, (-)-**195** {$[\alpha]_D^{20}$ = -57o (c 1 toluene), Lit.[95] $[\alpha]_D$ = +47o (c 1 toluene) for 87% ee opposite enantiomer} and (-)-**196** {$[\alpha]_D^{20}$ = -34o (c 1 CHCl3)} respectively. It follows that the absolute configuration of arenes (-)-**194**, (-)-**195** and (-)-**196** is (*S*), which in the case of (-)-**194** and (-)-**195** confirms the previous assignment based on Horeau's method.[96]



(-)-**188** R = Me
(-)-**191** R = Et
(-)-**193** R = Ph

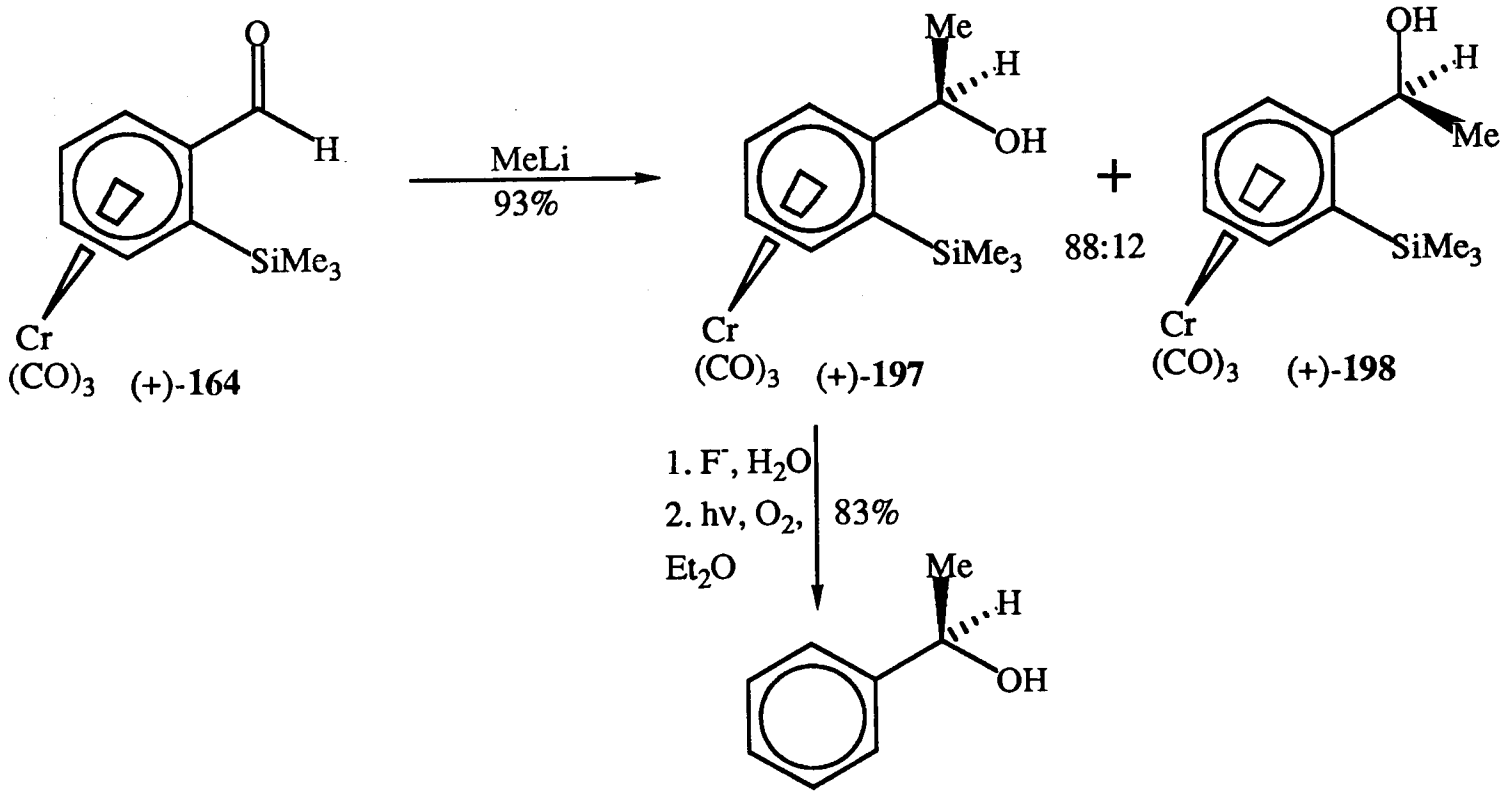
(-)-**194** R = Me 67%
(-)-**195** R = Et 95%
(-)-**196** R = Ph 67%

Enantiomeric purities of the free alcohols (-)-**194** and (-)-**195** were checked by ^{1}H n.m.r. spectroscopic analysis of their (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetate esters [(*R*)-Mosher's esters].[97] Authentic racemic alcohols **194** and **195**, (prepared from *o*-anisaldehyde **158** and the corresponding alkyllithium or Grignard reagent), were similarly esterified, to show no kinetic resolution was occurring on esterification and used as standards. Alcohols (-)-**194** and (-)-**195** were enantiomerically pure by this method (>99.5%). Arene (-)-**196** failed to generate the required ester under suitable conditions, but was assumed to be homochiral by analogy with alcohols (-)-**194** and (-)-**195**.

c. *Addition of Nucleophiles to (o-Trimethylsilylbenzaldehyde)Cr(CO)3.*

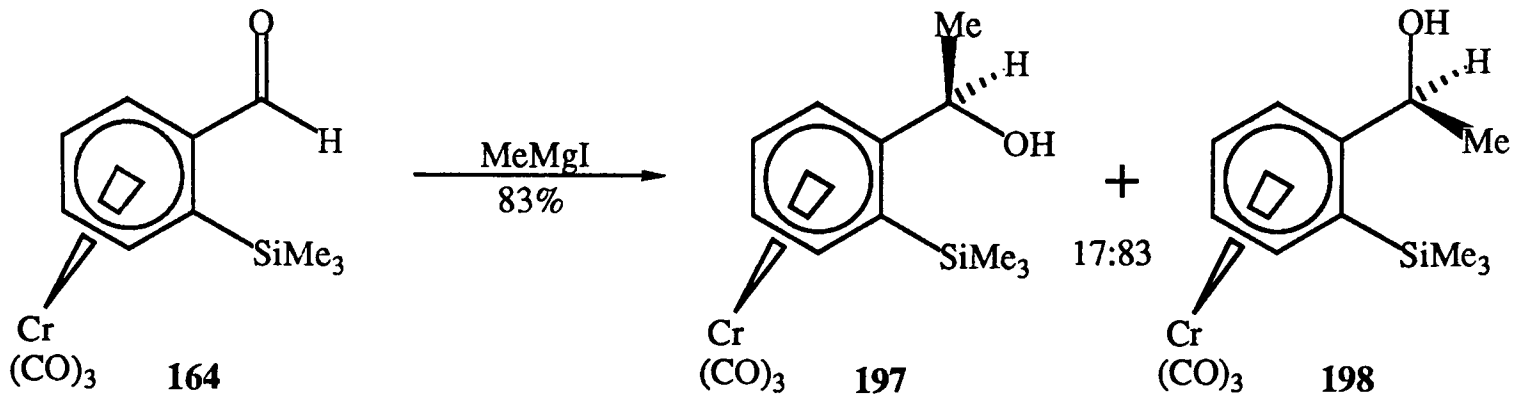
Treatment of (+)-(*o*-trimethylsilylbenzaldehyde)Cr(CO)3 (+)-**164** with MeLi in THF at -78oC gave a yellow solution immediately. Work up and chromatography gave the two 1-phenethanol derivatives (+)-**197** and (+)-**198** in a ratio of 88:12. The ^{1}H n.m.r. spectrum of the major isomer (+)-**197** {$[\alpha]_D^{21}$ = +20o (c 1 CHCl3)} incorporated a three proton doublet (δ1.56, J = 6.53Hz), a benzylic proton multiplet (δ4.84-4.72) and a nine

proton silyl singlet (δ0.41). A molecular ion *m/z* 330 (M^+) in the mass spectrum and a correct elemental microanalysis confirmed the identity of the product. The ^{1}H n.m.r. of the minor isomer (+)-**198** contained a three proton doublet (δ1.48, J = 6.32Hz), a benzylic proton quartet (δ4.82, J = 6.32Hz) and a nine proton silyl singlet (δ0.41). A molecular ion *m/z* 330 (M^+) in the mass spectrum and a correct elemental microanalysis also confirmed the identity of the product. Treatment of complex (+)-**197** with excess TBAF.3H$_2$O quantitatively desilylated the complex to give a yellow oil. Standard decomplexation of the oil gave, following distillation, (+)-1-phenethanol as a clear oil (+)-**199** {$[\alpha]_D^{20}$ = +51o (c 1 CHCl3), Lit.[98] $[\alpha]_D$ = +39.5o (neat)} identified by comparison with an authentic sample. The absolute configuration of (+)-**199** was determined on the basis of the sign of the optical rotation - (+)-1-phenethanol has (*R*) stereochemistry.[98] Thus, the major isomer (+)-**197** produced on addition of MeLi to complex (+)-**164** must have the (*SR*) stereochemistry shown and the minor isomer (+)-**198** must be (*SS*). This is in contrast to the stereoselectivity observed in the addition of MeLi to (*o*-anisaldehyde)Cr(CO)3 **149** where the major product observed was the (*RR*,*SS*) diastereoisomer.



(+)-**199** 100% ee

Addition of MeMgI to racemic **164** in THF at -78oC gave a yellow solution, which on work up gave a yellow oil. The ^{1}H n.m.r. spectrum of the product contained two sets of peaks, which were consistent with an 83:17 mixture of complexes **198** and **197**. Clearly the stereoselectivity of addition changes markedly from MeLi to MeMgI.



The change in the stereoselectivity of addition from MeLi to MeMgI can be attributed to greater Lewis acidity of metal ion species in the Grignard reagent. The ionic radii of Mg^{2+} and Li^{+} are similar and therefore as the charge density is greater on Mg^{2+} than on Li^{+}, the former ion is the stronger Lewis acid. Two types of addition can be envisaged, Lewis acid free and Lewis acid coordinated mechanisms, Figures IX and X respectively. In the Lewis acid free mechanism whilst the lowest energy conformer is **200**, there will be an equilibrium population of conformer **201**, possibly somewhat stabilised by a direct oxygen lone pair-silicon d-orbital interaction. Analysis of molecular models predicts that addition of the nucleophile to the carbonyl group will be much faster in conformer **201**. In conformer **200** the preferred 109° angle of attack of the nucleophile[99] is sterically hindered by the bulky trialkylsilyl group, whereas in conformer **201**, the nucleophile can approach through free space. Thus, since the rate limiting step of this reaction is presumably the addition of the nucleophile and the equilibrium between the conformers is rapidly established, the major product will arise from addition to conformer **201** to give complex **197**. This is in accord with the Curtin-Hammett principle.[100]

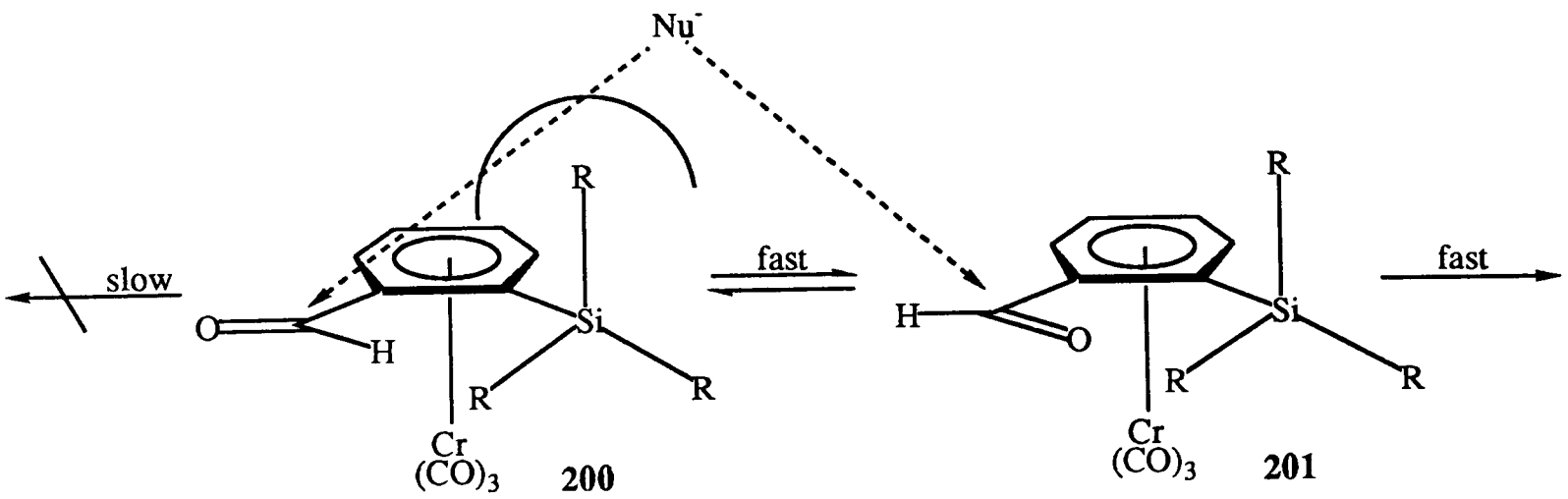


Figure IX. Lewis acid free mechanism for the addition of nucleophiles to (*o*-trialkylsilylbenzaldehyde)Cr(CO)3 complexes.

In the presence of strong Lewis acids, however, the first step of the reaction is coordination of the Lewis acid to the carbonyl oxygen. This drastically increases the size of the group and thus conformer **203**, Figure X, is very strongly destabilised with respect to conformer **202**. Consequently, the inaccessibility of conformer **203** means that the major product isomer will result from a slow addition of nucleophile to conformer **202**, at 109° to the carbonyl group, to give complex **198**. Alternatively the Lewis acid coordinated species may have some chromium stabilised benzylic carbonium ion character with an exocyclic double bond to the benzylic carbon. The minimum energy trajectory of approach of nucleophiles onto this species would presumably not be at 109° to the carbonyl group and therefore not pass as close to the bulky silyl unit. The production of the minor diastereoisomers, complex **198** in the case of MeMgI and complex **197** in the case of MeLi addition, may result from the operation of both Lewis acid free and Lewis acid coordinated mechanisms to a greater or lesser extent.

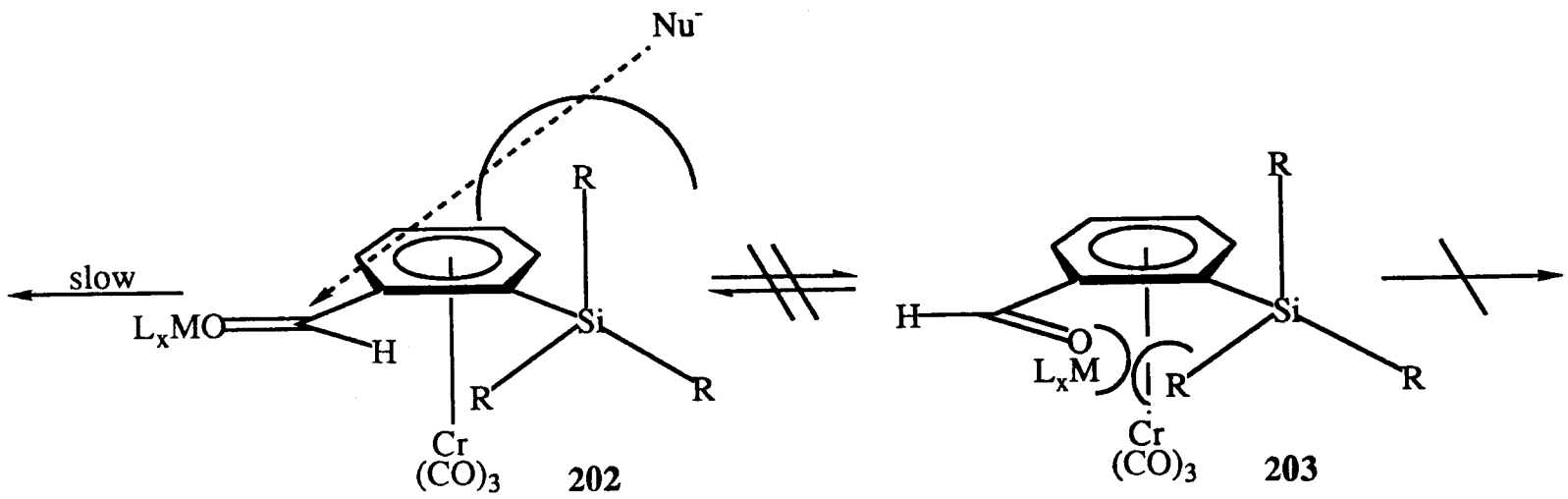
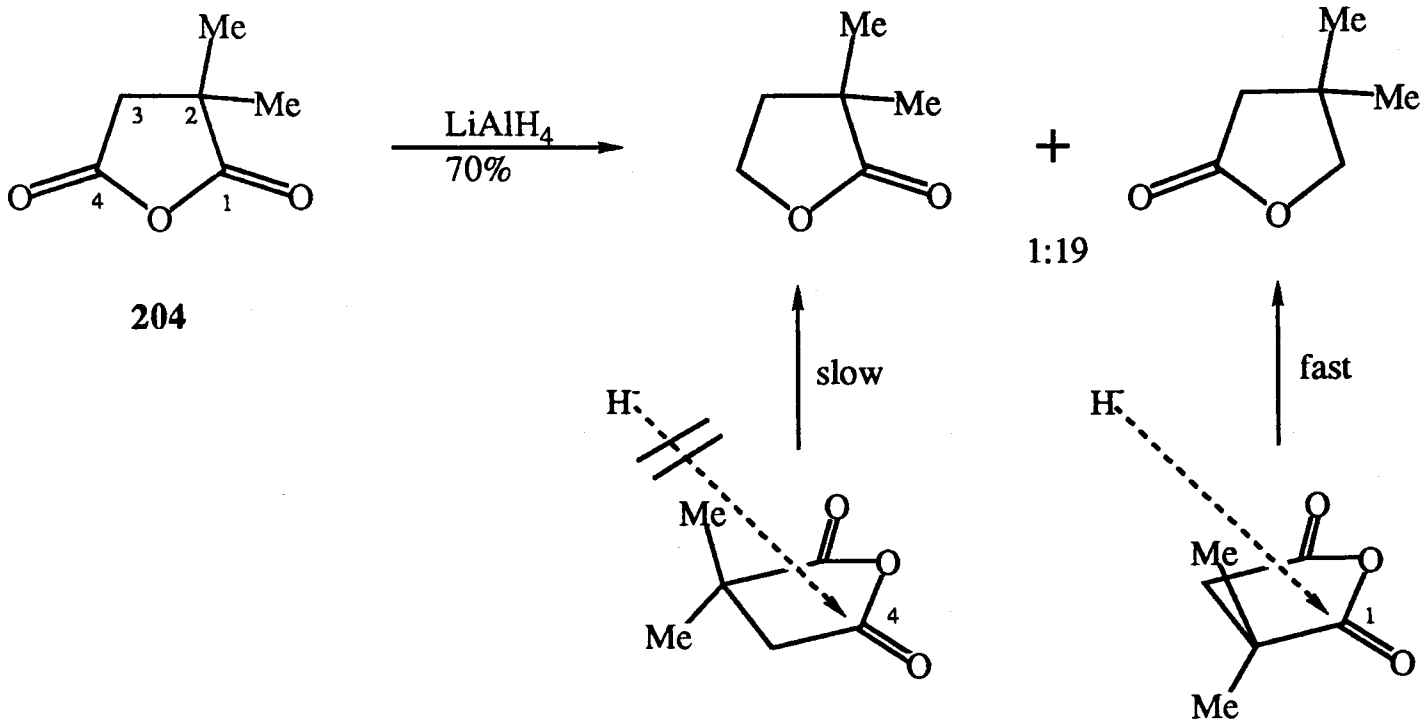


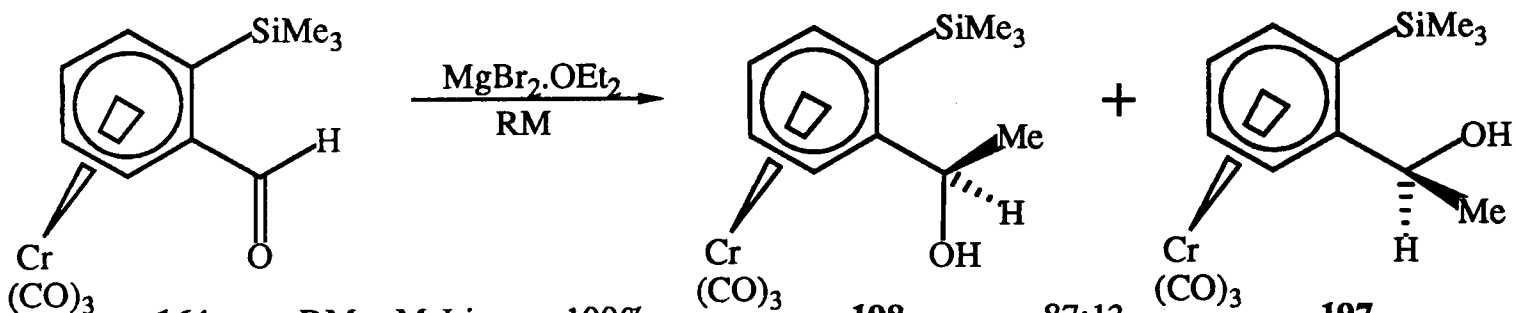
Figure X. Lewis acid coordinated mechanism for the addition of nucleophiles to (*o*-trialkylsilylbenzaldehyde)Cr(CO)3 complexes.

The succinic anhydride derivative **204** can be selectively reduced with metal hydrides at the C1 carbonyl group. The observed regioselectivity has been attributed to chelation of a Lewis acidic metal ion to the most electron rich carbonyl group, in this case that at C1, followed by selective attack of hydride at this activated carbonyl group. However, the observed product selectivity may also be rationalised in terms of a steric effect. The trajectory of approach of a nucleophile to the C4 carbonyl group at 109° to the CO bond is somewhat sterically blocked by the C2 *gem*-dimethyl groups. However, the approach to the C1 carbonyl group is not so congested and so selective reduction may proceed through this mode.[101]



If the two addition mechanisms to complex **164** depend entirely on the strength and concentration of Lewis acidic species, then addition of strong Lewis acids prior to the nucleophilic reagent should strongly favour the production of complex **198** over **197**.

Thus, pretreatment of complex **164** in Et_2O with $MgBr_2.OEt_2$, (prepared from Mg and 1,2-dibromoethane in dry Et_2O), gave a dark red solution, indicative of the formation of a strong Lewis acid coordinated species. Addition of MeLi, (to pretreated racemic **164**), or MeMgI, [to pretreated chiral (-)-**164**], at room temperature gave on work up, mixtures of complexes **197** and **198** identified by ^1H n.m.r. spectroscopy. In the case of MeLi addition the ratio of products **197** and **198** was 13:87, reflecting the expected changeover in selectivity, and in the case of MeMgI addition the ratio was 11:89.

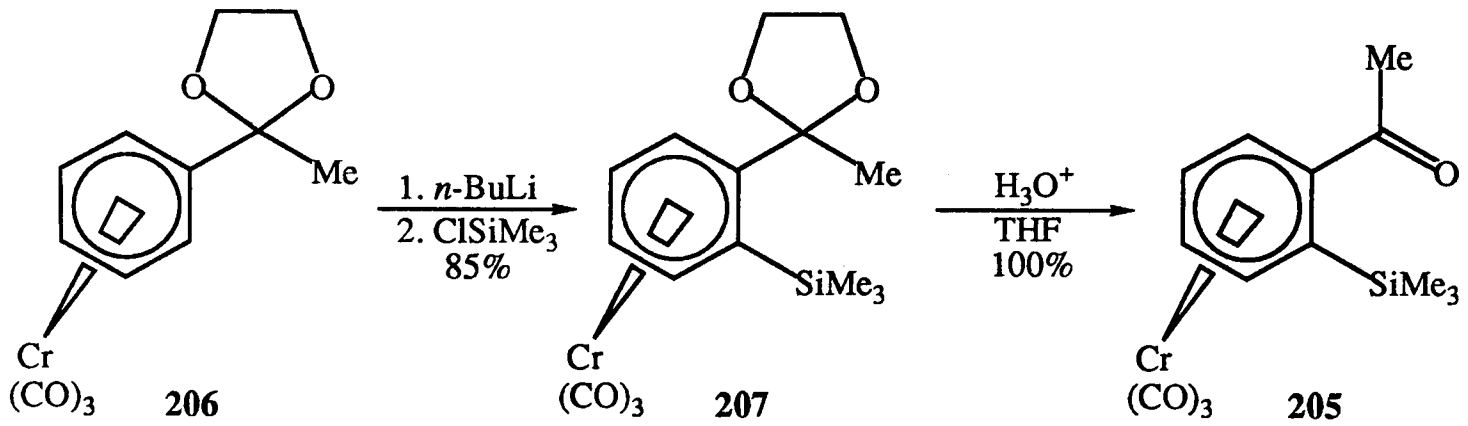


164	RM = MeLi	100%	**198**	87:13	**197**
(-)-**164**	RM = MeMgI	90%	(-)-**198**	89:11	(-)-**197**

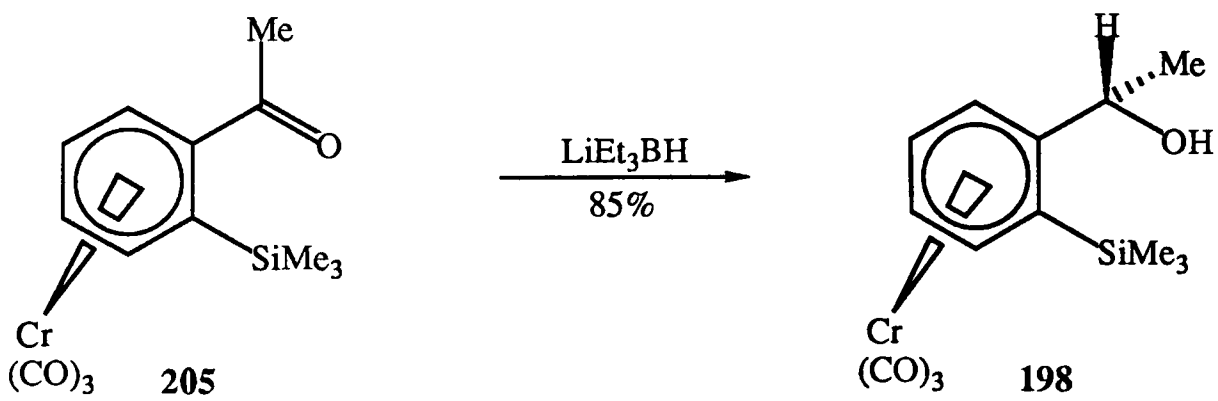
Mixtures of complexes **197** and **198** were separable by column chromatography (Al_2O_3). Treatment of complex (-)-**198** with $TBAF.3H_2O$ followed by standard decomplexation gave (*R*)-1-phenethanol (+)-**199** {$[\alpha]_D^{20}$ = +56o (c 0.5 $CHCl_3$), Lit.98 $[\alpha]_D$ = +39.5o (neat)} identified by comparison with an authentic sample.

The enantiomeric purities of samples of (+)-**199** were checked by ^1H n.m.r. spectroscopic analysis of their (*R*)-Mosher's esters (*vide supra*) and found to be homochiral.

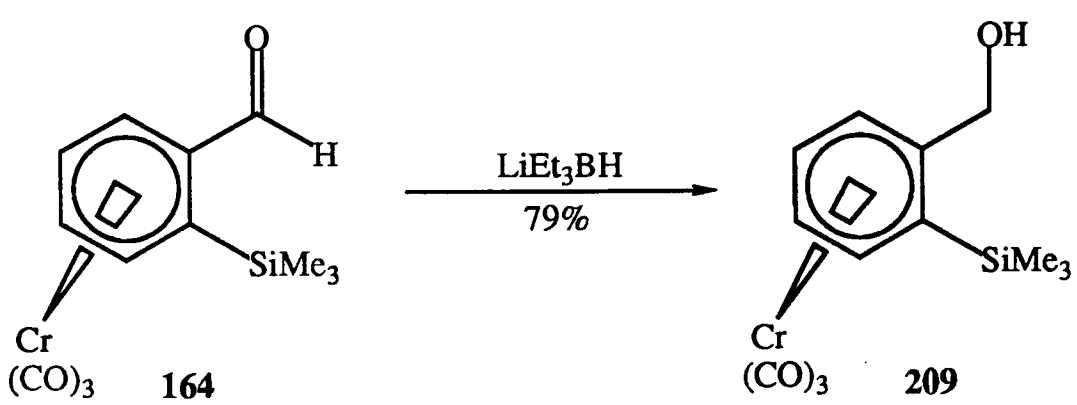
Another route through to complexes **197** and **198** was envisaged *via* a hydride reduction of (*o*-trimethylsilylacetophenone)$Cr(CO)_3$ **205**. In this complex the greater steric bulk of the α-methyl group over the carbonyl oxygen should favour conformations which place the carbonyl oxygen *syn* to the trimethylsilyl group. Use of hydride donors with weak Lewis acidic counterions such as Li^+ will presumably favour production of complex **198** over complex **197**. Treatment of (2-phenyl-2-methyl-1,3-dioxolane)$Cr(CO)_3$[102] **206** with *n*-BuLi followed by chlorotrimethylsilane gave, *via* a chelation controlled *o*-lithiation, the *o*-silylated complex **207**. The ^1H n.m.r. spectrum of complex **207** contained two aromatic proton multiplets (δ5.56-5.45, 5.28-5.20) integrating to four protons, a four proton multiplet (δ4.16-4.00) characteristic of the dioxolane ring protons, a three proton methyl singlet (δ1.62) and a nine proton silyl singlet (δ0.40). A molecular ion *m/z* 373 (M^++1) in the mass spectrum and a correct elemental microanalysis confirmed the identity of complex **207**. Treatment of complex **207** with acidic aqueous THF liberated the free acetophenone derivative **205**. The ^1H n.m.r. spectrum of complex **205** was similar to that of **207** but with the loss of the dioxolane ring proton multiplet and upfield shift of the methyl singlet (δ2.49).



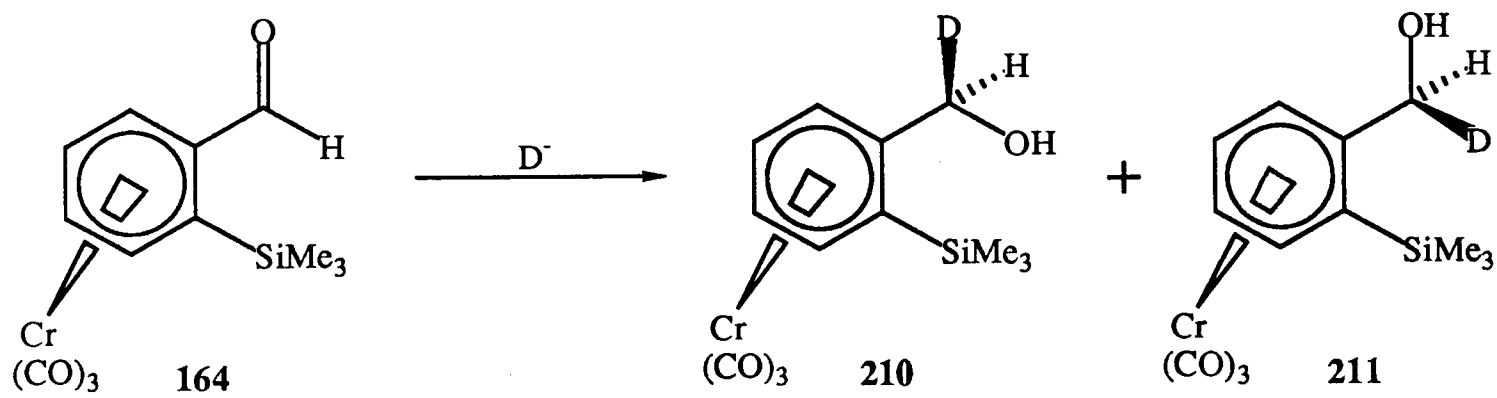
Treatment of complex **205** with $LiEt_3BH$ (super hydride) in THF at -78°C, gave on work up, a single compound in good yield identified by ^1H n.m.r. spectroscopy as complex **198**. None of the benzylic epimer **197** was detected under these reaction conditions. This stereoselective addition is consistent with a Lewis acid free mechanism, involving *exo* attack of hydride at the carbonyl group in conformations which place the carbonyl oxygen and not the α-methyl group *syn* to the bulky *o*-trimethylsilyl group.



The application of these stereoselective reactions of (*o*-trimethylsilyl-benzaldehyde)Cr(CO)3 **164** was envisaged as a possible route through to chiral α-deuteriobenzyl alcohol **208** *via* an addition of deuteride to complex **164** followed by desilylation and decomplexation of the adduct. As a test reaction a THF solution of complex **164** was treated with LiEt3BH under standard conditions. Work up gave the reduced benzyl alcohol product **209** in good yield. The ^1H n.m.r. spectrum (C_6D_6) of complex **209** contained an aromatic proton doublet (δ4.93-4.89), a two proton aromatic multiplet (δ4.78-4.67), an aromatic proton triplet (δ4.25-4.18), a two proton benzylic ABX system (δ4.07, 3.88, J_{AB} = 12.96Hz, J_{AX} = 5.96Hz, J_{BX} = 3.72Hz) and a nine proton silyl signal (δ0.10). A molecular ion *m/z* 316 (M^+) in the mass spectrum and a correct elemental microanalysis confirmed the identity of the product.



Addition of deuteride, from LiEt3BD (super deuteride) and LiAlD4, to racemic complex **164**, with and without MgBr2.OEt2 pretreatment, was studied. The ratios of products **210** and **211** were determined using ^1H n.m.r.spectroscopy (C_6D_6), by relative integration of the benzylic proton signals (**210**, δ4.06; **211**, δ3.88) and the results are summarised in Table IV below.

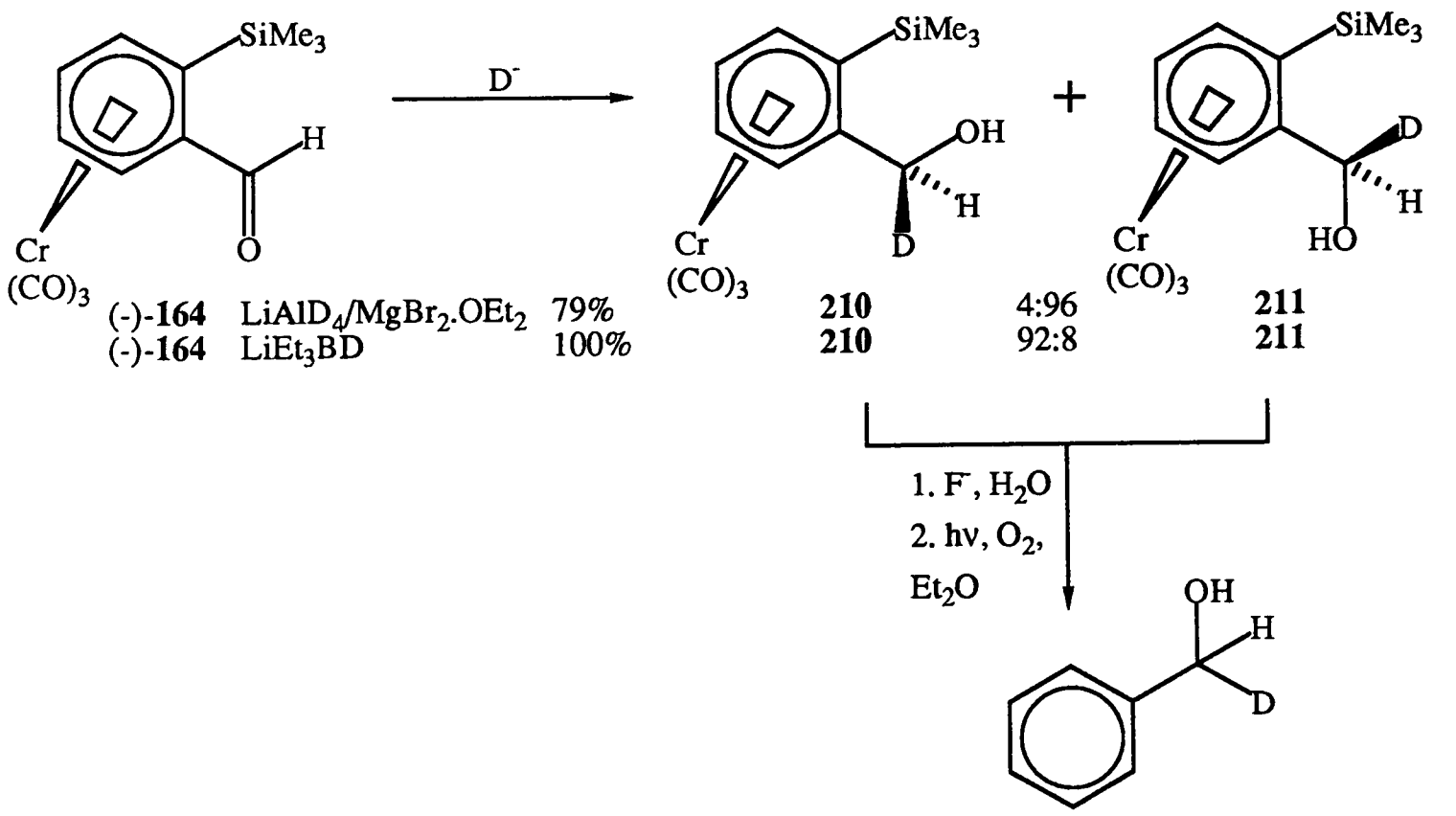


Entry	Reagent	Conditions	**210:211**	Yield(%)
1	$LiEt_3BD$	THF, -78°C	92:8	100%
2	$LiEt_3BD$	THF, -100°C	92:8	98%
3	$LiEt_3BD$	CH_2Cl_2, -100°C	75:25	99%
4	$LiEt_3BD$	toluene, -91°C	80:20	89%
5	$LiEt_3BD/MgBr_2.OEt_2$	Et_2O, 20°C	12:88	95%
6	$LiAlD_4$	THF, -78°C	38:62	100%
7	$LiAlD_4/MgBr_2.OEt_2$	Et_2O, 20°C	4:96	72%

Table IV. Addition of deuteride to (*o*-trimethylsilylbenzaldehyde)$Cr(CO)_3$ **164.**

Presumably LiEt3BD reacts primarily in the Lewis acid free mode, whilst the reverse is true for LiAlD4. This is consistent with the nature of the reagents - the aluminium species in LiAlD4 being more Lewis acidic due to their higher charge density.

The reactions in Entries 1 and 7 of Table IV, were repeated on homochiral (-)-**164**. The mixtures of diastereoisomers **210** and **211** were not separable and in both cases the mixture was desilylated with $TBAF.3H_2O$ and decomplexed under standard conditions to give α-deuteriobenzyl alcohol **208**. The enantiomeric purities of both samples of (*R*)- and (*S*)-**208** were checked by ^1H n.m.r. spectroscopic analysis of their (*R*)-Mosher's esters (*vide supra*) and found to range from 84% to 92% ee, in accord with the observed de of the products from the corresponding addition reactions.



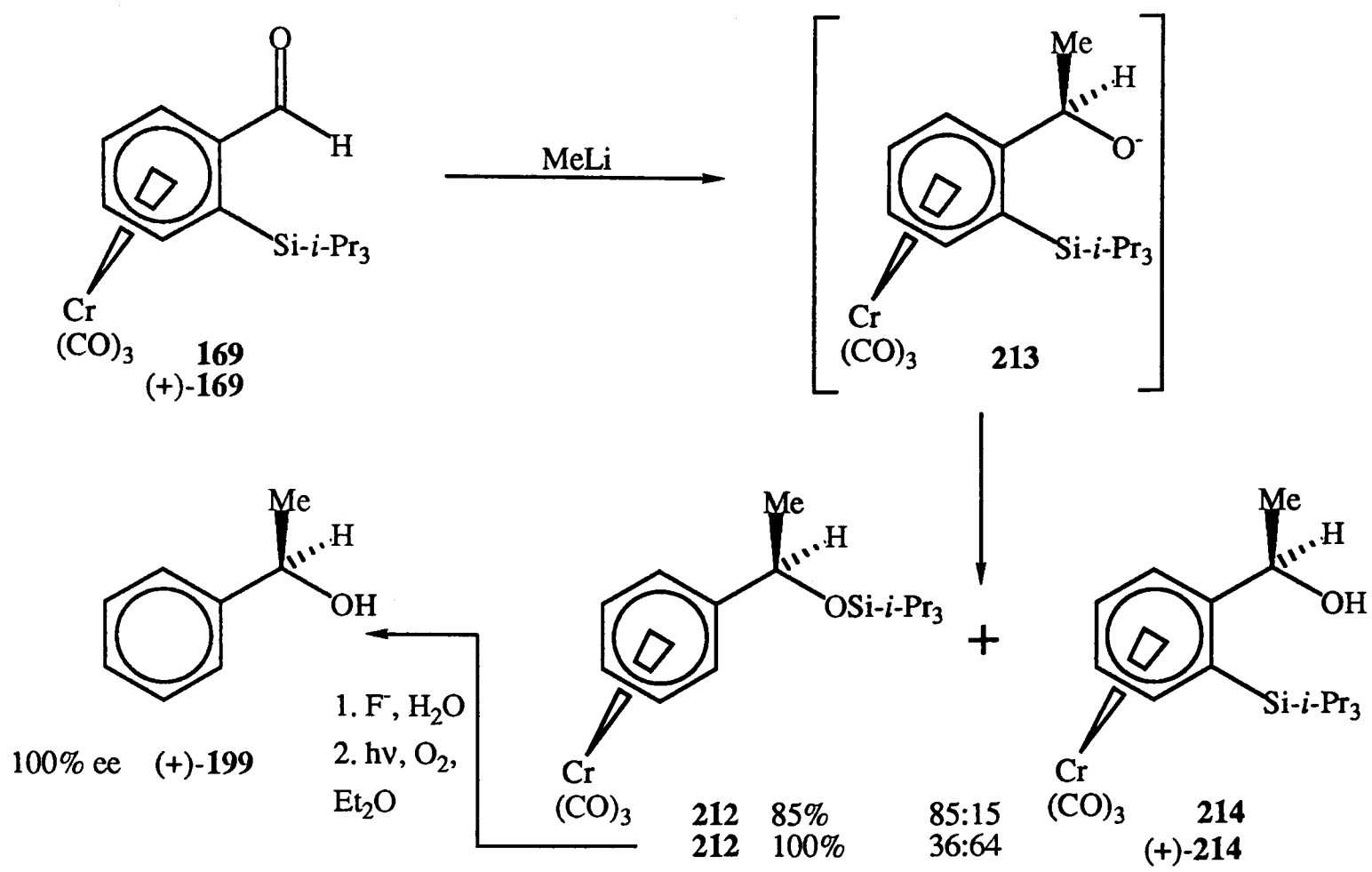
(-)-**164** $LiAlD_4/MgBr_2.OEt_2$ 79% **210** 4:96 **211**
(-)-**164** $LiEt_3BD$ 100% **210** 92:8 **211**

$LiAlD_4/MgBr_2.OEt_2$ (*R*)-**208** 92% ee 66%
$LiEt_3BD$ (*S*)-**208** 84% ee 44%

d. *Addition of Nucleophiles to (o-Tri-i-propylsilylbenzaldehyde)Cr(CO)3.*

Since the rationale for the stereoselectivity observed in the addition of nucleophiles to complex **164** depended upon the large steric bulk of the *o*-trimethylsilyl group, it may be predicted that increasing the size of the silyl group to tri-*i*-propylsilyl should increase the stereoselectivities observed.

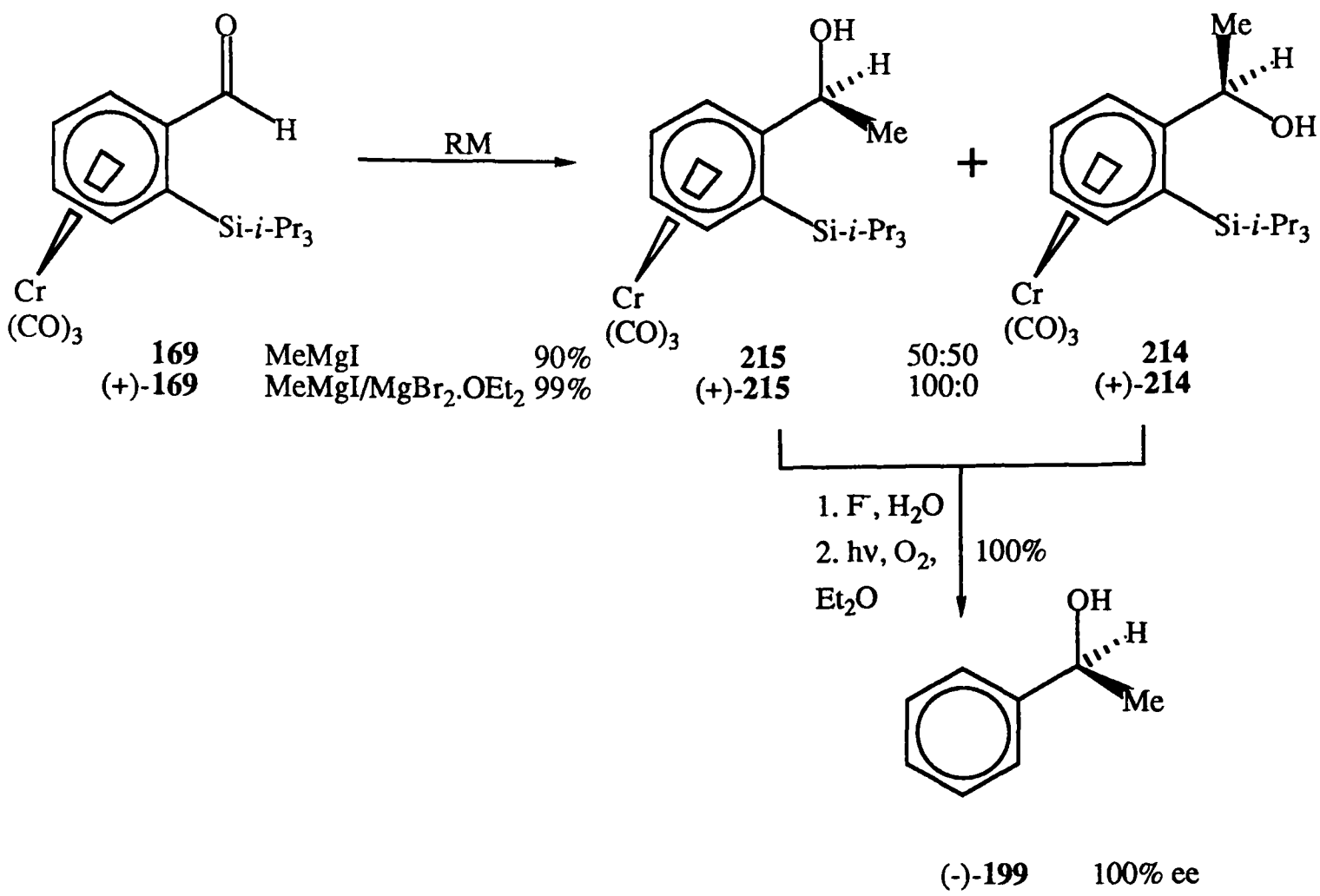
Addition of MeLi to a THF solution of racemic (*o*-tri-*i*-propylsilyl-benzaldehyde)Cr(CO)3 **169**, gave on quenching with *i*-PrOH and column chromatography, two fractions in a ratio of 85:15. The ^{1}H n.m.r. spectrum (C_6D_6) of fraction one contained two aromatic proton doublets (δ5.07-5.03, 4.73-4.71), three aromatic protons with a benzylic proton multiplet (δ4.45-4.35) and a three proton methyl doublet (δ1.17, J = 6.33Hz). The absence of an infrared hydroxyl absorption band, low melting point (45-46°C) and a correct elemental microanalysis confirmed the identity of the product as the O-tri-*i*-propylsilyl complex **212**, presumably formed by a transfer of the silyl group from the aromatic ring to the benzylic oxygen within anion **213**, generated after addition of the nucleophile. A similar migration in the reverse direction has been reported in the literature.[103] The second fraction was identified as the 1-phenethanol derivative **214** on the basis of its ^{1}H n.m.r. spectrum which clearly indicated the presence of two aromatic proton triplets (δ5.71-5.65, 5.25-5.19), two aromatic proton doublets (δ5.53-5.50, 5.46-5.43), a methyl doublet (δ1.59, J = 6.32Hz) and two silyl multiplets (δ1.54-1.34, 1.26-1.18). A molecular ion *m/z* 415 (M^++1) in the mass spectrum confirmed the identity of the product. Repeating the reaction on (+)-**169** but quenching with H_2O at -78°C to remove any phenethoxides before warming, followed by work up and chromatography, gave complexes **212** and (+)-**214** {$[\alpha]_D^{20}$ = +129° (c 0.1 CHCl3)} as separate fractions in a ratio of 36:64. Desilylation of separated samples of compounds **212** and (+)-**214** with TBAF.3H_2O followed by standard decomplexation gave in both cases homochiral, [by ^{1}H n.m.r. spectroscopic analysis of the (*R*)-Mosher's ester derivatives], (*R*)-1-phenethanol (+)-**199**. This confirmed that the absolute configurations at the benzylic sites within complexes **212** and **214** are the same and this is consistent with both complexes **212** and (+)-**214** arising from the common intermediate oxygen anion **213**. The stereochemistry of the products **212** and **214** is the same as that observed in the corresponding reaction using the trimethylsilyl analogue **164**. This confirms the assignment of the absolute configuration of (+)-**169** as that shown below.



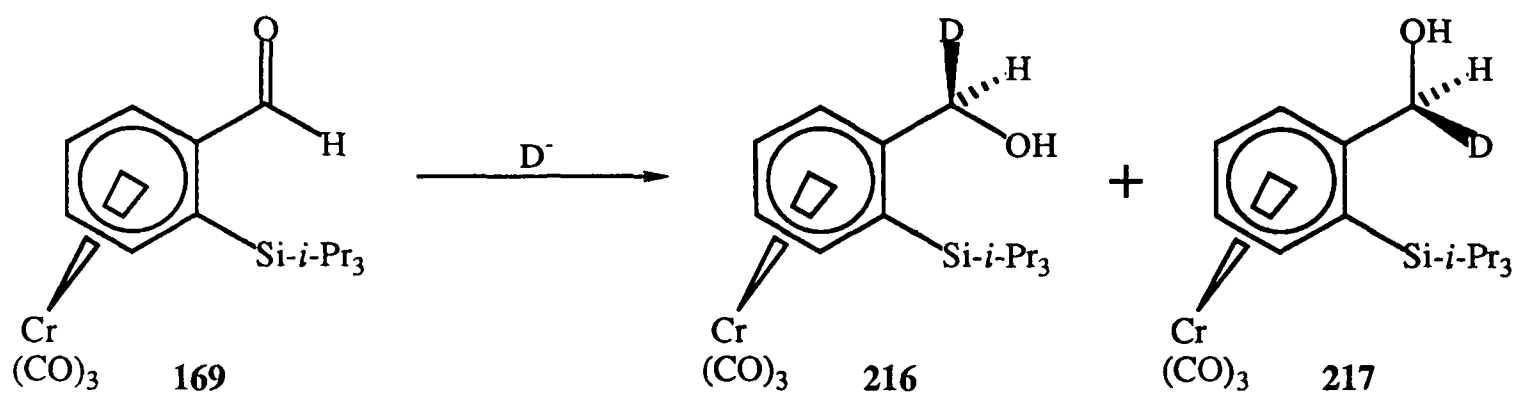
Treatment of racemic complex **169** with MeMgI at -78°C gave a mixture of products in a ratio of 50:50, identified as complex **214** and a new complex **215** by ^{1}H n.m.r. spectrocopy. Complex **215** had a similar spectrum to that of complex **214**, clearly containing two aromatic proton triplets (δ5.79-5.73, 5.22-5.15), two aromatic proton doublets (δ5.55-5.51, 5.48-5.45) and a three proton methyl doublet (δ1.47, J = 6.32Hz). Compound **215** was assigned as the benzylic epimer of complex **214** and gave a correct elemental microanalysis.

The increase in size of the silyl group has removed any selectivity in the Grignard addition reaction. Presumably the large silyl group sufficiently slows the rate of attack of nucleophile in conformer **202**, Figure X, so that products from the Lewis acid free pathway, Figure IX, are produced at an equivalent overall rate, despite the low concentration of uncoordinated aldehyde. Repeating the reaction but with $MgBr_2.OEt_2$ pretreatment of complex **169** should ensure that there is no uncoordinated aldehyde present and only a slow attack of nucleophile through conformer **202** of the Lewis acid coordinated pathway should be observed to give complex **215**.

Treatment of complex (+)-**169** with $MgBr_2.OEt_2$ in Et_2O gave a dark red solution, which slowly turned yellow on addition of MeMgI. Work up gave a single compound in essentially quantitative yield, identified by ^{1}H n.m.r.spectroscopy as (+)-**215** $\{[\alpha]_D^{20} = +79^o$ (c 0.8 $CHCl_3)\}$. Fluoride mediated desilylation followed by standard decomplexation gave (*S*)-1-phenethanol (-)-**199**, which was homochiral by ^{1}H n.m.r. spectroscopic analysis of the (*R*)-Mosher's ester derivative.



Addition of deuteride from $LiEt_3BD$ and $LiAlD_4$ to complex **169** with and without $MgBr_2.OEt_2$ pretreatment gave predictable results, Table V, the diastereoisomers **216** and **217** being distinguishable from their ^1H n.m.r. spectra. The ratios observed are similar to those obtained from the corresponding additions to the trimethylsilyl analogue **164**, see Table IV.



Entry	Reagent	Conditions	**216:217**	Yield(%)
1	$LiEt_3BD$	THF, -78°C	86:14	99%
2	$LiEt_3BD/MgBr_2.OEt_2$	Et_2O, 20°C	12:88	92%
3	$LiAlD_4$	THF, -78°C	30:70	100%
4	$LiAlD_4/MgBr_2.OEt_2$	Et_2O, 20°C	6:94	65%

Table V. Addition of deuteride to (*o*-tri-*i*-propylsilylbenzaldehyde)Cr(CO)3 **169**.

The reaction in Entry 4 of Table V was repeated on homochiral (-)-**169**. The 6:94 mixture of diastereoisomers **216** and **217** {$[\alpha]_D^{18}$ = -50o (c 0.7 CHCl3)} was desilylated with TBAF.3H_2O and decomplexed to give (*R*)-α-deuteriobenzyl alcohol **208** in 88% ee, determined by ^1H n.m.r.spectroscopy on the (*R*)-Mosher's ester derivative.

e. *Conclusion.*

The completely stereoselective addition of Grignard reagents to homochiral (*o*-anisaldehyde)Cr(CO)3 **149** has been achieved by performing the addition of the carbanion under kinetic conditions.

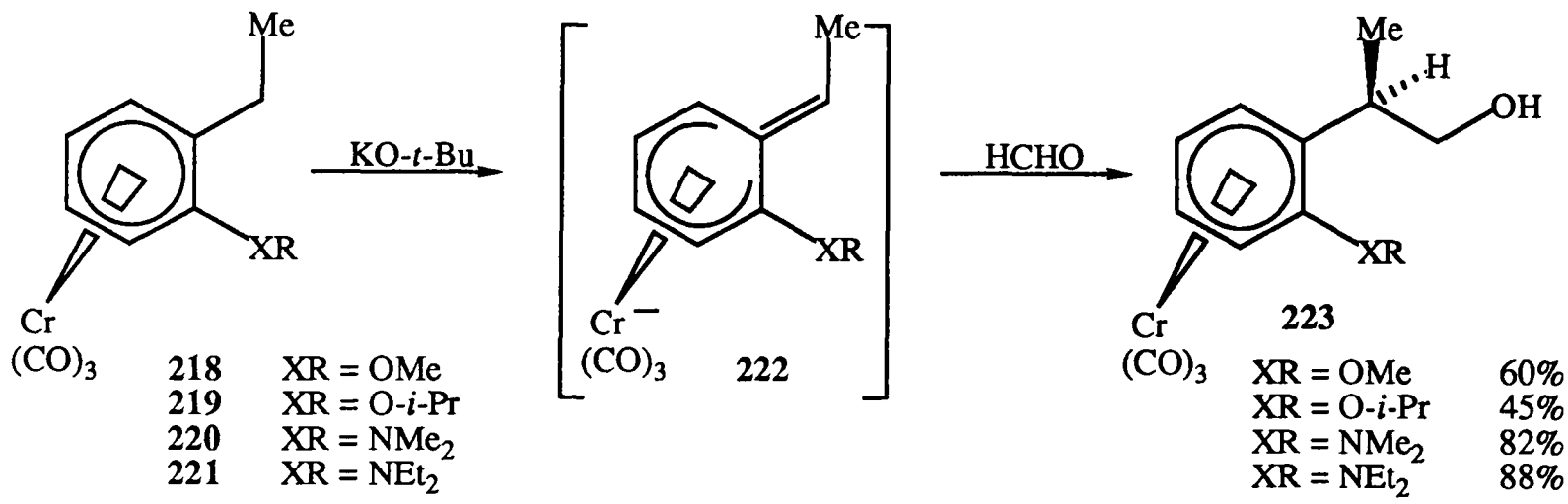
Stereoselective addition of nucleophiles to homochiral *o*-silylated (benzaldehyde)Cr(CO)3 complexes **164** and **169** has also been achieved. The direction of these addition reactions can be changed simply by a careful choice of reagents. Fluoride-mediated desilylation of the addition products followed by standard decomplexation gives either (*R*) or (*S*) substituted benzyl alcohol derivatives.

Chapter 8. Stereoselective Benzylic Elaboration of Arene Chromium Tricarbonyl Complexes.

a. *Introduction.*

Coordination of alkylbenzenes to the Cr(CO)3 group increases the acidity of the benzylic protons. Introducing a substituent into the *ortho* or *para* positions of these complexes decreases the benzylic proton acidity if the substituent is electron-donating and increases the acidity if it is electron-withdrawing. The benzylic protons of unsymmetrically *ortho* substituted (alkylbenzene)Cr(CO)3 complexes such as compounds **218-221** are rendered diastereotopic and benzylic deprotonation and alkylation can give rise to two possible diastereoisomers. The *ortho* substituent can have a profound influence on the ratio of product diastereoisomers observed.[104]

Addition of KO-*t*-Bu followed by HCHO to the *ortho* substituted ethylbenzene complexes **218-221** gave highly diastereoselective hydroxymethylation. For complexes **219** and **221** the reaction was completely stereoselective, whilst for compounds **218** and **220** only a small quantity of the other diastereoisomer was observed. The stereoselectivity is consistent with removal of a benzylic proton *antiperiplanar* to chromium from the least sterically crowded conformation with the methyl group of the ethyl substituent *anti* to the *ortho* substitutent, to give the configurationally stable anion **222**. Attack of the electrophile *exo* to chromium then generates the observed diastereoisomer **223**.[105]



218 XR = OMe
219 XR = O-*i*-Pr
220 XR = NMe_2
221 XR = NEt_2

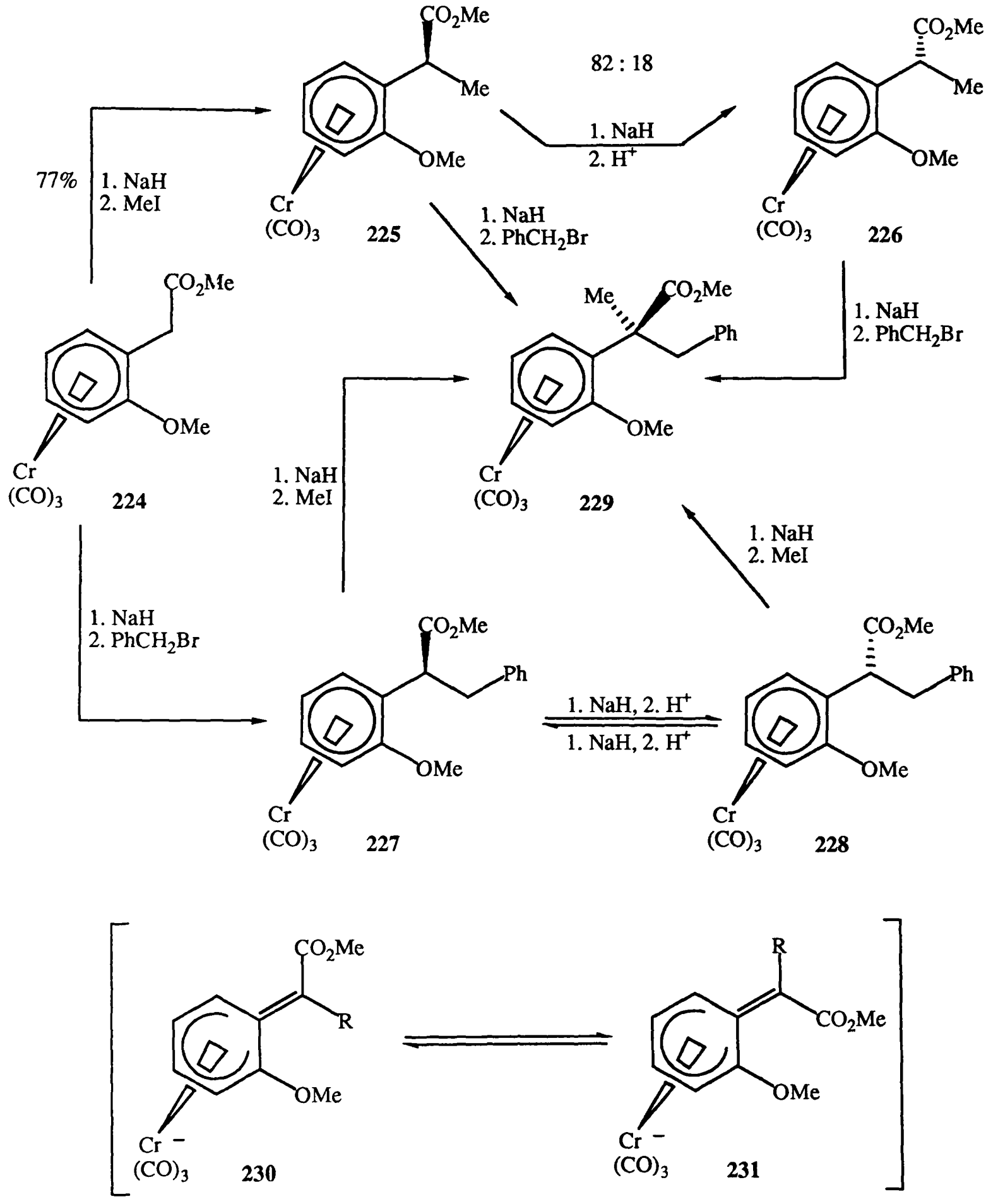
222

223

XR = OMe	60%
XR = O-*i*-Pr	45%
XR = NMe_2	82%
XR = NEt_2	88%

Treatment of (methyl *o*-methoxyphenylacetate)Cr(CO)3 **224** with NaH and MeI gave a 82:18 mixture of the two diastereoisomers **225** and **226**. Repeating the reaction with benzyl bromide gave a single diastereoisomer **227**. Epimerisation of complex **225** into **226** was achieved on deprotonation-protonation. Similar treatment of complex **227** gave a 72:28 mixture of itself with complex **228**, the benzylic epimer. Further metallation and alkylation of complexes **225** and **226** with benzyl bromide, and **227** and **228** with MeI gave exclusively the same complex **229**.[106] The stereoselectivities observed in the reactions of complex **224** and its derivatives indicate that the ester group facilitates

equilibration of the two geometric isomers of the benzylic carbanions **230** and **231**, alkylation occurring onto the *exo* face of the thermodynamically most stable isomer **230** (R = H, Me) or **231** (R = CH_2Ph), with the larger group *anti* to the *o*-methoxy substituent.

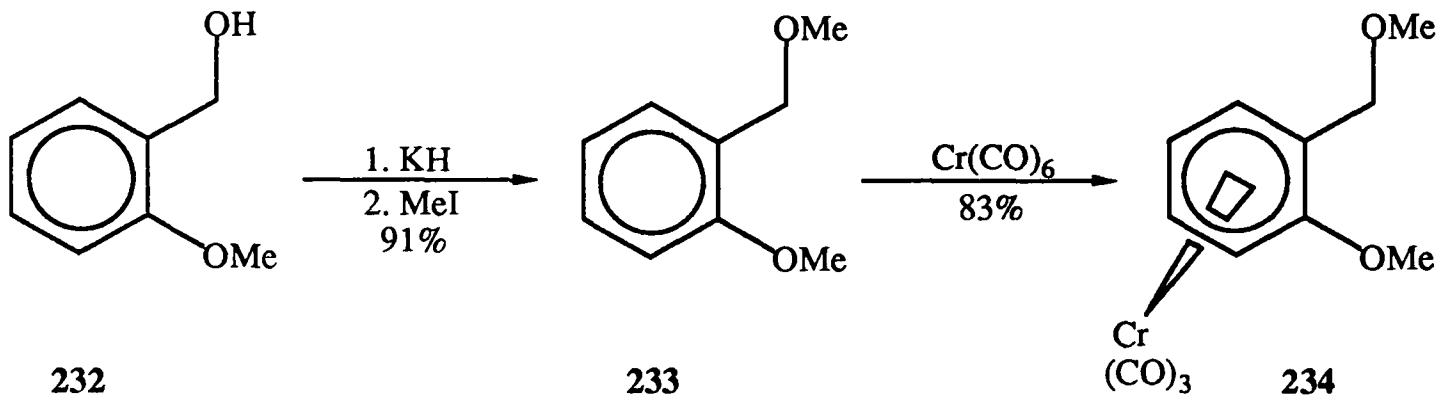


Complexation of benzyl alkyl ethers to the Cr(CO)3 group facilitates benzylic functionalisation *via* a stabilised carbanion with suppression of the Wittig rearrangement in most cases.[58,107,108] We wished to extend the above methodology to the stereoselective functionalisation of *ortho* substituted (benzyl methyl ether)Cr(CO)3

complexes. Use of homochiral starting materials, easily generated from homochiral *ortho* substituted (benzaldehyde)Cr(CO)3 complexes, see Chapters 6 and 7, would give rise, on decomplexation, to homochiral benzylically substituted arenes, with an overall transfer of chirality from the arene-metal centre to a side-chain.

b. *Preparation of (o-Methoxybenzyl Methyl Ether)Cr(CO)3.*

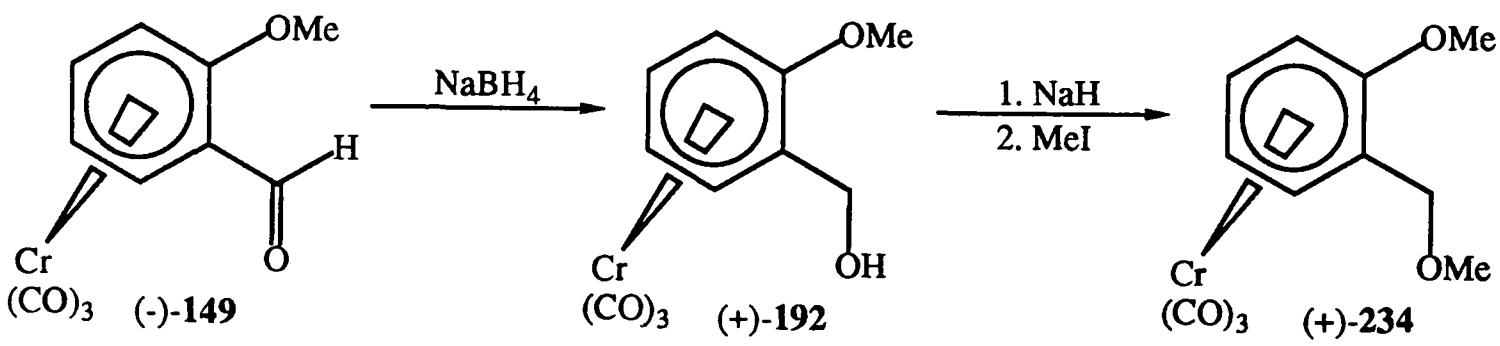
Treatment of *o*-methoxybenzyl alcohol **232** with KH in THF followed by addition of MeI gave, on work up and distillation, *o*-methoxybenzyl methyl ether **233** as a clear oil in good yield. The ^{1}H n.m.r. spectrum of arene **233** contained two aromatic proton doublets (δ7.47-7.44, 6.92-6.89), two aromatic proton triplets (δ7.35-7.29, 7.05-7.00), a benzylic proton singlet (δ4.59) and two methoxy singlets (δ3.85, 3.49). A molecular ion *m/z* 152 (*M*+) in the mass spectrum confirmed the identity of compound **233**. Complexation of arene **233** under standard conditions gave, on work up, a yellow oil in good yield, assigned as (*o*-methoxybenzyl methyl ether)Cr(CO)3 **234**. The ^{1}H n.m.r. spectrum of complex **234** contained two aromatic proton doublets (δ5.76-5.73, 5.08-5.06) and two aromatic proton triplets (δ5.54-5.49, 4.95-4.91). The two benzylic protons were diastereotopic and appeared as an AB system in the ^{1}H n.m.r. spectrum (δ4.53, 4.03, J_{AB} = 12.00Hz). A correct high resolution mass spectrum confirmed the assignment of complex **234**.



232 **233** **234**

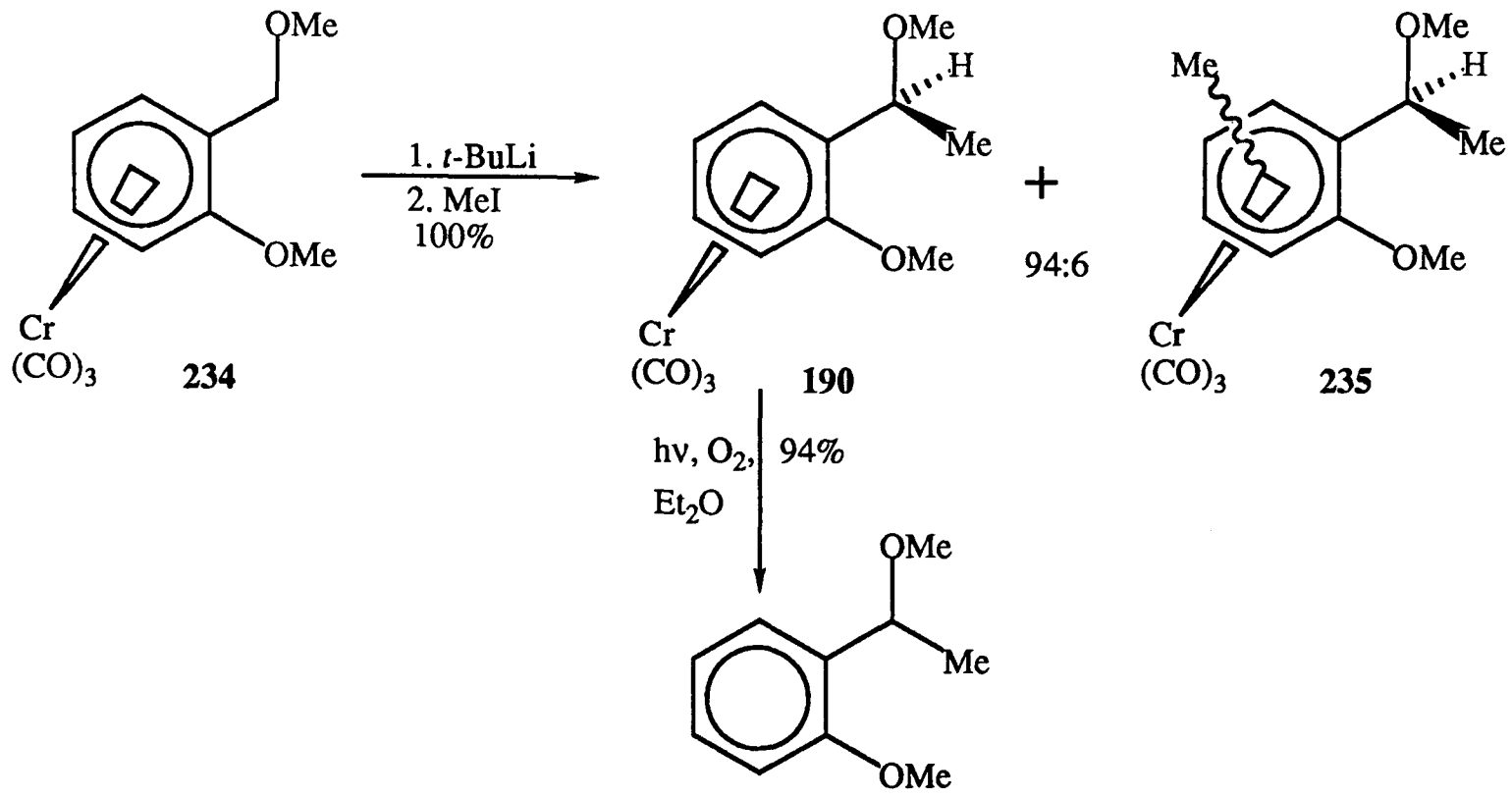
Preparation of homochiral (+)-**234** was achieved *via* a different route. Reduction of homochiral (-)-(*o*-anisaldehyde)Cr(CO)3 (-)-**149** with NaBH4 in THF:MeOH 3:1 gave a yellow solid (+)-**192** {$[\alpha]_D^{22}$ = +237o (c 1 CHCl3)}. The ^{1}H n.m.r. spectrum of the product contained a two proton AB system (δ4.64, 4.38, J_{AB} = 13.12Hz) characteristic of two diastereotopic benzylic protons. A broad hydroxyl singlet (δ1.96) confirmed the identity of (+)-**192** as (+)-(*o*-methoxybenzyl alcohol)Cr(CO)3. Conversion of compound (+)-**192** to (+)-**234** was achieved in good yield upon sequential treatment of (+)-**192** with NaH and MeI in THF. The product (+)-**234** {$[\alpha]_D^{22}$ = +200o (c 1 CHCl3)}, was spectroscopically identical with the racemic sample previously prepared. Since the starting aldehyde complex (-)-**149** was homochiral and subsequent transformations were

only performed on the aldehyde group, it follows that complex (+)-**234** is homochiral. Also since the absolute configuration of (-)-**149** is (*R*), it follows that that of complex (+)-**234** is also (*R*).

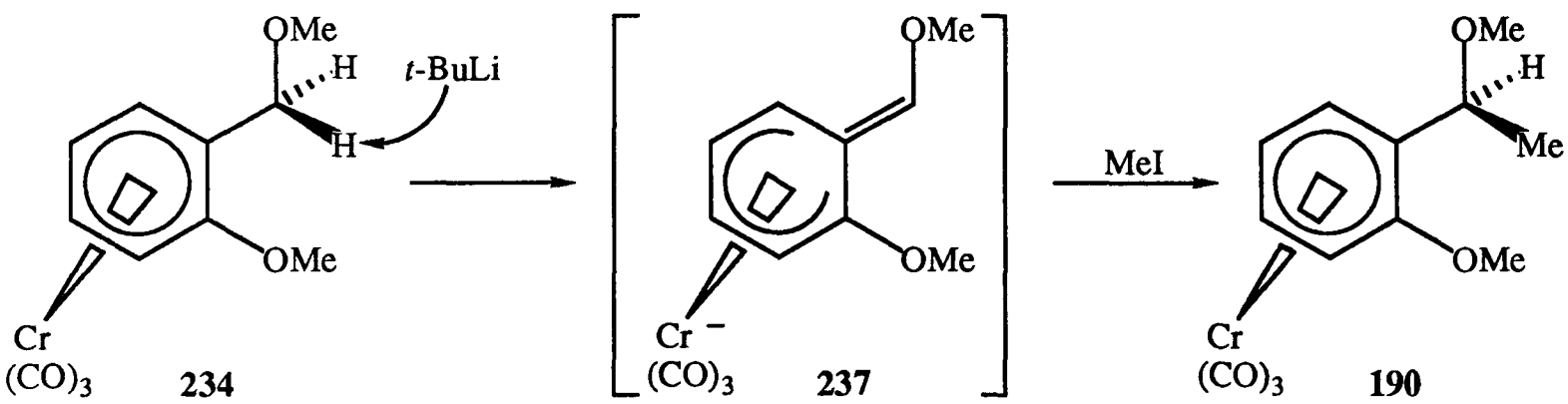


c. *Stereoselective Benzylic Elaboration of (o-Methoxybenzyl Methyl Ether)Cr(CO)3.*

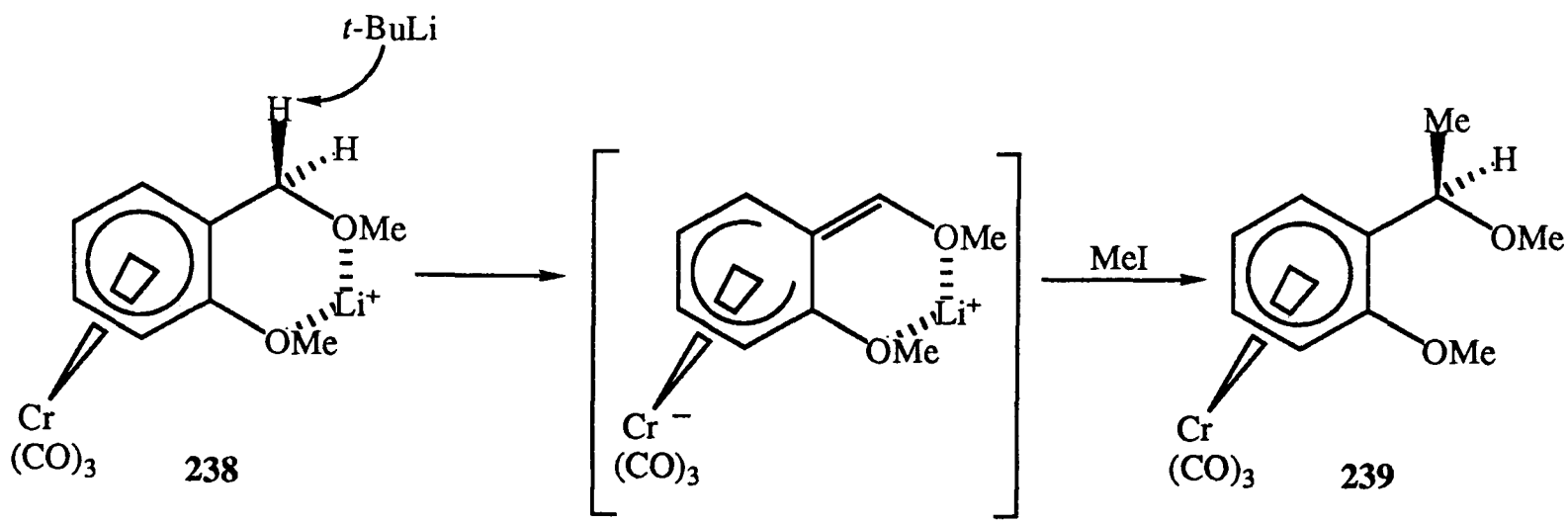
Addition of *t*-BuLi followed by MeI to complex **234** under standard alkylation conditions gave, on work up and chromatography, yellow crystals in quantitative yield. The ^{1}H n.m.r. spectrum of the product clearly showed two compounds **190** and **235** in a ratio of 94:6. The major set of peaks contained two aromatic proton doublets (δ5.86-5.84, 5.04-5.02), two aromatic proton triplets (δ5.51-5.47, 4.97-4.93), a one proton benzylic quartet (δ4.41, J = 6.34Hz) and three proton methyl doublet (δ1.37, J = 6.34Hz) and was consistent with a single diastereoisomer of (*o*-methoxy-α-methylbenzyl methyl ether)Cr(CO)3 **190**. The set of peaks corresponding to the minor product were similar to that of complex **190**, but contained two aromatic proton doublets (δ5.42-5.41, 5.18-5.15), an aromatic proton triplet (δ5.26-5.22) and a new three proton singlet (δ2.24) characteristic of an aromatic methyl group. Compound **235** was identified as a dimethylated derivative. The multiplet splitting pattern of three contiguous aromatic protons in the ^{1}H n.m.r. spectrum indicated that the second methyl group was *ortho* to either the methoxy or alkyl side-chains. Recrystallisation of the mixture from CH_2Cl_2:light petroleum gave large yellow blocks of complex **190**. Complex **190** gave a molecular ion *m/z* 302 (M^+) in the mass spectrum and a correct elemental microanalysis. Decomplexation of complex **190** under standard conditions gave the free racemic arene **236** in good yield. The ^{1}H n.m.r. spectrum of arene **236** contained two aromatic proton doublets (δ7.42-7.40, 6.90-6.88), two aromatic proton triplets (δ7.29-7.23, 7.03-6.93), a benzylic proton quartet (δ4.78, J = 6.39Hz) and a three proton methyl doublet (δ1.41, J = 6.42Hz).



Two mechanisms for this stereoselective benzylic alkylation are possible. In both, removal of a benzylic proton will occur preferentially from conformations which place the proton *antiperiplanar* to chromium, since delocalisation of the developing carbanion orbital over the ring and hence onto chromium will be maximised when the relevant orbitals have greatest overlap. In the first mechanism, the population of conformations which place the two methoxy groups *anti* are sterically favoured. The high energy dipolar interactions present between the lone pairs on the two oxygens will also favour the *anti* conformations over the *syn*. Removal of a benzylic proton *antiperiplanar* to the metal unit from these *anti* conformations gives the configurationally stable anion **237**. Subsequent *exo* alkylation would give rise to the product **190**.

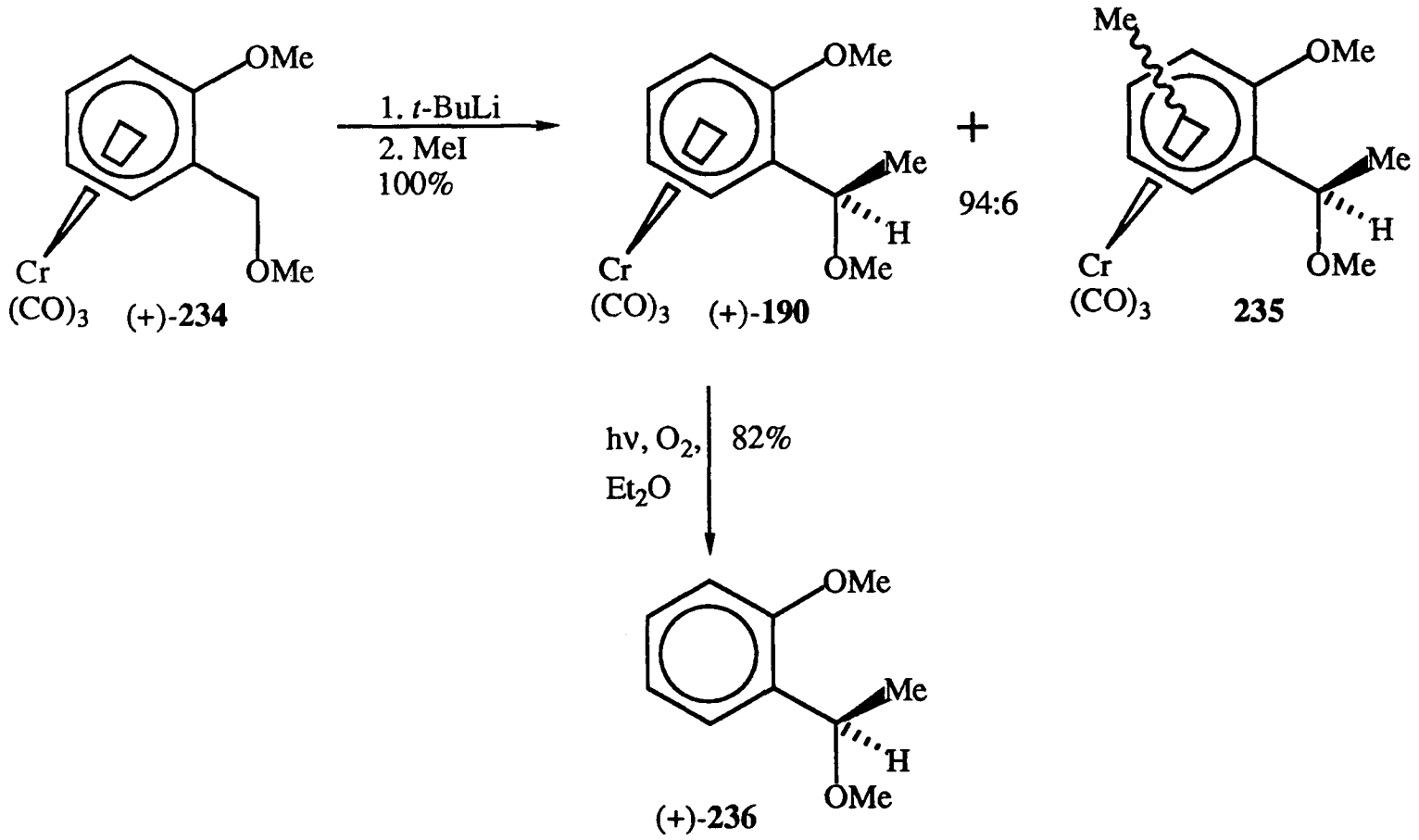


The second mechanism involves the formation of a Lewis acid chelated intermediate **238**, where the substrate **234** acts as a bidentate ligand towards Li^+. Benzylic deprotonation *antiperiplanar* to the chromium with a second molecule of base lead to loss of the other α-proton. Subsequent *exo* alkylation in this case would give rise to the product **239**.



The relative stereochemistry within the observed product **190** was unambiguously confirmed by a single crystal X-ray structure analysis, Figure XI. Final atomic coordinates, selected bond lengths, angles and torsional angles are presented in Appendix IV. The (*RR*,*SS*) configuration within complex **190** indeed confirms that only the first mechanism is operating.

Repetition of the stereoselective methylation reaction on homochiral (+)-**234** under the same conditions, similarly gave a 94:6 mixture of compounds (+)-**190** and **235**. Pure complex (+)-**190** {$[\alpha]_D^{22}$= +220° (c 0.8 CHCl3)}, was isolated after a single recrystallisation from CH_2Cl_2:light petroleum. Decomplexation of (+)-**190** gave free chiral (*R*)-*o*-methoxy-α-methylbenzyl methyl ether (+)-**236** as a clear oil.



Complexation of the free arene **236** with $Cr(CO)_6$ under standard conditions gave a mixture of products **190** and **239** in a ratio of 87:13. The major set of signals in the ^1H n.m.r. spectrum of the mixture was identical to that for pure complex **190**. The minor set

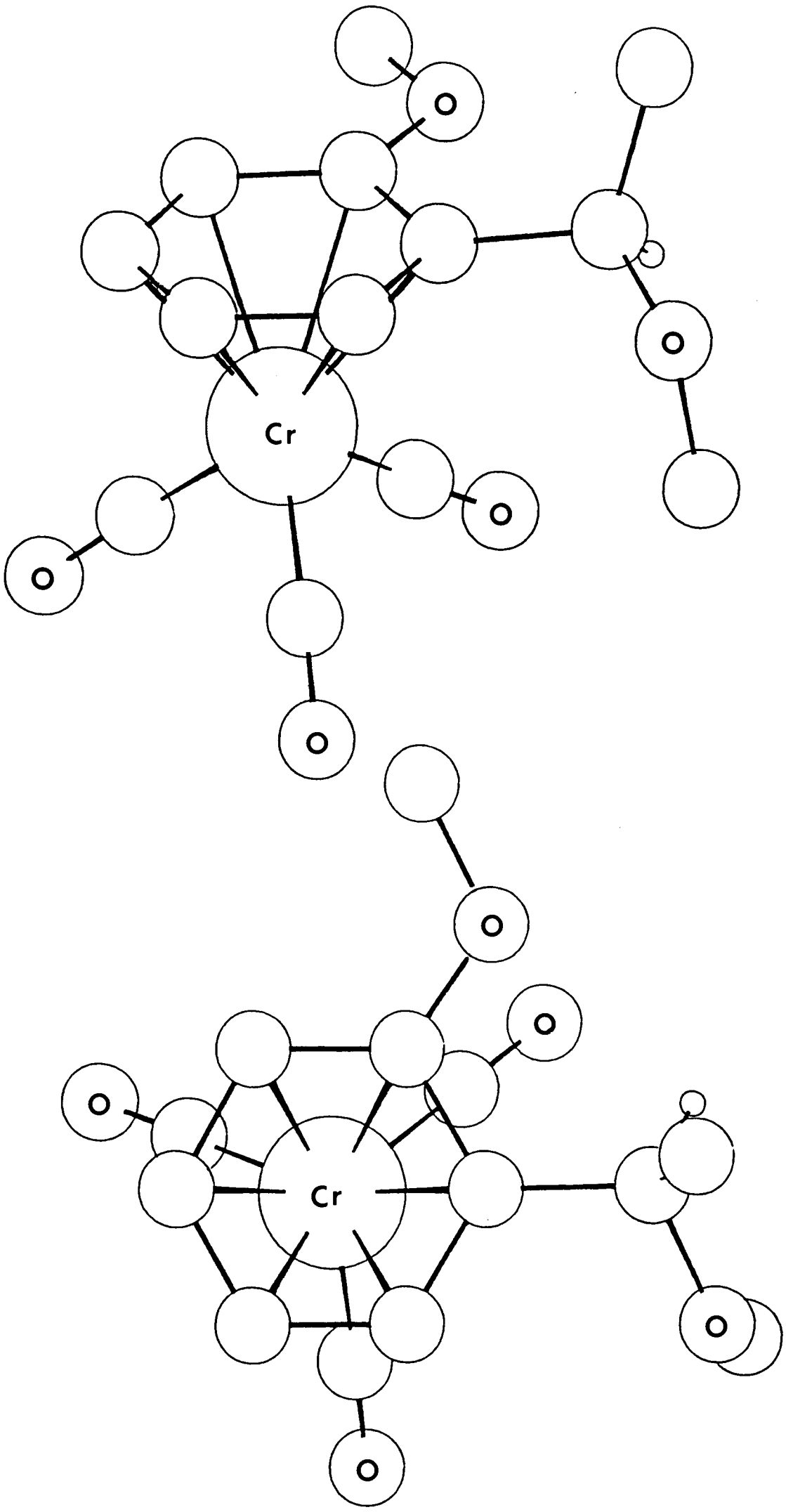
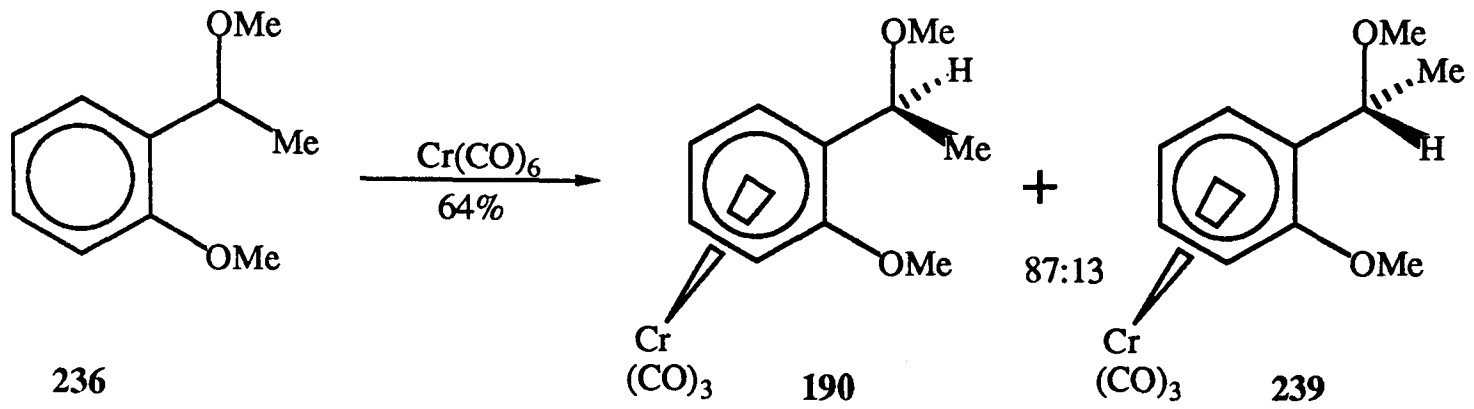


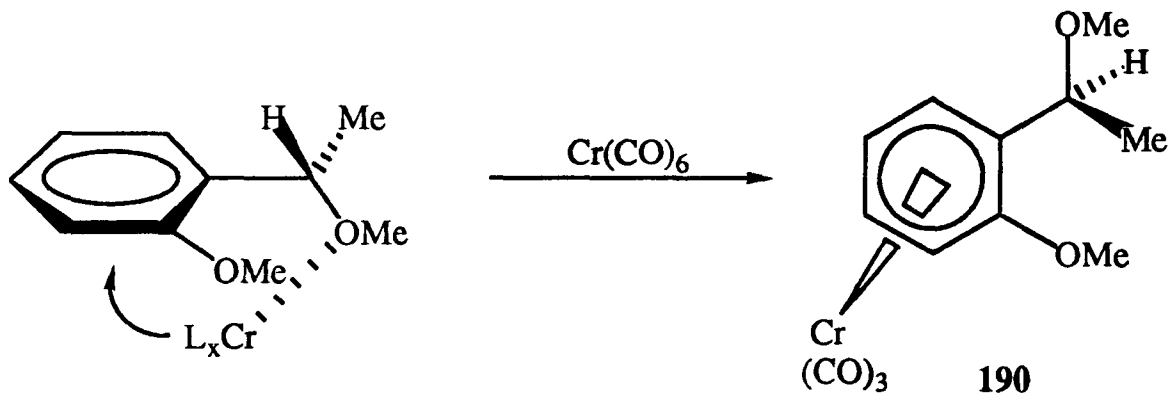
Figure XI. X-Ray crystal structure of (*RR*,*SS*)-(*o*-methoxy-α-methylbenzyl methyl ether)$Cr(CO)_3$ **190**.

of signals was similar to that of the major and contained two aromatic proton doublets (δ5.93-5.91, 5.13-5.10), two aromatic proton triplets (δ5.64-5.58, 4.91-4.87), a benzylic proton quartet (δ4.59, J = 6.50Hz) and a three proton methyl doublet (δ1.52, J = 6.52Hz). The minor product **239** was assigned as the epimeric complex.



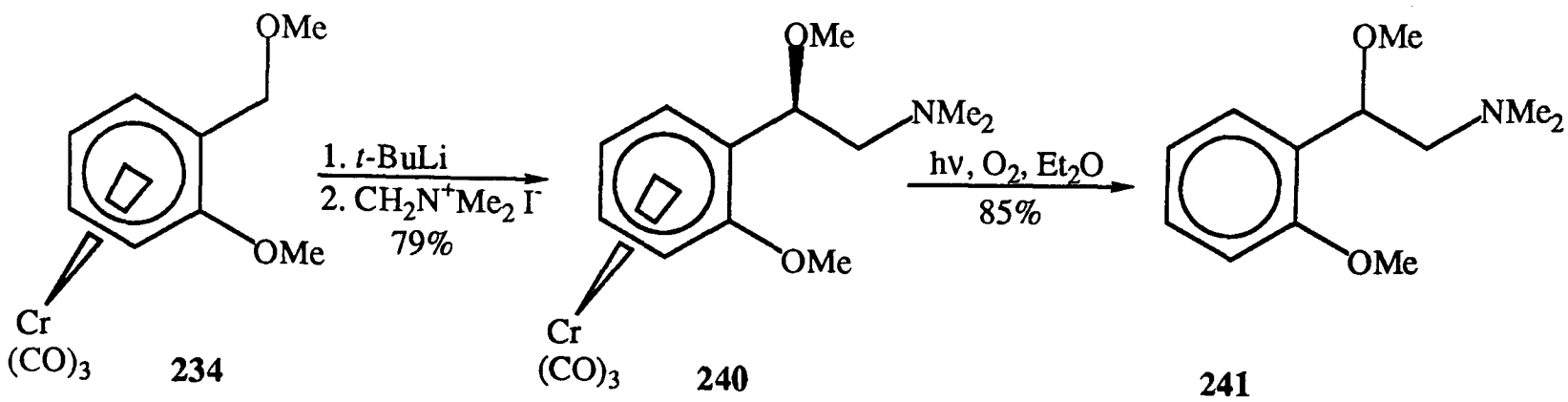
236 **190** **239**

The formation of predominantly one compound **190** is consistent with an oxygen-chelate directing effect in the complexation reaction, see Chapter 2. The benzylic oxygen function directs the incoming chromium unit onto the proximate face of the arene in less crowded conformations which place the α-proton and not α-methoxy group *syn* to the *o*-methoxy substituent.[34]

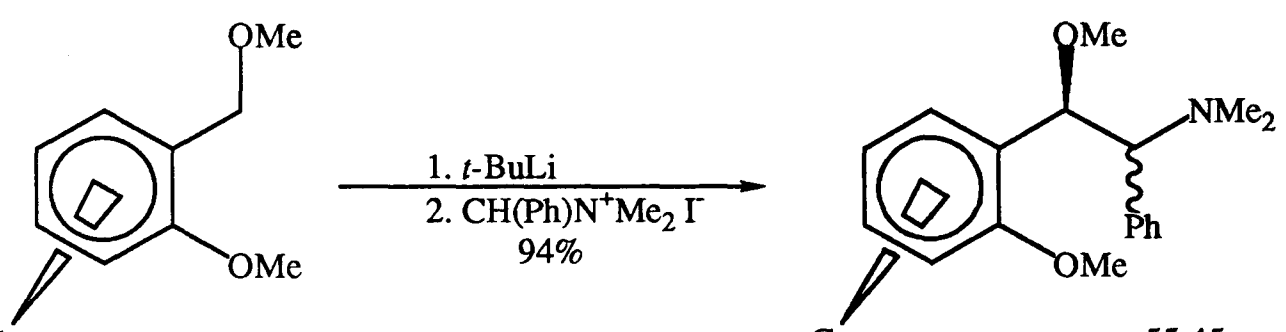


190

Addition of *t*-BuLi to racemic complex **234** followed by $CH_2NMe_2^+ I^-$ (Eschenmoser's salt), under standard conditions with warming to 0°C over 1h, gave on work up, a single product **240** as yellow needles. The ^1H n.m.r. spectrum of the product contained two aromatic proton doublets (δ5.87-5.84, 5.02-5.00), two aromatic proton triplets (δ5.54-5.49, 4.96-4.92), a benzylic proton doublet of doublets (δ4.50, J_{AX} = 8.48Hz, J_{AY} = 2.32Hz), a two proton ABX system (δ2.39, 2.52, J_{AB} = 13.15Hz, J_{AX} = 8.51Hz, J_{BX} = 2.31Hz) and a six proton N-methyl singlet (δ2.33). A molecular ion *m/z* 346 (M^++1) and a correct elemental microanalysis confirmed the identity of the product as the phenethanolamine derivative **240**. The relative stereochemistry within complex **240** was assigned by analogy with that observed in the stereoselective methylation reaction. Decomplexation of complex **240** under standard conditions gave the free racemic phenethanolamine **241** in good yield. The ^1H n.m.r. spectrum of arene **241** was similar to that of its $Cr(CO)_3$ complex **240** but with the two aromatic proton doublets (δ7.38-7.35, 6.88-6.85) and the two aromatic proton triplets (δ7.26-7.21, 7.00-6.95) shifted downfield.



Repeating the above reaction, using $PhCHNMe_2^+ I^-$ as the electrophile gave a mixture of the two products **242** and **243** in a ratio of 55:45 identified by ^1H n.m.r. spectroscopy. The presence of only two of the four possible diastereoisomeric products is consistent with the formation of only a single epimer at the α-centre, but with virtually no stereocontrol at the β-centre. The ^1H n.m.r. spectrum of the mixture contained two benzylic proton doublets (**242**, δ4.98, J = 3.82Hz; **243**, δ4.68, J = 6.13Hz), two beta proton doublets (**242**, δ3.15, J = 3.15Hz; **243**, δ3.50, J = 6.19Hz) and two six proton N-methyl singlets (**242**, δ2.28; **243**, δ2.26).

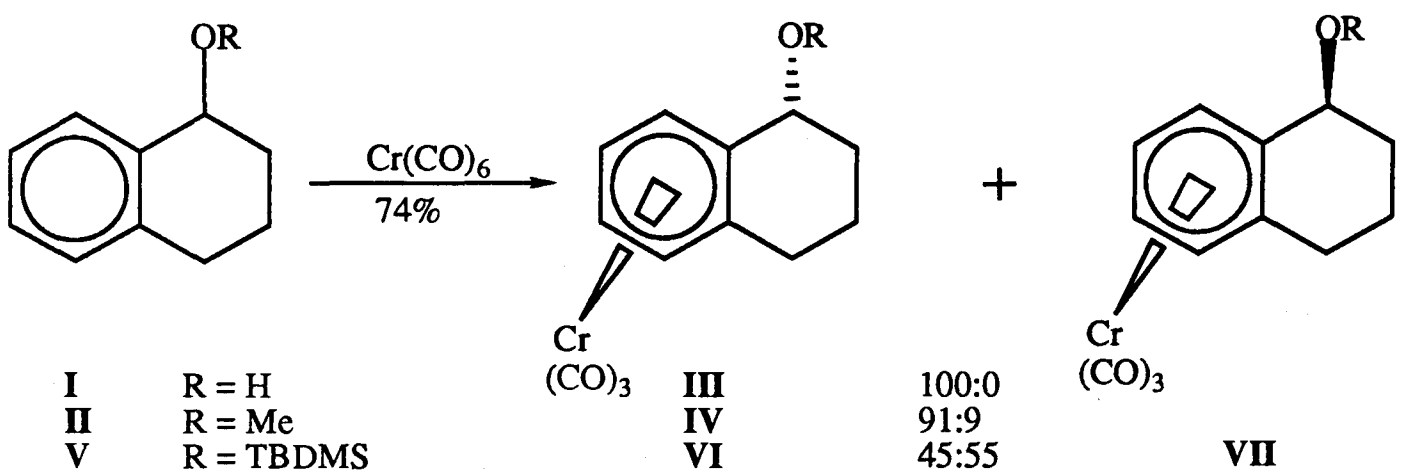


d. *Conclusion.*

The completely stereoselective benzylic elaboration of (*o*-methoxybenzyl methyl ether)Cr(CO)3 **234** has been achieved. The ready access to homochiral complex **234**, *via* homochiral (*o*-anisaldehyde)Cr(CO)3 **149**, see Chapters 6 and 7, potentially allows the synthesis of a wide range of α-substituted benzyl methyl ethers. This methodology involves the selective removal of a benzylic proton followed by electrophilic quench and is complementary to the stereoselective additions to (*o*-anisaldehyde)Cr(CO)3 **149** and (*o*-trialkylsilybenzaldehyde)Cr(CO)3 complexes **164** and **169** where nucleophilic species are used, see Chapter 7.

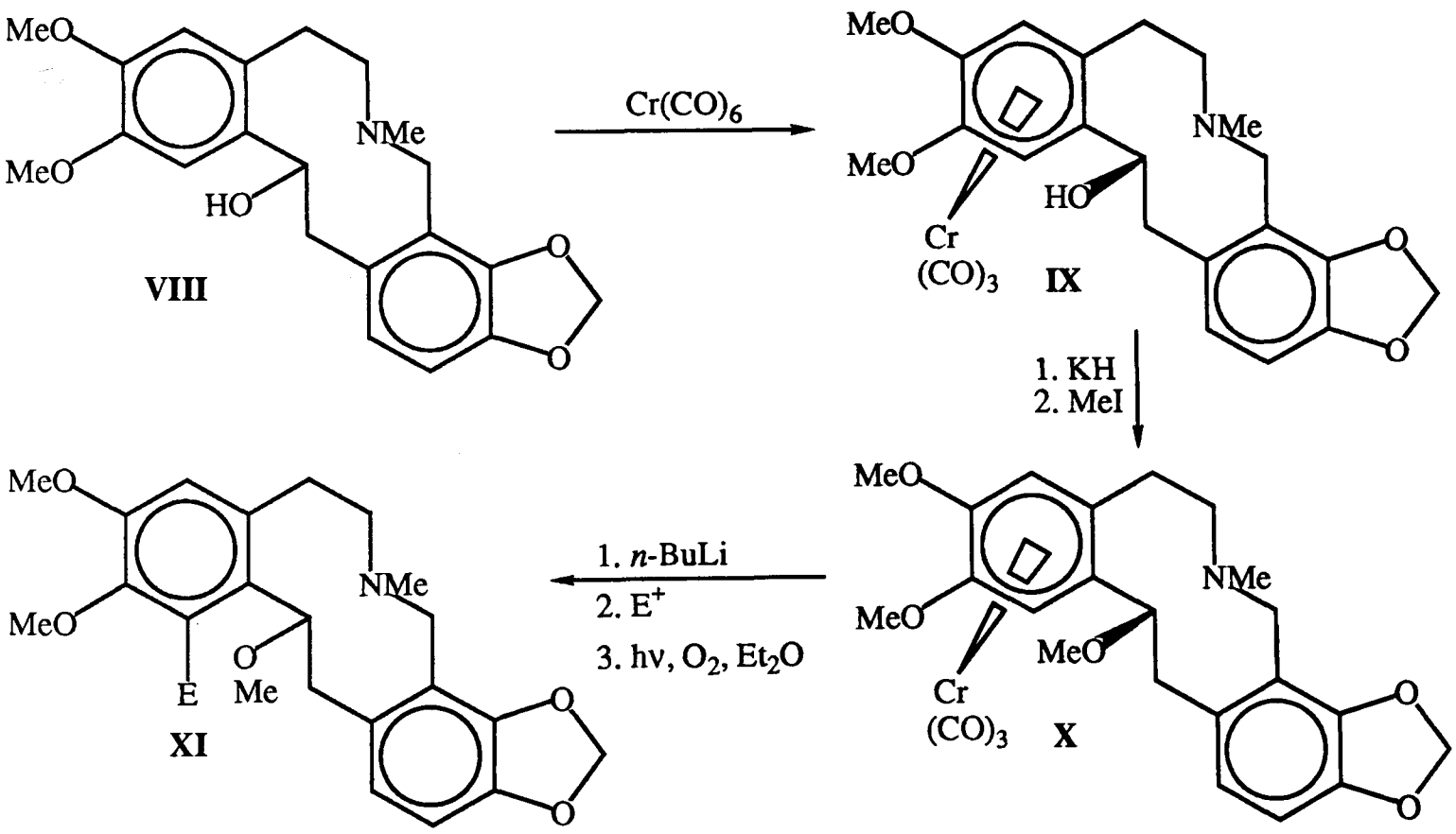
Summary

Complexation of arenes possessing diastereotopic faces to the $Cr(CO)_3$ group often give a predominance of one diastereoisomer. For arenes possessing an α-heteroatom substituent this can be due to both steric and chelate directing effects. Complexation of 1-tetralol **I** or 1-methoxytetralin **II** to the $Cr(CO)_3$ unit under standard conditions gives predominantly the *endo* complexes **III** and **IV**, indicating that the benzylic oxygen directing effect operates through a direct oxygen-chromium bond. Complexation of the *t*-butyldimethylsilyl derivative **V**, however, gives essentially a statistical mixture of diastereoisomers **VI** and **VII**, with suppression of the benzylic oxygen directing effect.[35]

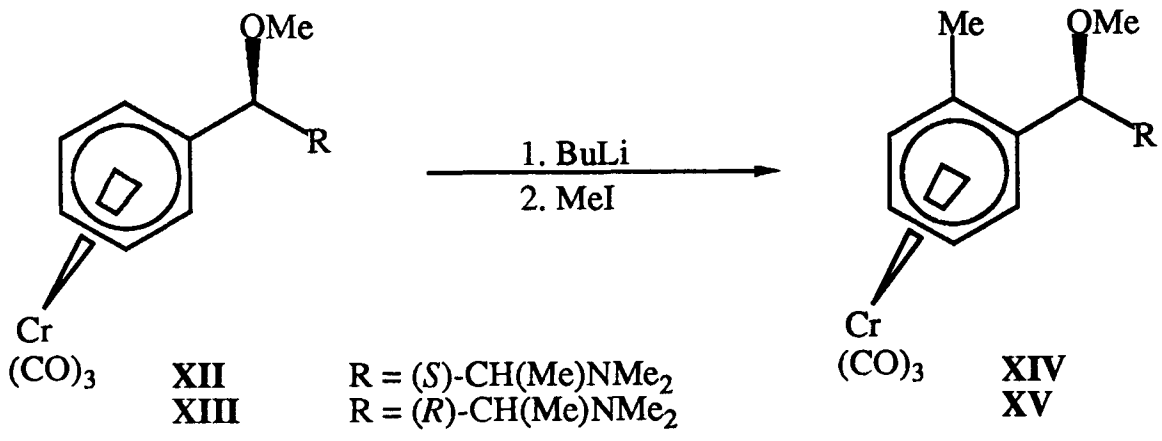


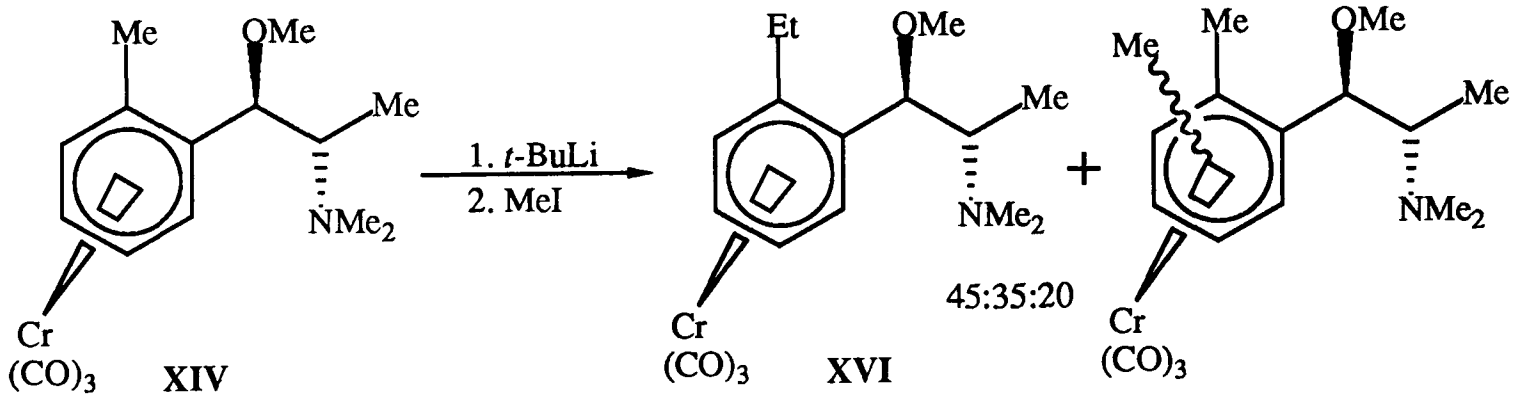
I R = H **III** 100:0
II R = Me **IV** 91:9
V R = TBDMS **VI** 45:55 **VII**

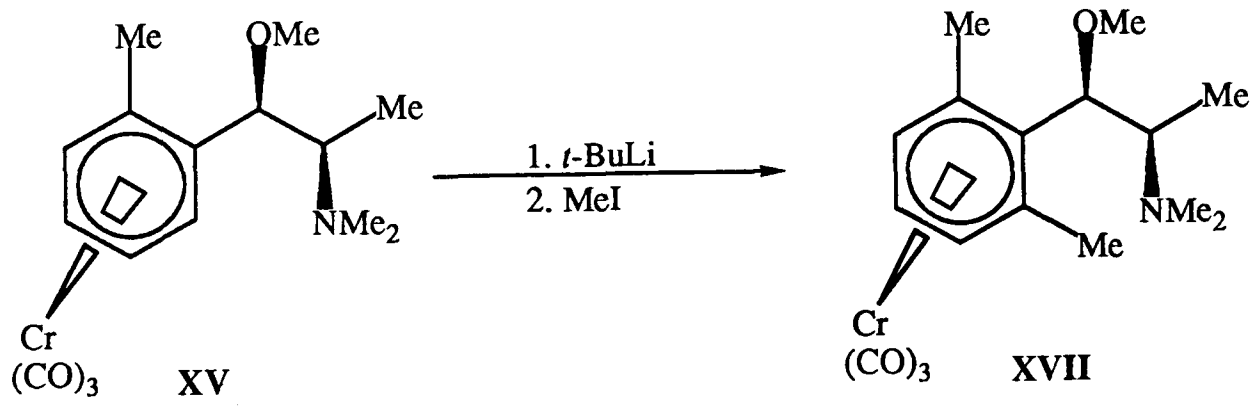
Extension of this methodology to dihydrocryptopine **VIII** allows the completely diastereoselective synthesis of *exo*-(dihydrocryptopine)$Cr(CO)_3$ **IX**, with the metal unit bound to the electron-rich dimethoxy arene ring.[46] O-Methylation of complex **IX** gives *exo*-(O-methyldihydrocryptopine)$Cr(CO)_3$ **X** which on treatment with *n*-BuLi followed by an electrophile, undergoes regioselective C1 alkylation *via* chelation of the base with the benzylic oxygen function. Oxidative decomplexation gives the C1 functionalised dihydrocrytopine derivatives **XI**.



Treatment of (1*S*,2*S*)-(N,O-dimethylephedrine)$Cr(CO)_3$ **XII** with *t*-BuLi and (1*S*,2*R*)-(N,O-dimethylpseudoephedrine)$Cr(CO)_3$ **XIII** with *n*-BuLi, followed by MeI in both cases, gives products **XIV** and **XV** resulting from exclusive removal of the *pro*-(*R*) *ortho* hydrogen. Further alkylation of products **XIV** and **XV** *via* sequential treatment with *t*-BuLi and an electrophile proceeds in complementary fashion. In the case of the ephedrine derivative **XIV**, a mixture of products is observed containing the *o*-ethyl complex **XVI** as the major isomer. Whereas in the case of the pseudoephedrine derivative **XV** only the *o*,*o*-dimethylated product **XVII** is observed. Assuming that the substrate acts as a bidentate ligand towards the alkyllithium, these results can be rationalised by analysis of conformations of the chelate leading to removal of either of the *ortho* protons.

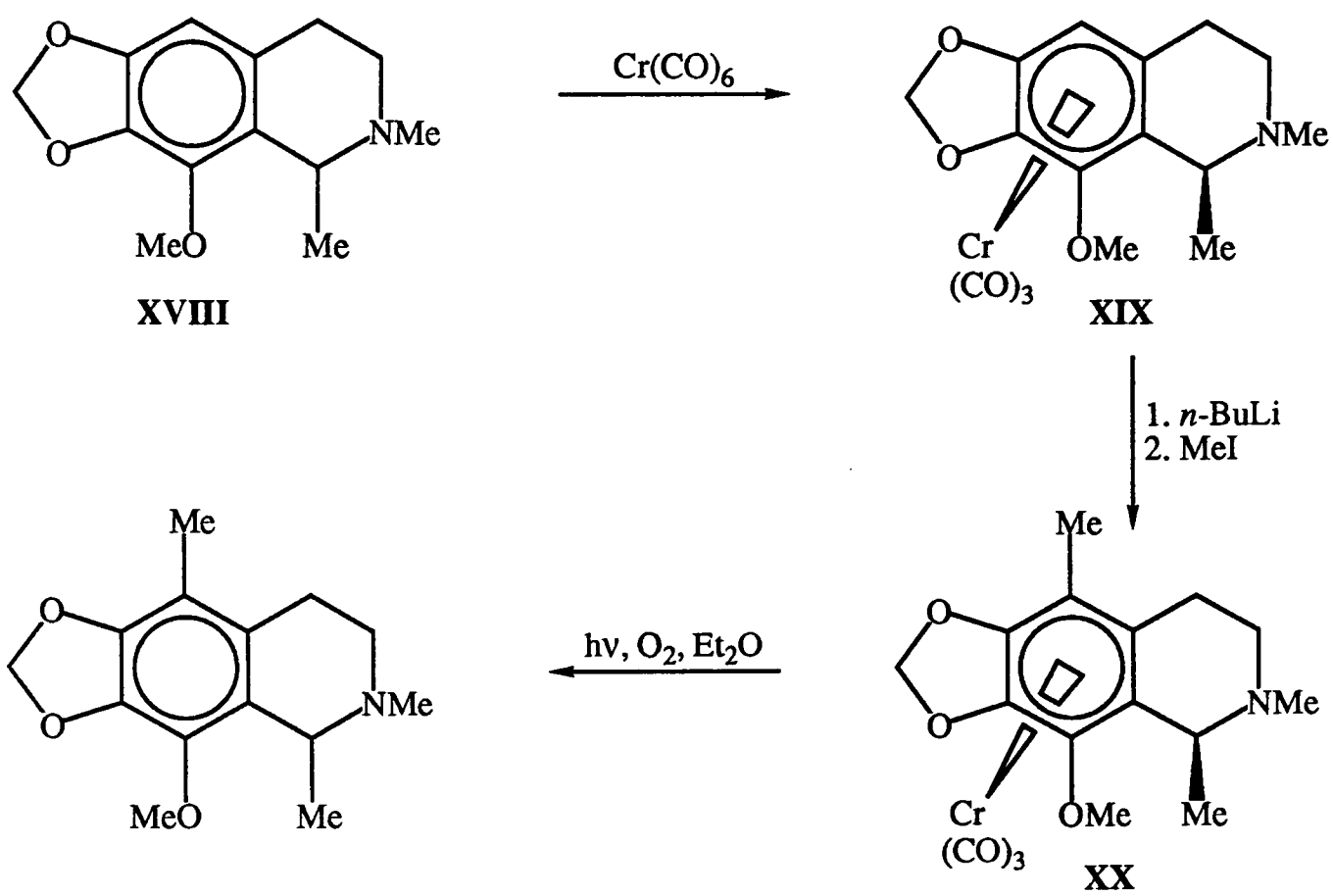




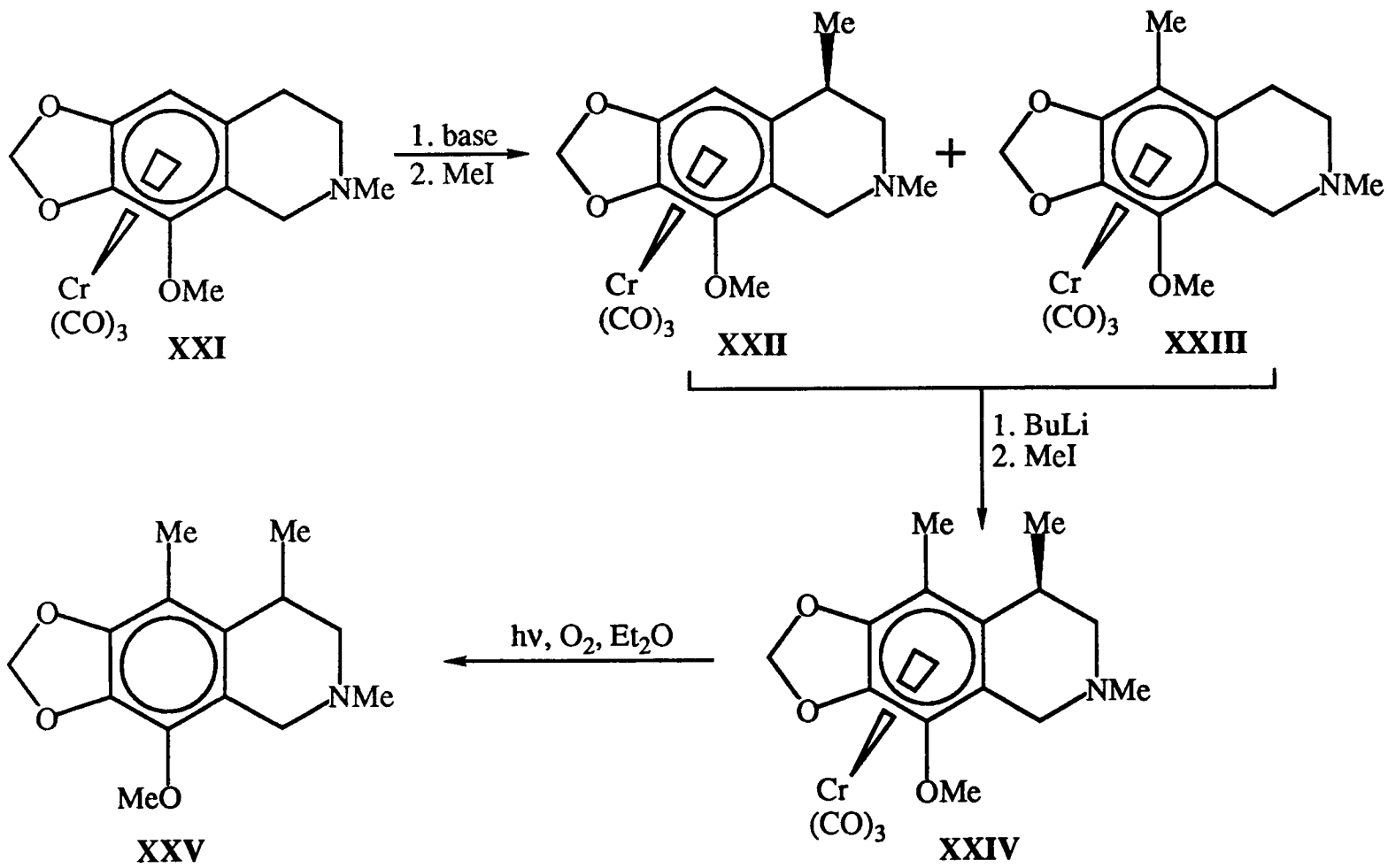


Diastereofacial selectivity in the complexation reaction, where the origins of the selectivity lie in the metal unit approaching the least hindered face of the arene,[64] is demonstrated in the coordination of 1-methylhydrocotarnine **XVIII** to the Cr(CO)3 unit

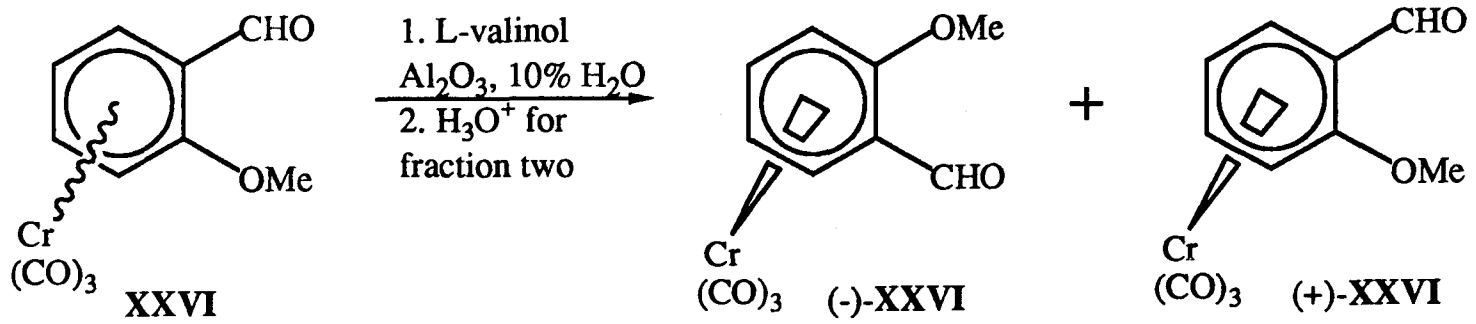
to give only *exo*-(1-methylhydrocotarnine)$Cr(CO)_3$ **XIX**. Treatment of complex **XIX** with *n*-BuLi followed by MeI gives only the *exo*-1,5-dimethylated product **XX**.

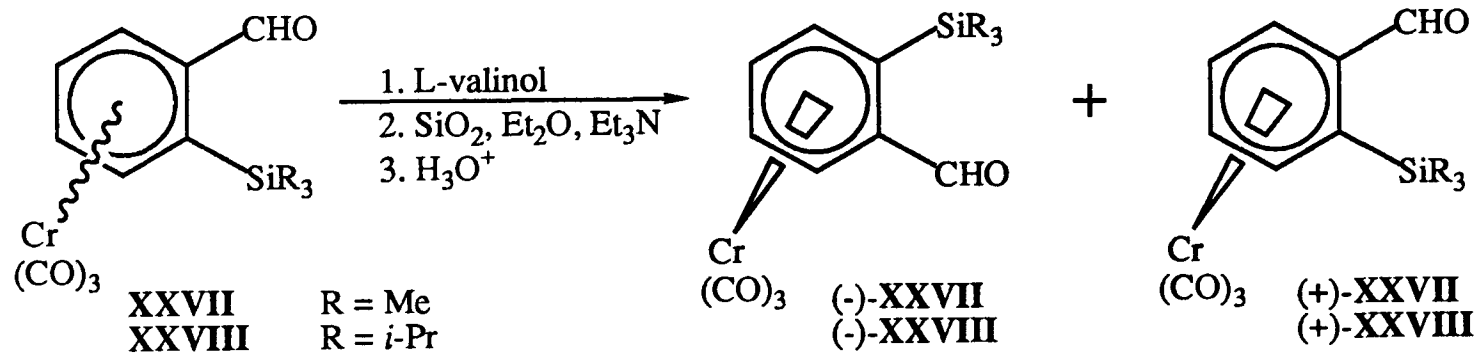


The parent complex (hydrocotarnine)$Cr(CO)_3$ **XXI** undergoes C4 and C5 alkylation on treatment with a variety of bases followed by electrophilic quench. The C4 alkylated product arises *via* exclusive *exo* attack of the electrophile onto the chromium stabilised benzylic anion. Treatment of *exo*-(4-methylhydrocotarnine)$Cr(CO)_3$ **XXII** or (5-methyl-hydrocotarnine)$Cr(CO)_3$ **XXIII** with BuLi followed by MeI gives, in both cases, the *exo*-4,5-dimethylated complex **XXIV**. Oxidative decomplexation gives the free arene **XXV**.

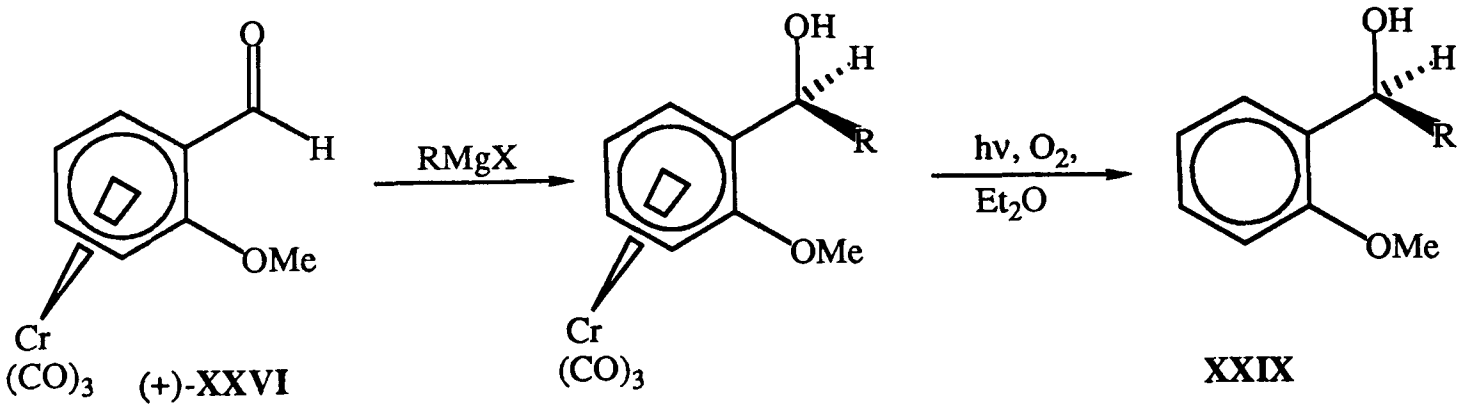


Homochiral *ortho* substituted (benzaldehyde)$Cr(CO)_3$ complexes are prepared by two routes. The first involves the kinetic resolution of (*o*-anisaldehyde)$Cr(CO)_3$ **XXVI** on an L-valinol doped deactivated alumina column. The method relies on the selective hydrolysis of the L-valinol derived imine of (-)-(*o*-anisaldehyde)$Cr(CO)_3$ (-)-**XXVI** combined with the large difference in R_f values of the free aldehyde and derived imine.[109,110] The second method involves a classical separation of the L-valinol derived imines of (*o*-trimethylsilylbenzaldehyde)$Cr(CO)_3$ **XXVII** and (*o*-tri-*i*-propylsilyl-benzaldehyde)$Cr(CO)_3$ **XXVIII** *via* a basified silica column, subsequent acidic hydrolysis releasing the free homochiral aldehyde complexes.

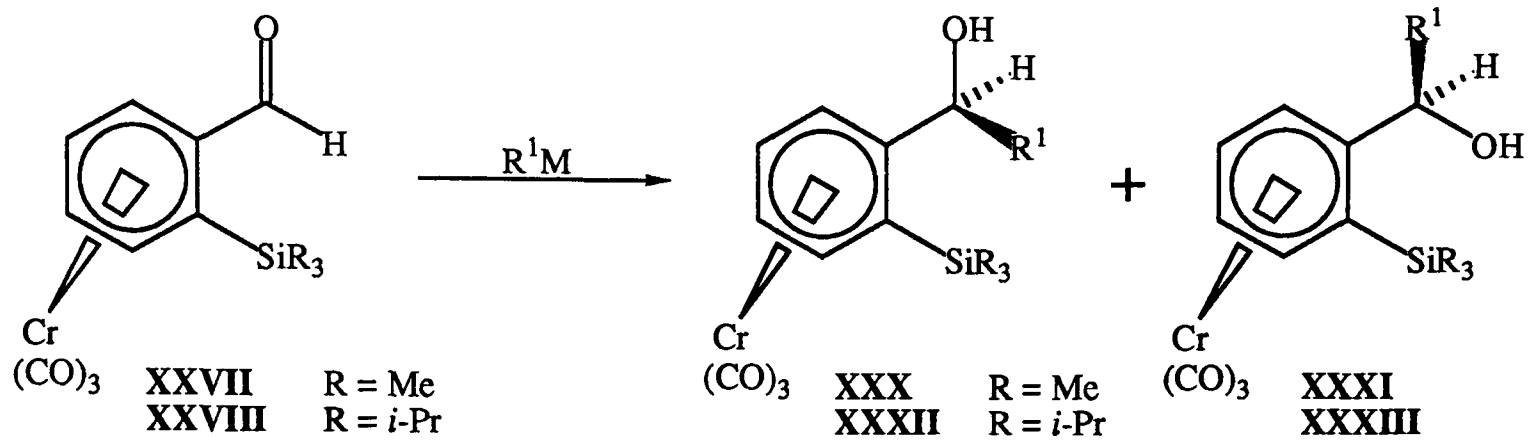




Addition of Grignard reagents to (+)-(*o*-anisaldehyde)$Cr(CO)_3$ (+)-**XXVI** proceeds under suitable conditions to give only the (*SS*) diastereoisomer with 100% asymmetric induction. Oxidative decomplexation gives homochiral (*S*)-*o*-methoxybenzyl alcohol derivatives **XXIX**.[109,110]



Addition of nucleophiles to complexes **XXVII** and **XXVIII** generally gives mixtures of both (*RR*,*SS*) and (*RS*,*SR*) products **XXX**-**XXXIII**. Performing the reaction in the presence of strong Lewis acids increases the proportion of the (*RR*,*SS*) diastereoisomers **XXX** and **XXXII**.

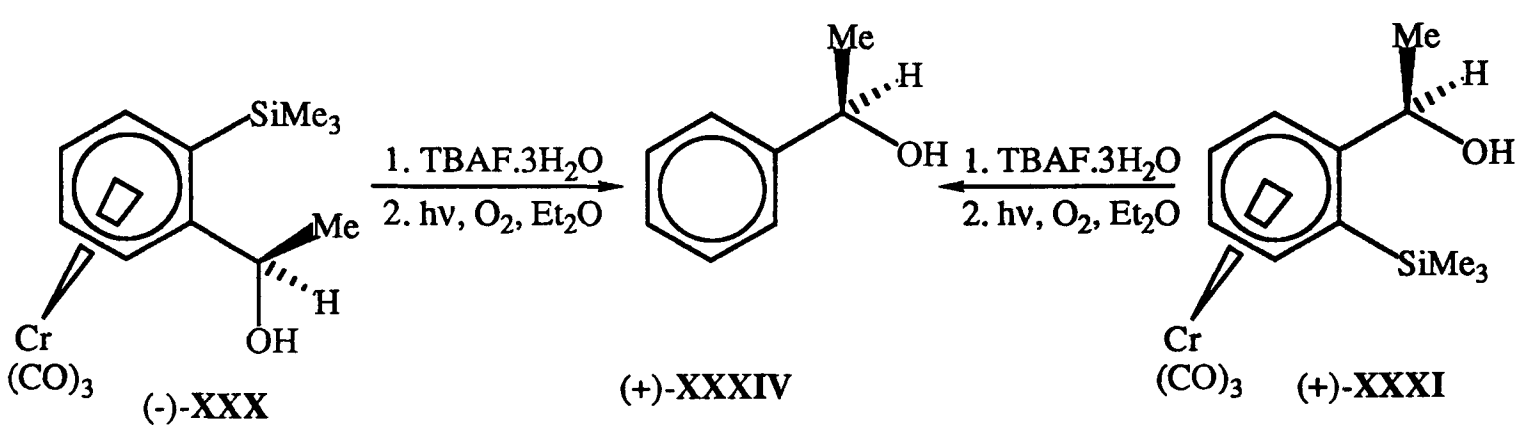


XXVII R = Me
XXVIII R = *i*-Pr

XXX R = Me
XXXII R = *i*-Pr

XXXI
XXXIII

Treatment of the homochiral (*RR*) or (*SR*) diastereoisomers (-)-**XXX** or (+)-**XXXI** respectively with TBAF.3H2O, followed by oxidative decomplexation, gives homochiral (*R*)-phenethanol (+)-**XXXIV.**

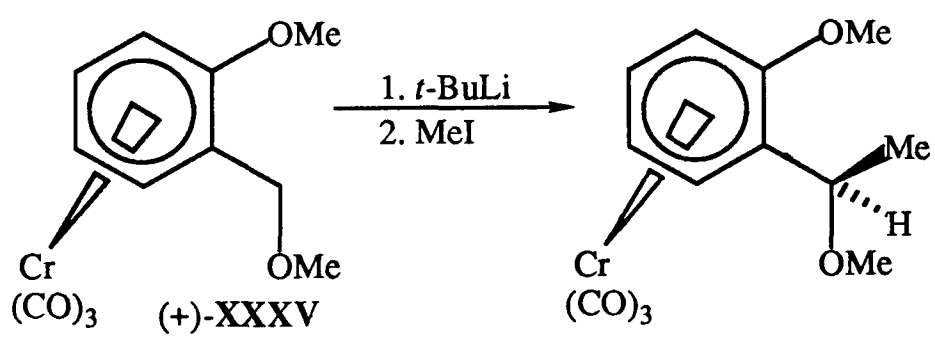


(-)-**XXX**

(+)-**XXXIV**

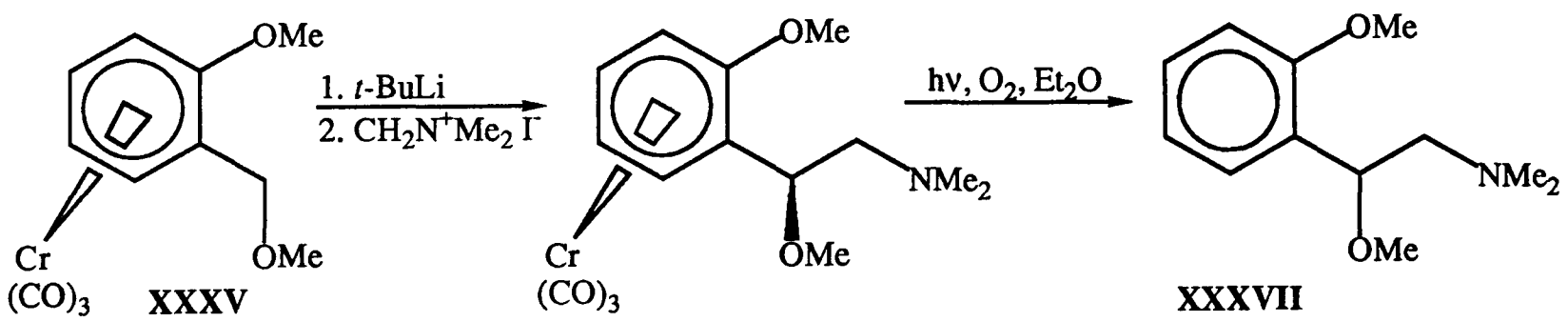
(+)-**XXXI**

Stereoselective benzylic elaboration of (*o*-methoxybenzyl methyl ether)Cr(CO)3 **XXXV** occurs on treatment with *t*-BuLi followed by addition of an electrophile. Only the (*RR*,*SS*) diastereoisomer is produced under these conditions. Performing the reaction on homochiral complex (+)-**XXXV**, easily accessible from (-)-(*o*-anisaldehyde)Cr(CO)3 (-)-**XXVI** in two steps, gives, following oxidative decomplexation, alpha substituted (*R*)-*o*-methoxybenzyl alcohol (+)-**XXXVI.** Using Eschenmoser's salt as the electrophile in these reactions provides a route through to the halostachine derivative **XXXVII.**[111]



(+)-**XXXV**

(+)-**XXXVI**



XXXV

XXXVII

Experimental

General Methods.

Reactions involving the preparation and utilisation of (arene)$Cr(CO)_3$ complexes were performed under an atmosphere of nitrogen using standard vacuum line and Schlenk techniques.[112] All solvents were rigorously degassed prior to use and solvent evaporation was performed under reduced pressure.

Reagents and Solvents.

THF was distilled from sodium benzophenone ketyl under an atmosphere of nitrogen. Diethyl ether was dried over sodium and di-*n*-butyl ether was sodium dried and distilled under an atmosphere of nitrogen. Dichloromethane was distilled from calcium hydride prior to use. Light petroleum refers to that fraction boiling between 60°C and 80°C and was redistilled prior to use. Hexane was dried over sodium wire.

Chromium hexacarbonyl was steam distilled and dried *in vacuo* prior to use. *n*-Butyllithium was used as a solution in hexanes, *t*-butyllithium as a solution in pentane and methyllithium as a solution in diethyl ether. LDA was freshly prepared from di-*i*-propylamine in THF, cooled to -78°C, treated with 0.95 equivalents of *n*-butyllithium and then warmed to 0°C.[113] Methylmagnesium iodide and phenylmagnesium bromide were used as diethyl ether solutions, prepared according to the literature procedure.[114] Ethyllithium was used as a solution in diethyl ether. Potassium hydride and sodium hydride were obtained as 35% and 50% dispersions in oil respectively from which the oil was removed by repeated washings with light petroleum followed by drying *in vacuo*. Methyl iodide was dried over 4$\overset{0}{A}$ molecular sieves and chlorotrimethylsilane and chlorotri-*i*-propylsilane were distilled from calcium hydride and stored under nitrogen. Eschenmoser's salt ($CH_2NMe_2^+ I^-$) was recrystallised from dichloromethane:light petroleum and dried before use.

All other commercially available reagents were purified according to standard procedures.[115]

Column Chromatography.

Column chromatography was performed on alumina (Grade V: Grade I 10% deactivated unless otherwise stated) or silica (Merck, 40-60μm) under a positive nitrogen pressure.

Melting points.

Melting points were recorded on a Kofler block and are uncorrected.

Elemental Microanalyses.

Elemental microanalyses were carried out by Mrs V. Lamburn in the Dyson Perrins Laboratory, Oxford.

Mass Spectra.

Mass spectra were obtained by Dr R.T. Aplin on a VG Micromass ZAB1F or an MM30F instrument using In Beam Electron Impact, Chemical Ionisation or ammonia Desorption Chemical Ionisation techniques.

Infrared Spectra.

Infrared Spectra were obtained on a Perkin-Elmer 781 or 297 spectrophotometer and were recorded as dichloromethane solutions in 0.1mm cells unless otherwise stated.

Optical Rotations.

Optical Rotations were obtained on a Perkin-Elmer 241 polarimeter.

^{1}H n.m.r. Spectra.

^{1}H n.m.r. spectra were obtained on a Varian Gemini-200 (200MHz), a Bruker WH300 (300MHz) or a Bruker WH500 (500MHz) instrument. Spectral data was recorded at 200MHz using d^{1}-chloroform solvent unless otherwise stated.

^{13}C and ^{2}H n.m.r. Spectra.

^{13}C and ^{2}H n.m.r. spectra were recorded on a Bruker AM250 (^{13}C, 62.9MHz; ^{2}H, 38.4MHz) instrument. ^{13}C n.m.r. spectral data were recorded using d^{1}-chloroform solvent and ^{2}H n.m.r. data were recorded using chloroform containing d^{1}-chloroform as an internal standard.

General procedure for preparation of (arene)Cr(CO)$_3$ complexes.

A deoxygenated 10:1 mixture of *n*-Bu$_2$O:THF, arene and Cr(CO)$_6$ was heated at reflux until the formation of the first trace of green precipitate was observed. The cooled solution was filtered through celite and the solvent evaporated to give the crude complex.

*(1-Tetralone)Cr(CO)$_3$ **13**.*[116]

Thermolysis of Cr(CO)$_6$ (3.92g, 17.8mmol) with 1-tetralone **48** (2.00g, 13.7mmol) under standard conditions (50ml solvent, 69h) gave after work up and column chromatography (Al$_2$O$_3$, CH$_2$Cl$_2$), (1-tetralone)Cr(CO)$_3$ **13** as red crystals (2.57g, 67%). *m/z* 282 (*M*$^+$); ν_{max} 1971, 1900br (-CO), 1682 (C=O) cm^{-1}; ^{1}H n.m.r. (500MHz) δ6.16-6.15, 5.15-5.14 (2d, 2H, Ar*H*), 5.64-5.62, 5.30-5.28 (2t, 2H, Ar*H*), 2.99-2.93, 2.48-2.41 (m, 2H, ArC*H*$_2$R), 2.76-2.74, 2.72-2.71 (m, 2H, ArCOC*H*$_2$R), 2.22-2.09 (m, 2H, ArCH$_2$C*H*$_2$R).

*endo-(1-Tetralol)Cr(CO)$_3$ **49**.*[91]

Method 1. To a solution of (1-tetralone)Cr(CO)3 **13** (500mg, 1.77mmol) in THF (20ml) and MeOH (5ml) was added NaBH$_4$ (1.00g, 26.4mmol) and the mixture stirred (2h). Acidification with aqueous HCl (2N), evaporation and column chromatography (Al$_2$O$_3$, Et$_2$O), gave *endo*-(1-tetralol)Cr(CO)$_3$ **49** as a yellow solid (409mg, 81%). *m/z* 284 (*M*$^+$); ν_{max} 3582 (-OH), 1955, 1875br (-CO), 1600 (arene ring) cm^{-1}; ^{1}H n.m.r. (300MHz) δ5.85-5.83, 5.11-5.09 (2d, 2H, Ar*H*), 5.54-5.50, 5.17-5.13 (2t, 2H, Ar*H*), 4.52 [m, 1H, ArC*H*(OH)R], 2.81-2.71, 2.65-2.56 [2m, 2H, ArCH(OH)C*H*$_2$R], 2.15-2.08, 2.03-1.93 (2m, 2H, ArC*H*$_2$R), 1.78-1.61 (m, 3H, RO*H*, ArCH$_2$C*H*$_2$R).

Method 2. Thermolysis of Cr(CO)$_6$ (3.86g, 17.6mmol) with 1-tetralol **45** (2.00g, 13.5mmol) under standard conditions (55ml solvent, 19h) gave after work up and column chromatography (Al$_2$O$_3$, Et$_2$O) *endo*-(1-tetralol)Cr(CO)$_3$ **49** as a yellow solid (1.37g, 36%), identified by comparison with an authentic sample.

Complexation of 1-methoxytetralin ***46***.

Thermolysis of $Cr(CO)_6$ (3.53g, 16.1mmol) with 1-methoxytetralin **46** (2.00g, 12.4mmol) under standard conditions (55ml solvent, 48h) gave after work up and column chromatography (Al_2O_3, Et_2O), a 91:9 mixture of *endo*- and *exo*-(1-methoxy-tetralin)$Cr(CO)_3$ **50** and **51** as a yellow solid (2.71g, 74%). ^1H n.m.r. (300MHz) **50**: δ5.71-5.69, 5.06-5.03 (2d, 2H, Ar*H*), 5.42-5.38, 5.14-5.10 (2t, 2H, Ar*H*), 4.10-4.06 [m, 1H, ArC*H*(OCH_3)R], 3.53 (s, 3H, ROC*H*$_3$), **51**: δ5.67-5.65, 5.21-5.20 (2d, 2H, Ar*H*), 5.40-5.36 (m, 1H, Ar*H*), 5.28-5.24 (t, 1H, Ar*H*), 4.18-4.15 [m, 1H, ArC*H*(OCH_3)R], 3.47 (s, 3H, ROC*H*$_3$), **50** and **51**: δ2.80-2.53 (m, 4H, ArC*H*$_2$R), 2.14-1.56 (m, 8H, $ArCH_2CH_2CH_2R$).

endo-(1-Methoxytetralin)Cr(CO)$_3$ ***50***.

A solution of *endo*-(1-tetralol)$Cr(CO)_3$ **49** (500mg, 1.76mmol) in THF (8ml) was added dropwise to a stirred suspension of KH (207mg, 5.18mmol) in THF (10ml). Stirring was continued (30min) followed by the addition of MeI (1.00g, 7.05mmol). After further stirring (1h), MeOH (1ml) was added and the solvent evaporated. Column chromatography (Al_2O_3, Et_2O) gave after recrystallisation from CH_2Cl_2:light petroleum, *endo*-(1-methoxytetralin)$Cr(CO)_3$ **50** as yellow needles (429mg, 82%). M.p. 122-124°C; Found: C 56.66, H 4.81%; $C_{14}H_{14}CrO_4$ requires: C 56.38, H 4.73%; *m/z* 298 (*M*+); ν_{max} 2818 (-OCH_3), 1954, 1875br (-CO), 1084 (C-O-C) cm^{-1}; ^1H n.m.r. (300MHz) δ5.71-5.69, 5.05-5.03 (2d, 2H, Ar*H*), 5.42-5.38, 5.14-5.10 (2t, 2H, Ar*H*), 4.10-4.06 [m, 1H, ArC*H*(OCH_3)R], 3.53 (s, 3H, ROC*H*$_3$), 2.80-2.69, 2.62-2.53 (2m, 2H, ArC*H*$_2$R), 2.12-1.94 [m, 2H, ArCH(OCH_3)C*H*$_2$R], 1.76-1.59 (m, 2H, $ArCH_2CH_2R$).

O-t-Butyldimethylsilyl-1-tetralol ***47***.

A solution of 1-tetralol **45** (1.50g, 10.1mmol) and imidazole (830mg, 12.2mmol) in DMF (5ml) was added dropwise to a cooled (0°C) solution of chloro-*t*-butyldimethyl-silane (1.66g, 11.0mmol) in DMF (5ml) and the mixture stirred (24h, 20°C). Water (85ml) was added and the mixture extracted with Et_2O (3 x 85ml). The organic extracts were combined, dried ($MgSO_4$) and evaporated to leave a colourless oil. Distillation gave O-*t*-butyldimethylsilyl-1-tetralol **47** as a clear, colourless oil (2.44g, 92%). B.p. 96-100°C (0.1mmHg); *m/z* 262 (*M*+); ^1H n.m.r. (300MHz) δ7.44-7.40, 7.11-7.08 (2m, 2H, Ar*H*), 7.24-7.16 (m, 2H, Ar*H*), 4.85-4.81 [m, 1H, ArC*H*$(OR)R^1$], 2.86-2.72 (m, 2H,

ArCH_2R), 2.07-2.00 [m, 2H, ArCH(OR)CH_2R^1], 1.88-1.76 (m, 2H, ArCH$_2$CH_2R), 0.99 [s, 9H, RC(CH_3)$_3$], 0.21, 0.20 (2s, 6H, RCH_3).

Complexation of O-t-butyldimethylsilyl-1-tetralol.

Thermolysis of Cr(CO)$_6$ (2.01g, 9.14mmol) with O-*t*-butyldimethylsilyl-1-tetralol **47** (2.00g, 7.63mmol) under standard conditions (55ml solvent, 75h) gave after work up and column chromatography (Al$_2$O$_3$ Et$_2$O:light petroleum 1:1) a 55:45 mixture of *exo*- and *endo*-(O-*t*-butyldimethylsilyl-1-tetralol)Cr(CO)$_3$ **52** and **53** (3.04g, 100%). *m/z* 398 (*M*$^+$); ^{1}H n.m.r. (300MHz) **52**: δ5.62-5.60, 5.18-5.16 (2d, 2H, Ar*H*), 5.37-5.32, 5.29-5.24 (2t, 2H, Ar*H*), 4.66-4.62 [m, 1H ArC*H*(OR)R^1], 2.78-2.53 (m, 2H, ArCH_2R), 2.05-1.90 (m, 4H, ArCH$_2$CH_2CH_2R), 0.93 [s, 9H, RC(CH_3)$_3$], 0.18, 0.17 (2s, 6H, RCH_3); **53**: δ5.66-5.64, 5.07-5.05 (2d, 2H, Ar*H*), 5.39-5.35, 5.15-5.11 (2t, 2H, Ar*H*), 4.59-4.54 [m, 1H, ArC*H*(OR)R^1], 2.84-2.72, 2.62-2.53 (2m, 2H, ArCH_2R), 2.05-1.91, 1.79-1.62 (2m, 4H, ArCH$_2$CH_2CH_2R), 0.99 [s, 9H, RC(CH_3)$_3$], 0.19, 0.17 (2s, 6H, RCH_3).

*Desilylation of exo- and endo-(O-t-butyldimethylsilyl-1-tetralol)Cr(CO)$_3$ **52** and **53** mixture.*

Tetra-*n*-butylammonium fluoride trihydrate (1.39g, 4.40mmol) was added to a 55:45 mixture of complexes **52** and **53** (1.75g, 4.39mmol) in THF (15ml) and the solution stirred (8h). Water was added (40ml) and the aqueous mixture extracted with Et$_2$O (3 x 40ml). The organic extracts were combined and evaporated to a yellow solid. Column chromatography (Al$_2$O$_3$, CH$_2$Cl$_2$) gave three fractions. Fraction one was evaporated to a yellow solid identified by ^{1}H n.m.r. spectroscopy as a 5:1 mixture of starting complexes **53** and **52** (665mg, 38%). Recrystallisation from CH$_2$Cl$_2$:light petroleum gave yellow needles of *endo*-(O-*t*-butyldimethylsilyl-1-tetralol)Cr(CO)$_3$ **53**. M.p. 132-134°C; Found: C 57.44, H, 6.72%; C$_{19}$H$_{26}$CrO$_4$Si requires: C 57.27, H 6.58%; *m/z* 398 (*M*$^+$); ν_{max} 1968, 1875br (-CO), 1600 (arene ring) cm^{-1}; ^{1}H n.m.r. (C$_6$D$_6$, 300MHz) δ5.44-5.42, 4.27-4.25 (2d, 2H, Ar*H*), 4.62-4.58, 4.39-4.35 (2t, 2H, Ar*H*), 4.12-4.07 [m, 1H, ArC*H*(OR)R^1], 2.47-2.35, 1.91-1.82 (2m, 2H, ArCH_2R), 1.63-1.52, 1.49-1.36 (2m, 4H, ArCH$_2$CH_2CH_2R), 1.05 [s, 9H, RC(CH_3)$_3$], 0.06, 0.05 (2s, 6H, RCH_3). Fraction two was evaporated to a yellow solid identified as *endo*-(1-tetralol)Cr(CO)$_3$ **49** by comparison with an authentic sample (162mg, 13%). Fraction three was evaporated to give *exo*-(1-tetralol)Cr(CO)$_3$ **54** as a yellow oil (486mg, 39%). *m/z* Found: 284.0241 (*M*$^+$); C$_{13}$H$_{12}$CrO$_4$ requires: 284.0241 (*M*$^+$); ν_{max} 3596, 3450br (-OH), 1961, 1882br (-CO) cm^{-1}; ^{1}H n.m.r. (C$_6$D$_6$, 300MHz) δ5.11-5.08, 4.29-4.27 (2d,

2H, Ar*H*), 4.47-4.43, 4.41-4.37 (2d of t, 2H, Ar*H*), 4.14 [q, 1H, J = 5.98Hz, ArC*H*(OH)R], 2.13, 1.92 (ABX$_2$ system, 2H, J_{AB} = 16.78Hz, J_{AX} = 6.10Hz, J_{BX} = 6.57Hz, ArCH_2R), 1.62-1.51, 1.42-1.21, 1.15-1.04 (3m, 4H, ArCH$_2$CH_2CH_2R), 1.08 (d, 1H, J = 6.15Hz, RO*H*).

Complexation of cryptopine ***55***.

Thermolysis of Cr(CO)$_6$ (1.43g, 6.50mmol) with cryptopine **55** (2.00g, 5.42mmol) under standard conditions (44ml solvent, 34h) followed by work up gave a yellow solid. Column chromatography (Al$_2$O$_3$, Grade II) gave two yellow fractions. Fraction one (CH_2Cl_2) was evaporated to give, after recrystallisation from CH_2Cl_2:light petroleum, (cryptopine)*bis*Cr(CO)$_3$ **67** as a yellow powder (104mg, 3%). M.p. decomposes >183^{o}C; Found: C 49.93, H 3.54, N 2.03%; $C_{27}H_{23}Cr_2NO_{11}$ requires: C 50.56, H 3.61, N 2.18%; *m/z* 642 (*M*$^+$+1); ν_{max} 1965, 1882br (-CO), 1666 (C=O) cm^{-1}; ^{1}H n.m.r. (300MHz) δ6.01, 5.85 (2s, 2H, -OCH_2O-), 5.67, 4.94 (2s, 2H, *H1*, *H4*), 5.52, 4.99 (AB system, 2H, J_{AB} = 6.37Hz, *H11*, *H12*), 3.90, 3.34 (AB system, 2H, J_{AB} = 13.55Hz, *H8* or *H13*), 3.84, 2.98 (AB system, 2H, J_{AB} = 16.42Hz, *H8* or *H13*), 3.88, 3.81 (2s, 6H, ArOCH_3), 3.32-3.24, 3.06-3.00, 2.53-2.47, 2.37-2.29 (4m, 4H, *H5*, *H6*), 1.95 (s, 3H, RR^{1}NCH_3). Fraction two (MeOH:CH_2Cl_2 1:1) was evaporated to give (cryptopine)Cr(CO)$_3$ as a mixture of regioisomers **65** and **66** (74:26, 1.18g, 43%). Recystallisation from CH_2Cl_2:light petroleum gave complex **65** as a yellow powder. *m/z* 506 (*M*$^+$+1); ν_{max} 1959, 1879br (-CO), 1660 (C=O) cm^{-1}; ^{1}H n.m.r. (300MHz) δ6.75, 6.72 (AB system, 2H, J_{AB} = 7.83Hz, *H11*, *H12*), 5.96, 5.94 (AB system, 2H, J_{AB} = 1.39Hz, -OCH_2O-), 5.73, 4.97 (2s, 2H, *H1*, *H4*), 3.98-3.89, 3.71-3.65, 3.48-3.38, 3.01-2.96, 2.40-2.35 (5m, 6H, *H5*, *H6*, *H8*), 3.87 (s, 3H, ArOCH_3), 3.79 (s, 3H, ArOCH_3), 2.99, 2.47 (AB system, 2H, J_{AB} = 13.99Hz, *H13*), 1.83 (s, 3H, RR^{1}NCH_3).

Dihydrocryptopine ***58***.

To a THF (100ml) suspension of cryptopine **55** (5.00g, 13.6mmol) was added $LiAlH_4$ (1.03g, 27.1mmol) suspended in THF (100ml). The mixture was stirred (45h), cooled (0^{o}C) and MeOH (10ml) added slowly. Filtration through celite and evaporation of the solvent gave a viscous gum. Water (150ml) was added and the mixture extracted with CH_2Cl_2 (3 x 75ml). The organic extracts were combined, dried ($MgSO_4$) and evaporated to give dihydrocryptopine **58** as a white powder (5.02g, 100%). M.p. 192-193^{o}C; Found: C 68.00, H 6.94, N 3.70%; $C_{21}H_{25}NO_5$ requires: C 67.91, H 6.78,

N 3.77%; *m/z* 372 (M^++1); ν_{max} 3588sh (-OH), 2828 (-OCH_3), 2780 (-NCH_3), 1602 (arene ring) cm^{-1}; ^1H n.m.r. (300MHz) δ7.12, 6.64 (2s, 2H, *H1*, *H4*), 6.73, 6.66 (AB system, 2H, J_{AB} = 7.87Hz, *H11*, *H12*), 5.94, 5.92 (AB system, 2H, J_{AB} = 1.44Hz, -OC*H*$_2$O-), 5.32 (d, 1H, J = 7.46Hz, *H14*), 4.02, 3.46 (AB system, 2H, J_{AB} = 14.90Hz, *H8*), 3.94, 3.89 (2s, 6H, ArOC*H*$_3$), 3.07-2.99, 2.89-2.86, 2.84-2.50 (3m, 6H, *H5*, *H6*, *H13*), 2.14 (s, 3H, RR^{1}NC*H*$_3$); ^{13}C n.m.r. δ147.81, 147.53, 146.56, 145.46, 137.88, 133.45, 130.38, 119.29 (8s, Ar*C*), 123.57, 113.79, 109.91, 108.51 (4d, Ar*C*), 100.54 (t, -O*C*H$_2$O-), 71.17 (d, *C14*), 59.69, 52.33, 46.63, 32.93 (4t, -*C*H$_2$-), 55.91 (q, ArO*C*H$_3$), 42.40 (q, RR^{1}N*C*H$_3$).

exo-(Dihydrocryptopine)Cr(CO)$_3$ ***68***.

Thermolysis of $Cr(CO)_6$ (1.42g, 6.45mmol) with dihydrocryptopine **58** (2.00g, 5.39mmol) under standard conditions (110ml solvent, 39h) followed by work up gave a yellow powder. Column chromatography (Al_2O_3, CH_2Cl_2) gave *exo*-(dihydrocryptopine)Cr(CO)3 **68** as a yellow powder (2.24g, 82%). M.p. decomposes >175°C; Found: C 56.74, H 4.90, N 2.64%; $C_{24}H_{25}CrNO_8$ requires: C 56.81, H 4.97, N 2.76%; *m/z* 507 (M^+); ν_{max} 3590sh (-OH), 2836 (-OCH_3), 2784 (-NCH_3), 1954, 1870br (-CO) cm^{-1}; ^1H n.m.r. (500MHz) δ6.68, 6.65 (AB system, 2H, J_{AB} = 7.9Hz, *H11*, *H12*), 5.93, 5.92 (AB system, 2H, J_{AB} = 1.0Hz, -OC*H*$_2$O-), 5.76 (s, 1H, *H1*), 5.10 (s, 1H, *H4*), 4.88 (d, 1H, J = 6.5Hz, *H14*), 3.91, 3.47 (AB system, 2H, J_{AB} = 14.9Hz, *H8*), 3.86, 3.86 (2s, 6H, ArOC*H*$_3$), 3.58-3.56, 2.90-2.81, 2.77-2.72, 2.62-2.57, 2.28-2.25 (5m, 6H, *H5*, *H6*, *H13*), 2.16 (s, 3H, RR^{1}NC*H*$_3$), 1.61 (s, br, 1H, RO*H*). Recrystallisation from CH_2Cl_2:light petroleum gave small yellow blocks. For X-ray crystal structure data see Appendix I.

O-Methyldihydrocryptopine ***70***.

A solution of dihydrocryptopine **58** (9.60g, 25.9mmol) in THF (200ml) was added dropwise to a stirred suspension of KH (2.41g, 60.3mmol) in THF (200ml). The solution was stirred and heated at reflux (20h). After cooling (0°C), MeI (4.78g, 33.7mmol) was added and the solution stirred (20°C, 1.5h). MeOH (5ml) was added cautiously and the solution filtered through celite and evaporated to a pale brown oil. Water (120ml) was added and the aqueous mixture extracted with CH_2Cl_2 (3 x 100ml). The organic extracts were combined, dried ($MgSO_4$) and evaporated to give a white powder. Recrystallisation from CH_2Cl_2:light petroleum gave O-methyldihydrocryptopine **70** as a white powder (8.46g, 85%). M.p. 158-160°C; Found: C 68.38, H 7.26, N 3.47%; $C_{22}H_{27}NO_5$ requires:

C 68.55, H 7.06, N 3.63%; *m/z* 386 (M^++1); ν_{max} 2828, 2818 (-OCH_3), 2781 (-NCH_3), 1601 (arene ring), 1091 (C-O-C) cm^{-1}; ^1H n.m.r. (300MHz) δ7.01, 6.65 (2s, 2H, *H1*, *H4*), 6.70, 6.63 (AB system, 2H, J_{AB} = 7.87Hz, *H11*, *H12*), 5.94, 5.91 (AB system, 2H, J_{AB} = 1.36Hz, -O*C*H_2O-), 4.82 (d, 1H, J = 7.13Hz, *H14*), 4.07, 3.45 (AB system, 2H, J_{AB} = 14.89Hz, *H8*), 3.92, 3.89 (2s, 6H, ArO*C*H_3), 3.45-3.41, 2.83-2.80, 2.79-2.74, 2.61-2.44 (4m, 6H, *H5*, *H6*, *H13*), 3.10 (s, 3H, RO*C*H_3), 2.10 (s, 3H, RR^{1}N*C*H_3); ^{13}C n.m.r. δ148.01, 147.57, 146.50, 145.26, 135.59, 133.59, 131.90, 119.10 (8s, Ar*C*), 124.02, 113.38, 108.14, 106.19 (4d, Ar*C*), 100.48 (t, -O*C*H_2O-), 80.12 (d, *C14*), 59.67, 52.11, 45.29, 32.51 (4t, -*C*H_2-), 56.74, 55.94, 55.86 (3q, RO*C*H3), 42.54 (q, RR^{1}N*C*H3).

exo-(O-Methyldihydrocryptopine)Cr(CO)3 ***69***.

Method 1. A solution of *exo*-(dihydrocryptopine)Cr(CO)3 **68** (500mg, 0.99mmol) in THF (15ml) was added dropwise to a stirred suspension of KH (103mg , 2.58mmol) in THF (15ml) to give an orange solution. Stirring was continued (2h) followed by addition of MeI (356mg, 2.51mmol). After further stirring (3.5h), MeOH (2ml) was added and the solution filtered through celite. Evaporation of the solvent, column chromatography (Al_2O_3, CH_2Cl_2) and recrystallisation of the product from CH_2Cl_2:light petroleum gave *exo*-(O-methyldihydrocryptopine)Cr(CO)3 **69** as a yellow powder (445mg, 86%). M.p. decomposes >194°C; Found: C 57.35, H 4.97, N 2.67%; $C_{25}H_{27}CrNO_8$ requires: C 57.58, H 5.22, N 2.69%; *m/z* 522 (M^++1); ν_{max} 2837 (-OCH_3), 2785 (-NCH_3), 1958, 1870br (-CO) cm^{-1}; ^1H n.m.r. (500MHz) δ6.67, 6.63 (AB system, 2H, J_{AB} = 7.45Hz *H11*, *H12*), 5.94, 5.91 (2s, 2H, -O*C*H_2O-), 5.73 (s, 1H, *H1*), 4.98 (s, 1H, *H4*), 4.31 (d, 1H, J = 5.74Hz, *H14*), 3.91, 3.46 (AB system, 2H, J_{AB} = 14.81Hz, *H8*), 3.86, 3.84 (2s, 6H, ArO*C*H_3), 3.41 (s, 3H, RO*C*H_3), 3.46-3.38, 2.90-2.83, 2.79-2.75, 2.62-2.57, 2.27-2.24 (5m, 6H, *H5*, *H6*, *H13*), 2.15 (s, 3H, RR^{1}N*C*H_3).

Method 2. Thermolysis of $Cr(CO)_6$ (1.00g, 4.55mmol) with O-methyldihydrocryptopine **70** (1.00g, 2.60mmol) under standard conditions (55ml solvent, 23h) gave after work up and column chromatography (SiO_2, CH_2Cl_2) *exo*-(O-methyldihydrocryptopine)Cr(CO)3 **69** as a yellow powder (1.00g, 74%), identified by comparison with an authentic sample.

exo-(1,O-Dimethyldihydrocryptopine)Cr(CO)3 ***71***.

n-BuLi (1.6M, 0.53ml, 0.85mmol) was added to a cooled (-78°C) THF (10ml) solution of *exo*-(O-methyldihydrocryptopine)Cr(CO)3 **69** (400mg, 0.77mmol) and the mixture stirred (10min). After warming (-40°C) and further stirring (2h), MeI (584mg,

4.11mmol) was added and stirring continued (-40°C, 2h). The solution was allowed to warm slowly (20°C) and MeOH (1ml) added. Evaporation and column chromatography (Al_2O_3, CH_2Cl_2) gave *exo*-(1,O-dimethyldihydrocryptopine)$Cr(CO)_3$ **71** as a yellow powder (402mg, 98%). M.p. decomposes >210°C; Found: C 58.40, H 5.45, N 2.11%; $C_{26}H_{29}CrNO_8$ requires: C 58.32, H 5.46, N 2.62%; *m/z* 535 (*M*+); ν_{max} 2839 (-OCH_3), 2792 (-NCH_3), 1950, 1870br (-CO) cm^{-1}; ^1H n.m.r. (300MHz) δ6.65, 6.63 (AB system, 2H, J_{AB} = 8.65Hz, *H11*, *H12*), 5.95, 5.92 (AB system, 2H, J_{AB} = 1.16Hz, -O*CH*$_2$O-), 4.73 (s, 1H, *H4*), 4.49 (m, br, 1H, *H14*), 3.98, 3.52 (AB system, 2H, J_{AB} = 15.23Hz, *H8*), 3.85, 3.44 (2s, 6H, ArO*CH*$_3$), 3.43-3.37, 2.64-2.56, 2.28-2.23 (3m, 3H, *H5*, *H6* or *H13*), 3.37 (s, 3H, RO*CH*$_3$), 3.16-2.87 (m, 3H, *H5*, *H6* or *H13*), 2.57 (s, 3H, Ar*CH*$_3$), 2.15 (s, 3H, RR^{1}N*CH*$_3$). Recrystallisation from CH_2Cl_2:light petroleum gave tiny yellow crystals.

exo-(O-Methyl-1-dimethylaminomethyldihydrocryptopine)Cr(CO)$_3$ **72**.

n-BuLi (1.6M, 0.66ml, 1.06mmol) was added to a cooled (-78°C) THF (12ml) solution of *exo*-(O-methyldihydrocryptopine)$Cr(CO)_3$ **69** (500mg, 0.96mmol) and the mixture stirred (10min). After warming (-40°C) and further stirring (2h), $CH_2N^+Me_2$ I^- (Eschenmoser's salt, 303mg, 1.64mmol) was added and stirring continued (-40°C, 2h). After warming slowly (20°C), MeOH (1ml) was added. Evaporation, column chromatography (SiO_2, CH_2Cl_2) and recrystallisation from MeOH:CH_2Cl_2, gave the title compound **72** as yellow plates (495mg, 89%). M.p. decomposes >140°C; Found: C 58.04, H 5.91, N 4.51%; $C_{28}H_{34}CrN_2O_8$ requires: C 58.13, H 5.92, N 4.84%; *m/z* 579 (*M*++1); ν_{max} 2834, 2817 (-OCH_3), 2774, 2760 (-NCH_3), 1951, 1868br (-CO) cm^{-1}; ^1H n.m.r. (300MHz) δ6.69, 6.63 (AB system, 2H, J_{AB} = 7.85Hz, *H11*, *H12*), 5.95, 5.91 (AB system, 2H, J_{AB} = 1.29Hz, -O*CH*$_2$O-), 4.84 (s, 1H, *H4*), 4.45 (d, 1H, J = 8.78Hz, *H14*), 4.38, 3.14 (AB system, 2H, J_{AB} = 11.91Hz, Ar*CH*$_2$NR$_2$), 4.01, 3.49 (AB system, 2H, J_{AB} = 15.22Hz, *H8*), 3.89-3.80, 3.36-3.31, 3.21-3.10, 2.96-2.91, 2.72-2.64, 2.30-2.18 (6m, 6H, *H5*, *H6*, *H13*), 3.87, 3.83 (2s, 6H, ArO*CH*$_3$), 3.31 (s, 3H, RO*CH*$_3$), 2.36, [s, 6H, RN(*CH*$_3$)$_2$], 2.16 (s, 3H, RR^{1}N*CH*$_3$).

1,O-Dimethyldihydrocryptopine ***73***.

exo-(1,O-Dimethyldihydrocryptopine)$Cr(CO)_3$ **71** (250mg, 0.47mmol) was suspended in Et_2O (100ml) and CH_2Cl_2 added until the solid just dissolved. Decomplexation in air and sunlight (96h) gave on work up and recrystallisation from CH_2Cl_2:light petroleum, 1,O-dimethyldihydrocryptopine **73** as fine white needles

(140mg, 75%). M.p. 168-170°C; Found: C 69.21, H 7.40, N 3.30%; $C_{23}H_{29}NO_5$ requires: C 69.15, H 7.32, N 3.51%; *m/z* 399 (*M*+); ν_{max} 2838 (-OCH_3), 2784 (-NCH_3), 1268 (C-O-C) cm^{-1}; ^1H n.m.r. (300MHz) δ6.71, 6.62 (AB system, 2H, J_{AB} = 7.88Hz, *H11*, *H12*), 6.55 (s, 1H, *H4*), 5.05 (d, 1H, J = 7.99Hz, *H14*), 4.11, 3.48 (AB system, 2H, J_{AB} = 15.14Hz, *H8*), 3.86, 3.80 (2s, 6H, ArOCH_3), 3.53-3.48, 2.84-2.78 (2m, 2H, *H5*, *H6* or *H13*), 3.26-3.10, 2.56-2.43 (2m, 4H, *H5*, *H6* or *H13*), 3.09 (s, 3H, ROCH_3), 2.53 (s, 3H, ArCH_3), 2.09 (s, 3H, RR^1NCH_3); ^{13}C n.m.r. δ151.13, 146.63, 146.53, 145.31, 136.93, 133.46, 132.67, 131.14, 118.76 (9s, Ar*C*), 124.43, 111.80, 106.23 (3d, Ar*C*), 100.52 (t, -OCH_2O-), 80.92 (d, *C14*), 59.96, 56.47, 55.54 (3q, ArOCH_3, ROCH_3), 59.96, 52.14, 42.74, 33.78 (4t, -CH_2-), 43.18 (q, RR^1NCH_3), 12.31 (q, ArCH_3).

O-Methyl-1-dimethylaminomethyldihydrocryptopine ***74***.

exo-(O-Methyl-1-dimethylaminomethyldihydrocryptopine)$Cr(CO)_3$ **72** (238mg, 0.41mmol) was dissolved in a 1:1 mixture of Et_2O:CH_2Cl_2 (100ml). Decomplexation in air and sunlight (96h) gave on work up and recrystallisation from CH_2Cl_2:light petroleum, the title compound **74** as white blocks (120mg, 66%). M.p. 100-103°C; *m/z* 442 (*M*+); ν_{max} 2834, 2810 (-OCH_3), 2781, 2761 (-NCH_3), 1589 (arene ring) cm^{-1}; ^1H n.m.r. (300MHz) δ6.71, 6.62 (AB system, 2H, J_{AB} = 7.87Hz, *H11*, *H12*), 6.65 (s, 1H, *H4*), 5.94, 5.91 (2s, 2H, -OCH_2O-), 5.08 (d, 1H, J = 7.33Hz, *H14*), 4.07-4.02, 3.49-3.43, 2.86-2.82 (3m, 3H, *H5*, *H6*, *H8*, *H13* or ArCH_2NR_2), 3.87, 3.86 (2s, 6H, ArOCH_3), 3.65-3.60, 2.65-2.47 (2m, 4H, *H5*, *H6*, *H8*, *H13* or ArCH_2NR_2), 3.28-3.18 (m, 3H, *H5*, *H6*, *H8*, *H13* or ArCH_2NR_2), 3.09 (s, 3H, ROCH_3), 2.11 [s, 6H, RN(CH_3)2], 2.02 (s, 3H, RR^1NCH_3).

(1R,2R)-N,O-Dimethylpseudoephedrine ***91***.[59]

Formaldehyde solution (37% aqueous solution, 250ml) followed by formic acid (250ml) were added dropwise to (1*R*,2*R*)-pseudoephedrine **79** (41.2g, 250mmol) and the mixture heated at reflux (18h). The solution was cooled, concentrated and basified with aqueous KOH (2N). Extraction of the aqueous mixture with Et_2O (3 x 200ml) gave on removal of the solvent and distillation under reduced pressure (1*R*,2*R*)-N-methylpseudo-ephedrine **90** as a low melting point solid (43.1g, 96%), identical in every respect to an authentic sample. B.p. 81°C (0.1mmHg); ν_{max} (neat) 3350br (-OH), 2788 (-NCH_3), 1605 (arene ring), 751, 702 (monosubstituted arene) cm^{-1}; ^1H n.m.r. (300MHz) δ7.39-7.27 (m, 5H, Ar*H*), 5.06 [s, br, 1H, ArCH(O*H*)R], 4.21 [d, 1H, J = 9.73Hz, ArC*H*(OH)R], 2.58 [d of q, 1H, J_d = 9.72Hz, J_q = 6.73Hz, $R^1CH(CH_3)NR_2$], 2.31 [s, 6H, RN(CH_3)2],

0.73 [d, 3H, J = 6.70Hz, $R^1CH(CH_3)NR_2$]. (1*R*,2*R*)-N-Methylpseudoephedrine **90** (4.00g, 22.3mmol) in THF (100ml) was added slowly to a stirred suspension of KH (1.36g, 34.0mmol) in THF (100ml). The mixture was heated at reflux (3.5h), cooled (20°C) and MeI (3.81g, 26.8mmol) added with stirring (1h). Addition of MeOH (4ml) followed by filtration and evaporation left a brown oily residue. Flash chromatography (SiO_2, 39:10:1 toluene:EtOH:c.NH_3) gave two fractions. Fraction one was evaporated and distilled to give *E*-α-methoxy-β-methylstyrene **92** as a clear, colourless oil (231mg, 7%), identified by comparison with an authentic sample. B.p. 45-48°C (0.1mmHg); ^1H n.m.r. (300MHz) δ7.47-7.24 (m, 5H, Ar*H*), 5.40 [q, 1H, J = 6.90Hz, 1H, $ArC(OCH_3)=CHCH_3$], 3.56 (s, 3H, $ROCH_3$), 1.82 [d, 3H, J = 6.88Hz, $ArC(OCH_3)=CHCH_3$]; n.O.e. irradiation of δ3.56 ($ROCH_3$) gave enhancements of δ7.47-7.24 (Ar*H*, 5.20%) and δ5.40 [$ArC(OCH_3)=CHCH_3$, 4.83%]. Fraction two was evaporated and distilled to give (1*R*,2*R*)-N,O-dimethylpseudoephedrine **91** as a clear, colourless oil (3.27g, 76%), identified by comparison with an authentic sample. B.p. 49-53°C (0.1mmHg); Found: C 74.25, H 10.27, N 7.80%; $C_{12}H_{19}NO$ requires: C 74.57, H 9.91, N 7.25%; *m/z* 194 (M^++1); ν_{max} (liquid film) 2808 ($-OCH_3$), 2783 ($-NCH_3$), 1599 (arene ring), 1094 (C-O-C), 749, 699 (monosubstituted arene) cm^{-1}; $[\alpha]_D^{21}$ = -98° (c 4.62 MeOH); ^1H n.m.r. (300MHz) δ7.36-7.27 (m, 5H, Ar*H*), 3.99 [d, 1H, J = 9.11Hz, $ArCH(OCH_3)R$], 3.15 (s, 3H, $ROCH_3$), 2.92 [m, 1H, $R^1CH(CH_3)NR_2$], 2.36 [s, 6H, $RN(CH_3)_2$], 0.61 [d, 3H, J = 6.81Hz, $R^1CH(CH_3)NR_2$].

(1S,2R)-(N,O-Dimethylpseudoephedrine)Cr(CO)3 ***89***.[59]

Thermolysis of $Cr(CO)_6$ (2.05g, 9.33mmol) with (1*R*,2*R*)-N,O-dimethylpseudoephedrine **91** (1.50g, 7.77mmol) under standard conditions (60ml solvent, 24h) gave after work up, column chromatography (Al_2O_3, Et_2O) and recrystallisation from CH_2Cl_2:light petroleum, the title compound **89** as yellow cubic crystals (2.11g, 83%), identified by comparison with an authentic sample. M.p. 73-74°C; Found: C 54.63, H 5.98, N 4.52%; $C_{15}H_{19}CrNO_4$ requires: C 54.71, H 5.82, N 4.25%; *m/z* 329 (M^+); ν_{max} 2810 ($-OCH_3$), 2778 ($-NCH_3$), 1967, 1883br (-CO), 1086 (C-O-C) cm^{-1}; $[\alpha]_D^{22}$ = -81° (c 0.98 $CHCl_3$); ^1H n.m.r. (300MHz) δ5.63-5.23 (m, 5H, Ar*H*), 3.91 [d, 1H, J = 4.67Hz, $ArCH(OCH_3)R$], 3.58 (s, 3H, $ROCH_3$), 2.64 [m, 1H, $R^1CH(CH_3)NR_2$], 2.27 [s, 6H, $RN(CH_3)_2$], 0.91 [d, 3H, J = 6.83Hz, $R^1CH(CH_3)NR_2$].

General procedure for alkylation of (arene)Cr(CO)$_3$ complexes.

BuLi or LDA was added dropwise to a cooled (-78°C) THF solution of the complex and the mixture stirred (-78°C, 2h). The alkyl halide was added and stirring continued (-78°C, 2h). Sufficient MeOH was slowly added to quench and the mixture warmed (20°C) and evaporated to give a residue containing the crude alkylated complex.

*(R,1S,2R)-(N,O,o-Trimethylpseudoephedrine)Cr(CO)$_3$ **93**.*

(1*S*,2*R*)-(N,O-Dimethylpseudoephedrine)Cr(CO)3 **89** (339mg, 1.03mmol) in THF (15ml) was treated with *n*-BuLi (1.6M, 1.35ml, 2.16mmol) and MeI (616mg, 4.34mmol) under standard conditions. Work up and column chromatography (Al_2O_3, Et_2O) gave on recrystallisation from CH_2Cl_2:light petroleum, the title compound **93** as yellow needles (318mg, 90%). M.p. 74-75°C; Found: C 55.73, H 6.29, N 3.71%; $C_{16}H_{21}CrNO_4$ requires: C 55.97, H 6.17, N 4.08%; *m/z* 344 (*M*+1); ν_{max} 2816 (-OCH_3), 2778 (-NCH_3), 1961, 1880br (-CO), 1600 (arene ring), 1089 (C-O-C) cm^{-1}; $[\alpha]_D^{22}$ = -60° (c 0.70 $CHCl_3$); ^{1}H n.m.r. (300MHz) δ5.57-5.53, 5.04-4.98 (2m, 4H, Ar*H*), 3.66 [d, 1H, J = 7.85Hz, ArC*H*(OCH_3)R], 3.51 (s, 3H, ROC*H*$_3$), 3.01-2.92 [m, 1H, R^{1}C*H*(CH_3)NR_2], 2.35 [s, 6H, RN(C*H*$_3$)$_2$], 2.33 (s, 3H, ArC*H*$_3$), 0.91 [d, 3H, J = 6.77Hz, R^{1}CH(C*H*$_3$)NR_2]. For X-ray crystal structure data see Appendix II.

*Methylation of (R,1S,2S)-(N,O,o-trimethylephedrine)Cr(CO)$_3$ **88** under standard conditions.*

(*R*,1*S*,2*S*)-(N,O,*o*-Trimethylephedrine)Cr(CO)3 **88** (prepared according to the literature route,[59] 300mg, 0.88mmol) in THF (12ml) was treated with *t*-BuLi (4.28M, 0.21ml, 0.90mmol) and MeI (310mg, 2.18mmol) under standard conditions. Work up and column chromatography gave a mixture of (*R*,1*S*,2*S*)-(N,O-dimethyl-*o*-ethyl-ephedrine)Cr(CO)3 **94** and two unassigned ring methylated isomers in ratio 45:35:20 (309mg, 98%). ^{1}H n.m.r. (500MHz) **94**: δ5.56-5.55, 4.92-4.91 (2d, 2H, Ar*H*), 5.08-5.05, 5.05-5.02 (2t, 2H, Ar*H*), 3.84 [d, 1H, J = 4.5Hz, ArC*H*(OCH_3)R], 3.35 (s, 3H, ROC*H*$_3$), 2.87-2.72, 2.46-2.39 [2m, 3H, ArC*H*$_2$$CH_3$, R^{1}C*H*($CH_3$)$NR_2$], 2.28 [s, 6H, RN(C*H*$_3$)$_2$], 1.25 (t, 3H, J = 7.4Hz, $ArCH_2$C*H*$_3$), 1.10 [d, 3H, J = 6.5Hz, R^{1}CH(C*H*$_3$)NR_2]; (300MHz) major ring methylated isomer: δ3.30 (s, 3H, ROC*H*$_3$), 2.28, 2.21 (2s, 6H, ArC*H*$_3$), 2.27 [s, 6H, RN(C*H*$_3$)$_2$], 1.13 [d, 3H, J = 6.63Hz, R^{1}CH(C*H*$_3$)NR_2]; (300MHz) minor ring methylated isomer: δ3.39 (s, 3H, ROC*H*$_3$), 2.27 [s, 6H, RN(C*H*$_3$)$_2$], 2.23, 2.13 (2s, 6H, ArC*H*$_3$). Repeating the reaction with *n*-BuLi gave identical results.

*(1S,2R)-(N,O,o,o-Tetramethylpseudoephedrine)Cr(CO)$_3$ **95**.*

(*R*,1*S*,2*R*)-(N,O,*o*-Trimethylpseudoephedrine)Cr(CO)3 **93** (222mg, 0.65mmol) in THF (8ml) was treated with *t*-BuLi (4.28M, 0.15ml, 0.65mmol) and MeI (230mg, 1.62mmol) under standard conditions. Work up and column chromatography (Al_2O_3, Et_2O) gave on recrystallisation from CH_2Cl_2:light petroleum the title compound **95** as yellow needles (183mg, 79%). M.p. 134-136°C; Found: C 57.08, H 6.59, N 3.79%; $C_{17}H_{23}CrNO_4$ requires: C 57.14, H 6.49, N 3.92%; *m/z* 357 (M^+); ν_{max} 2820 (-OCH_3), 2776 (-NCH_3), 1960, 1880br (-CO), 1602 (arene ring), 1092 (C-O-C) cm^{-1}; $[\alpha]_D^{21}$ = +18° (c 1.01 $CHCl_3$); ^{1}H n.m.r. (300MHz) δ5.58-5.54 (t, 1H, Ar*H*), 4.89-4.87, 4.86-4.84 (2d, 2H, Ar*H*), 4.08 [d, 1H, J = 8.99Hz, ArC*H*(OCH_3)R], 3.62 (s, 3H, ROC*H*$_3$), 3.18-3.12 [m, 1H, R^{1}C*H*(CH_3)NR_2], 2.42, 2.28 (2s, 6H, ArC*H*$_3$), 2.41 [s, 6H, RN(C*H*$_3$)2], 0.77 [d, 3H, J = 6.54Hz, R^{1}CH(C*H*$_3$)NR_2].

General procedure for decomplexation of (arene)Cr(CO)$_3$ complexes.

A Et_2O solution of the complex was stood in air and sunlight until a colourless solution with a green or brown precipitate resulted. Filtration through celite followed by removal of the solvent by distillation or evaporation, gave the crude arene.

*(1R,2R)-N,O,o,o-Tetramethylpseudoephedrine **100**.*

(1*S*,2*R*)-(N,O,*o*,*o*-Tetramethylpseudoephedrine)Cr(CO)3 **95** (71mg, 0.20mmol) was dissolved in Et_2O (25ml) and allowed to decomplex under standard conditions (72h). Work up gave the title compound **100** as a clear, colourless oil (42mg, 95%). ^{1}H n.m.r. ($CDCl_3$, 300MHz) δ7.14-7.09 (t, 1H, Ar*H*), 7.04-6.99 (m, 2H, Ar*H*), 4.82 [d, 1H, J = 9.18Hz, ArC*H*(OCH_3)R], 3.78-3.63 [m, 1H, R^{1}C*H*(CH_3)NR_2], 3.16 (s, 3H, ROC*H*$_3$), 2.77 [s, 6H, RN(C*H*$_3$)2], 2.47, 2.39 (2s, 6H, ArC*H*$_3$), 0.99 [d, 3H, J = 6.48Hz, R^{1}CH(C*H*$_3$)NR_2]; (C_6D_6, 300MHz) δ6.98-6.93 (t, 1H, Ar*H*), 6.89-6.81 (m, 2H, Ar*H*), 4.74-4.67 [d, 1H, J = 6.9Hz, ArC*H*(OCH_3)R], 3.60-3.49 [m, 1H, R^{1}C*H*(CH_3)NR_2], 2.90 (s, 3H, ROC*H*$_3$), 2.56 [s, 6H, RN(C*H*$_3$)2], 2.41, 2.22 (2s, 6H, ArC*H*$_3$), 0.88 [d, 3H, J = 6.9Hz, R^{1}CH(C*H*$_3$)NR_2].

*Hydrocotarnine **125**.*

Trifluoroacetic acid (2.83g, 54.8mmol) was added to a suspension of cotarnine hydrochloride **124** (7.50g, 27.4mmol) in CH_2Cl_2 (250ml) to give a clear yellow solution. Sodium cyanoborohydride (5.17g, 82.1mmol) was added and a vigorous effervescence ensued. After stirring (1.5h), 15% NaOH solution (100ml) was added and the organic layer separated. The aqueous layer was washed with CH_2Cl_2 (100ml) and the organic extracts combined, dried ($MgSO_4$) and evaporated to a pale orange oil. Distillation gave the title compound **125** as a clear, colourless oil (4.88g, 81%). B.p. 132-136°C (0.1mmHg); *m/z* 221 (*M*+); ^{1}H n.m.r. δ6.34 (s, 1H, Ar*H*), 5.88, 5.88 (2s, 2H, -OC*H*$_2$O-), 4.00 (s, 3H, ROC*H*$_3$), 3.46 (s, 2H, ArC*H*$_2$NRR^1), 2.85-2.79, 2.64-2.59 (2m, 4H, ArC*H*$_2$C*H*$_2$NRR^1), 2.48 (s, 3H, RR^{1}NC*H*$_3$).

*(Hydrocotarnine)Cr(CO)$_3$ **123**.*

Thermolysis of $Cr(CO)_6$ (156mg, 0.71mmol) with hydrocotarnine **125** (132mg, 0.60ml) under standard conditions (110ml solvent, 24h) followed by work up and column chromatography (Al_2O_3, Et_2O:light petroleum 1:1) gave a yellow solid. Recrystallisation from CH_2Cl_2:light petroleum gave the title compound **123** as large yellow needles (145mg, 68%). M.p. decomposes >141-145°C; Found: C 50.23, H 4.14, N 3.61%; $C_{15}H_{15}CrNO_6$ requires: C 50.43, H 4.23, N 3.92%; *m/z* 357 (*M*+); ν_{max} 2784 (-NCH_3), 1955, 1868br (-CO), 1086, 1030 (C-O-C) cm^{-1}; ^{1}H n.m.r. δ5.97, 5.81 (2s, 2H, -OC*H*$_2$O-), 5.04 (s, 1H, Ar*H*), 4.11 (s, 3H, ArOC*H*$_3$), 3.73, 3.15 (AB system, 2H, J_{AB} = 15.63Hz, ArC*H*$_2$NRR^1), 3.01-2.48 (m, 4H, ArC*H*$_2$C*H*$_2$NRR^1), 2.44 (s, 3H, RR^{1}NC*H*$_3$).

*1-Methylhydrocotarnine **128**.*

MeMgI (4M in Et_2O, 45.8ml, 183mmol) was added to a cooled (-40°C) THF (40ml) solution of cotarnine hydrochloride **124** (10.0g, 36.6mmol) and the mixture stirred (-40°C, 1h then 20°C, 12h). Water (20ml) was added cautiously and the solution filtered through celite and concentrated. A further quantity of water (150ml) was added and the aqueous mixture extracted with CH_2Cl_2 (3 x 150ml). The pink organic extracts were combined, dried ($MgSO_4$) and evaporated to give a pink solid.

Method 1. Recrystallisation from MeOH:Et_2O gave purple granular crystals of the phenethanol derivative **130** (6.98g, 75%). *m/z* 236 (*M*+-17); ν_{max} 3420 (-OH, -NH), 2764 (-NCH_3), 1620 (arene ring), 1040 (C-O-C) cm^{-1}; ^{1}H n.m.r. δ6.35 (s, 1H, Ar*H*),

5.92 (s, 2H, -OCH_2O-), 4.53 [q, 1H, J = 6.69Hz, ArCH(OH)CH_3], 4.05 (s, 3H, ArOCH_3), 3.57-2.95 (m, 4H, ArCH_2CH_2NRR^1), 2.83 (s, 3H, RR^{1}NCH_3), 1.72 [d, 3H, J = 6.32Hz, ArCH(OH)CH_3]. Compound **130** (1.75g, 6.92mmol) was dissolved in CH_2Cl_2 (50ml) and c.HCl (20 drops) added. The solution was stirred (6h) and 10% NaOH solution (5ml) added. The red organic layer was separated, dried ($MgSO_4$) and evaporated to a red oil. Distillation under reduced pressure gave the title compound **128** as a clear, colourless viscous oil (800mg, 49%). *m/z* 236 (*M*+1); ^{1}H n.m.r. δ6.32 (s, 1H, Ar*H*), 5.88, 5.87 (AB system, 2H, J_{AB} = 1.41Hz, -OCH_2O-), 4.01 (s, 3H, ArOCH_3), 3.93 [q, 1H, J = 6.57Hz, ArCH(CH_3)NRR^1], 3.12-2.51 (m, 4H, ArCH_2CH_2NRR^1), 2.47 (s, 3H, RR^{1}NCH_3), 1.25 [d, 3H, J = 6.45Hz, ArCH(CH_3)NRR^1].

Method 2. Column chromatography (SiO_2, toluene:EtOH:c.NH_3 39:10:1) of the crude solid (925mg, 3.66mmol) gave a pale pink oil. Distillation under reduced pressure gave the title compound **128** as a clear, colourless viscous oil (244mg, 28%), identified by comparison with an authentic sample.

exo-(1-Methylhydrocotarnine)Cr(CO)$_3$ ***129***.

Thermolysis of $Cr(CO)_6$ (516mg, 2.35mmol) with 1-methylhydrocotarnine **128** (500mg, 2.13mmol) under standard conditions (66ml solvent, 16h) followed by work up and column chromatography (Al_2O_3, Et_2O) gave a single compound as a yellow solid. Recrystallisation from CH_2Cl_2:light petroleum gave the title complex **129** as a yellow powder (186mg, 24%). M.p. decomposes >156°C; Found: C 51.85, H 4.58, N 3.52%; $C_{16}H_{17}CrNO_6$ requires: C 51.76, H 4.61, N 3.77%; *m/z* 371 (*M*+); ν_{max} 1954, 1868br (-CO), 1033 (C-O-C) cm^{-1}; ^{1}H n.m.r. (C_6D_6) δ5.00, 4.79 (2s, 2H, -OCH_2O-), 4.00 (s, 1H, Ar*H*), 3.62 (s, 3H, ArOCH_3), 3.57 [q, 1H, J = 6.35Hz, ArCH(CH_3)NRR^1], 2.96-2.80, 1.95-1.85 (2m, 2H, ArCH_2CH_2NRR^1), 2.42-2.13 (m, 2H, ArCH_2CH_2NRR^1), 1.99 (s, 3H, RR^{1}NCH_3), 1.32 [d, 3H, J = 6.32Hz, ArCH(CH_3)NRR^1].

Methylation of (hydrocotarnine)Cr(CO)$_3$ ***123***.

Method 1 with LDA. (Hydrocotarnine)Cr(CO)$_3$ **123** (92mg, 0.26mmol) in THF (5ml) was treated with LDA (0.28mmol) in THF (5ml) and MeI (109mg, 0.77mmol) under standard conditions. Work up and column chromatography (Al_2O_3, Et_2O) gave a single compound as a yellow solid. Recrystallisation from CH_2Cl_2:light petroleum gave (5-methylhydrocotarnine)Cr(CO)$_3$ **134** as yellow needles (62mg, 64%). M.p. decomposes >140°C; Found : C 51.74, H 4.74, N 3.87%; $C_{16}H_{17}CrNO_6$ requires: C 51.76, H 4.61,

N 3.77%; *m/z* 371 (M^+); ν_{max} 1955, 1868br (-CO), 1129, 1038 (C-O-C) cm^{-1}; ^1H n.m.r. δ5.99, 5.87 (2s, 2H, -OCH_2O-), 4.05 (s, 3H, ArOCH_3), 3.70, 3.24 (AB system, 2H, J_{AB} = 15.44Hz, ArCH_2NRR^1), 2.86-2.73 (m, 3H, ArCH_2CH_2NRR^1), 2.59-2.51 (m, 1H, ArCH_2CH_2NRR^1), 2.45 (s, 3H, RR^{1}NCH_3), 2.14 (s, 3H, ArCH_3).

Method 2 with *n*-BuLi. (Hydrocotarnine)Cr(CO)3 **123** (276mg, 0.77mmol) in THF (6ml) was treated with *n*-BuLi (1.65M, 0.52ml, 0.86mmol) and MeI (362mg, 2.55mmol) under standard conditions. Work up and column chromatography (Al_2O_3, Et_2O:light petroleum 1:1) gave two fractions, both as yellow solids. Fraction one was identified as *exo*-(4-methylhydrocotarnine)Cr(CO)3 **133** (43mg, 15%). M.p. decomposes >120°C; *m/z* Found: 371.0456 (M^+); $C_{16}H_{17}CrNO_6$ requires: 371.0461 (M^+); ν_{max} 1960, 1872br (-CO), 1091 (C-O-C) cm^{-1}; ^1H n.m.r. δ5.89, 5.74 (2s, 2H, -OCH_2O-), 5.08 (s, 1H, Ar*H*), 4.11 (s, 3H, ArOCH_3), 3.66, 3.12 (AB system, 2H, J_{AB} = 15.62Hz, ArCH_2NRR^1), 2.86-2.74 [m, 1H, ArC*H*(CH3)R], 2.69-2.58, 2.50-2.42 [2m, 2H, ArCH(CH3)CH_2NRR^1], 2.41 (s, 3H, RR^{1}NCH_3), 1.36 [d, 3H, J = 7.15Hz, ArCH(CH_3)R]. Fraction two was identified as complex **134** (161mg, 56%) by comparison with an authentic sample.

Method 3 with *t*-BuLi. (Hydrocotarnine)Cr(CO)3 **123** (113mg, 0.32mmol) in THF (8ml) was treated with *t*-BuLi (2.6M, 0.13ml, 0.34mmol) and MeI (135mg, 0.95mmol) under standard conditions. Work up and column chromatography (Al_2O_3, Et_2O:light petroleum 1:1) gave two fractions both as yellow solids. Fraction one was identified as complex **133** (49mg, 42%) and fraction two as complex **134** (35mg, 30%), both by comparison with authentic samples.

exo-(1,5-Dimethylhydrocotarnine)Cr(CO)3 ***135***.

exo-(1-Methylhydrocotarnine)Cr(CO)3 **129** (23mg, 62μmol) in THF (4ml) was treated with *n*-BuLi (1.65M, 43μl, 71μmol) and MeI (27mg, 0.19mmol) under standard conditions. Work up and column chromatography (Al_2O_3, Et_2O) gave a single compound as a yellow solid. Recrystallisation from CH_2Cl_2:light petroleum gave the title compound **135** as a yellow powder (19mg, 80%). M.p. decomposes >147-149°C; *m/z* Found: 385.0618 (M^+); $C_{17}H_{19}CrNO_6$ requires: 385.0617 (M^+); ν_{max} 1954, 1868br (-CO) cm^{-1}; ^1H n.m.r. δ5.97, 5.77 (2s, 2H, -OCH_2O-), 4.12 (s, 3H, ArOCH_3), 3.82 [q, 1H, J = 5.95Hz, ArC*H*(CH3)NRR^1], 3.12-3.06, 2.62-2.51 (2m, 2H, ArCH_2CH_2R), 2.84-2.75 (m, 2H, ArCH_2CH_2R), 2.45 (s, 3H, RR^{1}NCH_3), 2.09 (s, 3H, ArCH_3), 1.34 [d, 3H, J = 5.63Hz, ArCH(CH_3)NRR^1].

exo-(4,5-Dimethylhydrocotarnine)Cr(CO)$_3$ ***136***.

Method 1. *exo*-(4-Methylhydrocotarnine)Cr(CO)3 **133** (59mg, 0.16mmol) in THF (8ml) was treated with *n*-BuLi (1.65M, 0.11ml, 0.18mmol) and MeI (68mg, 0.48mmol) under standard conditions. Work up and column chromatography (Al_2O_3, Et_2O:light petroleum 2:1) gave a single compound as a yellow solid. Recrystallisation from CH_2Cl_2:hexane gave the title compound **136** as yellow blocks (43mg, 70%). M.p. decomposes >130°C; Found: C 53.14, H 5.07, N 3.53%; $C_{17}H_{19}CrNO_6$ requires: C 52.99, H 4.97, N 3.63%; *m/z* 385 (*M*+); ν_{max} 1950, 1863br (-CO) cm^{-1}; ^1H n.m.r. δ5.99, 5.89 (2s, 2H, -OC*H*$_2$O-), 4.06 (s, 3H, ArOC*H*$_3$), 3.87, 3.08 (AB system, 2H, J_{AB} = 15.67Hz, ArC*H*$_2$NRR^1), 2.92-2.86 [m, 1H, ArC*H*(CH$_3$)R], 2.69-2.54 [m, 2H, ArCH(CH$_3$)C*H*$_2$NRR^1], 2.42 (s, 3H, RR^{1}NC*H*$_3$), 2.21 (s, 3H, ArC*H*$_3$), 1.37 [d, 3H, J = 6.69Hz, ArCH(C*H*$_3$)R].

Method 2. (5-Methylhydrocotarnine)Cr(CO)3 **134** (52mg, 0.14mmol) in THF (6ml) was treated with *t*-BuLi (2.6M, 59μl, 0.15mmol) under standard conditions. Work up and column chromatography (Al_2O_3, Et_2O:light petroleum 1:1) gave the title compound **136** as a yellow solid (45mg, 83%), identified by comparison with an authentic sample.

1,5-Dimethylhydrocotarnine ***137***.

exo-(1,5-Dimethylhydrocotarnine)Cr(CO)3 **135** (4mg, 10μmol) was dissolved in Et_2O (10ml) and allowed to decomplex under standard conditions (48h). Work up gave the title compound **137** as a clear, colourless oil. *m/z* 250 (*M*++1); ^1H n.m.r. δ5.89, 5.87 (2s, 2H, -OC*H*$_2$O-), 3.97 [q, 1H, J = 6.48Hz, ArC*H*(CH$_3$)R], 3.97 (s, 3H, ArOC*H*$_3$), 3.14-3.00, 2.51-2.39 (2m, 2H, ArC*H*$_2$C*H*$_2$R), 2.84-2.62 (m, 2H, ArC*H*$_2$C*H*$_2$R), 2.47 (s, 3H, RR^{1}NC*H*$_3$), 2.05 (s, 3H, ArC*H*$_3$), 1.26 [d, 3H, J = 6.57Hz, ArCH(C*H*$_3$)R].

4,5-Dimethylhydrocotarnine ***138***.

exo-(4,5-Dimethylhydrocotarnine)Cr(CO)3 **136** (14mg, 36μmol) was dissolved in Et_2O (25ml) and allowed to decomplex under standard conditions (24h). Work up gave the title compound **138** as a clear, colourless oil (6mg, 67%). *m/z* 250 (*M*++1); ^1H n.m.r. δ5.89 (s, 2H, -OC*H*$_2$O-), 3.97 (s, 3H, ArOC*H*$_3$), 3.95, 2.94 (AB system, 2H, J_{AB} = 14.93Hz, ArC*H*$_2$NRR^1), 2.90-2.86 [m, 1H, ArC*H*(CH$_3$)R], 2.72-2.65, 2.41-2.33 [2m, 2H, ArCH(CH$_3$)C*H*$_2$NRR^1], 2.45 (s, 3H, RR^{1}NC*H*$_3$), 1.30 [d, 3H, J = 6.91Hz, ArCH(C*H*$_3$)R].

(o-Anisaldehyde)Cr(CO)$_3$ ***149***.

Thermolysis of $Cr(CO)_6$ (3.88g, 17.6mmol) with *o*-anisaldehyde **158** (2.00g, 14.7mmol) under standard conditions (55ml solvent, 5h) followed by work up and column chromatography (Al_2O_3, Et_2O), gave (*o*-anisaldehyde)$Cr(CO)_3$ **149** as a red solid (164mg, 4%), spectroscopically identical with the literature.[3] ^1H n.m.r. ($CDCl_3$, 300MHz) δ10.05 (s, 1H, ArC*H*O), 6.25-6.23, 5.07-5.05 (2d, 2H, Ar*H*), 5.87-5.82, 5.02-4.98 (2t, 2H, Ar*H*), 3.87 (s, 3H, ArOC*H*$_3$); (C_6D_6, 300MHz) δ9.90 (s, 1H, ArC*H*O), 5.91-5.88, 3.75-3.73 (2d, 2H, Ar*H*), 4.73-4.61, 3.92-3.88 (2t, 2H, Ar*H*), 2.79 (s, 3H, ArOC*H*$_3$).

2-(o-Anisyl)-1,3-dioxolane ***159***.[3]

A mixture of *o*-anisaldehyde **158** (30.0g, 221mmol) and ethane-1,2-diol (15.0g, 242mmol) in benzene (250ml), containing a catalytic quantity of *p*-TsOH.H_2O (1.39g, 7.32mmol), was heated at reflux in a Dean-Stark trap until water ceased to be evolved (4h). Evaporation of the solvent followed by distillation of the crude oil gave 2-(*o*-anisyl)-1,3-dioxolane **159** as a clear, colourless oil (29.0g, 73%). B.p. 118-122°C (0.1mmHg); ^1H n.m.r. (300MHz) δ7.46-7.43, 6.80-6.77 (2d, 2H, Ar*H*), 7.24-7.19, 6.90-6.77 (2t, 2H, Ar*H*), 6.07 [s, 1H, ArC*H*(OR)$_2$], 4.03-3.98, 3.91-3.87 (2m, 4H, -OC*H*$_2$C*H*$_2$O-), 3.73 (s, 3H, ArOC*H*$_3$).

[2-(o-Anisyl)-1,3-dioxolane]Cr(CO)$_3$ ***160***.[3]

Thermolysis of $Cr(CO)_6$ (5.75g, 26.1mmol) with 2-(*o*-anisyl)-1,3-dioxolane **159** (3.92g, 21.8mmol) under standard conditions (110ml solvent, 40h) followed by work up and column chromatography (Al_2O_3, Et_2O), gave a yellow solid. Recrystallisation from CH_2Cl_2:light petroleum gave the title compound **160** as yellow blocks (3.86g, 56%). *m/z* 316 (*M*+); ^1H n.m.r. (300MHz) δ5.95-5.92, 5.04-5.02 (2d, 2H, Ar*H*), 5.92 [s, 1H, ArC*H*(OR)$_2$], 5.59-5.55, 4.90-4.86 (2t, 2H, Ar*H*), 4.20-4.03 (m, 4H, -OC*H*$_2$C*H*$_2$O-), 3.80 (s, 3H, ArOC*H*$_3$).

Hydrolysis of [2-(o-anisyl)-1,3-dioxolane]Cr(CO)$_3$ ***160***.[3]

[2-(*o*-Anisyl)-1,3-dioxolane]$Cr(CO)_3$ **160** (2.00g, 6.33mmol) was dissolved in a 1:1 mixture of THF:water (30ml) and *p*-TsOH.H_2O (241mg, 1.27mmol) added. The solution

was stirred (4.5h) and slowly turned red. The mixture was concentrated and extracted with Et_2O (2 x 30ml). The organic extracts were combined, dried ($MgSO_4$) and evaporated to a red solid. Recrystallisation from CH_2Cl_2:light petroleum gave (*o*-anisaldehyde)$Cr(CO)_3$ **149** as large red needles (1.57g, 91%), identified by comparison with an authentic sample.

*2-(o-Tolyl)-1,3-dioxolane **162**.*[3]

A mixture of *o*-tolualdehyde **161** (5.00g, 41.7mmol) and ethane-1,2-diol (2.84g, 45.8mmol) in benzene (250ml), containing a catalytic quantity of *p*-TsOH.H_2O (792mg, 4.17mmol), was heated at reflux in a Dean-Stark trap until water ceased to be evolved (24h). Evaporation of the solvent followed by distillation of the crude oil gave 2-(*o*-tolyl)-1,3-dioxolane **162** as a clear, colourless oil (5.60g, 82%). B.p. 80-83°C (0.1mmHg); ^{1}H n.m.r. (300MHz) δ7.58-7.56 (d, 1H, Ar*H*), 7.31-7.19 (m, 3H, Ar*H*), 6.00 [s, 1H, ArC*H*$(OR)_2$], 4.19-4.14, 4.08-4.02 (2m, 4H, -OCH_2CH_2O-), 2.46 (s, 3H, ArCH_3).

*[2-(o-Tolyl)-1,3-dioxolane]Cr(CO)$_3$ **163**.*[3]

Thermolysis of $Cr(CO)_6$ (4.03g, 18.3mmol) with 2-(*o*-tolyl)-1,3-dioxolane **162** (2.00g, 12.2mmol) under standard conditions (88ml solvent, 24h) followed by work up and column chromatography (Al_2O_3, Et_2O), gave a yellow solid. Recrystallisation from CH_2Cl_2:light petroleum gave the title compound **163** as yellow needles (2.46g, 67%). ^{1}H n.m.r. (300MHz) δ5.83-5.81, 5.11-5.09 (2d, 2H, Ar*H*), 5.72 [s, 1H, ArC*H*$(OR)_2$], 5.45-5.40, 5.17-5.13 (2t, 2H, Ar*H*), 4.19-4.01 (m, 4H, -OCH_2CH_2O-), 2.29 (s, 3H, ArCH_3).

*(o-Tolualdehyde)Cr(CO)$_3$ **83**.*[3]

[2-(*o*-Tolyl)-1,3-dioxolane]$Cr(CO)_3$ **163** (550mg, 1.83mmol) was dissolved in a 3:1 mixture of THF:water (20ml) and *p*-TsOH.H_2O (70mg, 0.37mmol) added. The solution was stirred (60h) and slowly turned red. The mixture was concentrated and extracted with Et_2O (2 x 30ml). The organic extracts were combined, dried ($MgSO_4$) and evaporated to a red solid. Column chromatography (Al_2O_3, Et_2O) followed by recrystallisation from CH_2Cl_2:light petroleum gave the title compound **83** as large red blocks (421mg, 90%). *m/z* 256 (*M*$^+$); ν_{max} 1981, 1966, 1895br (-CO), 1684 (C=O) cm^{-1}; ^{1}H n.m.r. ($CDCl_3$, 300MHz) δ9.81 (s, 1H, ArC*H*O), 6.07-6.04, 5.05-5.03 (2d, 2H, Ar*H*), 5.75-5.70, 5.25-

5.21 (2t, 2H, Ar*H*), 2.54 (s, 3H, ArCH_3); (C_6D_6) δ9.10 (s, 1H, ArC*H*O), 5.32-5.28, 3.80-3.77 (2d, 2H, Ar*H*), 4.54-4.47, 4.03-3.97 (2t, 2H, Ar*H*), 1.70 (s, 3H, ArCH_3).

α,α-Dimethoxytoluene ***166***.[84]

Benzaldehyde **165** (35.0g, 330mmol) was added to trimethylorthoformate (37.5g, 354mmol) and the mixture stirred. On addition of c.H_2SO_4 (2 drops) the solution rapidly darkened. After stirring (24h), Na_2CO_3 (200mg) was added and the mixture distilled to give α,α-dimethoxytoluene **166** as a clear, colourless oil (42.2g, 84%), spectroscopically identical with a commercially available sample.[98] B.p. 90°C (13mmHg); ^{1}H n.m.r. (300MHz) δ7.50-7.34 (m, 5H, Ar*H*), 5.42 [s, 1H, ArC*H*$(OR)_2$], 3.35 (s, 6H, ROCH_3).

(α,α-Dimethoxytoluene)Cr(CO)$_3$ ***167***.

Thermolysis of $Cr(CO)_6$ (4.78g, 21.7mmol) with α,α-dimethoxytoluene **166** (3.00g, 19.7mmol) under standard conditions (110ml solvent, 72h) followed by work up and column chromatography (Al_2O_3, Et_2O:light petroleum 1:1), gave a yellow solid. Recrystallisation from CH_2Cl_2:light petroleum gave (α,α-dimethoxytoluene)$Cr(CO)_3$ **167** as yellow granules (4.89g, 86%). *m/z* 288 (*M*+); ν_{max} 2828 (-OCH_3), 1969, 1889br (-CO) cm^{-1}; ^{1}H n.m.r. (300MHz) δ5.54-5.52 (d, 2H, Ar*H*), 5.38-5.34 (t, 2H, Ar*H*), 5.31-5.29 (d, 1H, Ar*H*), 5.12 [s, 1H, ArC*H*$(OR)_2$], 3.39 [s, 6H, ROCH_3].

(α,α-Dimethoxy-o-trimethylsilyltoluene)Cr(CO)$_3$ ***168***.

(α,α-Dimethoxytoluene)$Cr(CO)_3$ **167** (2.50g, 8.68mmol) in THF (12ml) was treated with *n*-BuLi (1.65M, 5.79ml, 9.55mmol) and chlorotrimethylsilane (2.83g, 26.1mmol) under standard conditions. Work up and column chromatography (Al_2O_3, Et_2O:light petroleum 1:1) gave a red solid. Recrystallisation from CH_2Cl_2:light petroleum gave the title compound **168** as yellow needles (2.81g, 90%). M.p. 86-87°C; Found: C 49.95, H 5.82%; $C_{15}H_{20}CrO_5Si$ requires: C 49.99, H 5.56%; *m/z* 360 (*M*+); ν_{max} 2825 (-OCH_3), 1971, 1965, 1890br (-CO) cm^{-1}; ^{1}H n.m.r. ($CDCl_3$, 300MHz) δ5.61-5.59 (m, 2H, Ar*H*), 5.47-5.45 (d, 1H, Ar*H*), 5.32 [s, 1H, ArC*H*$(OR)_2$], 5.20-5.15 (m, 1H, Ar*H*), 3.53, 3.15 [2s, 6H, ROCH_3], 0.37 [s, 9H, ArSi(CH_3)$_3$]; (C_6D_6) δ5.30 [s, 1H, ArC*H*$(OR)_2$], 5.29-5.24, 4.93-4.89 (2d, 2H, Ar*H*), 4.77-4.70, 4.29-4.23 (2t, 2H, Ar*H*), 3.13, 2.72 (2s, 6H, ROCH_3), 0.24 [s, 9H, ArSi(CH_3)$_3$].

(o-Trimethylsilylbenzaldehyde)$Cr(CO)_3$ ***164***.

(α,α-Dimethoxy-*o*-trimethylsilyltoluene)$Cr(CO)_3$ **168** (3.80g, 10.6mmol) was dissolved in THF (50ml) and aqueous HCl (1N, 10ml) added. The solution was stirred (72h) and then concentrated. The aqueous residue was extracted with Et_2O (3 x 30ml) and the organic extracts combined, dried ($MgSO_4$) and evaporated to a red oil. Column chromatography (Al_2O_3, Et_2O:light petroleum 1:1) gave the title compound **164** as a low melting point red solid (3.34g, 100%). *m/z* 314 (*M*+); ν_{max} 1979, 1905br (-CO), 1705, 1688 (C=O) cm^{-1}; ^1H n.m.r. ($CDCl_3$, 300MHz) δ9.73 (s, 1H, ArC*H*O), 5.81-5.78, 5.44-5.42 (2d, 2H, Ar*H*), 5.59-5.54, 5.53-5.49 (2t, 2H, Ar*H*), 0.42 [s, 9H, ArSi(C*H*$_3$)$_3$]; (C_6D_6) δ9.09 (s, 1H, ArC*H*O), 4.79-4.73, 4.48-4.41 (2m, 4H, Ar*H*), 0.18 [s, 9H, ArSi(C*H*$_3$)$_3$].

2-Phenyl-1,3-dioxolane ***170***.

A mixture of benzaldehyde **165** (20.0g, 189mmol) and ethane-1,2-diol (12.0g, 193mmol) in benzene (250ml), containing a catalytic quantity of *p*-TsOH.H_2O (1.90g, 10.0mmol), was heated at reflux in a Dean-Stark trap until water ceased to be evolved (6h). Evaporation of the solvent followed by distillation of the crude oil gave 2-phenyl-1,3-dioxolane **170** as a clear, colourless oil (19.7g, 69%). ^1H n.m.r. δ7.55-7.39 (m, 5H, Ar*H*), 5.85 [s, 1H, ArC*H*(OR)$_2$], 4.21-4.02 (m, 4H, -OC*H*$_2$C*H*$_2$O-).

(2-Phenyl-1,3-dioxolane)$Cr(CO)_3$ ***171***.

Thermolysis of $Cr(CO)_6$ (7.33g, 33.3mmol) with 2-phenyl-1,3-dioxolane **170** (5.00g, 33.3mmol) under standard conditions (275ml solvent, 72h) followed by work up and column chromatography (SiO_2, Et_2O) gave a yellow solid. Recrystallisation from Et_2O:hexane gave the title compound **171** as yellow plates (4.51g, 47%). ^1H n.m.r. δ5.58-5.54, 5.37-5.29 [2m, 6H, Ar*H*, ArC*H*(OR)$_2$], 4.19-4.11, 4.09-4.01 (2m, 4H, -OC*H*$_2$C*H*$_2$O-).

[2-(o-Tri-i-propylsilylphenyl)-1,3-dioxolane]$Cr(CO)_3$ ***172***.

(2-Phenyl-1,3-dioxolane)$Cr(CO)_3$ **171** (1.00g, 3.50mmol) in THF (10ml) was treated with *n*-BuLi (2.5M, 1.47ml, 3.68mmol) and chlorotri-*i*-propylsilane (1.35g, 7.00mmol) under standard conditions. Work up and column chromatography (Al_2O_3, Et_2O:hexane

1:3) gave a single compound as a yellow solid. Recrystallisation from Et_2O:light petroleum gave the title compound **172** as yellow needles (703mg, 45%). ^1H n.m.r. δ5.72-5.66, 5.18-5.12 (2t, 2H, Ar*H*), 5.56 [s, 1H, ArC*H*$(OR)_2$], 5.54-5.51, 5.44-5.41 (2d, 2H, Ar*H*), 4.19-3.95 (m, 4H, -O*CH*$_2$*CH*$_2$O-), 1.50-1.32 [m, 3H, RC*H*$(CH_3)_2$], 1.23, 1.18 [2d, 18H, J_1 = 7.07Hz, J_2 = 7.07Hz, RCH(C*H*$_3)_2$].

(o-Tri-i-propylsilylbenzaldehyde)Cr(CO)$_3$ ***169***.

[2-(*o*-Tri-*i*-propylsilylphenyl)-1,3-dioxolane]$Cr(CO)_3$ **172** (1.40g, 3.17mmol) was dissolved in THF (25ml) and aqueous HCl (2.5N, 10ml) added. The solution was stirred (6 days) and then evaporated to a red oil. Column chromatography (SiO_2, Et_2O:hexane 1:3) followed by recrystallisation from hexane, gave the title compound **169** as red granules (1.20g, 95%). M.p. 64-66°C; Found: C 57.01, H 6.88%; $C_{19}H_{26}CrO_4Si$ requires: C 57.27, H 6.58%; *m/z* 398 (*M*+); ν_{max} 1980, 1910br (-CO), 1699 (C=O) cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ9.80 (s, 1H, ArC*H*O), 5.79-5.76, 5.57-5.54 (2d, 2H, Ar*H*), 5.71-5.65, 5.48-5.42 (2t, 2H, Ar*H*), 1.52-1.34 [m, 3H, RC*H*$(CH_3)_2$], 1.19, 1.17 [2d, 18H, J_1 = 7.07Hz, J_2 = 7.11Hz, RCH(C*H*$_3)_2$]; (C_6D_6) δ9.57 (s, 1H, ArC*H*O), 5.20-5.16, 4.96-4.92 (2d, 2H, Ar*H*), 4.60-4.54, 4.37-4.31 (2t, 2H, Ar*H*), 1.14-0.99 [m, 3H, RC*H*$(CH_3)_2$], 0.94, 0.93 [2d, 18H, J_1 = 6.41Hz, J_2 = 6.41Hz, RCH(C*H*$_3)_2$].

L-Valinol.

A suspension of L-valine (25.0g, 214mmol) in THF (250ml) was slowly added to a cooled (0°C), stirred suspension of $LiAlH_4$ (20.0g, 526mmol) in THF (250ml). The mixture was heated at reflux (17h), cooled (0°C) and water added dropwise to quench. 5% NaOH solution (40ml) was added and the mixture filtered through celite, washing with copious quantities of CH_2Cl_2. The filtrate was evaporated to a clear oil. Distillation gave L-valinol as a low melting point white solid (18.6g, 84%). ^1H n.m.r. (300MHz) δ3.53, 3.22 (ABX system, 2H, J_{AB} = 9.69Hz, J_{AX} = 7.62Hz, J_{BX} = 10.43Hz, RC*H*$_2$OH), 2.50-2.44 (m, br, 4H, RCH$_2$O*H*, RN*H*$_2$, RR^{1}C*H*NH$_2$), 1.50 [m, 1H, RC*H*$(CH_3)_2$], 0.83, 0.82 [2d, 6H, J_1 = 6.75Hz, J_2 = 6.79Hz, RCH(C*H*$_3)_2$].

Kinetic resolution of (o-anisaldehyde)Cr(CO)$_3$ ***149***.

L-Valinol (379mg, 3.68mmol) was added to a Et_2O (10ml) solution of

(*o*-anisaldehyde)$Cr(CO)_3$ **149** (1.00g, 3.68mmol) and the mixture stirred (4.5h), the initial red solution turning orange. Column chromatography (Al_2O_3) of the crude solution without evaporation of the solvent, gave two fractions. Fraction one (Et_2O) was evaporated to a red solid and fraction two (MeOH:CH_2Cl_2 1:10) to an orange oil. Both products were separately dissolved in THF (8ml). Water (2ml) was added followed by c.HCl (5 drops) and the darkened solutions stirred until they turned crimson (30min). Evaporation of the solvent followed by filtration of a Et_2O (10ml) solution through a plug of alumina gave both products as red solids. Fraction one was identified as (-)-(*o*-anisaldehyde)$Cr(CO)_3$ (-)-**149** (460mg, 46%) by comparison with an authentic racemic sample. $[\alpha]_D^{23}$ = -1015o (c 0.06 $CHCl_3$) Lit.[3] $[\alpha]_D$ = -1020o (c 0.09 $CHCl_3$). Fraction two was identified as (+)-(*o*-anisaldehyde)$Cr(CO)_3$ (+)-**149** (380mg, 38%), also by comparison with an authentic racemic sample. $[\alpha]_D^{23}$ = +1016o (c 0.06 $CHCl_3$) Lit.[3] $[\alpha]_D$ = +1015o (c 0.06 $CHCl_3$).

*L-Valinol derived imine of (+)-(o-anisaldehyde)$Cr(CO)_3$ (+)-**149**, complex **173**.*

(+)-(*o*-Anisaldehyde)$Cr(CO)_3$ (+)-**149** (250mg, 0.92mmol) was dissolved in Et_2O (12ml) and L-valinol (95mg, 0.92mmol) added. After stirring (4.5h) a portion of the solution was evaporated to give an orange oil. ^1H n.m.r. (C_6D_6) δ8.34 (s, 1H, Ar*CH*=NR), 6.34-6.31, 3.95-3.93 (2d, 2H, Ar*H*), 4.76-4.71, 4.11-4.06 (2t, 2H, Ar*H*), 3.67-3.61, 3.56-3.53 (2m, br, 2H, RCH_2OH), 2.92 (s, 3H, ArOCH_3), 2.78-2.72 (m, 1H, RR^1CHN=CHAr), 1.87-1.76 [m, 1H, RC*H*$(CH_3)_2$], 1.06 (s, br, RCH_2OH), 0.97, 0.86 [2d, 6H, J_1 = 6.80Hz, J_2 = 6.81Hz, RCH(CH_3)$_2$]. The remainder of the solution was evaporated to an orange solid and recrystallised from Et_2O:light petroleum to give the L-valinol derived imine of (+)-(*o*-anisaldehyde)$Cr(CO)_3$ (+)-**149**, complex **173** as orange blocks (295mg, 90%). M.p. 96-97oC; Found: C 54.10, H 5.58, N 3.92%; $C_{16}H_{19}CrNO_5$ requires: C 53.78, H 5.36, N 3.92%; *m/z* 325 (*M*$^+$-32); ν_{max} 1970, 1891br (-CO), 1633 (C=N), 1014 (C-O-C) cm^{-1}; $[\alpha]_D^{21}$ = +512o (c 0.204 $CHCl_3$). For X-ray crystal structure data see Appendix III. Treatment of a THF (5ml) solution of imine **173** (200mg, 0.56mmol) with water (2ml) and c.HCl (5 drops) with stirring (30min), gave, on evaporation of the solvent, followed by filtration of a Et_2O (10ml) solution through a plug of alumina, starting material (+)-**149** as a red solid (145mg, 95%), identified by comparison with an authentic sample. $[\alpha]_D^{21}$= +1017o (c 0.06 $CHCl_3$).

*L-Valinol derived imine of (-)-(o-anisaldehyde)Cr(CO)$_3$ (-)-**149**, complex **175**.*

(-)-(*o*-Anisaldehyde)Cr(CO)3 (-)-**149** (160mg, 0.59mmol) was dissolved in Et_2O (10ml) and L-valinol (61mg, 0.59mmol) added. Excess 4^0_A molecular sieves (10g) were added to the solution and the mixture gently stirred (17h). After filtration through celite, the solution was evaporated to give the L-valinol derived imine of (-)-(*o*-anisaldehyde)Cr(CO)3 (-)-**149**, complex **175** as an orange oil (190mg, 90%). *m/z* 358 (*M*+1); ν_{max} 1966, 1888br (-CO), 1631 (C=N), cm^{-1}; ^1H n.m.r. (C_6D_6) δ8.28 (s, 1H, ArC*H*=NR), 6.26-6.22, 4.06-4.02 (2d, 2H, Ar*H*), 4.75-4.69, 4.17-4.11 (2t, 2H, Ar*H*), 3.69-3.58 (m, 2H, RCH_2OH), 2.96 (s, 3H, ArOCH_3), 2.82-2.74 (m, 1H, RR^{1}C*H*N=CHAr), 1.87-1.72 [m, 1H, RC*H*(CH3)2], 0.80, 0.77 [2d, 6H, J_1 = 6.61Hz, J_2 = 6.57Hz, RCH(CH_3)2].

*Kinetic resolution of (o-anisaldehyde)Cr(CO)3 **149** via an L-valinol doped alumina column.*

A slurry of L-valinol (400mg, 3.88mmol), deactivated alumina (40g) and Et_2O (15ml) was evaporated to give a free-flowing white powder. A chromatography column was half packed with alumina (120g) in Et_2O and half the doped alumina (20g) added. After further packing with alumina (120g), the remaining doped alumina was added to the top of the column. A solution of (*o*-anisaldehyde)Cr(CO)3 **149** (500mg, 1.84mmol) in Et_2O (10ml) was adsorbed onto the top of the column and allowed to stand (10min). Elution with Et_2O gave fraction one as a red oil. The remaining two bands were eluted (MeOH:Et_2O 1:5) and evaporated to give fraction two as an orange oil. Both products were separately dissolved in THF (8ml). Water (2ml) was added followed by c.HCl (15 drops) and the darkened solutions stirred until they turned crimson (1h). Evaporation of the solvent followed by filtration of a Et_2O (10ml) solution through a plug of alumina gave both products as red solids. Fraction one was identified as (-)-(*o*-anisaldehyde)Cr(CO)3 (-)-**149** (212mg, 42%), by comparison with an authentic sample. $[\alpha]_D^{25}$ = -1006o (c 0.063 CHCl3). Fraction two was identified as (+)-(*o*-anisaldehyde)Cr(CO)3 (+)-**149** (171mg, 34%), also by comparison with an authentic sample. $[\alpha]_D^{24}$ = +1020o (c 0.06 CHCl3).

*Kinetic resolution of (o-tolualdehyde)Cr(CO)3 **83**.*

L-Valinol (109mg, 1.06mmol) was added to a Et_2O (10ml) solution of (*o*-tolualdehyde)Cr(CO)3 **83** (270mg, 1.05mmol) and the mixture stirred (4h). Column chromatography (Al_2O_3) of the crude solution without evaporation of the solvent, gave

two fractions. Fraction one (Et_2O) was evaporated to a red solid and fraction two (MeOH:CH_2Cl_2 1:10) to a red oil. Both products were separately dissolved in THF (10ml). Water (1ml) was added followed by c.HCl (10 drops) and the solutions stirred (fraction one, 15min; fraction two, 35min). Evaporation of the solvent followed by column chromatography (Al_2O_3, Et_2O) gave both products as red solids. Fraction one was identified as (-)-(*o*-tolualdehyde)$Cr(CO)_3$ (-)-**83** (90mg, 33%) by comparison with an authentic racemic sample. $[\alpha]_D^{22}$ = -542o (c 0.26 $CHCl_3$) Lit.[3] $[\alpha]_D$ = -664o (c 0.26 $CHCl_3$). Fraction two was identified as (+)-(*o*-tolualdehyde)$Cr(CO)_3$ (+)-**83** (105mg, 39%), also by comparison with an authentic racemic sample. $[\alpha]_D^{22}$ = +619o (c 0.22 $CHCl_3$) Lit.[3] $[\alpha]_D$ = +665o (c 0.22 $CHCl_3$).

Kinetic resolution of (o-trimethylsilylbenzaldehyde)Cr(CO)3 ***164****.*

L-Valinol (113mg, 1.10mmol) was added to a Et_2O (12ml) solution of (*o*-trimethylsilylbenzaldehyde)$Cr(CO)_3$ **164** (344mg, 1.10mmol) and the mixture stirred (4h). Column chromatography (Al_2O_3) of the crude solution without evaporation of the solvent, gave two fractions. Fraction one (Et_2O) was evaporated to a red oil and fraction two (MeOH:Et_2O 1:10) to an orange oil. Both products were separately dissolved in THF (8ml). Water (2ml) was added followed by c.HCl (10 drops) and the solutions stirred (fraction one, 30min; fraction two, 1h). Evaporation of the solvent followed by column chromatography (Al_2O_3, Et_2O) gave both products as red oils. Fraction one was identified as (-)-(*o*-trimethylsilylbenzaldehyde)$Cr(CO)_3$ (-)-**164** (164mg, 48%) by comparison with an authentic racemic sample. $[\alpha]_D^{21}$ = -107o (c 0.049 $CHCl_3$). Fraction two was identified as (+)-(*o*-trimethylsilylbenzaldehyde)$Cr(CO)_3$ (+)-**164** (128mg, 37%), also by comparison with an authentic racemic sample. $[\alpha]_D^{21}$ = +143o (c 0.049 $CHCl_3$).

Classical resolution of (o-trimethylsilylbenzaldehyde)Cr(CO)3 ***164****.*

L-Valinol (981mg, 9.52mmol) was added to a Et_2O (30ml) solution of (*o*-trimethylsilylbenzaldehyde)$Cr(CO)_3$ **164** (2.99g, 9.52mmol) containing excess 4^0_A molecular sieves (10g). The mixture was stirred (18h), filtered through celite and evaporated to an orange oil. Addition of hexane gave orange crystals. Column chromatography (SiO_2, Et_2O:Et_3N 10:1) gave two fractions. Fraction one was crystallised from hexane to give the L-valinol derived imine of (-)-(*o*-trimethylsilylbenzaldehyde)$Cr(CO)_3$ (-)-**164**, complex **177** as orange needles (870mg, 23%). M.p. 92-94oC; Found: C 53.93, H 6.29, N 3.29%; $C_{18}H_{25}CrNO_4Si$ requires: C 54.12, H 6.31, N 3.51%; *m/z* 399 (M^+);

ν_{max} 3588 (-OH), 1968, 1892br (-CO), 1632 (C=N) cm^{-1}; $[\alpha]_D^{19}$ = -601o (c 1.11 $CHCl_3$); ^1H n.m.r. δ8.24 (s, 1H, ArC*H*=NR), 6.10-6.07, 5.54-5.50 (2d, 2H, Ar*H*), 5.70-5.63, 5.31-5.25 (2t, 2H, Ar*H*), 3.81-3.75 (m, 2H, RCH_2OH), 3.03-2.94 (m, 1H, RR^{1}C*H*N=CHAr), 1.99-1.85 [m, 2H, RC*H*$(CH_3)_2$, RO*H*], 0.96, 0.88 [2d, 6H, J_1 = 6.78Hz, J_2 = 6.70Hz, RCH(CH_3)2], 0.44 [s, 9H, ArSi(CH_3)3]. Fraction two was crystallised from hexane to give the L-valinol derived imine of (+)-(*o*-trimethylsilylbenzaldehyde)Cr(CO)3 (+)-**164**, complex **178** as orange needles (1.40g, 37%). M.p. 96-97oC; Found: C 54.28, H 6.47, N 3.20%; $C_{18}H_{25}CrNO_4Si$ requires: C 54.12, H 6.31, N 3.51%; *m/z* 399 (*M*+); ν_{max} 1974, 1899br (-CO), 1640 (C=N) cm^{-1}; $[\alpha]_D^{19}$ = +455o (c 0.875 $CHCl_3$); ^1H n.m.r. δ8.22 (s, 1H, ArC*H*=NR), 5.98-5.95, 5.48-5.31 (2d, 2H, Ar*H*), 5.66-5.59, 5.31-5.24 (2t, 2H, Ar*H*), 3.83-3.78 (m, 2H, RCH_2OH), 3.05-2.97 (m, 1H, RR^{1}C*H*N=CHAr), 1.99-1.85 [m, 1H, RC*H*$(CH_3)_2$], 1.46 (t, 1H, J = 6.14Hz, RCH$_2$O*H*), 0.98, 0.94 [2d, 6H, J_1 = 7.69Hz, J_2 = 6.98Hz, RCH(CH_3)2], 0.43 [s, 9H, ArSi(CH_3)3].

Complex **177** (399mg, 1.00mmol) was dissolved in THF (5ml) containing water (1ml) and c.HCl (6 drops). After stirring (2h), evaporation of the solvent and column chromatography (SiO_2, Et_2O), the product was isolated as a red oil and identified as (-)-(*o*-trimethylsilylbenzaldehyde)Cr(CO)3 (-)-**164** (310mg, 99%), by comparison with an authentic sample. $[\alpha]_D^{18}$ = -154o (c 1.14 $CHCl_3$). Complex **178** (399mg, 1.00mmol) was dissolved in THF (5ml) containing water (1ml) and c.HCl (6 drops). After stirring (1.5h), evaporation of the solvent and column chromatography (SiO_2, Et_2O), the product was isolated as a red oil and identified as (+)-(*o*-trimethylsilylbenzaldehyde)Cr(CO)3 (+)-**164** (314mg, 100%) by comparison with an authentic sample. $[\alpha]_D^{20}$ = +146o (c 0.116 $CHCl_3$).

Resolution of (o-tri-i-propylsilylbenzaldehyde)Cr(CO)3 ***169***.

L-Valinol (142mg, 1.38mmol) was added to a Et_2O (10ml) solution of (*o*-tri-*i*-propylsilylbenzaldehyde)Cr(CO)3 **169** (550mg, 1.38mmol) containing excess 4^0_A molecular sieves (10g). The mixture was stirred (96h), filtered through celite and evaporated to an orange oil. Column chromatography (SiO_2, Et_2O:hexane:Et_3N 10:10:1) gave three fractions. Fraction one was evaporated to a red solid and identified as (-)-(*o*-tri-*i*-propylsilylbenzaldehyde)Cr(CO)3 (-)-**169** (77mg, 14%) by comparison with an authentic racemic sample. $[\alpha]_D^{19}$= -384o (c 0.824 $CHCl_3$). Fraction two was evaporated to give the L-valinol derived imine of (-)-(*o*-tri-*i*-propylsilylbenzaldehyde)Cr(CO)3 (-)-**169**, complex **179** as a red oil (253mg, 38%). ^1H n.m.r. (C_6D_6) δ8.17 (s, 1H, ArC*H*=NR), 5.84-5.80, 5.13-5.10 (2d, 2H, Ar*H*), 4.84-4.78, 4.34-4.28 (2t, 2H, Ar*H*), 3.66-3.54 (m, 2H, RCH_2OH), 2.95-2.87 (m, 1H, RR^{1}C*H*N=CHAr), 1.84-1.68 [m, 1H, RC*H*$(CH_3)_2$], 1.43-0.73 {m, 27H, RCH(CH_3)2, ArSi[C*H*(CH_3)2]3}. Fraction three was evaporated to give the L-valinol derived imine of (+)-(*o*-tri-*i*-propylsilylbenzaldehyde)Cr(CO)3 (+)-**169**,

complex **180** as a red oil (293mg, 44%). ^{1}H n.m.r. (C_6D_6) δ8.21 (s, 1H, ArC*H*=NR), 5.82-5.78, 5.11-5.08 (2d, 2H, Ar*H*), 4.86-4.80, 4.35-4.29 (2t, 2H, Ar*H*), 3.55-3.51 (m, 2H, RC*H*$_2$OH), 2.87-2.78 (m, 1H, RCH$_2$O*H*), 2.41-2.30 (m, 1H, RR^{1}C*H*N=CHAr), 1.82-1.72 [m, 1H, RC*H*(CH$_3$)$_2$], 1.39-0.78 {m, 27H, RCH(C*H*$_3$)$_2$, ArSi[C*H*(C*H*$_3$)$_2$]$_3$}.

Complex **179** (253mg, 0.52mmol) was dissolved in THF (5ml) containing water (2ml) and c.HCl (40 drops). After stirring (5h), evaporation of the solvent and column chromatography (Al$_2$O$_3$, Et$_2$O:hexane 1:1), the product was isolated as a red solid and identified as (-)-(*o*-tri-*i*-propylsilylbenzaldehyde)Cr(CO)$_3$ (-)-**169** (166mg, 80%), by comparison with an authentic racemic sample. $[\alpha]_D^{19}$ = -485o (c 0.095 CHCl3). Complex **180** (293mg, 0.61mmol) was dissolved in THF (5ml) containing water (1ml) and c.HCl (0.5ml). After stirring (15h), evaporation of the solvent and column chromatography (Al$_2$O$_3$, Et$_2$O:hexane 1:1), the product was isolated as a red solid and identified as (+)-(*o*-tri-*i*-propylsilylbenzaldehyde)Cr(CO)$_3$ (+)-**169** (170mg, 70%), by comparison with an authentic sample. $[\alpha]_D^{21}$ = +515o (c 0.14 CHCl3).

General procedure for addition of nucleophiles to substituted (benzaldehyde)Cr(CO)3 complexes.

A Et$_2$O or THF solution of the nucleophile was added dropwise to a cooled (-78^{o}C) THF solution of the complex and the mixture stirred (-78^{o}C, 1h). Sufficient MeOH was slowly added to quench and the mixture warmed (20^{o}C) and evaporated to gave a residue containing the crude product.

(o-Methoxy-1-phenethanol)Cr(CO)3 ***188.93***

Method 1. (+)-(*o*-Anisaldehyde)Cr(CO)$_3$ (+)-**149** (960mg, 3.53mmol) in THF (20ml) was treated with MeMgI (4.0M, 1.77ml, 7.08mmol) under standard conditions. Work up and column chromatography (Al$_2$O$_3$, Et$_2$O) gave (*SS*)-(*o*-methoxy-1-phenethanol)Cr(CO)$_3$ (-)-**188** as a yellow solid (1.01g, 99%). *m/z* 288 (*M*+); ν_{max} 3590 (-OH), 2860 (-OCH$_3$), 1960, 1878br (-CO), 1021 (C-O-C) cm^{-1}; ^{1}H n.m.r. (C_6D_6) δ5.55-5.52, 3.95-3.91 (2d, 2H, Ar*H*), 4.70 [d of q, 1H, J_d = 3.99Hz, J_q = 6.35Hz, ArC*H*(OH)CH3], 4.59-4.51, 4.08-4.02 (2t, 2H, Ar*H*), 2.83 (s, 3H, ArOC*H*$_3$), 1.49 [d, 1H, J = 3.81Hz, ArCH(O*H*)CH3], 1.15 [d, 3H, J = 6.37Hz, ArCH(OH)C*H*$_3$].

Method 2. (*o*-Anisaldehyde)Cr(CO)$_3$ **149** (500mg, 1.84mmol) in THF (10ml) was treated with MeLi (1.4M, 2.63ml, 3.68mmol) under standard conditions. Work up and column chromatography (Al$_2$O$_3$, Et$_2$O) gave a 94:6 mixture of (*RR*,*SS*)- and (*RS*,*SR*)-(*o*-

methoxy-1-phenethanol)$Cr(CO)_3$ complexes **188** and **189** respectively (530mg, 100%), the major product **188** being identified by comparison with an authentic sample. ^1H n.m.r. (C_6D_6) **189**: δ5.41-5.38, 4.25-4.22 (2d, 2H, Ar*H*), 4.50-4.45, 4.41-4.37 (2t, 2H, Ar*H*), 1.46 [s, 1H, ArCH(O*H*)CH_3], 0.94 [d, 3H, J = 6.40Hz, ArCH(OH)C*H*$_3$]. Recrystallisation of the mixture from CH_2Cl_2:light petroleum gave complex **188** as yellow needles.

(RR,SS)-(o-Methoxy-1-phenethyl methyl ether)$Cr(CO)_3$ ***190***.

(*RR,SS*)-(*o*-Methoxy-1-phenethanol)$Cr(CO)_3$ **188** (325mg, 1.13mmol) was dissolved in THF (3ml) and added to a suspension of KH (79mg, 19.97mmol) in THF (3ml) and the mixture stirred (10min). MeI (642mg, 4.52mmol) was added and the orange solution turned yellow. After further stirring (30min), MeOH (1ml) was added and the solvent evaporated to give a yellow solid. Column chromatography and recrystallisation from CH_2Cl_2:light petroleum gave the title complex **190** as yellow cubic crystals (315mg, 92%), identified by comparison with an authentic sample (*vide infra*). ^1H n.m.r. (300MHz) δ5.87-5.84, 5.04-5.01 (2d, 2H, Ar*H*), 5.51-5.46, 4.97-4.93 (2t, 2H, ArH), 4.41 [q, 1H, J = 6.40Hz, ArC*H*(OCH$_3$)CH$_3$], 3.74 (s, 3H, ArOC*H*$_3$), 3.57 [s, 3H, ArCH(OC*H*$_3$)CH$_3$], 1.37 [d, 3H, J = 6.42Hz, ArCH(OCH$_3$)C*H*$_3$].

*(SS)-[1-(o-Anisyl)propanol]$Cr(CO)_3$ (-)-**191**.*

(+)-(*o*-Anisaldehyde)$Cr(CO)_3$ (+)-**149** (300mg, 1.10mmol) in THF (10ml) was treated with EtMgI (0.79M, 2.53ml, 2.00mmol) under standard conditions. Column chromatography (Al_2O_3, Et_2O) gave three fractions. Fraction one was evaporated to give (*SS*)-[1-(*o*-anisyl)propanol]$Cr(CO)_3$ (-)-**191** as a yellow solid (205mg, 62%). $[\alpha]_D^{21}$ = -201° (c 1.17 $CHCl_3$); ^1H n.m.r. (300MHz) δ5.90-5.88, 5.06-5.04 (2d, 2H, Ar*H*), 5.56-5.51, 4.98-4.94 (2t, 2H, Ar*H*), 4.80 [s, br, 1H, ArC*H*(OH)R], 3.74 (s, 3H, ArOC*H*$_3$), 1.80 [s, br, 1H, ArCH(O*H*)R], 1.79-1.59 (m, 2H, RC*H*$_2$CH$_3$), 1.01 (t, 3H, J = 7.40Hz, RCH$_2$C*H*$_3$). Fraction two was evaporated to give (+)-(*o*-anisaldehyde)$Cr(CO)_3$ (+)-**149** (36mg, 12%) identified by comparison with an authentic sample. Fraction three was evaporated to give (-)-(*o*-methoxybenzyl alcohol)$Cr(CO)_3$ (-)-**192** as a yellow solid (78mg, 26%). $[\alpha]_D^{21}$ = -216° (c 1.03 $CHCl_3$); ^1H n.m.r. (300MHz) δ5.78-5.76, 5.09-5.07 (2d, 2H, Ar*H*), 5.55-5.51, 4.95-4.91 (2t, 2H, Ar*H*), 4.64, 4.38 (AB system, 2H, J_{AB} = 13.12Hz, ArC*H*$_2$OH), 3.78 (s, 3H, ArOC*H*$_3$), 1.96 (s, br, 1H, ArCH$_2$O*H*).

*(SS)-(α-Phenyl-2-methoxybenzyl alcohol)Cr(CO)$_3$ (-)-**193**.*[93]

(+)-(*o*-Anisaldehyde)Cr(CO)3 (+)-**149** (470mg, 1.73mmol) in THF (10ml) was treated with PhMgBr (0.78M, 6.65ml, 5.19mmol) under standard conditions. Work up and column chromatography (Al_2O_3, Et_2O) gave (*SS*)-(α-phenyl-2-methoxybenzyl alcohol)Cr(CO)3 (-)-**193** as a yellow solid (605mg, 100%). M.p. 113-114°C; Found: C 58.52, H 4.21%; $C_{17}H_{14}CrO_5$ requires: C 58.29, H 4.03%; *m/z* 350 (*M*+); ν_{max} 1970, 1888br (-CO), 1608 (arene ring) cm^{-1}; $[\alpha]_D^{24}$ = -178° (c 1.46 $CHCl_3$); ^{1}H n.m.r. δ7.48-7.44 (m, 2H, Ar*H*), 7.40-7.29 (m, 3H, Ar*H*), 6.06-6.02, 5.05-5.02 (2d, 2H, Ar*H*), 5.96 [s, 1H, ArC*H*(OH)Ar^1], 5.58-5.50, 4.99-4.92 (2t, 2H, Ar*H*), 3.77 (s, 3H, ArOCH_3), 2.19 [d, 1H, J = 2.27Hz, ArCH(O*H*)Ar^1].

*(S)-o-Methoxy-1-phenethanol (-)-**194**.*

(*SS*)-(*o*-Methoxy-1-phenethanol)Cr(CO)3 (-)-**188** (191mg, 0.66mmol) was dissolved in Et_2O (100ml) and allowed to decomplex under standard conditions (48h). Work up and distillation gave the title compound (-)-**194** as a clear, colourless oil (67mg, 67%). $[\alpha]_D^{20}$ = -59° (c 1.18 toluene); ^{1}H n.m.r. δ7.38-7.34, 6.93-6.89 (2d, 2H, Ar*H*), 7.32-7.23, 7.02-6.94 (2t, 2H, Ar*H*), 5.14-5.06 [m, 1H, ArC*H*(OH)CH_3], 3.88 (s, 3H, ArOCH_3), 2.70 [s, br, 1H, ArCH(O*H*)CH_3], 1.53 [d, 3H, J = 6.49Hz, ArCH(OH)CH_3].

*(S)-1-(o-Anisyl)propanol (-)-**195**.*

(*SS*)-[1-(*o*-Anisyl)propanol]Cr(CO)3 (-)-**191** (110mg, 0.36mmol) was dissolved in Et_2O (100ml) and allowed to decomplex under standard conditions (48h). Work up and distillation gave the title compound (-)-**195** as a clear, colourless oil (57mg, 95%). $[\alpha]_D^{20}$ = -57° (c 1.02 toluene) Lit.[95] $[\alpha]_D$ = +47° (c 1 toluene) for 87% ee opposite enantiomer; ^{1}H n.m.r. (300MHz) δ7.31-7.28, 6.90-6.87 (2d, 2H, Ar*H*), 7.27-7.21, 6.98-6.93 (2t, 2H, Ar*H*), 4.79 [t, 1H, J = 6.64Hz, ArC*H*(OH)R], 3.85 (s, 3H, ArOCH_3), 2.53 [s, br, ArCH(O*H*)R], 1.87-1.78 (m, 2H, RCH_2CH3), 0.96 (t, 3H, J = 7.42Hz, RCH_2CH_3).

*(S)-α-Phenyl-2-methoxybenzyl alcohol (-)-**196**.*

(*SS*)-(α-Phenyl-2-methoxybenzyl alcohol)Cr(CO)3 (-)-**193** (297mg, 0.85mmol) was dissolved in Et_2O (100ml) and allowed to decomplex under standard conditions (72h). Work up and distillation gave the title compound (-)-**196** as a clear, colourless oil

(122mg, 67%). *m/z* 197 (M^+-17); $[\alpha]_D^{20}$ = -34o (c 1.2 $CHCl_3$); ^{1}H n.m.r. δ7.49-7.23 (m, 7H, Ar*H*), 7.00-6.89 (m, 2H, Ar*H*), 6.08 [s, 1H, ArC*H*(OH)Ar^1], 3.83 (s, 3H, $ArOCH_3$), 3.74 (s, br, 1H, RO*H*).

(R,S)-o-Methoxy-1-phenethanol ***194***.

o-Anisaldehyde **158** (2.00g, 14.7mmol) in THF (20ml) was treated with MeLi (1.10M, 18.7ml, 20.6mmol) under standard conditions. Work up gave a brown oil. Water (100ml) was added and the aqueous mixture extracted with Et_2O (3 x 100ml). The organic extracts were combined, dried ($MgSO_4$) and evaporated to a clear oil. Distillation gave the title compound **194** as a clear, colourless oil (1.80g, 81%), identified by comparison with an authentic sample. B.p. 72-76oC (0.1mmHg).

(R,S)-1-(o-Anisyl)propanol ***195***.

o-Anisaldehyde **158** (2.00g, 14.7mmol) in THF (20ml) was treated with EtLi (1.43M, 14.4ml, 20.6mmol) under standard conditions. Work up gave a yellow oil. Water (100ml) was added and the aqueous mixture extracted with Et_2O (3 x 100ml). The organic extracts were combined, dried ($MgSO_4$) and evaporated to a clear oil. Distillation gave the title compound **195** as a clear, colourless oil (1.83g, 75%), identified by comparison with an authentic sample. B.p. 78-80oC (0.1mmHg).

General procedure for preparation of (R)-α-methoxy-α-(trifluoromethyl)phenylacetate esters (Mosher's esters).[97]

A sample of chiral or racemic alcohol (0.15mmol) was dissolved in CH_2Cl_2 (0.25ml) containing 4-dimethylaminopyridine (1 crystal) and pyridine (6 drops), and (*R*)-α-methoxy-α-(trifluormethyl)phenylacetyl chloride (1.55M in CH_2Cl_2, 0.17ml, 0.26mmol) added. The solution was stirred (24h) and aqueous H_2SO_4 (1N, 2ml) added. The mixture was extracted with Et_2O (3 x 2ml) and the organic extracts combined, dried ($MgSO_4$) and evaporated to give an oil. A $CDCl_3$ (0.5ml) solution of the ester was filtered through a short plug of silica prior to ^{1}H n.m.r spectroscopy.

(R)-α-Methoxy-α-(trifluoromethyl)phenylacetate esters of o-methoxy-1-phenethanol ***194*** *and 1-(o-anisyl)propanol* ***195****.*

The (*R*)-α-Methoxy-α-(trifluoromethyl)phenylacetate esters of racemic and chiral *o*-methoxy-1-phenethanol **194** and 1-(*o*-anisyl)propanol **195** were prepared under standard conditions. The ^{1}H n.m.r. chemical shifts used to check diastereoisomeric excesses of the esters, and hence enantiomeric excesses of the free alcohols, are presented below in Table VI.

(*R*)-α-methoxy-α-(trifluoro-methyl)phenylacetate ester	^{1}H n.m.r. chemical shift					
	ROCH_3			RCH_3		
	(*RR*)	ratio	(*SR*)	(*RR*)	ratio	(*SR*)
(*R,S*)-*o*-methoxy-1-phenethanol **194**	δ3.86, s	50:50	δ3.83, s	δ1.56, d	50:50	δ1.61, d
(*S*)-*o*-methoxy-1-phenethanol (-)-**194**	—	0:100	δ3.83, s	—	0:100	δ1.61, d
(*R,S*)-1-(*o*-anisyl)propanol **195**	δ3.86, s	50:50	δ3.84, s	δ0.86, t	50:50	δ0.96, t
(*S*)-1-(*o*-anisyl)propanol (-)-**195**	—	0:100	δ3.85, s	—	0:100	δ0.98, t

Table VI. ^{1}H n.m.r. chemical shifts used to check diastereoisomeric excesses of the (*R*)-Mosher's esters of prepared samples of (*S*)-*o*-methoxy-1-phenethanol (-)-**194** and (*S*)-1-(*o*-anisyl)propanol (-)-**195**.

*Addition of MeLi to (+)-(o-trimethylsilylbenzaldehyde)Cr(CO)3 (+)-****164****.*

(+)-(*o*-Trimethylsilylbenzaldehyde)Cr(CO)3 (+)-**164** (157mg, 0.50mmol) in THF (10ml) was treated with MeLi (1.4M, 0.71ml, 0.99mmol) under standard conditions. Column chromatography (Al_2O_3, Et_2O:light petroleum 2:1) gave two product fractions in ratio 12:88. Fraction one, the minor isomer, was evaporated to give a yellow solid. Recrystallisation from CH_2Cl_2:light petroleum gave (*SS*)-(*o*-trimethylsilyl-1-phenethanol)Cr(CO)3 (+)-**198** as yellow needles (18mg, 10%). M.p. 75°C; Found: C 50.80, H 5.68%; $C_{14}H_{18}CrO_4Si$ requires: C 50.90, H 5.49%; *m/z* 330 (*M*+); ν_{max} 1968, 1888br (-CO), 1607 (arene ring) cm^{-1}; $[\alpha]_D^{20}$ = +36° (c 0.765 CHCl3); ^{1}H n.m.r. δ5.75-5.68, 5.22-5.15 (2t, 2H, Ar*H*), 5.52-5.47 (m, 2H, Ar*H*), 4.82 [q, 1H, J = 6.32Hz, ArC*H*(OH)CH3], 2.13 [s, br, 1H, ArCH(O*H*)CH3], 1.48 [d, 3H, J = 6.32Hz, ArCH(OH)C*H*3], 0.41 [s, 9H, ArSi(C*H*3)3]. Fraction two, the major isomer, was evaporated to give a yellow solid. Recrystallisation from CH_2Cl_2:light petroleum gave (*SR*)-(*o*-trimethylsilyl-1-phenethanol)Cr(CO)3 (+)-**197** as yellow blocks (137mg, 83%). M.p. 39-40°C; Found: C 51.18, H 5.53%; $C_{14}H_{18}CrO_4Si$ requires: C 50.90, H 5.49%; *m/z* 330 (*M*+); ν_{max} 3595 (-OH), 1970, 1889br (-CO), 1610 (arene ring) cm^{-1}; $[\alpha]_D^{21}$

= +20° (c 1.01 $CHCl_3$); ^1H n.m.r. ($CDCl_3$) δ5.63-5.56, 5.23-5.17 (2t, 2H, Ar*H*), 5.51-5.48, 5.29-5.26 (2d, 2H, Ar*H*), 4.84-4.72 [m, 1H, ArC*H*(OH)CH_3], 1.78 [d, 1H, J = 5.29Hz, ArCH(O*H*)CH_3], 1.56 [d, 3H, J = 6.53Hz, ArCH(OH)C*H*$_3$], 0.41 [s, 9H, ArSi(C*H*$_3$)$_3$]; (C_6D_6) δ4.97-4.94, (d, 1H, Ar*H*), 4.72-4.65 (t, 1H, Ar*H*), 4.41-4.38 (m, 2H, Ar*H*), 4.31 [q, 1H, J = 6.31Hz, ArC*H*(OH)CH_3], 0.99 [d, 3H, J = 6.45Hz, ArCH(OH)C*H*$_3$], 0.22 [s, 9H, ArSi(C*H*$_3$)$_3$].

*Desilylation and decomplexation of (SR)-(o-trimethylsilyl-1-phenethanol)Cr(CO)3 (+)-**197**.*

Tetra-*n*-butylammonium fluoride trihydrate (301mg, 0.96mmol) was added to a CH_2Cl_2 (5ml) solution of (*SR*)-(*o*-trimethylsilyl-1-phenethanol)Cr(CO)3 (+)-**197** (210mg, 0.64mmol) and the solution stirred (2h). After filtration (Al_2O_3, Et_2O) and evaporation of the solvent, Et_2O (10ml) was added and the mixture allowed to decomplex under standard conditions (72h). Work up and distillation gave (*R*)-1-phenethanol (+)-**199** as a clear, colourless oil (65mg, 83%), identified by comparison with a commercially available sample.[98] $[\alpha]_D^{20}$ = +51° (c 1.35 CHCl3) Lit.[98] $[\alpha]_D$ = +39.5° (neat); ^1H n.m.r. δ7.43-7.29 (m, 5H, Ar*H*), 4.93 [q, 1H, J = 6.45Hz, ArC*H*(OH)CH_3], 1.90 [s, br, 1H, ArCH(O*H*)CH_3], 1.53 (d, 3H, J = 6.36Hz, ArCH(OH)C*H*$_3$].

*Addition of MeMgI to (o-trimethylsilylbenzaldehyde)Cr(CO)3 **164**.*

(*o*-Trimethylsilylbenzaldehyde)Cr(CO)3 **164** (600mg, 1.91mmol) in THF (8ml) was treated with MeMgI (2.0M, 2.00ml, 4.00mmol) under standard conditions. Column chromatography (Al_2O_3, Et_2O:light petroleum 1:1) gave two fractions both as yellow solids in ratio 83:17. Fraction one, the major isomer, was identified as (*RR,SS*)-(*o*-trimethylsilyl-1-phenethanol)Cr(CO)3 **198** (523mg, 83%), and fraction two, the minor isomer, was identifed as (*RS,SR*)-(*o*-trimethylsilyl-1-phenethanol)Cr(CO)3 **197** (105mg, 17%), both by comparison with authentic samples.

Magnesium bromide etherate.[117]

Magnesium (192mg, 8.00mmol) was stirred vigorously under nitrogen until the metal surface darkened. Dry Et_2O (10ml) was added followed by 1,2-dibromoethane (1.36g, 7.23mmol). The solution was gently warmed to initiate reaction and then stirred (10min)

until no further reaction was observed. The resultant crude solution of $MgBr_2.OEt_2$ (~0.8M) was used without further purification.

General procedure for the addition of nucleophiles to (o-trialkylsilyl-benzaldehyde)Cr(CO)3 complexes in the presence of MgBr2.OEt2.

$MgBr_2.OEt_2$ in Et_2O was added to a solution of the complex in Et_2O and the darkened mixture was stirred (10min). A Et_2O or THF solution of the nucleophile was added slowly to the mixture and the resultant yellow solution stirred (30min). Sufficient MeOH was added to quench and the solvent evaporated to give a residue containing the crude product.

Addition of MeLi to (o-trimethylsilylbenzaldehyde)Cr(CO)3 ***164*** *pretreated with MgBr2.OEt2.*

(*o*-Trimethylsilylbenzaldehyde)$Cr(CO)_3$ **164** (518mg, 1.65mmol) in Et_2O (10ml) was treated with $MgBr_2.OEt_2$ (0.8M, 10.0ml, 8.00mmol) followed by MeLi (1.5M, 1.60ml, 2.40mmol) under standard conditions. Work up and column chromatography (Al_2O_3, Et_2O:light petroleum 1:1) gave two fractions, both as yellow solids in ratio 87:13. Fraction one, the major isomer, was identified as (*RR*,*SS*)-(*o*-trimethylsilyl-1-phenethanol)$Cr(CO)_3$ **198** (474mg, 87%) and fraction two, the minor isomer, was identified as (*RS*,*SR*)-(*o*-trimethylsilyl-1-phenethanol)$Cr(CO)_3$ **197** (71mg, 13%), both by comparison with authentic samples.

*Addition of MeMgI to (-)-(o-trimethylsilylbenzaldehyde)Cr(CO)3 (-)-****164*** *pretreated with MgBr2.OEt2.*

(-)-(*o*-Trimethylsilylbenzaldehyde)$Cr(CO)_3$ (-)-**164** (100mg, 0.32mmol) in Et_2O (8ml) was treated with $MgBr_2.OEt_2$ (0.8M, 3.33ml, 2.66mmol) followed by MeMgI (1.0M, 0.51ml, 0.51mmol) under standard conditions. Work up and column chromatography (Al_2O_3, Et_2O:light petroleum 1:1) gave two fractions both as yellow solids in ratio 89:11. Fraction one, the major isomer, was identified as (*RR*)-(*o*-trimethyl-silyl-1-phenethanol)$Cr(CO)_3$ (-)-**198** (84mg, 80%) by comparison with an authentic sample. $[\alpha]_D^{21} = -360$ (c 0.765 CHCl3). Fraction two, the minor isomer, was identified as (*RS*)-(*o*-trimethylsilyl-1-phenethanol)$Cr(CO)_3$ (-)-**197** (10mg, 10%), also by comparison with an authentic sample.

*Desilylation and decomplexation of (RR)-(o-trimethylsilyl-1-phenethanol)Cr(CO)$_3$ (-)-**198**.*

Tetra-*n*-butylammonium fluoride trihydrate (115mg, 0.37mmol) was added to a CH_2Cl_2 (5ml) solution of (*RR*)-(*o*-trimethylsilyl-1-phenethanol)Cr(CO)$_3$ (-)-**198** (80mg, 0.24mmol) and the solution stirred (3h). After filtration (Al_2O_3, Et_2O) and evaporation of the solvent, Et_2O (100ml) was added and the mixture allowed to decomplex under standard conditions (72h). Work up and distillation gave (*R*)-1-phenethanol (+)-**199** as a clear, colourless oil (12mg, 41%) identified by comparison with an authentic sample. $[\alpha]_D^{20}$ = +56° (c 0.46 $CHCl_3$) Lit.[98] $[\alpha]_D$ = +39.5° (neat).

*[2-(o-Trimethylsilylphenyl)-2-methyl-1,3-dioxolane]Cr(CO)$_3$ **207**.*

(2-Phenyl-2-methyl-1,3-dioxolane)Cr(CO)$_3$ **206** (200mg, 0.67mmol)[102] in THF (8ml) was treated with *n*-BuLi (1.65M, 0.43ml, 0.71mmol) and chlorotrimethylsilane (228mg, 2.10mmol) under standard conditions. Work up and column chromatography (Al_2O_3, Et_2O:light petroleum 3:1) gave a single compound as a yellow solid. Recrystallisation from Et_2O:hexane gave the title compound **207** as yellow needles (213mg, 85%). M.p. 98-100°C; Found: C 51.36, H 5.32%; $C_{16}H_{20}CrO_5Si$ requires: C 51.60, H 5.41%; *m/z* 373 (*M*+1); ν_{max} 1963, 1882br (-CO), 1601 (arene ring) cm^{-1}; ^{1}H n.m.r. δ5.56-5.45 (m, 3H, Ar*H*), 5.28-5.20 (m, 1H, Ar*H*), 4.16-4.00 (m, 4H, -O*CH*$_2$*CH*$_2$O-), 1.62 [s, 3H, ArC(OR)$_2$*CH*$_3$], 0.40 [s, 9H, ArSi(*CH*$_3$)$_3$].

*(o-Trimethylsilylacetophenone)Cr(CO)$_3$ **205**.*

[2-(*o*-Trimethylsilylphenyl)-2-methyl-1,3-dioxolane]Cr(CO)$_3$ **207** (120mg, 0.32mmol) was dissolved in THF (5ml) and aqueous HCl (3N, 3ml) added. The solution was stirred (24h) and removal of the solvent gave an orange oil. Column chromatography (SiO_2, Et_2O:light petroleum 1:1) gave, on evaporation of the solvent, the title compound **205** as an orange solid (106mg, 100%). *m/z* 328 (*M*+); ν_{max} 1979, 1908br (-CO), 1696 (C=O) cm^{-1}; ^{1}H n.m.r. δ5.71-5.68 (d, 1H, Ar*H*), 5.60-5.55 (m, 2H, Ar*H*), 5.45-5.39 (t, 1H, Ar*H*), 2.49 (s, 3H, RC*H*$_3$), 0.32 [s, 9H, ArSi(*CH*$_3$)$_3$].

Addition of $LiEt_3BH$ to (o-trimethylsilylacetophenone)$Cr(CO)_3$ ***205***.

(*o*-Trimethylsilylacetophenone)$Cr(CO)_3$ **205** (100mg, 0.30mmol) in THF (8ml) was treated with $LiEt_3BH$ (1.0M in THF, 0.90ml, 0.90mmol) under standard conditions (-78°C, 30min). Work up and column chromatography (Al_2O_3, Et_2O) gave, on evaporation of the solvent, (*RR*,*SS*)-(*o*-trimethylsilyl-1-phenethanol)$Cr(CO)_3$ **198** as a yellow solid (84mg, 85%), identified by comparison with an authentic sample.

(o-Trimethylsilylbenzyl alcohol)$Cr(CO)_3$ ***209***.

(*o*-Trimethylsilylbenzaldehyde)$Cr(CO)_3$ **164** (324mg, 1.03mmol) in THF (8ml) was treated with $LiEt_3BH$ (1.0M in THF, 0.50ml, 0.50mmol) under standard conditions (-78°C, 20min) with MeOH (3 drops) quench. Column chromatography (SiO_2, Et_2O) gave, on evaporation of the solvent, a single compound as a yellow solid. Recrystallisation from CH_2Cl_2:hexane gave the title compound **209** as pale yellow flakes (258mg, 79%). M.p. 97-98°C; Found: C 49.60, H 5.06%; $C_{13}H_{16}CrO_4Si$ requires: C 49.36, H 5.10%; *m/z* 316 (*M*+); ν_{max} 3600 (-OH), 1968, 1888br (-CO), 1603 (arene ring) cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ5.69-5.63, 5.18-5.12 (2t, 2H, Ar*H*), 5.55-5.51, 5.42-5.38 (2d, 2H, Ar*H*), 4.62, 4.52 (ABX system, 2H, J_{AB} = 13.50Hz, J_{AX} = 7.11Hz, J_{BX} = 4.49Hz, ArCH_2OH), 1.91 (t, 1H, J = 6.10Hz, ArCH$_2$O*H*), 0.38 [s, 9H, ArSi(CH_3)3]; (C_6D_6) δ4.93-4.89 (d, 1H, Ar*H*), 4.78-4.67 (m, 2H, Ar*H*), 4.25-4.18 (t, 1H, Ar*H*), 4.07, 3.88 (ABX system, 2H, J_{AB} = 12.96Hz, J_{AX} = 5.96Hz, J_{BX} = 3.72Hz, ArCH_2OH), 0.94 (t, 1H, J = 5.36Hz, ArCH$_2$O*H*), 0.10 [s, 9H, ArSi(CH_3)3].

Addition of $LiEt_3BD$ to (o-trimethylsilylbenzaldehyde)$Cr(CO)_3$ ***164***.

Method 1. (*o*-Trimethylsilylbenzaldehyde)$Cr(CO)_3$ **164** (320mg, 1.02mmol) in THF (8ml) was treated with $LiEt_3BD$ (1.0M in THF, 1.60ml, 1.60mmol) under standard conditions (-78°C, 20min). Column chromatography (Al_2O_3, Et_2O) gave, on evaporation of the solvent, a yellow solid, identified as a 92:8 mixture of (*RS*,*SR*)-(*o*-trimethylsilyl-α-deuteriobenzyl alcohol)$Cr(CO)_3$ **210** and (*RR*,*SS*)-(*o*-trimethylsilyl-α-deuteriobenzyl alcohol)$Cr(CO)_3$ **211** respectively (323mg, 100%). *m/z* 317 (*M*+); ^1H n.m.r. ($CDCl_3$) **210**: δ4.61 [m, 1H, ArC*H*(OH)D], **211**: δ4.50 [m, 1H, ArC*H*(OH)D], **210** and **211**: δ5.70-5.64, 5.19-5.13 (2t, 2H, Ar*H*), 5.55-5.52, 5.42-5.39 (2d, 2H, Ar*H*), 1.87 [s, br, ArCH(O*H*)D], 0.39 [s, 9H, ArSi(CH_3)3]; (C_6D_6) **210**: δ4.06 [m, 1H, ArC*H*(OH)D], **211**: δ3.88 [m, 1H, ArC*H*(OH)D], **210** and **211**: δ4.93-4.90, 4.76-4.71 (2d, 2H, Ar*H*), 4.79-4.67, 4.25-4.18 (2t, 2H, Ar*H*), 0.97 [d, 1H, J = 6.33Hz, ArCH(O*H*)D], 0.10 [s, 9H,

ArSi(CH_3)$_3$]; ^{2}H n.m.r. **210**: δ4.60 [s, 1D, ArCH(OH)*D*], **211**: δ4.50 [s, 1D, ArCH(OH)*D*].

Method 2. (*o*-Trimethylsilylbenzaldehyde)Cr(CO)3 **164** (292mg, 0.93mmol) in THF (8ml) (cooled to -100°C) was treated with LiEt3BD (1.0M in THF, 2.00ml, 2.00mmol) under standard conditions (-100°C, 20min). Column chromatography (Al_2O_3, Et_2O) gave, on evaporation of the solvent, a yellow solid, identified as a 92:8 mixture of complexes **210** and **211** (289mg, 98%), by comparison with an authentic mixture.

Method 3. (*o*-Trimethylsilylbenzaldehyde)Cr(CO)3 **164** (309mg, 0.98mmol) in CH_2Cl_2 (15ml) (cooled to -100°C) was treated with LiEt3BD (1.0M in THF, 2.00ml, 2.00mmol) under standard conditions (-100°C, 5min). Column chromatography (Al_2O_3, Et_2O) gave, on evaporation of the solvent, a yellow solid, identified as a 75:25 mixture of complexes **210** and **211** (309mg, 99%), by comparison with an authentic mixture.

Method 4. (*o*-Trimethylsilylbenzaldehyde)Cr(CO)3 **164** (600mg, 1.91mmol) in toluene (15ml) (cooled to -91°C) was treated with LiEt3BD (1.0M in THF, 3.30ml, 3.30mmol) under standard conditions (-91°C, 20min). Column chromatography (Al_2O_3, Et_2O) gave, on evaporation of the solvent, a yellow solid, identified as an 80:20 mixture of complexes **210** and **211** (540mg, 89%), by comparison with an authentic mixture.

Addition of LiEt3BD to (o-trimethylsilylbenzaldehyde)Cr(CO)3 ***164*** *pretreated with MgBr2.OEt2.*

(*o*-Trimethylsilylbenzaldehyde)Cr(CO)3 **164** (240mg, 0.76mmol) in Et_2O (5ml) was treated with MgBr2.OEt2 (0.8M, 6.80ml, 5.44mmol) followed by LiEt3BD (1.0M in THF, 4.00ml, 4.00mmol) under standard conditions. Work up and column chromatography (Al_2O_3, Et_2O) gave, on evaporation of the solvent, a yellow solid, identified as a 12:88 mixture of complexes **210** and **211** (229mg, 95%), by comparison with an authentic mixture.

Addition of LiAlD4 to (o-trimethylsilylbenzaldehyde)Cr(CO)3 ***164****.*

(*o*-Trimethylsilylbenzaldehyde)Cr(CO)3 **164** (335mg, 1.07mmol) in THF (8ml) was treated with powdered LiAlD4 (100mg, 2.38mmol) under standard conditions (-78°C, 10min). Column chromatography (Al_2O_3, Et_2O) gave, on evaporation of the solvent, a

yellow solid, identified as a 38:62 mixture of complexes **210** and **211** (339mg, 100%), by comparison with an authentic mixture.

*Addition of $LiAlD_4$ to (o-trimethylsilylbenzaldehyde)$Cr(CO)_3$ **164** pretreated with $MgBr_2.OEt_2$.*

(*o*-Trimethylsilylbenzaldehyde)$Cr(CO)_3$ **164** (369mg, 1.18mmol) in Et_2O (5ml) was treated with $MgBr_2.OEt_2$ (0.8M, 6.80ml, 5.44mmol) followed by powdered $LiAlD_4$ (110mg, 2.62mmol) under standard conditions. Work up and column chromatography (Al_2O_3, Et_2O) gave, on evaporation of the solvent, a yellow solid, identified as a 4:96 mixture of complexes **210** and **211** (270mg, 72%), by comparison with an authentic sample.

*Addition of $LiEt_3BD$ to (-)-(o-trimethylsilylbenzaldehyde)$Cr(CO)_3$ (-)-**164**.*

(-)-(*o*-Trimethylsilylbenzaldehyde)$Cr(CO)_3$ (-)-**164** (310mg, 0.99mmol) in THF (8ml) was treated with $LiEt_3BD$ (1.0M in THF, 1.60ml, 1.60mmol) under standard conditions (-78°C, 20min). Column chromatography (Al_2O_3, Et_2O) gave, on evaporation of the solvent, a yellow solid, identified as a 92:8 mixture of (*RS*)-(*o*-trimethylsilyl-α-deuteriobenzyl alcohol)$Cr(CO)_3$ **210** and (*RR*)-(*o*-trimethylsilyl-α-deuteriobenzyl alcohol)$Cr(CO)_3$ **211** (313mg, 100%), by comparison with an authentic racemic mixture. $[\alpha]_D^{20} = \sim 0°$ (c 0.865 $CHCl_3$).

*Addition of $LiAlD_4$ to (-)-(o-trimethylsilylbenzaldehyde)$Cr(CO)_3$ (-)-**164** pretreated with $MgBr_2.OEt_2$.*

(-)-(*o*-Trimethylsilylbenzaldehyde)$Cr(CO)_3$ (-)-**164** (100mg, 0.32mmol) in Et_2O (5ml) was treated with $MgBr_2.OEt_2$ (0.8M, 3.33ml, 2.66mmol) followed by powdered $LiAlD_4$ (25mg, 0.60mmol) under standard conditions. Work up and column chromatography (Al_2O_3, Et_2O) gave, on evaporation of the solvent, a yellow solid, identified as a 4:96 mixture of (*RS*)-(*o*-trimethylsilyl-α-deuteriobenzyl alcohol)$Cr(CO)_3$ **210** and (*RR*)-(*o*-trimethylsilyldeuteriobenzyl alcohol)$Cr(CO)_3$ **211** (80mg, 79%), by comparison with an authentic racemic mixture. $[\alpha]_D^{20} = \sim 0°$ (c 0.60 $CHCl_3$).

*Desilylation and decomplexation of a 92:8 mixture of (RS)- and (RR)-(o-trimethylsilyl-α-deuteriobenzyl alcohol)Cr(CO)3 complexes **210** and **211**.*

Tetra-*n*-butylammonium fluoride trihydrate (299mg, 0.95mmol) was added to a CH_2Cl_2 (8ml) solution of a 92:8 mixture of (*RS*)- and (*RR*)-(*o*-trimethylsilyl-α-deuteriobenzyl alcohol)Cr(CO)3 complexes **210** and **211** (200mg, 0.63mmol) and the solution stirred (1h). After filtration (Al_2O_3, Et_2O) and evaporation of the solvent, Et_2O (75ml) was added and the mixture allowed to decomplex under standard conditions (60h). Work up and distillation gave (*S*)-α-deuteriobenzyl alcohol (*S*)-**208** as a clear, colourless oil (46mg, 44%), identified by comparison with an authentic racemic sample.[118] B.p. 80°C (21mmHg); *m/z* 109 (*M*+); ^{1}H n.m.r. δ7.40-7.25 (m, 5H, Ar*H*), 4.99 [s, 1H, ArC*H*(OH)D], 1.71 [s, 1H, ArCH(O*H*)D].

*Desilylation and decomplexation of a 4:96 mixture of (RS)- and (RR)-(o-trimethylsilyl-α-deuteriobenzyl alcohol)Cr(CO)3 complexes **210** and **211**.*

Tetra-*n*-butylammonium fluoride trihydrate (100mg, 0.32mmol) was added to a CH_2Cl_2 (5ml) solution of a 4:96 mixture of (*RS*)- and (*RR*)-(*o*-trimethylsilyl-α-deuteriobenzyl alcohol)Cr(CO)3 complexes **210** and **211** (80mg, 0.25mmol) and the solution stirred (12h). After filtration (Al_2O_3, Et_2O) and evaporation of the solvent, Et_2O (25ml) was added and the mixture allowed to decomplex under standard conditions (48h). Work up and distillation gave (*R*)-α-deuteriobenzyl alcohol (*R*)-**208** as a clear, colourless oil (18mg, 66%), identified by comparison with an authentic racemic sample.[118]

*Addition of MeLi to (o-tri-i-propylsilylbenzaldehyde)Cr(CO)3 **169**.*

Method 1. (*o*-Tri-*i*-propylsilylbenzaldehyde)Cr(CO)3 **169** (84mg, 0.21mmol) in THF (8ml) was treated with MeLi (1.5M, 0.28ml, 0.42mmol) under standard conditions with *i*-PrOH (0.50ml) quench. Column chromatography (Al_2O_3) gave two fractions in 85:15 ratio. Fraction one (Et_2O:hexane 1:1) was evaporated to give a yellow oil. Crystallisation from hexane gave (O-tri-*i*-propylsilyl-1-phenethanol)Cr(CO)3 **212** as yellow plates (63mg, 72%). M.p. 45-46°C; Found: C 58.21, H 7.44%; $C_{20}H_{30}CrO_4Si$ requires: C 57.95, H 7.29%; *m/z* 414 (*M*+); ν_{max} 1970, 1890br (-CO) cm^{-1}; ^{1}H n.m.r. (C_6D_6) δ5.07-5.03, 4.73-4.71 (2d, 2H, Ar*H*), 4.45-4.35 [m, 4H, Ar*H*, ArC*H*(OH)CH_3], 1.17 [d, 3H, J = 6.33Hz, ArCH(OH)C*H*3], 1.11-0.94 {m, 21H, ArSi[C*H*(C*H*3)2]3}. Fraction two (Et_2O) was evaporated to give a yellow oil. Crystallisation from hexane gave (*RS*,*SR*)-(*o*-tri-*i*-propylsilyl-1-phenethanol)Cr(CO)3 **214** as tiny yellow crystals (11mg, 13%).

m/z 415 (M^++1); ^{1}H n.m.r. δ5.71-5.65, 5.25-5.19 (2t, 2H, Ar*H*), 5.53-5.50, 5.46-5.43 (2d, 2H, Ar*H*), 4.72 [m, 1H, ArC*H*(OH)CH_3], 1.72 [d, 1H, J = 4.75Hz, ArCH(O*H*)CH_3], 1.59 [d, 3H, J = 6.32Hz, ArCH(OH)C*H*$_3$], 1.54-1.34 {m, 3H, ArSi[C*H*$(CH_3)_2]_3$}, 1.26-1.18 {m, 18H, ArSi[CH(C*H*$_3)_2]_3$}.

Method 2. (+)-(*o*-Tri-*i*-propylsilylbenzaldehyde)Cr(CO)$_3$ (+)-**169** (60mg, 0.15mmol) in THF (5ml) was treated with MeLi (1.5M, 0.20ml, 0.30mmol) under standard conditions with water (1 drop) quench. Column chromatography (Al_2O_3) gave two fractions in 36:64 ratio. Fraction one (Et_2O:hexane 1:1) was evaporated to give (*R*)-(O-tri-*i*-propylsilyl-1-phenethanol)Cr(CO)$_3$ **212** as a yellow oil (22mg, 36%), identified by comparison with an authentic racemic sample. Fraction two (Et_2O) was evaporated to a yellow solid (40mg, 64%). Recrystallisation from hexane gave (*SR*)-(*o*-tri-*i*-propylsilyl-1-phenethanol)Cr(CO)$_3$ (+)-**214** as tiny yellow crystals, identified by comparison with an authentic racemic sample. $[\alpha]_D^{20}$ = +129o (c 0.14 $CHCl_3$).

Desilylation and decomplexation of (R)-(O-tri-i-propylsilyl-1-phenethanol)Cr(CO)$_3$ ***212****.*

Tetra-*n*-butylammonium fluoride trihydrate (114mg, 0.36mmol) was added to a CH_2Cl_2 (2ml) solution of (*R*)-(O-tri-*i*-propylsilyl-1-phenethanol)Cr(CO)$_3$ **212** (22mg, 53μmol) and the solution stirred (2h). After filtration (Al_2O_3, Et_2O) and evaporation of the solvent, Et_2O (10ml) was added and the mixture allowed to decomplex under standard conditions (24h). Work up gave (*R*)-1-phenethanol (+)-**199** as a clear, colourless oil (6mg, 93%), identified by comparison with an authentic sample.

*Desilylation and decomplexation of (SR)-(o-tri-i-propylsilyl-1-phenethanol)Cr(CO)$_3$ (+)-****214****.*

Tetra-*n*-butylammonium fluoride trihydrate (38mg, 0.12mmol) was added to a CH_2Cl_2 (2ml) solution of (*SR*)-(*o*-tri-*i*-propylsilyl-1-phenethanol)Cr(CO)$_3$ (+)-**214** (5mg, 12μmol) and the solution stirred (30min). After filtration (Al_2O_3, Et_2O) and evaporation of the solvent, Et_2O (10ml) was added and the mixture allowed to decomplex under standard conditions (24h). Work up gave (*R*)-1-phenethanol (+)-**199** as a clear, colourless oil (1.4mg, 96%), identified by comparison with an authentic sample.

*Addition of MeMgI to (o-tri-i-propylsilylbenzaldehyde)Cr(CO)$_3$ **169**.*

(*o*-Tri-*i*-propylsilylbenzaldehyde)Cr(CO)3 **169** (98mg, 0.25mmol) in THF (8ml) was treated with MeMgI (1.0M, 1.00ml, 1.00mmol) under standard conditions with *i*-PrOH (0.5ml) quench. Column chromatography (Al_2O_3) gave two fractions in 50:50 ratio. Fraction one (Et_2O:hexane 1:2) was evaporated to a yellow solid (47mg, 45%). Recrystallisation from hexane gave (*RR*,*SS*)-(*o*-tri-*i*-propylsilyl-1-phenethanol)Cr(CO)3 **215** as yellow needles. M.p. 67-68°C; Found: C 58.29, H 7.27%; $C_{20}H_{30}CrO_4Si$ requires: C 57.95, H 7.29%; *m/z* 415 (*M*+1); ν_{max} 1965, 1890br (-CO) cm^{-1}; ^1H n.m.r. δ5.79-5.73, 5.22-5.15 (2t, 2H, Ar*H*), 5.55-5.51, 5.48-5.45 (2d, 2H, Ar*H*), 4.68 [d of q, 1H, J_d = 2.08Hz, J_q = 6.12Hz, ArC*H*(OH)CH3], 2.03 [d, 1H, J = 2.10Hz, ArCH(O*H*)CH3], 1.47 [d, 3H, J = 6.32Hz, ArCH(OH)C*H*3], 1.41-1.31 {m, 3H, ArSi[C*H*(CH3)2]3}, 1.27, 1.19 {2d, 18H, J_1 = 5.95Hz, J_2 = 6.62Hz, ArSi[CH(C*H*3)2]3}. Fraction two (Et_2O) was evaporated to give (*RS*,*SR*)-(*o*-tri-*i*-propylsilyl-1-phenethanol)Cr(CO)3 **214** as a yellow oil (47mg, 45%), identified by comparison with an authentic sample.

*Addition of MeMgI to (+)-(o-tri-i-propylsilylbenzaldehyde)Cr(CO)3 (+)-**169** pretreated with MgBr2.OEt2.*

(+)-(*o*-Tri-*i*-propylsilylbenzaldehyde)Cr(CO)3 (+)-**169** (65mg, 0.16mmol) in Et_2O (5ml) was treated with $MgBr_2.OEt_2$ (0.8M, 3.33ml, 2.66mmol) followed by MeMgI (1.0M, 0.30ml, 0.30mmol) under standard conditions. Work up and column chromatography (Al_2O_3, Et_2O) gave, on evaporation of the solvent, a single fraction as a yellow solid. Recrystallisation from hexane gave (*SS*)-(o-tri-*i*-propylsilyl-1-phenethanol)Cr(CO)3 (+)-**215** as a yellow powder (66mg, 99%), identified by comparison with an authentic sample. $[\alpha]_D^{20}$ = +79o (c 0.835 CHCl3).

*Desilylation and decomplexation of (SS)-(o-tri-i-propylsilyl-1-phenethanol)Cr(CO)3 (+)-**215**.*

Tetra-*n*-butylammonium fluoride trihydrate (107mg, 0.34mmol) was added to a CH_2Cl_2 (2ml) solution of (*SS*)-(*o*-tri-*i*-propylsilyl-1-phenethanol)Cr(CO)3 (+)-**215** (64mg, 0.15mmol) and the solution stirred (30min). After filtration (Al_2O_3, Et_2O) and evaporation of the solvent, Et_2O (10ml) was added and the mixture allowed to decomplex under standard conditions (24h). Work up gave (*S*)-1-phenethanol (-)-**199** as a clear, colourless oil (18mg, 100%), identified by comparison with an authentic sample.

*(R)-α-Methoxy-α-(trifluoromethyl)phenylacetate ester of 1-phenethanol **199**.*

The (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetate esters of racemic and chiral samples of 1-phenethanol **199** were prepared under standard conditions. The ^{1}H n.m.r. chemical shifts used to check diastereoisomeric excesses of the esters, and hence enantiomeric excesses of the free alcohols, are presented below in Table VII.

(*R*)-α-methoxy-α-(trifluoro-methyl)phenylacetate ester	^{1}H n.m.r. chemical shift					
	ROCH_3			RCH_3		
	(*RS*)	ratio	(*RR*)	(*RS*)	ratio	(*RR*)
(*R,S*)-1-phenethanol **199**	δ3.59, s	50:50	δ3.50, s	δ1.66, d	50:50	δ1.60, d
(*R*)-1-phenethanol (+)-**199** from (+)-**197**	—	0:100	δ3.49, s	—	0:100	δ1.60, d
(*R*)-1-phenethanol (+)-**199** from (-)-**198**	—	0:100	δ3.49, s	—	0:100	δ1.60, d
(*R*)-1-phenethanol (+)-**199** from **212**	—	0:100	δ3.49, s	—	0:100	δ1.59, d
(*R*)-1-phenethanol (+)-**199** from (+)-**214**	—	0:100	δ3.49, s	—	0:100	δ1.59, d
(*S*)-1-phenethanol (-)-**199** from (+)-**215**	δ3.59, s	100:0	—	δ1.66, d	100:0	—

Table VII. ^{1}H n.m.r. chemical shifts used to check diastereomeric excesses of the (*R*)-Mosher's esters of prepared samples of chiral 1-phenethanol **199**.

(o-Tri-i-propylsilylbenzyl alcohol)Cr(CO)3.

(*o*-Tri-*i*-propylsilylbenzaldehyde)Cr(CO)3 **169** (100mg, 0.25mmol) in THF (5ml) was treated with LiEt3BH (1.0M in THF, 0.50ml, 0.50mmol) under standard conditions (-78°C, 5min) with water (3 drops) quench. Column chromatography (Al_2O_3, Et_2O:hexane 1:1) gave, on evaporation of the solvent, the title compound as a yellow oil (95mg, 95%). ^{1}H n.m.r. (CD_3COCD_3) δ6.03-5.96, 5.41-5.34 (2t, 2H, Ar*H*), 5.79-5.76, 5.67-5.64 (2d, 2H, Ar*H*), 4.73-4.68 (m, 1H, $ArCH_2O$*H*), 4.54, 4.45 (ABX system, 2H, J_{AX} = 5.38HZ, J_{BX} = 5.07Hz, J_{AB} = 13.24Hz, ArCH_2OH), 1.53-1.32 {m, 3H, ArSi[C*H*(CH_3)2]3}, 1.26-1.12 {m, 18H, ArSi[CH(C*H*3)2]3}.

Addition of $LiEt_3BD$ to (o-tri-i-propylsilylbenzaldehyde)$Cr(CO)_3$ ***169****.*

(*o*-Tri-*i*-propylsilylbenzaldehyde)Cr(CO)3 **169** (100mg, 0.25mmol) in THF (8ml) was treated with LiEt3BD (1.0M in THF, 0.45ml, 0.45mmol) under standard conditions (-78°C, 5min) with water (3 drops) quench. Column chromatography (SiO_2, Et_2O) gave, on evaporation of the solvent, an 86:14 mixture of (*RS*,*SR*)-(*o*-tri-*i*-propylsilyl-α-deuteriobenzyl alcohol)Cr(CO)3 and (*RR*,*SS*)-(*o*-tri-*i*-propylsilyl-α-deuteriobenzyl alcohol)Cr(CO)3 complexes **216** and **217** respectively as a yellow oil (99mg, 99%). *m/z* 402 (M^++1); ^{1}H n.m.r. **216**: δ4.53 [s, 1H, ArC*H*(OH)D], **217**: δ4.43 [s, 1H, ArC*H*(OH)D], **216** and **217**: δ6.03-5.96, 5.41-5.35 (2t, 2H, Ar*H*), 5.79-5.76, 5.68-5.63 (2d, 2H, Ar*H*), 4.70-4.67 [m, 1H, ArCH(O*H*)D], 1.53-1.32 {m, 3H, ArSi[C*H*(CH_3)2]3}, 1.26-1.09 {m, 18H, ArSi{CH(C*H*$_3$)2]3}.

Addition of $LiEt_3BD$ to (o-tri-i-propylsilylbenzaldehyde)$Cr(CO)_3$ ***169*** *pretreated with $MgBr_2.OEt_2$.*

(*o*-Tri-*i*-propylsilylbenzaldehyde)Cr(CO)3 **169** (100mg, 0.25mmol) in Et_2O (5ml) was treated with $MgBr_2.OEt_2$ (0.8M, 3.33ml, 2.66mmol) followed by LiEt3BD (1.0M, 0.50ml, 0.50mmol) under standard conditions. Work up and column chromatography (Al_2O_3, Et_2O:hexane 2:1) gave on evaporation of the solvent, a 12:88 mixture of complexes **216** and **217** as a yellow oil (92mg, 92%), identified by comparison with an authentic mixture.

Addition of $LiAlD_4$ to (o-tri-i-propylsilylbenzaldehyde)$Cr(CO)_3$ ***169****.*

(*o*-Tri-*i*-propylsilylbenzaldehyde)Cr(CO)3 **169** (120mg, 0.30mmol) in THF (8ml) was treated with powdered $LiAlD_4$ (60mg, 1.43mmol) under standard conditions (-78°C, 10min). Column chromatography (Al_2O_3, Et_2O:hexane 1:1) gave, on evaporation of the solvent, a 30:70 mixture of complexes **216** and **217** as a yellow oil (120mg, 100%), identified by comparison with an authentic mixture.

Addition of $LiAlD_4$ to (o-tri-i-propylsilylbenzaldehyde)$Cr(CO)_3$ ***169*** *pretreated with $MgBr_2.OEt_2$.*

(*o*-Tri-*i*-propylsilylbenzaldehyde)Cr(CO)3 **169** (100mg, 0.25mmol) in Et_2O (5ml) was treated with $MgBr_2.OEt_2$ (0.8M, 3.33ml, 2.66mmol) followed by powdered $LiAlD_4$

(50mg, 1.19mmol) under standard conditions. Work up and column chromatography (Al_2O_3, Et_2O:hexane 1:1) gave, on evaporation of the solvent, a 6:94 mixture of complexes **216** and **217** (65mg, 65%), identified by comparison with an authentic mixture.

*Addition of LiAlD4 to (-)-(o-tri-i-propylsilylbenzaldehyde)Cr(CO)3 (-)-**169** pretreated with $MgBr_2.OEt_2$.*

(-)-(*o*-Tri-*i*-propylsilylbenzaldehyde)$Cr(CO)_3$ (-)-**169** (60mg, 0.15mmol) in Et_2O (5ml) was treated with $MgBr_2.OEt_2$ (0.8M, 3.33ml, 2.66mmol) followed by powdered $LiAlD_4$ (50mg, 1.19mmol) under standard conditions. Work up and column chromatography (Al_2O_3, Et_2O:hexane 1:1) gave, on evaporation of the solvent, a 6:94 mixture of (*RS*)-(*o*-tri-*i*-propylsilyl-α-deuteriobenzyl alcohol)$Cr(CO)_3$ **216** and (*RR*)-(*o*-tri-*i*-propylsilyl-α-deuteriobenzyl alcohol)$Cr(CO)_3$ **217** as a yellow solid (60mg, 100%), identified by comparison with an authentic racemic mixture. $[\alpha]_D^{18}$ = -50o (c 0.715 $CHCl_3$).

*Desilylation and decomplexation of a 6:94 mixture of (RS)- and (RR)-(o-tri-i-propylsilyl-α-deuteriobenzyl alcohol)Cr(CO)3 complexes **216** and **217**.*

Tetra-*n*-butylammonium fluoride trihydrate (98mg, 0.31mmol) was added to a CH_2Cl_2 (2ml) solution of a 6:94 mixture of (*RS*)- and (*RR*)-(*o*-tri-*i*-propylsilyl-α-deuteriobenzyl alcohol)$Cr(CO)_3$ comlpexes **216** and **217** (25mg, 63μmol) and the solution stirred (30min). After filtration (Al_2O_3, Et_2O) and evaporation of the solvent, Et_2O (10ml) was added and the mixture allowed to decomplex under standard conditions (24h). Work up gave (*R*)-α-deuteriobenzyl alcohol (*R*)-**208** as a clear, colourless oil (7mg, 100%), identified by comparison with an authentic racemic sample.[118]

*(R)-α-Methoxy-α-(trifluoromethyl)phenylacetate esters of benzyl alcohol and α-deuteriobenzyl alcohol **208**.*

The (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetate esters of benzyl alcohol and chiral samples of (*R*)- and (*S*)-α-deuteriobenzyl alcohol (*R*)- and (*S*)-**208** were prepared under standard conditions. The ^1H n.m.r. chemical shifts used to check diastereoisomeric excesses of the esters, and hence enantiomeric excesses of the free alcohols, are presented below in Table VIII.

(*R*)-α-methoxy-α-(trifluoromethyl)-phenylacetate ester	^{1}H n.m.r. chemical shift (C_6D_6)		
	ArC*H*(OH)R		
benzyl alcohol	δ4.96, 4.86 AB system		
	(*RS*)	ratio	(*RR*)
(*S*)-α-deuteriobenzyl alcohol (*S*)-**208** from a 92:8 mixture of (*RS*)- and (*RR*)-(*o*-trimethylsilyl-α-deuterio benzyl alcohol)$Cr(CO)_3$ complexes **210** and **211**	δ4.83, s	92:8	δ4.93, s
(*R*)-α-deuteriobenzyl alcohol (*R*)-**208** from a 4:96 mixture of (*RS*)- and (*RR*)-(*o*-trimethylsilyl-α-deuterio benzyl alcohol)$Cr(CO)_3$ complexes **210** and **211**	δ4.82, s	4:96	δ4.92, s
(*R*)-α-deuteriobenzyl alcohol (*R*)-**208** from a 6:94 mixture of (*RS*)- and (*RR*)-(*o*-tri-*i*-propylsilyl-α-deuterio benzyl alcohol)$Cr(CO)_3$ complexes **216** and **217**	δ4.83, s	6:94	δ4.93, s

Table VIII. ^{1}H n.m.r. chemical shifts used to check diastereoisomeric excesses of the (*R*)-Mosher's esters of prepared samples of (*R*)- and (*S*)-α-deuteriobenzyl alcohol (*R*)- and (*S*)-**208**.

o-Methoxybenzyl methyl ether ***233***.

A solution of *o*-methoxybenzyl alcohol **232** (8.73g, 63.3mmol) in THF (250ml) was added dropwise to a stirred suspension of KH (3.80g, 95.0mmol) in THF (250ml). The solution was stirred (21h) and MeI (18.2g, 129mmol) added. After further stirring (1h), MeOH (5ml) was added cautiously and the solution filtered through celite and evaporated to a clear oil. Distillation gave the title compound **233** as a clear, colourless oil (8.72g, 91%). B.p. 54-58°C (0.1mmHg); *m/z* 152 (*M*+); ν_{max} 2838, 2824 (-OCH_3), 754 (disubstituted arene) cm^{-1}; ^{1}H n.m.r. (300MHz) δ7.47-7.44, 6.92-6.89 (2d, 2H, Ar*H*), 7.35-7.29, 7.05-7.00 (2t, 2H, Ar*H*), 4.59 (s, 2H, ArCH_2OR), 3.85 (s, 3H, ArOCH_3), 3.49 (s, 3H, ROCH_3).

(o-Methoxybenzyl methyl ether)Cr(CO)3 ***234***.

Thermolysis of $Cr(CO)_6$ (6.50g, 29.5mmol) with *o*-methoxybenzyl methyl ether **233** (3.00g, 19.7mmol) under standard conditions (110ml solvent, 68h) followed by work up gave a brown oil. Column chromatography (Al_2O_3, Et_2O) gave the title compound **234** as a yellow oil (4.73g, 83%). *m/z* Found: 288.0090 (*M*+); $C_{12}H_{12}CrO_5$ requires: 288.0090 (*M*+); ν_{max} ($CHCl_3$) 2850 (-OCH_3), 1971, 1891br (-CO) cm^{-1}; ^{1}H n.m.r.

(300MHz) δ5.76-5.73, 5.08-5.06 (2d, 2H, Ar*H*), 5.54-5.49, 4.95-4.91 (2t, 2H, Ar*H*), 4.53, 4.03 (AB system, 2H, J_{AB} = 12.00Hz, ArCH_2OR), 3.77 (s, 3H, ArOCH_3), 3.47 (s, 3H, ROCH_3).

*(+)-(o-Methoxybenzyl alcohol)Cr(CO)3 (+)-**192**.*

To a solution of (-)-(*o*-anisaldehyde)Cr(CO)3 (-)-**149** (400mg, 1.47mmol) in THF (15ml) and MeOH (5ml) was added $NaBH_4$ (167mg, 4.41mmol) and the mixture stirred (30min). Saturated aqueous NH_4Cl (10 drops) was added and the solution evaporated to a yellow oily solid. Column chromatography (Al_2O_3, Et_2O) gave the title compound (+)-**192** as a yellow solid (280mg, 70%), identified by comparison with an authentic sample. $[\alpha]_D^{22}$ = +237o (c 1.04 $CHCl_3$).

*(+)-(o-Methoxybenzyl methyl ether)Cr(CO)3 (+)-**234**.*

A solution of (+)-(*o*-methoxybenzyl alcohol)Cr(CO)3 (+)-**192** (230mg, 0.85mmol) in THF (3ml) was added dropwise to a stirred suspension of NaH (74mg, 3.08mmol) in THF (3ml). The solution was stirred (20min) and MeI (477mg, 3.36mmol) added. After further stirring (40min), MeOH (0.5ml) was added cautiously and the solution evaporated to a yellow oily solid. Column chromatography (Al_2O_3, Et_2O:light petroleum 3:1) gave the title complex (+)-**234** as a yellow solid (220mg, 90%), identified by comparison with an authentic racemic sample. $[\alpha]_D^{22}$ = +200o (c 1.26 $CHCl_3$).

*(RR,SS)-(o-Methoxy-α-methylbenzyl methyl ether)Cr(CO)3 **190**.*

(*o*-Methoxybenzyl methyl ether)Cr(CO)3 **234** (600mg, 2.08mmol) in THF (20ml) was treated with *t*-BuLi (2.36M, 0.97ml, 2.29mmol) and MeI (1.18g, 8.32mmol) under standard conditions. Work up and column chromatography (Al_2O_3, Et_2O) gave a 94:6 mixture of (*RR,SS*)-(*o*-methoxy-α-methylbenzyl methyl ether)Cr(CO)3 and a dimethylated derivative **190** and **235** respectively as yellow crystals (617mg, 100%). ^1H n.m.r. (300MHz) **190**: δ5.86-5.84, 5.04-5.02 (2d, 2H, Ar*H*), 5.51-5.47, 4.97-4.93 (2t, 2H, Ar*H*), 4.41 [q, 1H, J = 6.34Hz, ArC*H*(CH3)OR], 3.74 (s, 3H, ArOCH_3), 3.57 (s, 3H, ROCH_3), 1.37 [d, 3H, J = 6.34Hz, ArCH(CH_3)OR], **235**: δ5.42-5.41, 5.18-5.15 (2d, 2H, Ar*H*), 5.26-5.22 (t, 1H, Ar*H*), 3.83 (s, 3H, ArOCH_3), 3.54 (s, 3H, ROCH_3), 2.24 (s, 3H, ArCH_3), 1.45 [d, 3H, J = 6.34Hz, ArCH(CH_3)OR]. Recrystallisation of the mixture from CH_2Cl_2:light petroleum gave complex **190** as large yellow cubic crystals. M.p. 114-

115°C; Found: C 51.75, H 4.64%; $C_{13}H_{14}CrO_5$ requires: C 51.66, H 4.67%; *m/z* 302 (*M*+); ν_{max} ($CHCl_3$) 1969, 1888br (-CO). For X-ray crystal structure data see Appendix IV.

o-Methoxy-α-methylbenzyl methyl ether ***236***.

(*RR*,*SS*)-(*o*-Methoxy-α-methylbenzyl methyl ether)$Cr(CO)_3$ **190** (750mg, 2.48mmol) was dissolved in Et_2O (100ml) and allowed to decomplex under standard conditions (120h). Work up and distillation gave the title compound **236** as a clear, colourless oil (385mg, 94%). B.p. 60-70°C (0.1mmHg); *m/z* 165 (*M*+-1); ν_{max} (neat) 2824, 2816 (-OCH_3), 1596 (arene ring), 1238, 1111 (C-O-C), 763 (disubstituted arene) cm^{-1}; ^1H n.m.r. δ7.42-7.40, 6.90-6.88 (2d, 2H, Ar*H*), 7.29-7.23, 7.03-6.98 (2t, 2H, Ar*H*), 4.78 [q, 1H, J = 6.39Hz, ArC*H*(CH_3)OR], 3.85 (s, 3H, ArOC*H*$_3$), 3.28 (s, 3H, ROC*H*$_3$), 1.41 [d, 3H, J = 6.42Hz, ArCH(C*H*$_3$)OR].

(RR)-(o-Methoxy-α-methylbenzyl methyl ether)$Cr(CO)_3$ *(+)-****190***.

(+)-(*o*-Methoxybenzyl methyl ether)$Cr(CO)_3$ (+)-**234** (100mg, 0.35mmol) in THF (6ml) was treated with *t*-BuLi (2.6M, 0.13ml, 0.35mmol) and MeI (196mg, 1.38mmol) under standard conditions. Work up and column chromatography (Al_2O_3, Et_2O) gave a 94:6 mixture of (*RR*)-(*o*-methoxy-α-methylbenzyl methyl ether)$Cr(CO)_3$ and a dimethylated derivative (+)-**190** and **235** respectively as a yellow solid (105mg, 99%), identified by comparison with an authentic racemic mixture. Recrystallisation of the mixture from CH_2Cl_2:light petroleum gave complex (+)-**190** as large yellow cubic crystals, identified by comparison with an authentic racemic sample. $[\alpha]_D^{22}$ = +220° (c 0.795 $CHCl_3$).

*(R)-o-Methoxy-α-methylbenzyl methyl ether (+)-****236***.

(*RR*)-(*o*-Methoxy-α-methylbenzyl methyl ether)$Cr(CO)_3$ (+)-**190** (67mg, 0.22mmol) was dissolved in Et_2O (25ml) and allowed to decomplex under standard conditions (24h). Work up and distillation gave the title compound (+)-**236** as a clear, colourless oil (30mg, 82%), identified by comparison with an authentic racemic sample. $[\alpha]_D^{23}$ = +109° (c 1.19 $CHCl_3$).

*Complexation of o-methoxy-α-methylbenzyl methyl ether **236**.*

Thermolysis of $Cr(CO)_6$ (421mg, 1.91mmol) with *o*-methoxy-α-methylbenzyl methyl ether **236** (212mg, 1.28mmol) under standard conditions (44ml solvent, 22h) gave after work up and column chromatography (Al_2O_3, Et_2O) an 87:13 mixture of (*RR,SS*)-(*o*-methoxy-α-methylbenzyl methyl ether)$Cr(CO)_3$ and (*RS,SR*)-(*o*-methoxy-α-methylbenzyl methyl ether)$Cr(CO)_3$ **190** and **239** respectively as a yellow oil (246mg, 43%). *m/z* 302 (*M*+); ^{1}H n.m.r. (300MHz) **190**: δ5.88-5.85, 5.05-5.02 (2d, 2H, Ar*H*) 5.51-5.47, 4.98-4.94 (2t, 2H, Ar*H*), 4.42 [q, 1H, J = 6.37Hz, ArC*H*(CH$_3$)OR], 3.75 (s, 3H, ArOC*H*$_3$), 3.58 (s, 3H, ROC*H*$_3$), 1.38 [d, 3H, J = 6.41Hz, ArCH(C*H*$_3$)OR], **239**: δ5.93-5.91, 5.13-5.10 (2d, 2H, Ar*H*), 5.64-5.58, 4.91-4.87 (2t, 2H, Ar*H*), 4.59 [q, 1H, J = 6.50Hz, ArC*H*(CH$_3$)OR], 3.79 (s, 3H, ArOC*H*$_3$), 3.33 (s, 3H, ROC*H*$_3$), 1.52 [d, 3H, J = 6.52Hz, ArCH(C*H*$_3$)OR].

*(RR,SS)-(o-Methoxy-N,O-dimethylhalostachine)Cr(CO)$_3$ **240**.*

(*o*-Methoxybenzyl methyl ether)$Cr(CO)_3$ **234** (200mg, 0.69mmol) in THF (15ml) was treated with *t*-BuLi (2.6M, 0.29ml, 0.75mmol) and $CH_2N^+Me_2$ I$^-$ (Eschenmoser's salt, 271mg, 1.47mmol) under standard conditions with warming (-78 to 0^{o}C, 1h) prior to MeOH (1ml) quench. Work up and column chromatography (Al_2O_3, Et_2O) gave, on evaporation of the solvent, a single compound as a yellow oil. Crystallisation from CH_2Cl_2:light petroleum gave the title compound **240** as yellow needles (189mg, 79%). M.p. 89-90^{o}C; Found: C 52.15, H 5.54, N 3.63%; $C_{15}H_{19}CrNO_5$ requires: C 52.17, H 5.55, N 4.06%; *m/z* 346 (*M*++1); ν_{max} 2820 (-OCH$_3$), 2769 (-NCH$_3$), 1960, 1878br (-CO) cm^{-1}; ^{1}H n.m.r (300MHz) δ5.87-5.84, 5.02-5.00 (2d, 2H, Ar*H*), 5.54-5.49, 4.96-4.92 (2t, 2H, Ar*H*), 4.50 [d of d, 1H, J_{AX} = 8.48Hz, J_{AY} = 2.32Hz, ArC*H*(OCH$_3$)R], 3.75 (s, 3H, ArOC*H*$_3$), 3.65 [s, 3H, ArCH(OC*H*$_3$)R], 2.39, 2.52 (ABX system, 2H, J_{AB} = 13.15Hz, J_{AX} = 8.51Hz, J_{BX} = 2.31Hz, R^{1}C*H*$_2$NR$_2$), 2.33 [s, 6H, RN(C*H*$_3$)2].

*o-Methoxy-N,O-dimethylhalostachine **241**.*

(*RR,SS*)-(*o*-Methoxy-N,O-dimethylhalostachine)$Cr(CO)_3$ **240** (58mg, 0.17mmol) was dissolved in Et_2O (25ml) and allowed to decomplex under standard conditions (72h). Work up gave the title compound as a clear, colourless oil (30mg, 84%). ^{1}H n.m.r. (300MHz) δ7.38-7.35, 6.88-6.85 (2d, 2H, Ar*H*), 7.26-7.21, 7.00-6.95 (2t, 2H, Ar*H*), 4.81 [d of d, 1H, J_{AX} = 9.10Hz, J_{AY} = 2.26Hz, ArC*H*(OCH$_3$)R], 3.83 (s, 3H, ArOC*H*$_3$), 3.26

[s, 3H, ArCH(OC*H*$_3$)R], 2.60, 2.30 (ABX system, 2H, J_{AB} = 13.17Hz, J_{AX} = 9.15Hz, J_{BX} = 2.41Hz, R^{1}C*H*$_2$NR$_2$), 2.34 [s, 6H, RN(C*H*$_3$)$_2$]; ^{13}C n.m.r. δ150.96, 128.85 (2s, Ar*C*), 128.32, 126.55, 120.73, 110.35 (4d, Ar*C*), 75.53 [d, Ar*C*H(OCH$_3$)R], 65.33 (t, R^1*C*H$_2$NR$_2$), 56.91, 55.30 (2q, ArO*C*H$_3$, RO*C*H$_3$), 45.79 [q, RN(*C*H$_3$)$_2$].

Treatment of (o-methoxybenzyl methyl ether)Cr(CO)$_3$ ***234*** *with t-BuLi and PhCHN$^+$Me$_2$ I$^-$.*

(*o*-Methoxybenzyl methyl ether)Cr(CO)$_3$ **234** (546mg, 1.90mmol) in THF (12ml) was treated with *t*-BuLi (2.6M, 0.74ml, 1.92mmol) and PhCHN$^+$Me$_2$ I$^-$ (1.14g, 4.37mmol) under standard conditions with warming (-78 to 0°C, 1h) prior to MeOH (1ml) quench. Work up and column chromatography (Al$_2$O$_3$, Et$_2$O) gave, on evaporation of the solvent, a 55:45 mixture of (*R*1*R*2*R*,*S*1*S*2*S*)- and (*R*1*R*2*S*,*S*1*S*2*R*)-(*o*-methoxy-2-phenyl-N,O-dimethylhalostachine)Cr(CO)$_3$ complexes **242** and **243** with unknown relative assignments, as a yellow solid (755mg, 94%). ^{1}H n.m.r. (300MHz) **242**: δ4.98 [d, 1H, J = 3.82Hz, ArC*H*(OCH$_3$)R], 3.78, 3.68 (2s, 6H, ArOC*H*$_3$, ROC*H*$_3$), 3.15 [d, 1H, J = 3.15Hz, R^{1}C*H*(Ar^1)NR$_2$], 2.28 [s, 6H, RN(C*H*$_3$)$_2$], **243**: δ4.68 [d, 1H, J = 6.13Hz, ArC*H*(OCH$_3$)R], 3.66, 3.56 (2s, 6H, ArOC*H*$_3$, ROC*H*$_3$), 3.50 [d, 1H, J = 6.19Hz, R^{1}C*H*(Ar^1)NR$_2$], 2.26 [s, 6H, RN(C*H*$_3$)$_2$], **242** and **243**: δ7.90-7.07 (m, 10H, Ar*H*), 5.82-5.79, 5.74-5.72 (2d, 2H, Ar*H*), 5.45-5.38, 5.11-5.05, 4.81-4.76 (3m, 6H, Ar*H*).

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Appendix

X-Ray crystal structure analyses.

The following general procedure describes the X-ray crystal structure analysis methodology applied to the four complexes **68**, **93**, **173** and **190**.

The cell parameter and the reflection intensities were measured using graphite monochromated copper-Kα (1.5418$\overset{0}{A}$) radiation on an Enraf-Nonius CAD4-F 4-circle diffractometer operating in ω/2θ mode. Reflection intensities were collected out to a maximum Bragg angle of θ = 75°. The space group was determined unambiguously as a result of the structure analysis, but in the case of the homochiral complexes was initially indicated by the optical activity of the sample. The ω scan angle was calculated from [1.00 + (0.14tanθ)]° and increased by 25% on each side for background determination. Three standard reflections, measured each hour, were used to scale the intensity data and to correct for any crystal decay. The data were corrected for Lorentz polarisation and absorption effects[1] and equivalent reflections were merged. Reflections for which $I>3\sigma(I)$ were considered to be observed and used in the subsequent structure analysis. The structures were solved by either Patterson or direct methods followed by electron density Fourier synthesis in each case.

Final full-matrix least squares refinement included parameters for atomic positions, anisotropic temperature factors (for non-hydrogen atoms), an overall scale factor and an extinction parameter.[2] Hydrogen atoms were located by difference Fourier synthesis, placed in calculated positions and allowed to ride on their respective atoms. Refinement was terminated when the r.m.s. (shift/θ) was less than 0.001°. Weights for each reflection were calculated using Chebyshev series of either 3, 4 or 5 terms.[3] Final fourier difference synthesis showed no significant residual electron density and a detailed analysis failed to reveal any systematic errors in each structure. Calculations were performed using the CRYSTALS package[4] on the Chemical Crystallography Laboratory VAX 11/750 computer.

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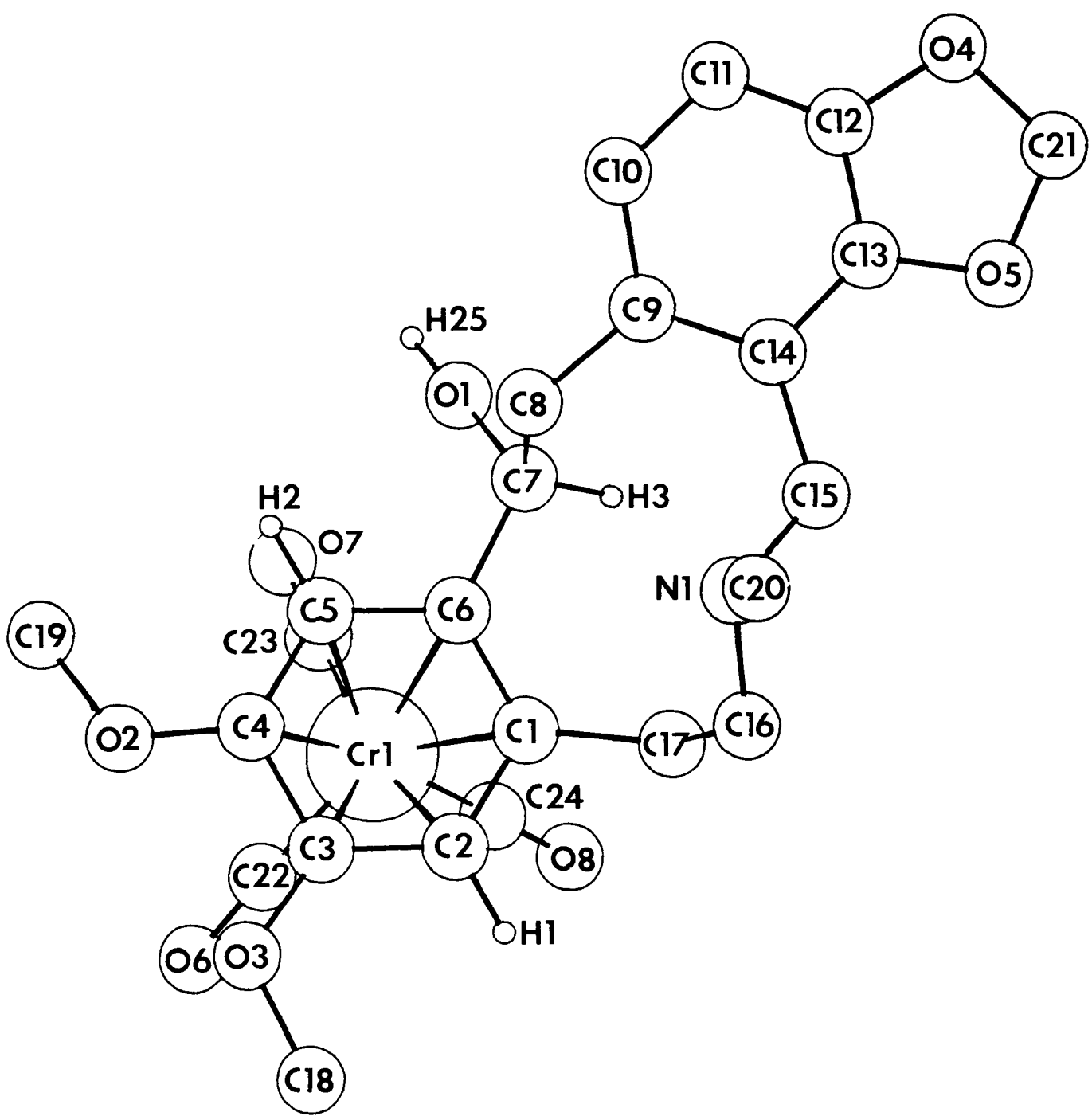
Appendix I. X-Ray Crystal Structure Data for *exo*-(Dihydrocryptopine)Cr(CO)3.

X-Ray crystal structure data for complex ***68****.*

Copper-Kα radiation, $C_{24}H_{25}CrNO_8$, M = 507.46, monoclinic, a = 7.573, b = 46.059, c = 7.017 $\overset{0}{A}$, $\alpha = \gamma = 90^o$, $\beta = 110.39^o$, U = 2294.2$\overset{0}{A}^3$, D_{calc} = 1.47gcm^{-3}, μ(Cu-Kα) = 45.90cm^{-1}, space group $P2_1/a$, number of independent reflections measured 3667, number of reflections with $I>3\sigma(I)$ 1999, R = 0.046, R_w = 0.059.

The structure was solved by direct methods and electron density Fourier synthesis. Reflections were weighted by applying a 3 term Chebyshev series of the form $w = [11.353t_0(X) - 3.746t_1(X) + 7.752t_2(X)]$ where $X = F_o/F_{max}$.



Atomic coordinates (e.s.d's) for complex **68**.

Atom	x/a	y/b	z/c	U(iso)
CR(1)	8611(1)	3287.2(2)	724(1)	483
N(1)	6789(5)	4163.3(9)	-4228(6)	492
O(1)	11636(5)	3949.2(9)	1522(6)	635
O(2)	11067(6)	2910.9(9)	-1575(7)	760
O(3)	7534(6)	2816.9(9)	-3194(6)	726
O(4)	10532(7)	5303.9(9)	-2375(7)	726
O(5)	7693(5)	5058.6(8)	-3140(6)	648
O(6)	8169(10)	2687(1)	2114(9)	1046
O(7)	11625(7)	3393(1)	4749(7)	986
O(8)	5728(7)	3454(1)	2532(8)	915
C(1)	7347(6)	3595(1)	-1812(7)	450
C(2)	6748(7)	3312(1)	-2553(7)	513
C(3)	7983(8)	3086(1)	-2492(8)	561
C(4)	9963(8)	3142(1)	-1595(9)	602
C(5)	10570(7)	3422(1)	-845(8)	543
C(6)	9288(6)	3651(1)	-1000(7)	465
C(7)	10085(7)	3952(1)	-369(8)	514
C(8)	10787(7)	4081(1)	-1997(8)	520
C(9)	10725(7)	4409(1)	-2095(8)	508
C(10)	12414(7)	4564(1)	-1672(8)	595
C(11)	12500(8)	4865(1)	-1761(9)	610
C(12)	10828(9)	5009(1)	-2255(8)	595
C(13)	9156(7)	4863(1)	-2676(7)	508
C(14)	9011(7)	4566(1)	-2647(7)	465
C(15)	7069(7)	4432(1)	-3086(8)	510
C(16)	5248(6)	3985(1)	-4036(8)	478
C(17)	5827(6)	3821(1)	-2022(8)	487
C(18)	5598(10)	2747(1)	-4118(11)	855
C(19)	12921(9)	2922(2)	-346(13)	881
C(20)	6546(9)	4219(2)	-6341(9)	712
C(21)	8529(10)	5337(1)	-3002(10)	705
C(22)	8374(10)	2923(1)	1573(10)	726
C(23)	10433(9)	3353(2)	3166(10)	745
C(24)	6865(8)	3391(1)	1829(9)	618
H(1)	5365(7)	3273(1)	-3138(7)	500
H(2)	11951(7)	3458(1)	-172(8)	500
H(3)	9076(7)	4069(1)	-117(8)	500
H(4)	12121(7)	4018(1)	-1689(8)	500
H(5)	9986(7)	4003(1)	-3353(8)	500
H(6)	13617(7)	4452(1)	-1290(8)	500
H(7)	13725(8)	4969(1)	-1469(9)	500
H(8)	6095(7)	4575(1)	-3881(8)	500
H(9)	6902(7)	4392(1)	-1759(8)	500
H(10)	4148(6)	4113(1)	-4158(8)	500
H(11)	4878(6)	3839(1)	-5163(8)	500
H(12)	6325(6)	3965(1)	-897(8)	500
H(13)	4695(6)	3722(1)	-1899(8)	500
H(14)	5453(10)	2541(1)	-4583(11)	500
H(15)	5004(10)	2878(1)	-5309(11)	500
H(16)	4968(10)	2776(1)	-3094(11)	500
H(17)	13559(9)	2737(2)	-477(13)	500
H(18)	13543(9)	3089(2)	-776(13)	500
H(19)	13019(9)	2949(2)	1101(13)	500
H(20)	6351(9)	4031(2)	-7104(9)	500
H(21)	7694(9)	4318(2)	-6419(9)	500
H(22)	5423(9)	4347(2)	-6953(9)	500
H(23)	8047(10)	5434(1)	-4361(10)	500
H(24)	8210(10)	5458(1)	-1984(10)	500
H(25)	12737(5)	3945.8(9)	2824(6)	800

Thermal parameters (e.s.d's) for complex **68**.

Atom	U(11)	U(22)	U(33)	U(23)	U(13)	U(12)
CR(1)	501(5)	438(5)	472(5)	21(4)	98(3)	19(4)
N(1)	501(23)	495(25)	504(23)	-24(19)	169(19)	-118(20)
O(1)	564(22)	658(26)	647(24)	2(20)	-143(18)	-49(19)
O(2)	812(30)	654(28)	918(30)	-44(22)	286(24)	211(22)
O(3)	969(31)	495(24)	736(27)	-113(20)	92(23)	-38(22)
O(4)	1082(36)	533(26)	871(31)	-68(21)	386(27)	-338(24)
O(5)	755(25)	435(21)	829(28)	12(19)	273(21)	-18(19)
O(6)	2103(66)	591(32)	1130(42)	296(30)	645(42)	178(35)
O(7)	902(35)	1882(65)	549(28)	104(30)	-38(26)	-378(35)
O(8)	1029(35)	1006(38)	986(36)	-49(29)	571(31)	100(29)
C(1)	431(27)	463(29)	439(26)	4(21)	126(21)	-3(22)
C(2)	531(28)	474(30)	484(27)	20(25)	77(22)	-20(26)
C(3)	756(39)	422(29)	532(31)	4(24)	188(27)	-24(27)
C(4)	678(37)	538(35)	625(34)	43(27)	233(28)	110(29)
C(5)	454(27)	562(32)	624(33)	55(27)	176(24)	38(26)
C(6)	460(28)	465(29)	471(28)	7(22)	157(22)	42(23)
C(7)	408(26)	536(32)	557(30)	-7(25)	68(22)	16(23)
C(8)	391(25)	591(34)	667(34)	-19(27)	225(24)	-33(24)
C(9)	455(28)	551(32)	534(29)	-56(24)	167(23)	-75(25)
C(10)	463(30)	708(40)	648(35)	-38(29)	174(25)	-99(28)
C(11)	591(36)	856(47)	603(34)	-89(31)	201(28)	-362(35)
C(12)	813(43)	588(37)	514(31)	-58(27)	232(29)	-251(34)
C(13)	643(32)	496(32)	439(27)	-40(23)	191(24)	-133(28)
C(14)	521(29)	449(28)	451(27)	-54(22)	153(22)	-124(23)
C(15)	459(28)	437(30)	639(32)	-3(24)	160(24)	-27(22)
C(16)	384(25)	489(31)	537(29)	24(23)	97(22)	-5(22)
C(17)	389(25)	482(30)	607(31)	69(24)	149(22)	0(22)
C(18)	1137(60)	563(43)	905(50)	-43(35)	91(43)	-166(38)
C(19)	773(46)	709(48)	1394(68)	-69(44)	402(46)	161(36)
C(20)	909(44)	789(44)	565(34)	47(31)	184(32)	-308(37)
C(21)	1143(55)	507(36)	667(39)	-57(30)	353(37)	-168(35)
C(22)	1028(48)	596(41)	682(39)	79(32)	301(35)	216(36)
C(23)	699(38)	998(56)	577(37)	90(34)	164(31)	-85(34)
C(24)	730(39)	560(35)	569(34)	-19(27)	211(30)	-11(29)

Bond lengths in $\overset{0}{A}$ (e.s.d's) for complex **68**.

CR(1)	C(1)	2.216(5)	C(6)	C(7)	1.514(7)
CR(1)	C(2)	2.243(5)	C(7)	C(8)	1.538(7)
CR(1)	C(3)	2.330(5)	C(7)	H(3)	1.00
CR(1)	C(4)	2.303(6)	C(8)	C(9)	1.512(7)
CR(1)	C(5)	2.222(5)	C(8)	H(4)	1.00
CR(1)	C(6)	2.229(5)	C(8)	H(5)	1.00
CR(1)	C(22)	1.812(7)	C(9)	C(10)	1.404(7)
CR(1)	C(23)	1.812(6)	C(9)	C(14)	1.418(7)
CR(1)	C(24)	1.814(6)	C(10)	C(11)	1.388(8)
N(1)	C(15)	1.450(6)	C(10)	H(6)	1.00
N(1)	C(16)	1.471(6)	C(11)	C(12)	1.363(8)
N(1)	C(20)	1.451(7)	C(11)	H(7)	1.00
O(1)	C(7)	1.434(6)	C(12)	C(13)	1.371(7)
O(1)	H(25)	1.00	C(13)	C(14)	1.372(7)
O(2)	C(4)	1.351(7)	C(14)	C(15)	1.524(7)
O(2)	C(19)	1.369(8)	C(15)	H(8)	1.00
O(3)	C(3)	1.334(6)	C(15)	H(9)	1.00
O(3)	C(18)	1.418(8)	C(16)	C(17)	1.528(7)
O(4)	C(12)	1.376(7)	C(16)	H(10)	1.00
O(4)	C(21)	1.432(8)	C(16)	H(11)	1.00
O(5)	C(13)	1.377(6)	C(17)	H(12)	1.00
O(5)	C(21)	1.417(7)	C(17)	H(13)	1.00
O(6)	C(22)	1.176(8)	C(18)	H(14)	1.00
O(7)	C(23)	1.177(7)	C(18)	H(15)	1.00
O(8)	C(24)	1.169(7)	C(18)	H(16)	1.00
C(1)	C(2)	1.418(7)	C(19)	H(17)	1.00
C(1)	C(6)	1.402(6)	C(19)	H(18)	1.00
C(1)	C(17)	1.518(7)	C(19)	H(19)	1.00
C(2)	C(3)	1.391(7)	C(20)	H(20)	1.00
C(2)	H(1)	1.00	C(20)	H(21)	1.00
C(3)	C(4)	1.433(8)	C(20)	H(22)	1.00
C(4)	C(5)	1.405(8)	C(21)	H(23)	1.00
C(5)	C(6)	1.413(7)	C(21)	H(24)	1.00
C(5)	H(2)	1.00			

Bond angles in degrees (e.s.d's) for complex **68**.

C(2)	CR(1)	C(1)	37.1(2)	C(7)	C(6)	C(5)	117.9(4)
C(3)	CR(1)	C(1)	65.9(2)	C(6)	C(7)	O(1)	112.2(4)
C(3)	CR(1)	C(2)	35.4(2)	C(8)	C(7)	O(1)	107.8(4)
C(4)	CR(1)	C(1)	78.0(2)	C(8)	C(7)	C(6)	110.0(4)
C(4)	CR(1)	C(2)	64.3(2)	H(3)	C(7)	O(1)	105.7(3)
C(4)	CR(1)	C(3)	36.0(2)	H(3)	C(7)	C(6)	107.1(3)
C(5)	CR(1)	C(1)	66.4(2)	H(3)	C(7)	C(8)	114.0(3)
C(5)	CR(1)	C(2)	76.6(2)	C(9)	C(8)	C(7)	114.0(4)
C(5)	CR(1)	C(3)	65.0(2)	H(4)	C(8)	C(7)	108.2(3)
C(5)	CR(1)	C(4)	36.1(2)	H(4)	C(8)	C(9)	108.2(3)
C(6)	CR(1)	C(1)	36.8(2)	H(5)	C(8)	C(7)	108.4(3)
C(6)	CR(1)	C(2)	65.5(2)	H(5)	C(8)	C(9)	108.4(3)
C(6)	CR(1)	C(3)	77.4(2)	H(5)	C(8)	H(4)	109.47
C(6)	CR(1)	C(4)	65.9(2)	C(10)	C(9)	C(8)	119.3(5)
C(6)	CR(1)	C(5)	37.0(2)	C(14)	C(9)	C(8)	122.3(4)
C(22)	CR(1)	C(1)	142.5(3)	C(14)	C(9)	C(10)	118.5(5)
C(22)	CR(1)	C(2)	106.6(3)	C(11)	C(10)	C(9)	123.6(5)
C(22)	CR(1)	C(3)	86.5(2)	H(6)	C(10)	C(9)	118.1(3)
C(22)	CR(1)	C(4)	94.8(3)	H(6)	C(10)	C(11)	118.3(3)
C(22)	CR(1)	C(5)	125.5(3)	C(12)	C(11)	C(10)	116.2(5)
C(22)	CR(1)	C(6)	160.6(2)	H(7)	C(11)	C(10)	121.6(3)
C(23)	CR(1)	C(1)	128.8(3)	H(7)	C(11)	C(12)	122.2(3)
C(23)	CR(1)	C(2)	163.9(2)	C(11)	C(12)	O(4)	127.8(5)
C(23)	CR(1)	C(3)	144.4(3)	C(13)	C(12)	O(4)	110.6(6)
C(23)	CR(1)	C(4)	109.7(3)	C(13)	C(12)	C(11)	121.5(6)
C(23)	CR(1)	C(5)	90.1(2)	C(12)	C(13)	O(5)	109.7(5)
C(23)	CR(1)	C(6)	98.3(2)	C(14)	C(13)	O(5)	126.4(4)
C(24)	CR(1)	C(1)	90.0(2)	C(14)	C(13)	C(12)	123.9(5)
C(24)	CR(1)	C(2)	97.6(2)	C(13)	C(14)	C(9)	116.3(4)
C(24)	CR(1)	C(3)	125.8(2)	C(15)	C(14)	C(9)	125.1(5)
C(24)	CR(1)	C(4)	161.4(2)	C(15)	C(14)	C(13)	118.5(5)
C(24)	CR(1)	C(5)	148.3(2)	C(14)	C(15)	N(1)	113.7(4)
C(24)	CR(1)	C(6)	112.0(2)	H(8)	C(15)	N(1)	108.4(3)
C(23)	CR(1)	C(22)	88.5(3)	H(8)	C(15)	C(14)	108.6(3)
C(24)	CR(1)	C(22)	86.2(3)	H(9)	C(15)	N(1)	108.3(3)
C(24)	CR(1)	C(23)	88.9(3)	H(9)	C(15)	C(14)	108.3(3)
C(16)	N(1)	C(15)	113.2(4)	H(9)	C(15)	H(8)	109.47
C(20)	N(1)	C(15)	110.9(4)	C(17)	C(16)	N(1)	112.4(4)
C(20)	N(1)	C(16)	111.7(4)	H(10)	C(16)	N(1)	109.0(3)
H(25)	O(1)	C(7)	178.7(3)	H(10)	C(16)	C(17)	109.6(3)
C(19)	O(2)	C(4)	118.2(5)	H(11)	C(16)	N(1)	108.3(3)
C(18)	O(3)	C(3)	118.0(5)	H(11)	C(16)	C(17)	108.0(3)
C(21)	O(4)	C(12)	104.8(4)	H(11)	C(16)	H(10)	109.47
C(21)	O(5)	C(13)	105.8(4)	C(16)	C(17)	C(1)	113.1(4)
C(2)	C(1)	CR(1)	72.5(3)	H(12)	C(17)	C(1)	108.2(3)
C(6)	C(1)	CR(1)	72.1(3)	H(12)	C(17)	C(16)	108.0(3)
C(6)	C(1)	C(2)	118.2(4)	H(13)	C(17)	C(1)	109.0(3)
C(17)	C(1)	CR(1)	128.1(3)	H(13)	C(17)	C(16)	109.1(2)
C(17)	C(1)	C(2)	117.2(4)	H(13)	C(17)	H(12)	109.47
C(17)	C(1)	C(6)	124.5(4)	H(14)	C(18)	O(3)	110.1(3)
C(1)	C(2)	CR(1)	70.4(3)	H(15)	C(18)	O(3)	109.8(3)
C(3)	C(2)	CR(1)	75.7(3)	H(15)	C(18)	H(14)	109.48
C(3)	C(2)	C(1)	123.5(5)	H(16)	C(18)	O(3)	108.5(4)
H(1)	C(2)	CR(1)	127.3(1)	H(16)	C(18)	H(14)	109.48
H(1)	C(2)	C(1)	118.2(3)	H(16)	C(18)	H(15)	109.48
H(1)	C(2)	C(3)	118.3(3)	H(17)	C(19)	O(2)	109.4(3)
O(3)	C(3)	CR(1)	131.8(4)	H(18)	C(19)	O(2)	109.1(4)
C(2)	C(3)	CR(1)	68.9(3)	H(18)	C(19)	H(17)	109.48
C(2)	C(3)	O(3)	127.1(5)	H(19)	C(19)	O(2)	109.9(4)
C(4)	C(3)	CR(1)	70.9(3)	H(19)	C(19)	H(17)	109.48
C(4)	C(3)	O(3)	115.1(5)	H(19)	C(19)	H(18)	109.48
C(4)	C(3)	C(2)	117.9(5)	H(20)	C(20)	N(1)	109.7(3)
O(2)	C(4)	CR(1)	130.3(4)	H(21)	C(20)	N(1)	109.5(3)
C(3)	C(4)	CR(1)	73.0(3)	H(21)	C(20)	H(20)	109.47
C(3)	C(4)	O(2)	114.2(5)	H(22)	C(20)	N(1)	109.2(3)
C(5)	C(4)	CR(1)	68.8(3)	H(22)	C(20)	H(20)	109.48
C(5)	C(4)	O(2)	126.7(5)	H(22)	C(20)	H(21)	109.48
C(5)	C(4)	C(3)	119.0(5)	O(5)	C(21)	O(4)	109.0(5)
C(4)	C(5)	CR(1)	75.1(3)	H(23)	C(21)	O(4)	109.6(3)
C(6)	C(5)	CR(1)	71.8(3)	H(23)	C(21)	O(5)	109.4(3)
C(6)	C(5)	C(4)	122.0(5)	H(24)	C(21)	O(4)	109.5(3)
H(2)	C(5)	CR(1)	125.5(1)	H(24)	C(21)	O(5)	109.8(3)
H(2)	C(5)	C(4)	118.7(3)	H(24)	C(21)	H(23)	109.47
H(2)	C(5)	C(6)	119.4(3)	O(6)	C(22)	CR(1)	178.2(7)
C(1)	C(6)	CR(1)	71.1(3)	O(7)	C(23)	CR(1)	179.4(7)
C(5)	C(6)	CR(1)	71.2(3)	O(8)	C(24)	CR(1)	179.1(5)
C(5)	C(6)	C(1)	119.3(5)				
C(7)	C(6)	CR(1)	132.3(3)				
C(7)	C(6)	C(1)	122.7(4)				

Selected torsional angles in degrees (e.s.d's) for complex **68**.

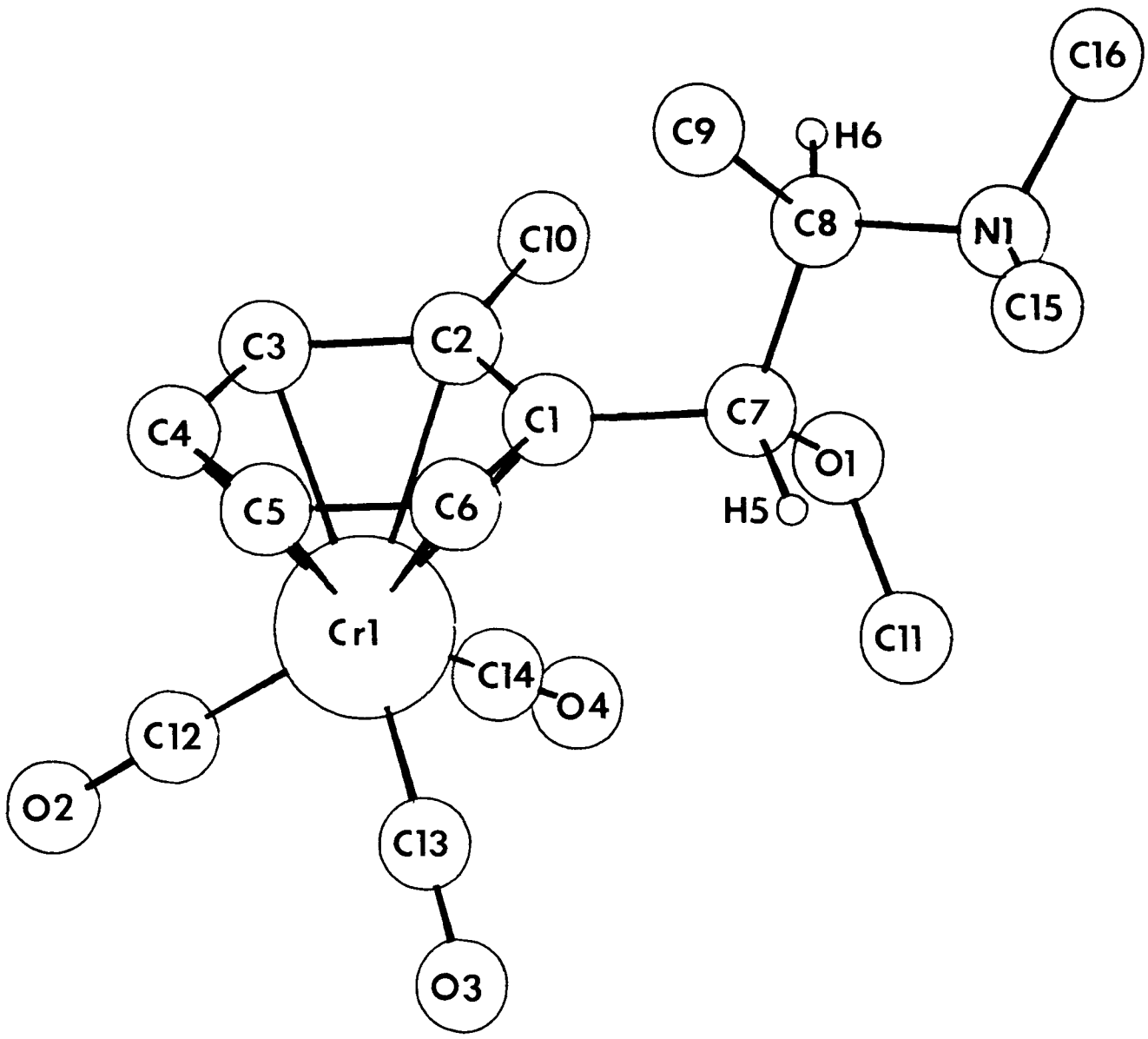
O(1)	-	C(7)	-	C(6)	-	C(5)	-45.47
H(2)	-	C(5)	-	C(6)	-	C(7)	7.53
C(19)	-	O(2)	-	C(4)	-	C(5)	15.20
C(18)	-	O(3)	-	C(3)	-	C(2)	0.24
H(1)	-	C(2)	-	C(3)	-	C(4)	-178.18
C(8)	-	C(7)	-	C(6)	-	C(5)	74.63
C(16)	-	C(17)	-	C(1)	-	C(6)	88.85

Appendix II. X-Ray Crystal Structure Data for (*R*,1*S*,2*R*)-(N,O,*o*-Trimethylpseudoephedrine)Cr(CO)3.

X-Ray crystal structure data for complex ***93***.

Copper-Kα radiation, $C_{16}H_{21}CrNO_4$, M = 343.34, rotation (-), orthorhombic, a = 7.964, b = 11.909, c = 17.958 Å, α = β = γ = 90°, U = 1703.2Å^3, scan speed 1.0 to 5.5°min^{-1}, D_{calc} = 1.34gcm^{-3}, μ(Cu-Kα) = 57.49cm^{-1}, space group $P2_12_12_1$, crystal dimensions 0.088mm x 0.11mm x 0.418mm, number of independent reflections measured 1448, number of reflections with I>3σ(I) 1448, R = 0.061, R_w = 0.079.

The structure was solved by Patterson methods and electron density Fourier synthesis. Reflections were weighted by applying a 4 term Chebyshev series of the form w = [494.943t_0(X) + 722.512t_1(X) + 325.684t_2(X) + 96.445t_3(X)] where X = F_o/F_{max}.



Atomic coordinates (e.s.d's) for complex **93**.

Atom	x/a	y/b	z/c	U(iso)
CR(1)	2141(2)	-1102(1)	2213.6(7)	557
N(1)	7495(9)	723(5)	305(4)	580
O(1)	6592(7)	-431(4)	1657(3)	532
O(2)	-188(10)	-2340(7)	3227(4)	912
O(3)	1756(13)	918(7)	3177(4)	1064
O(4)	4956(10)	-1967(8)	3148(4)	954
C(1)	3698(10)	-616(7)	1242(5)	539
C(2)	3538(11)	-1773(7)	1232(5)	547
C(3)	1872(13)	-2237(9)	1258(5)	654
C(4)	473(14)	-1559(14)	1285(6)	771
C(5)	626(12)	-417(12)	1281(6)	709
C(6)	2268(12)	54(9)	1269(5)	639
C(7)	5379(10)	6(6)	1163(4)	463
C(8)	6094(10)	-66(7)	373(4)	545
C(9)	4757(13)	94(9)	-241(5)	774
C(10)	4997(12)	-2568(7)	1173(6)	688
C(11)	6842(12)	223(9)	2302(5)	738
C(12)	687(11)	-1848(8)	2828(5)	662
C(13)	1917(12)	134(8)	2794(5)	706
C(14)	3885(12)	-1622(8)	2787(5)	675
C(15)	7047(15)	1878(7)	227(6)	792
C(16)	8687(13)	398(10)	-285(5)	776
H(1)	1759(13)	-3115(9)	1261(5)	1149(86)
H(2)	-708(14)	-1948(14)	1316(6)	1149(86)
H(3)	-468(12)	74(12)	1263(6)	1149(86)
H(4)	2411(12)	928(9)	1306(5)	1149(86)
H(5)	5224(10)	844(6)	1331(4)	1149(86)
H(6)	6612(10)	-866(7)	285(4)	1149(86)
H(7)	3809(13)	-507(9)	-165(5)	1149(86)
H(8)	5292(13)	-6(9)	-771(5)	1149(86)
H(9)	4242(13)	902(9)	-195(5)	1149(86)
H(10)	4551(12)	-3397(7)	1182(6)	1149(86)
H(11)	5803(12)	-2438(7)	1628(6)	1149(86)
H(12)	5655(12)	-2425(7)	675(6)	1149(86)
H(13)	7750(12)	-174(9)	2634(5)	1149(86)
H(14)	7270(12)	1025(9)	2150(5)	1149(86)
H(15)	5717(12)	298(9)	2603(5)	1149(86)
H(16)	8130(15)	2377(7)	184(6)	1149(86)
H(17)	6355(15)	2123(7)	697(6)	1149(86)
H(18)	6310(15)	1980(7)	-253(6)	1149(86)
H(19)	8984(13)	-452(10)	-203(5)	1149(86)
H(20)	9780(13)	885(10)	-235(5)	1149(86)
H(21)	8172(13)	507(10)	-818(5)	1149(86)

Thermal parameters (e.s.d's) for complex **93**.

Atom	U(11)	U(22)	U(33)	U(23)	U(13)	U(12)
CR(1)	458(7)	654(7)	587(7)	38(7)	32(6)	-58(7)
N(1)	582(47)	603(34)	609(36)	86(30)	135(31)	-55(32)
O(1)	472(29)	665(30)	485(24)	-31(25)	-46(22)	15(25)
O(2)	971(56)	1091(55)	904(47)	93(45)	265(46)	-326(49)
O(3)	1478(76)	963(51)	1027(52)	-254(46)	374(56)	-281(59)
O(4)	738(49)	1499(73)	1037(54)	483(56)	-284(45)	-73(55)
C(1)	398(45)	705(51)	565(42)	52(40)	28(38)	3(38)
C(2)	495(43)	554(43)	601(44)	-8(38)	5(39)	-47(38)
C(3)	670(69)	906(65)	651(48)	-144(48)	-56(45)	-378(55)
C(4)	475(58)	1545(117)	701(61)	10(74)	-92(45)	-247(70)
C(5)	419(58)	1141(87)	836(69)	286(69)	40(47)	107(56)
C(6)	414(47)	871(56)	793(55)	226(50)	30(44)	71(47)
C(7)	460(42)	484(37)	456(36)	64(31)	19(31)	-14(33)
C(8)	592(52)	613(43)	468(37)	24(35)	81(35)	-85(41)
C(9)	762(66)	1096(78)	579(47)	70(54)	-97(47)	-110(63)
C(10)	638(58)	586(46)	889(62)	33(48)	70(51)	60(45)
C(11)	659(61)	996(66)	655(47)	-167(51)	-36(46)	-103(50)
C(12)	592(52)	730(52)	708(53)	105(53)	63(47)	-89(43)
C(13)	782(66)	759(52)	653(46)	12(49)	118(54)	-194(50)
C(14)	731(64)	853(58)	545(43)	80(52)	-112(46)	-197(50)
C(15)	943(72)	602(48)	959(64)	155(47)	73(66)	-141(59)
C(16)	708(64)	1109(74)	756(59)	26(58)	321(53)	-113(63)

Bond lengths in $\overset{0}{A}$ (e.s.d's) for complex **93**.

CR(1)	C(1)	2.218(9)
CR(1)	C(2)	2.232(9)
CR(1)	C(3)	2.196(9)
CR(1)	C(4)	2.20(1)
CR(1)	C(5)	2.22(1)
CR(1)	C(6)	2.186(9)
CR(1)	C(12)	1.830(9)
CR(1)	C(13)	1.81(1)
CR(1)	C(14)	1.84(1)
N(1)	C(8)	1.46(1)
N(1)	C(15)	1.43(1)
N(1)	C(16)	1.47(1)
O(1)	C(7)	1.411(8)
O(1)	C(11)	1.411(9)
O(2)	C(12)	1.16(1)
O(3)	C(13)	1.17(1)
O(4)	C(14)	1.15(1)
C(1)	C(2)	1.38(1)
C(1)	C(6)	1.39(1)
C(1)	C(7)	1.54(1)
C(2)	C(3)	1.44(1)
C(2)	C(10)	1.50(1)
C(3)	C(4)	1.38(2)
C(3)	H(1)	1.05
C(4)	C(5)	1.37(2)
C(4)	H(2)	1.05
C(5)	C(6)	1.42(1)
C(5)	H(3)	1.05
C(6)	H(4)	1.05
C(7)	C(8)	1.530(9)
C(7)	H(5)	1.05
C(8)	C(9)	1.54(1)
C(8)	H(6)	1.05
C(9)	H(7)	1.05
C(9)	H(8)	1.05
C(9)	H(9)	1.05
C(10)	H(10)	1.05
C(10)	H(11)	1.05
C(10)	H(12)	1.05
C(11)	H(13)	1.05
C(11)	H(14)	1.05
C(11)	H(15)	1.05
C(15)	H(16)	1.05
C(15)	H(17)	1.05
C(15)	H(18)	1.05
C(16)	H(19)	1.05
C(16)	H(20)	1.05
C(16)	H(21)	1.05

Bond angles in degrees (e.s.d's) for complex **93**.

C(2)	CR(1)	C(1)	36.3(3)	C(8)	C(7)	C(1)	112.5(6)
C(3)	CR(1)	C(1)	66.4(3)	H(5)	C(7)	O(1)	104.5(4)
C(3)	CR(1)	C(2)	37.9(3)	H(5)	C(7)	C(1)	109.2(4)
C(4)	CR(1)	C(1)	78.8(4)	H(5)	C(7)	C(8)	111.3(4)
C(4)	CR(1)	C(2)	67.3(4)	C(7)	C(8)	N(1)	109.0(6)
C(4)	CR(1)	C(3)	36.5(4)	C(9)	C(8)	N(1)	112.7(7)
C(5)	CR(1)	C(1)	67.3(3)	C(9)	C(8)	C(7)	113.4(7)
C(5)	CR(1)	C(2)	78.9(4)	H(6)	C(8)	N(1)	105.7(4)
C(5)	CR(1)	C(3)	65.4(5)	H(6)	C(8)	C(7)	109.7(4)
C(5)	CR(1)	C(4)	36.0(4)	H(6)	C(8)	C(9)	105.9(5)
C(6)	CR(1)	C(1)	36.8(3)	H(7)	C(9)	C(8)	108.6(5)
C(6)	CR(1)	C(2)	65.8(3)	H(8)	C(9)	C(8)	110.7(5)
C(6)	CR(1)	C(3)	77.6(4)	H(8)	C(9)	H(7)	109.48
C(6)	CR(1)	C(4)	66.2(5)	H(9)	C(9)	C(8)	109.1(5)
C(6)	CR(1)	C(5)	37.7(4)	H(9)	C(9)	H(7)	109.48
C(12)	CR(1)	C(1)	162.7(4)	H(9)	C(9)	H(8)	109.48
C(12)	CR(1)	C(2)	128.1(4)	H(10)	C(10)	C(2)	109.3(5)
C(12)	CR(1)	C(3)	96.3(4)	H(11)	C(10)	C(2)	109.0(5)
C(12)	CR(1)	C(4)	87.4(4)	H(11)	C(10)	H(10)	109.48
C(12)	CR(1)	C(5)	106.8(4)	H(12)	C(10)	C(2)	110.1(5)
C(12)	CR(1)	C(6)	143.4(4)	H(12)	C(10)	H(10)	109.48
C(13)	CR(1)	C(1)	107.2(3)	H(12)	C(10)	H(11)	109.48
C(13)	CR(1)	C(2)	142.6(4)	H(13)	C(11)	O(1)	108.4(5)
C(13)	CR(1)	C(3)	160.1(4)	H(14)	C(11)	O(1)	109.6(5)
C(13)	CR(1)	C(4)	125.3(5)	H(14)	C(11)	H(13)	109.48
C(13)	CR(1)	C(5)	94.7(5)	H(15)	C(11)	O(1)	110.5(5)
C(13)	CR(1)	C(6)	86.6(4)	H(15)	C(11)	H(13)	109.48
C(14)	CR(1)	C(1)	96.1(4)	H(15)	C(11)	H(14)	109.48
C(14)	CR(1)	C(2)	86.9(4)	O(2)	C(12)	CR(1)	177.7(9)
C(14)	CR(1)	C(3)	107.7(4)	O(3)	C(13)	CR(1)	178.8(8)
C(14)	CR(1)	C(4)	142.9(5)	O(4)	C(14)	CR(1)	178.6(9)
C(14)	CR(1)	C(5)	163.4(4)	H(16)	C(15)	N(1)	110.3(6)
C(14)	CR(1)	C(6)	127.8(4)	H(17)	C(15)	N(1)	108.7(5)
C(13)	CR(1)	C(12)	89.1(4)	H(17)	C(15)	H(16)	109.48
C(14)	CR(1)	C(12)	88.7(4)	H(18)	C(15)	N(1)	109.4(5)
C(14)	CR(1)	C(13)	91.5(4)	H(18)	C(15)	H(16)	109.48
C(15)	N(1)	C(8)	115.9(8)	H(18)	C(15)	H(17)	109.48
C(16)	N(1)	C(8)	112.5(7)	H(19)	C(16)	N(1)	107.4(5)
C(16)	N(1)	C(15)	110.1(7)	H(20)	C(16)	N(1)	109.2(5)
C(11)	O(1)	C(7)	114.2(6)	H(20)	C(16)	H(19)	109.48
C(2)	C(1)	CR(1)	72.4(6)	H(21)	C(16)	N(1)	111.8(5)
C(6)	C(1)	CR(1)	70.3(5)	H(21)	C(16)	H(19)	109.48
C(6)	C(1)	C(2)	119.7(9)	H(21)	C(16)	H(20)	109.48
C(7)	C(1)	CR(1)	133.2(6)				
C(7)	C(1)	C(2)	124.0(8)				
C(7)	C(1)	C(6)	116.2(7)				
C(1)	C(2)	CR(1)	71.3(6)				
C(3)	C(2)	CR(1)	69.7(5)				
C(3)	C(2)	C(1)	117.8(9)				
C(10)	C(2)	CR(1)	131.8(7)				
C(10)	C(2)	C(1)	123.8(8)				
C(10)	C(2)	C(3)	118.3(8)				
C(2)	C(3)	CR(1)	72.5(5)				
C(4)	C(3)	CR(1)	71.9(6)				
C(4)	C(3)	C(2)	121.5(9)				
H(1)	C(3)	CR(1)	128.1(3)				
H(1)	C(3)	C(2)	117.5(6)				
H(1)	C(3)	C(4)	121.0(7)				
C(3)	C(4)	CR(1)	71.6(6)				
C(5)	C(4)	CR(1)	72.7(7)				
C(5)	C(4)	C(3)	120.8(11)				
H(2)	C(4)	CR(1)	127.6(3)				
H(2)	C(4)	C(3)	117.9(7)				
H(2)	C(4)	C(5)	121.3(7)				
C(4)	C(5)	CR(1)	71.3(7)				
C(6)	C(5)	CR(1)	69.9(5)				
C(6)	C(5)	C(4)	118.3(10)				
H(3)	C(5)	CR(1)	132.8(3)				
H(3)	C(5)	C(4)	118.7(7)				
H(3)	C(5)	C(6)	122.9(7)				
C(1)	C(6)	CR(1)	72.8(5)				
C(5)	C(6)	CR(1)	72.4(6)				
C(5)	C(6)	C(1)	121.8(9)				
H(4)	C(6)	CR(1)	125.5(3)				
H(4)	C(6)	C(1)	118.8(6)				
H(4)	C(6)	C(5)	119.3(7)				
C(1)	C(7)	O(1)	111.2(6)				
C(8)	C(7)	O(1)	107.9(6)				

Selected torsional angles in degrees (e.s.d's) for complex **93**.

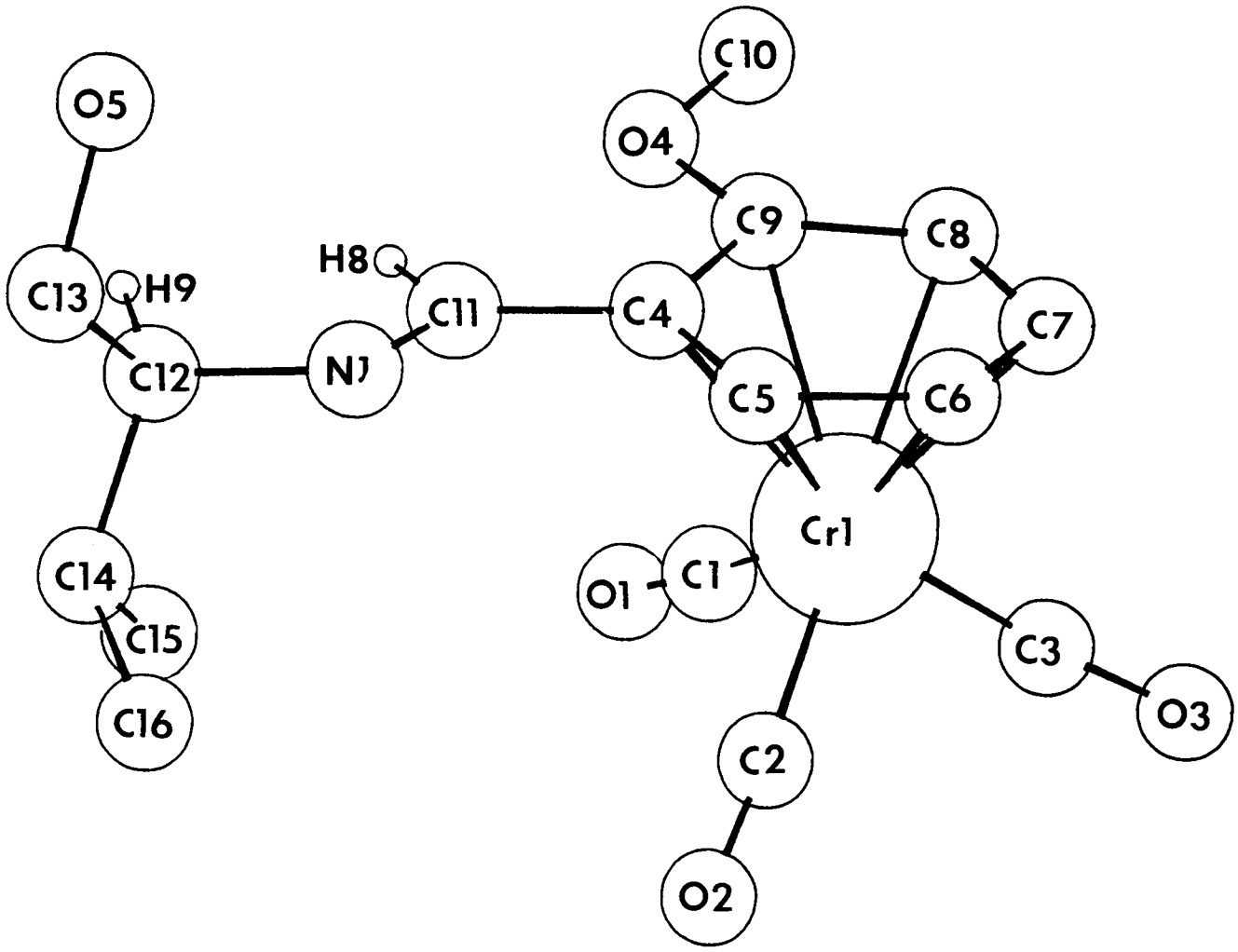
C(10)	-	C(2)	-	C(1)	-	C(7)		2.44
C(10)	-	C(2)	-	C(3)	-	H(1)		2.99
O(1)	-	C(7)	-	C(1)	-	C(2)		-49.88
H(5)	-	C(7)	-	C(1)	-	C(2)		-164.67
C(8)	-	C(7)	-	C(1)	-	C(6)		-104.04
C(9)	-	C(8)	-	C(7)	-	O(1)		165.17

Appendix III. X-Ray Crystal Structure Data for the L-Valinol Derived Imine of (+)-(*o*-Anisaldehyde)Cr(CO)3.

X-Ray crystal structure data for complex 173.

Copper-Kα radiation, $C_{16}H_{19}CrNO_5$, M = 357.33, rotation (+), orthorhombic, a = 12.743, b = 15.673, c = 17.383 $\overset{0}{A}$, $\alpha = \beta = \gamma = 90^o$, U = 3471.8$\overset{0}{A}^3$, scan speed 1.0 to 6.7^{o}min^{-1}, Z = 8, D_{calc} = 1.37gcm^{-3}, μ(Cu-Kα) = 57.0767cm-1, space group $P2_12_12_1$, crystal dimensions 0.61mm x 0.77mm x 0.97mm, number of independent reflections measured 3983, number of reflections with I>3σ(I) 2220, R = 0.049, R_w = 0.055.

The structure was solved by direct methods and electron density Fourier synthesis. Reflections were weighted by applying a 3 term Chebyshev series of the form $w = [7.768t_0(X) - 3.010t_1(X) + 4.269t_2(X)]$ where $X = F_o/F_{max}$.



Atomic coordinates (e.s.d's) for complex **173**.

Atom	x/a	y/b	z/c	U(iso)
CR(1	1602.6(9)	9641.5(7)	1305.1(6)	384
CR(2)	1878.0(9)	3786.1(8)	9511.1(7)	424
C(1)	728(8)	8805(6)	939(5)	565
C(2)	685(6)	10466(6)	950(5)	508
C(3)	884(7)	9618(7)	2240(5)	681
C(4)	2965(5)	10508(4)	1473(4)	314
C(5)	3059(6)	9804(4)	1949(4)	426
C(6)	3062(7)	8963(4)	1652(5)	466
C(7)	2856(7)	8848(5)	863(5)	528
C(8)	2776(6)	9542(4)	367(4)	397
C(9)	2857(5)	10368(5)	646(4)	361
C(10)	2630(9)	10977(5)	-595(4)	582
C(11)	2938(6)	11383(4)	1766(4)	360
C(12)	2991(8)	12461(4)	2690(5)	477
C(13)	3920(9)	12714(6)	3199(5)	595
C(14)	1925(9)	12600(5)	3083(5)	586
C(15)	1764(11)	12002(7)	3773(6)	858
C(16)	1031(9)	12530(9)	2521(7)	987
C(17)	2849(6)	3493(6)	10286(5)	539
C(18)	2735(7)	3250(5)	8832(5)	587
C(19)	2621(6)	4753(5)	9350(5)	510
C(20)	496(6)	4126(5)	8805(4)	382
C(21)	541(6)	3220(5)	8886(5)	443
C(22)	565(7)	2858(6)	9624(6)	595
C(23)	586(8)	3399(8)	10270(5)	603
C(24)	529(7)	4277(6)	10210(4)	505
C(25)	460(5)	4654(6)	9462(4)	444
C(26)	465(9)	6074(7)	9982(5)	700
C(27)	582(5)	4541(5)	8034(4)	386
C(28)	779(7)	4590(6)	6704(4)	488
C(29)	-6(8)	4339(6)	6102(4)	603
C(30)	1907(8)	4443(5)	6439(5)	603
C(31)	2178(9)	3501(6)	6349(6)	822
C(32)	2685(8)	4855(7)	6980(6)	839
O(1)	231	8237	675	776
O(2)	147	10990	698	767
O(3)	486	9637	2833	805
O(4)	2779	11092	223	405
O(5)	4899(6)	12647(4)	2821(4)	674
O(6)	3454	3312	10751	535
O(7)	3275	2881	8392	883
O(8)	3075	5381	9246	708
O(9)	389	5498	9356	459
O(10)	-1064(5)	4515(4)	6326(3)	554
N(1)	3118	11566	2463	320
N(2)	560	4096	7408	378

Thermal parameters (e.s.d's) for complex **173**.

Atom	U(11)	U(22)	U(33)	U(23)	U(13)	U(12)
CR(1)	418(6)	347(5)	413(6)	54(6)	-17(6)	-69(6)
CR(2)	386(6)	569(7)	404(6)	181(6)	-16(6)	-18(6)
C(1)	854(66)	562(52)	480(48)	85(45)	147(48)	-232(50)
C(2)	398(44)	581(53)	613(50)	84(47)	31(40)	-103(40)
C(3)	599(54)	834(62)	644(52)	88(59)	-37(46)	11(57)
C(4)	400(36)	228(31)	369(34)	-66(27)	59(29)	-34(28)
C(5)	500(42)	324(37)	493(40)	-29(31)	-80(37)	7(34)
C(6)	602(50)	257(34)	687(51)	-53(34)	-119(46)	30(39)
C(7)	688(58)	319(39)	692(55)	-76(42)	-3(46)	18(41)
C(8)	535(43)	332(36)	447(38)	-172(34)	-1(34)	-43(34)
C(9)	424(38)	363(34)	363(36)	-128(34)	77(29)	-24(34)
C(10)	1485(97)	532(47)	256(39)	15(35)	-69(50)	-98(57)
C(11)	589(46)	231(31)	356(33)	-31(27)	68(34)	-27(32)
C(12)	1126(76)	245(33)	407(40)	-14(31)	13(50)	93(43)
C(13)	1383(96)	416(46)	520(50)	-248(43)	96(60)	-44(56)
C(14)	1334(94)	450(44)	428(44)	43(38)	148(60)	334(60)
C(15)	1473(112)	994(76)	892(71)	431(66)	582(85)	669(87)
C(16)	1078(95)	1234(105)	879(81)	-211(81)	83(76)	395(88)
C(17)	501(50)	642(51)	571(52)	203(43)	99(39)	-3(41)
C(18)	531(49)	575(50)	679(57)	50(45)	79(45)	2(41)
C(19)	465(41)	537(47)	599(49)	189(42)	-26(38)	-5(39)
C(20)	406(39)	484(41)	294(35)	68(32)	-4(33)	-18(34)
C(21)	502(46)	484(46)	447(44)	194(39)	-66(37)	-73(39)
C(22)	570(50)	715(60)	758(65)	393(56)	-47(54)	-135(48)
C(23)	530(54)	1123(88)	484(56)	336(59)	-33(45)	-150(56)
C(24)	487(49)	863(65)	317(39)	97(42)	15(38)	-22(46)
C(25)	348(35)	677(49)	403(37)	40(46)	-98(34)	-40(41)
C(26)	1023(81)	932(74)	542(52)	-411(56)	30(58)	4(65)
C(27)	406(37)	433(40)	338(34)	2(33)	-61(31)	34(36)
C(28)	959(66)	426(40)	293(36)	31(38)	3(40)	88(49)
C(29)	1049(79)	668(55)	337(43)	91(40)	-71(46)	99(57)
C(30)	882(65)	565(49)	488(45)	140(39)	93(48)	-31(49)
C(31)	1046(85)	788(64)	960(74)	-22(62)	546(73)	12(61)
C(32)	894(74)	1035(85)	780(67)	221(63)	157(61)	-243(68)
O(1)	1251	856	752	-62	-37	-662
O(2)	645	870	1265	501	-67	245
O(3)	893	1671	481	149	322	-29
O(4)	714	301	350	-27	134	-101
O(5)	1206	441	753	-119	-206	-249
O(6)	717	863	558	310	-286	188
O(7)	1052	950	773	-60	266	115
O(8)	762	726	731	206	-127	-127
O(9)	586	543	388	-178	-26	152
O(10)	840	606	399	116	-154	96
N(1)	556	182	327	-17	-6	-29
N(2)	429	433	336	126	46	68

Bond lengths in $\overset{0}{A}$ (e.s.d's) for complex **173**.

CR(1)	C(1)	1.834(9)
CR(1)	C(2)	1.849(8)
CR(1)	C(3)	1.865(9)
CR(1)	C(4)	2.224(6)
CR(1)	C(5)	2.182(7)
CR(1)	C(6)	2.226(8)
CR(1)	C(7)	2.166(8)
CR(1)	C(8)	2.218(7)
CR(1)	C(9)	2.272(7)
CR(2)	C(17)	1.885(8)
CR(2)	C(18)	1.815(9)
CR(2)	C(19)	1.808(8)
CR(2)	C(20)	2.212(7)
CR(2)	C(21)	2.208(8)
CR(2)	C(22)	2.226(9)
CR(2)	C(23)	2.196(9)
CR(2)	C(24)	2.241(9)
CR(2)	C(25)	2.263(8)
C(1)	O(1)	1.186(9)
C(2)	O(2)	1.156(8)
C(3)	O(3)	1.149(9)
C(4)	C(5)	1.385(9)
C(4)	C(9)	1.461(9)
C(4)	C(11)	1.463(8)
C(5)	C(6)	1.415(9)
C(6)	C(7)	1.41(1)
C(7)	C(8)	1.39(1)
C(8)	C(9)	1.385(9)
C(9)	O(4)	1.356(7)
C(10)	O(4)	1.446(7)
C(11)	N(1)	1.267(6)
C(12)	C(13)	1.53(1)
C(12)	C(14)	1.54(1)
C(12)	N(1)	1.466(7)
C(13)	O(5)	1.41(1)
C(14)	C(15)	1.54(1)
C(14)	C(16)	1.50(1)
C(17)	O(6)	1.154(8)
C(18)	O(7)	1.180(9)
C(19)	O(8)	1.157(8)
C(20)	C(21)	1.43(1)
C(20)	C(25)	1.41(1)
C(20)	C(27)	1.493(9)
C(21)	C(22)	1.40(1)
C(22)	C(23)	1.41(1)
C(23)	C(24)	1.38(1)
C(24)	C(25)	1.43(1)
C(25)	O(9)	1.339(9)
C(26)	O(9)	1.418(8)
C(27)	N(2)	1.293(7)
C(28)	C(29)	1.50(1)
C(28)	C(30)	1.53(1)
C(28)	N(2)	1.475(7)
C(29)	O(10)	1.43(1)
C(30)	C(31)	1.52(1)
C(30)	C(32)	1.51(1)
O(5)	H(12)	1.01
O(10)	H(31)	1.16

Bond angles in degrees (e.s.d's) for complex **173**.

C(2)	CR(1)	C(1)	89.9(4)	O(1)	C(1)	CR(1)	174.8(8)
C(3)	CR(1)	C(1)	89.4(4)	O(2)	C(2)	CR(1)	176.5(6)
C(3)	CR(1)	C(2)	89.6(4)	O(3)	C(3)	CR(1)	175.9(8)
C(4)	CR(1)	C(1)	163.0(3)	C(5)	C(4)	CR(1)	70.1(4)
C(4)	CR(1)	C(2)	96.4(3)	C(9)	C(4)	CR(1)	72.8(4)
C(4)	CR(1)	C(3)	106.3(3)	C(9)	C(4)	C(5)	118.4(6)
C(5)	CR(1)	C(1)	141.1(4)	C(11)	C(4)	CR(1)	126.8(5)
C(5)	CR(1)	C(2)	128.9(3)	C(11)	C(4)	C(5)	122.8(6)
C(5)	CR(1)	C(3)	88.5(3)	C(11)	C(4)	C(9)	118.8(6)
C(5)	CR(1)	C(4)	36.6(2)	C(4)	C(5)	CR(1)	73.3(4)
C(6)	CR(1)	C(1)	105.1(4)	C(6)	C(5)	CR(1)	73.0(5)
C(6)	CR(1)	C(2)	162.4(3)	C(6)	C(5)	C(4)	121.7(6)
C(6)	CR(1)	C(3)	99.5(4)	C(5)	C(6)	CR(1)	69.6(4)
C(6)	CR(1)	C(4)	66.6(2)	C(7)	C(6)	CR(1)	69.0(5)
C(6)	CR(1)	C(5)	37.4(2)	C(7)	C(6)	C(5)	118.3(7)
C(7)	CR(1)	C(1)	85.1(4)	C(6)	C(7)	CR(1)	73.6(5)
C(7)	CR(1)	C(2)	138.6(4)	C(8)	C(7)	CR(1)	73.5(4)
C(7)	CR(1)	C(3)	131.3(4)	C(8)	C(7)	C(6)	121.0(7)
C(7)	CR(1)	C(4)	79.7(3)	C(7)	C(8)	CR(1)	69.5(5)
C(7)	CR(1)	C(5)	67.8(3)	C(9)	C(8)	CR(1)	74.2(4)
C(7)	CR(1)	C(6)	37.4(3)	C(9)	C(8)	C(7)	120.6(6)
C(8)	CR(1)	C(1)	96.0(3)	C(4)	C(9)	CR(1)	69.3(4)
C(8)	CR(1)	C(2)	103.3(3)	C(8)	C(9)	CR(1)	69.9(4)
C(8)	CR(1)	C(3)	165.9(3)	C(8)	C(9)	C(4)	119.5(6)
C(8)	CR(1)	C(4)	67.2(2)	O(4)	C(9)	CR(1)	129.9(4)
C(8)	CR(1)	C(5)	79.1(3)	O(4)	C(9)	C(4)	114.5(5)
C(8)	CR(1)	C(6)	66.6(3)	O(4)	C(9)	C(8)	125.9(5)
C(9)	CR(1)	C(1)	127.6(3)	N(1)	C(11)	C(4)	122.7(5)
C(9)	CR(1)	C(2)	85.8(3)	C(14)	C(12)	C(13)	112.9(7)
C(9)	CR(1)	C(3)	142.6(4)	N(1)	C(12)	C(13)	108.6(6)
C(9)	CR(1)	C(4)	37.9(2)	N(1)	C(12)	C(14)	110.6(6)
C(9)	CR(1)	C(5)	66.5(3)	O(5)	C(13)	C(12)	113.2(7)
C(9)	CR(1)	C(6)	77.8(3)	C(15)	C(14)	C(12)	112.3(8)
C(8)	CR(1)	C(7)	37.0(3)	C(16)	C(14)	C(12)	111.8(7)
C(9)	CR(1)	C(7)	65.8(3)	C(16)	C(14)	C(15)	111.2(10)
C(9)	CR(1)	C(8)	35.9(2)	O(6)	C(17)	CR(2)	179.0(6)
C(18)	CR(2)	C(17)	87.5(4)	O(7)	C(18)	CR(2)	178.2(7)
C(19)	CR(2)	C(17)	88.3(4)	O(8)	C(19)	CR(2)	178.4(6)
C(19)	CR(2)	C(18)	88.4(4)	C(21)	C(20)	CR(2)	71.0(5)
C(20)	CR(2)	C(17)	167.8(3)	C(25)	C(20)	CR(2)	73.6(4)
C(20)	CR(2)	C(18)	103.3(4)	C(25)	C(20)	C(21)	120.3(7)
C(20)	CR(2)	C(19)	97.4(3)	C(27)	C(20)	CR(2)	123.0(5)
C(21)	CR(2)	C(17)	139.5(3)	C(27)	C(20)	C(21)	121.3(7)
C(21)	CR(2)	C(18)	87.6(3)	C(27)	C(20)	C(25)	118.2(6)
C(21)	CR(2)	C(19)	131.7(3)	C(20)	C(21)	CR(2)	71.3(5)
C(21)	CR(2)	C(20)	37.7(3)	C(22)	C(21)	C(20)	119.6(8)
C(22)	CR(2)	C(17)	105.8(3)	C(21)	C(22)	CR(2)	70.9(5)
C(22)	CR(2)	C(18)	101.9(4)	C(23)	C(22)	CR(2)	70.3(5)
C(22)	CR(2)	C(19)	162.7(3)	C(23)	C(22)	C(21)	119.1(8)
C(22)	CR(2)	C(20)	66.9(3)	C(22)	C(23)	CR(2)	72.6(5)
C(22)	CR(2)	C(21)	36.9(3)	C(24)	C(23)	CR(2)	73.6(5)
C(23)	CR(2)	C(17)	89.7(3)	C(24)	C(23)	C(22)	122.5(8)
C(23)	CR(2)	C(18)	135.6(4)	C(23)	C(24)	CR(2)	70.1(6)
C(23)	CR(2)	C(19)	135.8(4)	C(25)	C(24)	CR(2)	72.3(5)
C(23)	CR(2)	C(20)	78.6(3)	C(25)	C(24)	C(23)	118.9(9)
C(23)	CR(2)	C(21)	66.8(3)	C(20)	C(25)	CR(2)	69.7(4)
C(23)	CR(2)	C(22)	37.1(4)	C(24)	C(25)	CR(2)	70.6(5)
C(24)	CR(2)	C(17)	101.5(3)	C(24)	C(25)	C(20)	119.4(8)
C(24)	CR(2)	C(18)	166.7(4)	O(9)	C(25)	CR(2)	130.8(4)
C(24)	CR(2)	C(19)	101.4(4)	O(9)	C(25)	C(20)	118.0(6)
C(24)	CR(2)	C(20)	66.9(3)	O(9)	C(25)	C(24)	122.5(7)
C(24)	CR(2)	C(21)	79.2(3)	N(2)	C(27)	C(20)	121.2(6)
C(24)	CR(2)	C(22)	66.4(4)	C(30)	C(28)	C(29)	112.3(7)
C(25)	CR(2)	C(17)	134.2(3)	N(2)	C(28)	C(29)	108.4(7)
C(25)	CR(2)	C(18)	137.2(3)	N(2)	C(28)	C(30)	110.5(6)
C(25)	CR(2)	C(19)	84.7(3)	O(10)	C(29)	C(28)	112.9(7)
C(25)	CR(2)	C(20)	36.7(3)	C(31)	C(30)	C(28)	112.9(8)
C(25)	CR(2)	C(21)	66.8(3)	C(32)	C(30)	C(28)	111.5(7)
C(25)	CR(2)	C(22)	78.2(3)	C(32)	C(30)	C(31)	109.2(9)
C(24)	CR(2)	C(23)	36.3(3)	C(10)	O(4)	C(9)	116.0(4)
C(25)	CR(2)	C(23)	65.8(3)	C(26)	O(9)	C(25)	121.3(6)
C(25)	CR(2)	C(24)	37.1(3)	C(12)	N(1)	C(11)	116.9(4)
				C(28)	N(2)	C(27)	114.3(4)

Selected torsional angles in degrees (e.s.d's) for complex **173**.

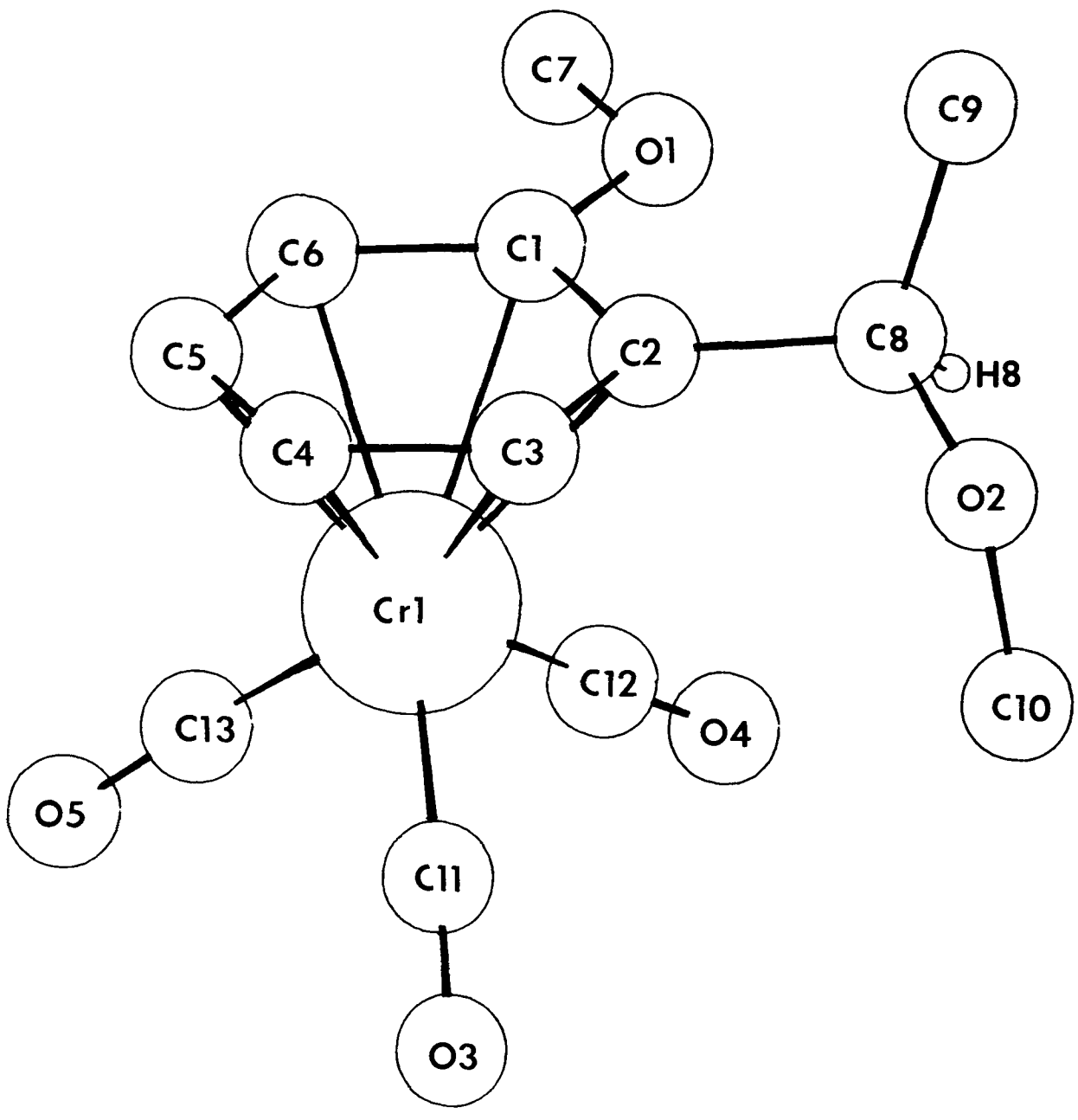
C(8)	-	C(9)	-	O(4)	-	C(10)	-1.83
N(1)	-	C(11)	-	C(4)	-	C(5)	8.33
C(12)	-	N(1)	-	C(11)	-	C(4)	-175.89
O(5)	-	C(13)	-	C(12)	-	C(14)	-175.74
O(5)	-	C(13)	-	C(12)	-	N(1)	61.31

Appendix IV. X-Ray Crystal Structure Data for (*RR*,*SS*)-(*o*-Methoxy-α-methylbenzyl Methyl Ether)Cr(CO)3.

*X-Ray crystal structure data for complex **190**.*

Copper-Kα radiation, $C_{13}H_{14}CrO_5$, M = 302.25, triclinic, a = 12.246, b = 8.169, c = 10.164 Å, α = 136.37°, β = 97.80°, γ = 92.42°, U = 680.21 Å^3, Scan speed 1.3 to 5.5°min^{-1}, D_{calc} = 1.48gcm^{-3}, μ(Cu-Kα) = 71.586cm^{-1}, space group $P\bar{1}$, number of independent reflections measured 2364, number of reflections with I>3σ(I) 2336, R = 0.042, R_w = 0.059.

The structure was solved by Patterson methods and electron density Fourier synthesis. Reflections were weighted by applying a 4 term Chebyshev series of the form w = [217.58t_0(X) + 309.34t_1(X) + 116.56t_2(X) + 21.10t_3(X)] where X = F_o/F_{max}.



Atomic coordinates (e.s.d's) for complex **190**.

Atom	x/a	y/b	z/c	U(iso)
CR(1)	1922.0(4)	1700.7(8)	4415.4(6)	299
O(1)	3852(2)	-912(4)	1820(3)	399
O(2)	2872(2)	4500(4)	2667(3)	416
O(3)	915(3)	6093(5)	7067(4)	648
O(4)	4212(2)	4644(5)	7064(4)	619
O(5)	1601(3)	1245(7)	7002(5)	708
C(1)	2757(2)	-780(5)	1844(4)	335
C(2)	2399(2)	980(5)	1981(4)	313
C(3)	1270(3)	1183(6)	1961(4)	374
C(4)	493(3)	-263(6)	1844(5)	451
C(5)	860(3)	-1901(6)	1787(5)	470
C(6)	1994(3)	-2177(5)	1789(5)	405
C(7)	4298(4)	-2387(8)	1945(7)	508
C(8)	3236(3)	2422(5)	1990(4)	334
C(9)	3358(3)	867(6)	-89(5)	464
C(10)	3185(4)	6567(6)	4739(5)	552
C(11)	1312(3)	4406(6)	6038(5)	435
C(12)	3321(3)	3514(6)	6047(4)	387
C(13)	1718(3)	1373(6)	5966(5)	455
H(1)	1002(3)	2453(6)	2044(4)	702(35)
H(2)	-355(3)	-109(6)	1796(5)	702(35)
H(3)	291(3)	-2949(6)	1740(5)	702(35)
H(4)	2268(3)	-3405(5)	1756(5)	702(35)
H(5)	5151(4)	-2308(8)	1911(7)	702(35)
H(6)	4226(4)	-1743(8)	3266(7)	702(35)
H(7)	3853(4)	-4188(8)	754(7)	702(35)
H(8)	4002(3)	3053(5)	2974(4)	702(35)
H(9)	3942(3)	1857(6)	-77(5)	702(35)
H(10)	3632(3)	-701(6)	-661(5)	702(35)
H(11)	2570(3)	373(6)	-968(5)	702(35)
H(12)	2882(4)	8033(6)	5150(5)	702(35)
H(13)	4068(4)	7019(6)	5201(5)	702(35)
H(14)	2851(4)	6171(6)	5401(5)	702(35)

Thermal parameters (e.s.d's) for complex **190**.

Atom	U(11)	U(22)	U(33)	U(23)	U(13)	U(12)
CR(1)	313(3)	345(3)	337(3)	274(2)	95(2)	108(2)
O(1)	492(12)	505(12)	630(14)	484(12)	300(11)	286(10)
O(2)	687(15)	403(11)	481(12)	376(11)	169(11)	194(10)
O(3)	783(20)	644(17)	580(16)	352(15)	229(14)	450(16)
O(4)	438(14)	696(17)	684(17)	488(15)	-59(12)	9(12)
O(5)	1024(25)	1273(30)	1055(26)	1067(26)	528(21)	473(22)
C(1)	452(15)	308(13)	369(14)	263(12)	173(12)	157(11)
C(2)	387(14)	319(13)	308(12)	243(11)	103(10)	124(11)
C(3)	392(15)	470(16)	355(14)	323(14)	33(11)	99(12)
C(4)	366(15)	549(18)	421(16)	350(16)	20(12)	44(13)
C(5)	509(18)	386(16)	453(17)	277(15)	88(14)	-39(13)
C(6)	583(19)	291(13)	418(15)	256(13)	175(14)	113(12)
C(7)	676(24)	764(25)	970(30)	772(26)	430(22)	463(21)
C(8)	444(15)	336(13)	368(14)	289(12)	118(12)	123(11)
C(9)	628(21)	526(18)	443(17)	385(16)	224(15)	155(15)
C(10)	1068(34)	358(16)	491(19)	312(16)	264(21)	205(19)
C(11)	433(16)	515(18)	418(16)	346(15)	94(13)	173(14)
C(12)	406(16)	460(16)	399(15)	339(14)	110(12)	146(13)
C(13)	526(18)	544(19)	523(18)	437(17)	224(15)	201(15)

Bond lengths in Å (e.s.d's) for complex **190**.

C(2)	C(8)	1.523(4)	CR(1)	C(1)	2.284(3)
C(3)	C(4)	1.409(5)	CR(1)	C(2)	2.263(3)
C(3)	H(1)	1.05	CR(1)	C(3)	2.223(3)
C(4)	C(5)	1.394(5)	CR(1)	C(4)	2.218(3)
C(4)	H(2)	1.05	CR(1)	C(5)	2.200(3)
C(5)	C(6)	1.417(5)	CR(1)	C(6)	2.240(3)
C(5)	H(3)	1.05	CR(1)	C(11)	1.833(3)
C(6)	H(4)	1.05	CR(1)	C(12)	1.827(3)
C(7)	H(5)	1.05	CR(1)	C(13)	1.825(3)
C(7)	H(6)	1.05	O(1)	C(1)	1.352(3)
C(7)	H(7)	1.05	O(1)	C(7)	1.422(4)
C(8)	C(9)	1.522(4)	O(2)	C(8)	1.418(3)
C(8)	H(8)	1.05	O(2)	C(10)	1.419(4)
C(9)	H(9)	1.05	O(3)	C(11)	1.157(4)
C(9)	H(10)	1.05	O(4)	C(12)	1.157(4)
C(9)	H(11)	1.05	O(5)	C(13)	1.157(4)
C(10)	H(12)	1.05	C(1)	C(2)	1.434(4)
C(10)	H(13)	1.05	C(1)	C(6)	1.408(4)
C(10)	H(14)	1.05	C(2)	C(3)	1.399(4)

Bond angles in degrees (e.s.d's) for complex **190**.

C(2)	CR(1)	C(1)	36.76(9)	C(2)	C(3)	CR(1)	73.4(2)
C(3)	CR(1)	C(1)	65.4(1)	C(4)	C(3)	CR(1)	71.3(2)
C(3)	CR(1)	C(2)	36.3(1)	C(4)	C(3)	C(2)	121.6(3)
C(4)	CR(1)	C(1)	77.6(1)	H(1)	C(3)	CR(1)	128.12(8)
C(4)	CR(1)	C(2)	66.3(1)	H(1)	C(3)	C(2)	118.8(2)
C(4)	CR(1)	C(3)	37.0(1)	H(1)	C(3)	C(4)	119.6(2)
C(5)	CR(1)	C(1)	65.9(1)	C(3)	C(4)	CR(1)	71.7(2)
C(5)	CR(1)	C(2)	78.5(1)	C(5)	C(4)	CR(1)	70.9(2)
C(5)	CR(1)	C(3)	66.3(1)	C(5)	C(4)	C(3)	119.4(3)
C(5)	CR(1)	C(4)	36.8(1)	H(2)	C(4)	CR(1)	129.55(9)
C(6)	CR(1)	C(1)	36.2(1)	H(2)	C(4)	C(3)	120.2(2)
C(6)	CR(1)	C(2)	66.3(1)	H(2)	C(4)	C(5)	120.4(2)
C(6)	CR(1)	C(3)	78.1(1)	C(4)	C(5)	CR(1)	72.3(2)
C(6)	CR(1)	C(4)	66.5(1)	C(6)	C(5)	CR(1)	72.9(2)
C(6)	CR(1)	C(5)	37.2(1)	C(6)	C(5)	C(4)	120.8(3)
C(11)	CR(1)	C(1)	149.5(1)	H(3)	C(5)	CR(1)	127.31(9)
C(11)	CR(1)	C(2)	112.9(1)	H(3)	C(5)	C(4)	119.9(2)
C(11)	CR(1)	C(3)	89.6(1)	H(3)	C(5)	C(6)	119.3(2)
C(11)	CR(1)	C(4)	93.0(1)	C(1)	C(6)	CR(1)	73.6(2)
C(11)	CR(1)	C(5)	121.4(1)	C(5)	C(6)	CR(1)	69.9(2)
C(11)	CR(1)	C(6)	158.4(1)	C(5)	C(6)	C(1)	119.4(3)
C(12)	CR(1)	C(1)	88.5(1)	H(4)	C(6)	CR(1)	128.12(9)
C(12)	CR(1)	C(2)	92.3(1)	H(4)	C(6)	C(1)	120.0(2)
C(12)	CR(1)	C(3)	121.3(1)	H(4)	C(6)	C(5)	120.6(2)
C(12)	CR(1)	C(4)	157.8(1)	H(5)	C(7)	O(1)	109.1(2)
C(12)	CR(1)	C(5)	148.1(1)	H(6)	C(7)	O(1)	109.4(2)
C(12)	CR(1)	C(6)	111.2(1)	H(6)	C(7)	H(5)	109.48
C(13)	CR(1)	C(1)	124.2(1)	H(7)	C(7)	O(1)	109.8(2)
C(13)	CR(1)	C(2)	161.0(1)	H(7)	C(7)	H(5)	109.48
C(13)	CR(1)	C(3)	151.0(1)	H(7)	C(7)	H(6)	109.48
C(13)	CR(1)	C(4)	114.5(1)	C(2)	C(8)	O(2)	111.9(2)
C(13)	CR(1)	C(5)	91.7(1)	C(9)	C(8)	O(2)	106.8(2)
C(13)	CR(1)	C(6)	96.0(1)	C(9)	C(8)	C(2)	109.9(2)
C(12)	CR(1)	C(11)	90.3(1)	H(8)	C(8)	O(2)	106.6(2)
C(13)	CR(1)	C(11)	86.1(1)	H(8)	C(8)	C(2)	108.7(1)
C(13)	CR(1)	C(12)	87.5(1)	H(8)	C(8)	C(9)	113.0(2)
C(7)	O(1)	C(1)	117.8(2)	H(9)	C(9)	C(8)	109.8(2)
C(10)	O(2)	C(8)	113.8(2)	H(10)	C(9)	C(8)	110.0(2)
O(1)	C(1)	CR(1)	130.7(2)	H(10)	C(9)	H(9)	109.48
C(2)	C(1)	CR(1)	70.8(1)	H(11)	C(9)	C(8)	108.6(2)
C(2)	C(1)	O(1)	115.0(2)	H(11)	C(9)	H(9)	109.48
C(6)	C(1)	CR(1)	70.2(2)	H(11)	C(9)	H(10)	109.48
C(6)	C(1)	O(1)	124.7(3)	H(12)	C(10)	O(2)	110.2(2)
C(6)	C(1)	C(2)	120.2(3)	H(13)	C(10)	O(2)	108.5(2)
C(1)	C(2)	CR(1)	72.4(2)	H(13)	C(10)	H(12)	109.48
C(3)	C(2)	CR(1)	70.3(2)	H(14)	C(10)	O(2)	109.7(2)
C(3)	C(2)	C(1)	118.5(3)	H(14)	C(10)	H(12)	109.48
C(8)	C(2)	CR(1)	132.7(2)	H(14)	C(10)	H(13)	109.48
C(8)	C(2)	C(1)	119.0(2)	O(3)	C(11)	CR(1)	178.8(3)
C(8)	C(2)	C(3)	122.3(2)	O(4)	C(12)	CR(1)	179.3(3)
				O(5)	C(13)	CR(1)	177.8(4)

Selected torsional angles in degrees (e.s.d's) for complex **190**.

C(9)	-	C(8)	-	C(2)	-	C(1)		77.74
C(8)	-	C(2)	-	C(1)	-	O(1)		2.90
C(7)	-	O(1)	-	C(1)	-	C(6)		-6.44
O(2)	-	C(8)	-	C(2)	-	C(3)		20.88