Asymmetric ligands for lanthanide(II) reagents

Phillip Damian Dent

Asymmetric Ligands for Lanthanide(II) Reagents

Philip Damian Dent, B.Sc.(Hons)

Ph.D. Thesis

University of Durham

Department of Chemistry

February 1999

Copyright

Declaration

This work was conducted in the Department of Chemistry at the University of Durham between October 1995 and September 1998 and has not been submitted for a degree in this, or any other, university. It is my own work, unless otherwise indicated.

Acknowledgements

Thanks to my supervisor: Dr. Parick. G. Steel for his constant advice and encouragement and also to the members of CG1- Alison, Craig, Bill, Ed, Russell and Darren.

Many thanks to: Liz Grayson; the glassblowers (Gordon, Malcolm and Ray); Jimmy, Joe and Mel (stores); Emma Smart; Tom Caygill; Mike Jones and Lara Turner (MS); Alan Kenwright, Ian McKeag and Julia Say (NMR); Lenny Lauchlin (chiral HPLC and GC) and members of Prof. David Parker's group (in particular: Mark, Alvaro and Steve) for useful advice over the last three years.

I wish to thank the EPSRC for funding and ICI for a Scholarship Award (1996-1998).

Abbreviations

Ac	: acetyl
Ar	: aromatic
Bn	: benzyl
b.p.	: boiling point
br	: broad
Bu	: butyl
BuLi	: butyl lithium
CI	: chemical ionisation
d	: doublet
DCE	: 1,2-dichloroethane
de	: diastereomeric excess
Δ	: reflux
DIBAL	: diisobutylaluminium hydride
DMA	: dimethylacetamide
DMAE	: dimethylaminoethanol
DMAP	: 4-dimethylaminopyridine
DME	: 1,2-dimethoxyethane
DMF	: N,N-dimethylformamide
DMPU	: 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone
DMS	: dimethylsulfide
DMSO	: dimethylsulfoxide
ee	: enantiomeric excess
EI	: electron impact ionisation
ESMS	: electrospray mass spectrometry
Et	: ethyl
FAB	: fast atom bombardment
GC	: gas chromatography

GC-MS	: gas chromatography-mass spectrometry
Hal	: halogen
hfc	: heptafluorohydroxymethylene-d-camphorato
HMPA	: hexamethylphosphoramide
HPLC	: high performance liquid chromatography
HRMS	: high resolution mass spectrometry
IR	: infrared
LDA	: lithium diisopropylamide
m	: multiplet
Me	: methyl
Ms	: methanesulfonyl
m.p.	: melting point
MS	: mass spectrometry
NMR	: nuclear magnetic resonance
Ph	: phenyl
q	: quartet
s	: singlet
t	: triplet
Tf	: trifluoromethanesulfonyl
THF	: tetrahydrofuran
THP	: tetrahydropyran
tlc	: thin layer chromatography
TBDPS	: *tert*- butyldiphenylsilyl
TMEDA	: trimethylethylenediamine
TMS	: trimethylsilyl
Ts	: toluenesulfonyl
p-TsCl	: *para*-toluenesulfonyl chloride
p-TsOH	: *para*-toluenesulfonic acid

ABSTRACT

Asymmetric Ligands for Lanthanide(II) Reagents

Philip Damian Dent

Ph.D. 1999

Although the use of Ln^{2+} species as one electron reducing agents has recently become popular, relatively few processes have focused on the control of stereochemistry by the incorporation of chiral auxiliaries at the metal centre. This thesis discusses work aimed at the synthesis of chiral bis(pentaalkylcyclopentadienyl) and polyaza/oxo ligands for Ln(II) ions, and their subsequent application in asymmetric organic synthesis.

Synthesis of enantiomerically pure bis(pentaalkylcyclopentadienyl) ligands was attempted *via* a novel double Nazarov cyclisation of 5,6-di-(methyl)-decane-3,8-dione. A competing intramolecular aldol reaction reduced the efficiency of this route, although subsequent work suggests that the alternative ketone, (3,4-*RR/SS*)-bis(2'-oxobutyl)tetrahydrofuran, could inhibit aldol formation. In addition, a route for bis(tetramethylcyclopentadienyl) ligands was developed *via* oxidative coupling of 4-(*S*)-isopropyl-3-propionyl-oxazolidin-2-one.

A range of tetradentate polyaza/oxo ligands have been prepared and their application in enantioselective carbon-carbon bond formation, in particular the Barbier reaction between 2-octanone and bromobutane, investigated. Using N,N'-bis(3'-propionamide)cyclohexane-1,2-diamine, asymmetric induction and a marked acceleration in reaction rate was observed. This represents the first enantioselective Sm(II)-mediated Barbier reaction. The use of aryl ketones affords pinacols with low enantioselectivity.

Contents

Section A: Introduction and Background

Section B: Results and Discussion

Section D: Appendix

SECTION A

INTRODUCTION AND BACKGROUND

SECTION A: INTRODUCTION AND BACKGROUND

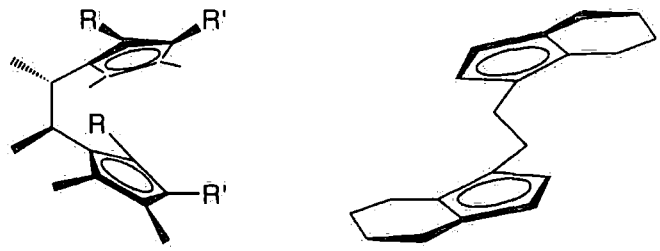
CHAPTER 1

Lanthanides in Organic Synthesis

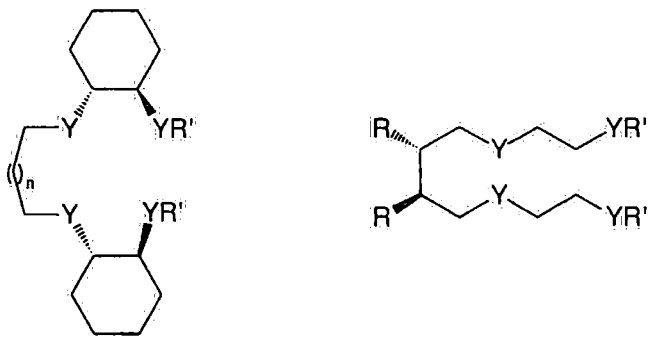
1.1 Introduction

Lanthanide reagents have become widely used for controlled organic synthesis. This chapter will give an overview of the use of these reagents, in particular Sm(II), in synthetic organic chemistry.

The aim of this work was the realisation of lanthanide(II) mediated enantioselective reactions, *via* reagent-based stereocontrol. This has been explored through the synthesis of two series of ligands, which will complex Ln^{2+} ions, Figure 1.1, and their subsequent application in asymmetric synthesis. Ligands belonging to Series One and Two are discussed in Chapters 2 and 3 respectively.



Series One: R,R'=H, alkyl



Series Two: Y=NH, NR", O; R'=H, alkyl.

Figure 1.1

1.2 General Properties of the Lanthanides

1.2.1 Oxidation states, lanthanide contraction and ligand field effects

The highly electropositive nature of these metals (comparable to that of Group I and II elements) leads to the formation of predominantly ionic compounds, with Ln(III) being the most common oxidation state. The existence of additional oxidation states–Sm(II), Eu(II), Yb(II) and Ce(IV)–has been attributed to favourable ionisation enthalpies, enthalpies of sublimation and lattice enthalpies in the associated Born-Haber cycles.[1]

Some of the properties of trivalent and divalent lanthanide ions, which are of particular relevance to this project, are summarised in Tables 1.1 and 1.2 respectively.[2]

Ion	E^0/V^a	Radius/Å	Configuration
Sm^{3+}	-2.30	0.96	$4f^5$
Eu^{3+}	-1.99	0.95	$4f^6$
Yb^{3+}	-2.22	0.85	$4f^{13}$

a) For $M^{3+}+3e=M$

Table 1.1

Ion	E^0/V^a	Radius/Å	Configuration
Sm^{2+}	-1.40	1.11	$4f^6$
Eu^{2+}	-0.34	1.10	$4f^7$
Yb^{2+}	-1.04	0.93	$4f^{14}$

a) For M^{3+}/M^{2+}

Table 1.2

As can be seen from these tables the ionic radii decrease with increasing atomic number, a property referred to as the "lanthanide contraction". This trend is generally ascribed to the poor shielding of the 4f electrons which leads to an increase in the effective nuclear charge experienced by each electron with successive increases in atomic number. This results in a reduction in the size of the total 4f shell.

This contraction and the minimal interaction of the 4f orbitals of lanthanide cations with the surrounding ligand orbitals, produces two effects:

(i) The bonding in lanthanide complexes is essentially ionic.

(ii) There is negligible crystal field splitting.

Consequently, lanthanide ions are classified as hard acids[3] and interact preferentially with hard bases, such as alkoxide/aryloxide, amide and cyclopentadienyl ligands. Large co-

ordination numbers (in the range 8-12) are adopted, with the geometry determined by the ability of the ligands to pack efficiently around the metal centre.

Electronic transitions from one f orbital to another are Laporte forbidden. Owing to little relaxation of the Laporte selection rules, most Ln^{3+} complexes are weakly coloured although Ln^{2+} can be intensely coloured.

Lanthanide cations are strongly Lewis acidic and this interaction between the metal and oxygen atoms on the substrate molecule usually controls the resulting chemo- and stereoselectivities in Ln-mediated reactions (*vide infra*).

1.3 Samarium Iodide in Organic Synthesis

1.3.1 Introduction

Lanthanide reagents, in a range of oxidation states (II-IV), have adopted an important role in organic synthesis. They have been employed selectively in hydrogenations[4], Barbier[5], Reformatsky[6], cyclopropanation[7], pinacol[8], aldol[9] and Diels-Alder[10] reactions. This chemistry has recently been reviewed[11] and the following section is intended to give an overview of the one-electron reduction processes initiated by samarium(II) iodide, SmI_2.

As can be seen from Table 1.2, Sm(II) is a more powerful reductant than europium or ytterbium. Consequently, SmI_2 is invariably the reagent of choice. It is typically used as a 0.1M solution in THF, prepared[12] by reaction of the metal with a suitable oxidant, Scheme 1.1. SmI_2 is air - and moisture- sensitive, so reactions employing this reductant are usually conducted under an inert atmosphere (although the use of Schlenk or glove-box techniques is not necessary)

$$Sm + ICH_2CH_2I \xrightarrow[3\text{-}4h]{THF,\ rt} SmI_2 + C_2H_4$$

$$Sm + ICH_2I \xrightarrow[3\text{-}4h]{THF,\ rt} SmI_2 + 0.5\ C_2H_4$$

$$Sm + I_2 \xrightarrow[24h]{THF,\ rt} SmI_2$$

Scheme 1.1

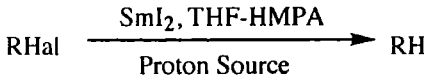
The redox potential of SmI_2 is influenced by additives. In particular, the use of HMPA as a co-solvent has been shown to dramatically accelerate reaction rate.[13] This presumably occurs by electron donation from the ligand to the metal, facilitating electron release by Sm^{2+}.

Although less well investigated than SmI_2, dicyclopentadienylsamarium(II) [Cp_2Sm] and bis-(pentamethylcyclopentadienyl)samarium(II) [Cp_2^*Sm] exhibit an enhanced reactivity relative to SmI_2. These systems are discussed in Chapter 2.

1.3.2. Functional Group Transformations: The Reduction of Organic Functionalities by SmI_2

1.3.2.i Halides, Sulfonates and Sulfones

Primary, secondary and tertiary alkyl halides can be efficiently reduced to alkanes in the presence of HMPA, Scheme 1.2.[14]

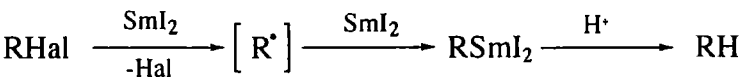


R	Hal	Proton Source	Conditions	Yield(%)
$C_{10}H_{21}$	Cl	^{i}PrOH	60°C, 8h	>95
$C_{10}H_{21}$	Br	^{i}PrOH	rt, 10 min	>95
$C_{10}H_{21}$	I	^{i}PrOH	rt, 5 min	>95
1-Adamantane	Br	^{i}PrOH	rt, 10 min	>95
2-Adamantane	Br	^{i}PrOH	rt, 10 min	>95

Scheme 1.2

The order of reactivity is I>Br>Cl»F (alkyl chlorides require heating for several hours). Fluoroalkanes are resistant to these conditions but can be reduced upon photochemical irradiation, in the presence of SmI_2.[15] Chemoselective reductions are possible.

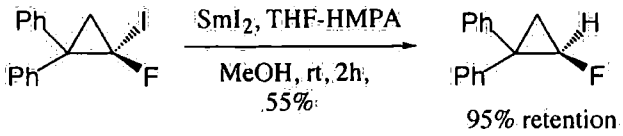
Deuterium labelling studies suggest that the reduction of primary and secondary alkyl halides proceeds *via* organosamarium(III) species, which are protonated upon work-up, Scheme 1.3.[16]



Scheme 1.3

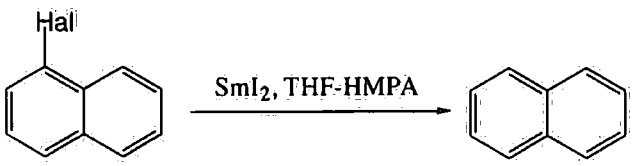
Interestingly, analogous studies with tertiary alkyl halides[16] failed to produce the corresponding deuterated alkanes, suggesting that tertiary radicals are not reduced rapidly enough by SmI_2 to prevent competing radical-radical and/or radical-solvent reactions.

Racemization generally occurs with chiral alkyl halides, which is consistent with a radical mechanism. Exceptions have been reported with fluorocyclopropanes, Scheme 1.4.[17]

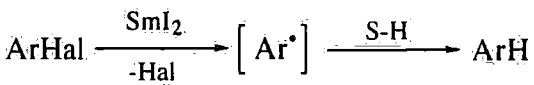


Scheme 1.4

Aryl chlorides, bromides and iodides and alkenyl halides undergo rapid reduction to alkanes, upon treatment with SmI_2-THF-HMPA, Scheme 1.5.[18] In this case, reduction occurs without the intermediacy of organosamarium(III) species, with the aromatic and alkenyl radicals rapidly abstracting hydrogen atoms from the solvent (THF).[19]

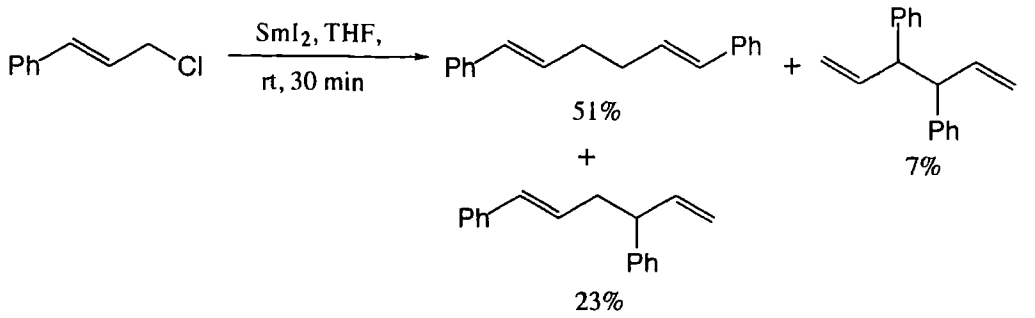


Hal	Conditions	Yield(%)
Cl	rt, 15 min	>95
Br	rt, 5 min	98
I	rt, 1 min	>95



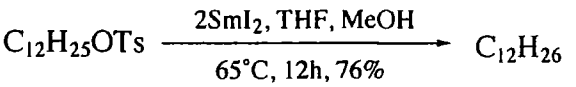
Scheme 1.5

Allylic and benzylic halides undergo a rapid dimerisation with no evidence of the simple reduction products, Scheme 1.6.[20]



Scheme 1.6

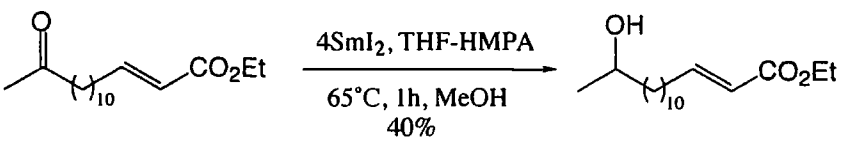
Alkyl tosylates are reduced to alkanes, Scheme 1.7.[20] The addition of NaI produces an increase in reactivity so a Finkelstein reaction must generate the alkyl iodide, which then undergoes reductive cleavage. Alkyl phenyl and alkenyl sulfones undergo similar reduction with SmI_2 (in the presence of HMPA).[21]



Scheme 1.7

1.3.2.ii Aldehydes and Ketones

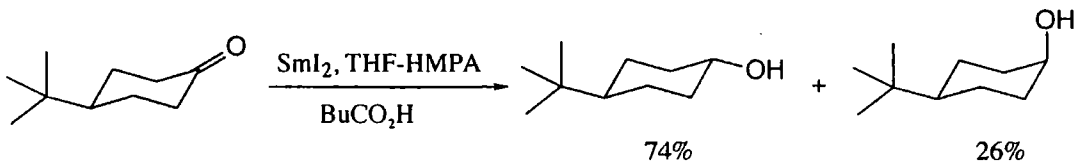
Initial studies by Kagan revealed that the SmI_2 reduction of carbonyl substrates to the corresponding alcohol has the following order of reactivity: aldehydes> ketones» esters> α,β–unsaturated esters>carboxylic acids.[22] Consequently, chemoselective reductions are possible, Scheme 1.8.[23]



Scheme 1.8

Successful reductions require the presence of an added proton source, otherwise pinacols are isolated (*vide infra*).

Although diastereoselectivity in the reduction of acyclic aldehydes and ketones is negligible, there is significant preference for the formation of the equatorial alcohol in the reduction of cyclohexanones and related species, Scheme 1.9.[24]



Scheme 1.9

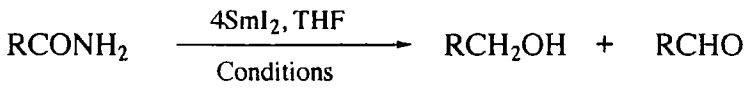
1.3.2.iii Carboxylic Acids and Derivatives

Carboxylic acids, esters and amides are generally inert to SmI_2 or SmI_2-THF-HMPA. A variety of reductions, however, are possible in the presence of aqueous acid or base, Scheme 1.10a and Scheme 1.10b.[25]

$$RCOR' \xrightarrow[\text{Conditions}]{4SmI_2,\ THF} RCH_2OH$$

R	R'	Conditions	Yield (%)
Ph	OH	H_3PO_4 (85%), rt, 3s	91
Ph	OH	H_2O, 8NaOH, rt, 60s	91
C_6H_{11}	OH	H_2O, 8NaOH, rt, 58s	78
Ph	OMe	H_3PO_4 (85%), rt, 3s	72
Ph	OMe	H_2O, 8KOH, rt, 8 min	68

Scheme 10a

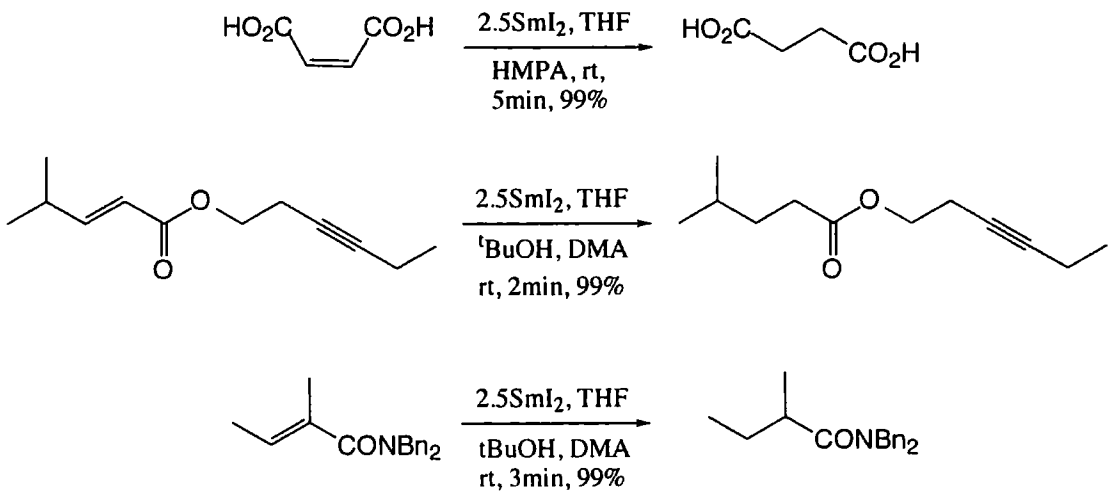


R	Conditions	Yield(%) {RCH_2OH : RCHO}
Ph	H_3PO_4 (85%), rt, 3s	0 : 99
Ph	H_2O, MeOH, 8KOH, rt, 123s	82 : 8

Scheme 1.10b

1.3.2.iv Conjugated Carbonyl Compounds

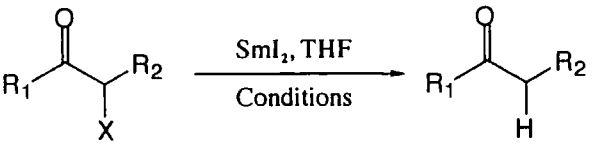
α,β-Unsaturated acids, esters and amides undergo selective 1,4-reduction with SmI_2 and a range of catalysts. Isolated double and triple bonds are tolerated, Scheme 1.11.[26]



Scheme 1.11

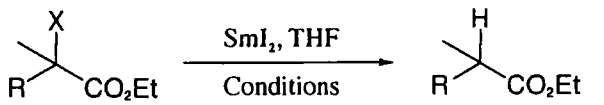
1.3.2.v α–Heterosubstituted Carbonyl Compounds

SmI_2 is used extensively in the reduction of α-heterosubstituted ketones and esters, Scheme 1.12.[27] The mild reaction conditions permit the removal of a wide range of α-heterosubstituents.



R_1	R_2	X	Conditions	Yield(%)
$-(CH_2)_4-$		Cl	MeOH, -40°C[a]	88
Et	Et	OH	Ac_2O, -78°C	59
Et	Et	OTMS	MeOH, -78°C	98
Et	Et	OAc	MeOH, -78°C	75
$-(CH_2)_4-$		SPh	MeOH, -78°C	76
$-(CH_2)_4-$		SOPh	MeOH, -78°C	64
$-(CH_2)_4-$		SO_2Ph	MeOH, -78°C	88

a) TMSCl, NaI, MeCN



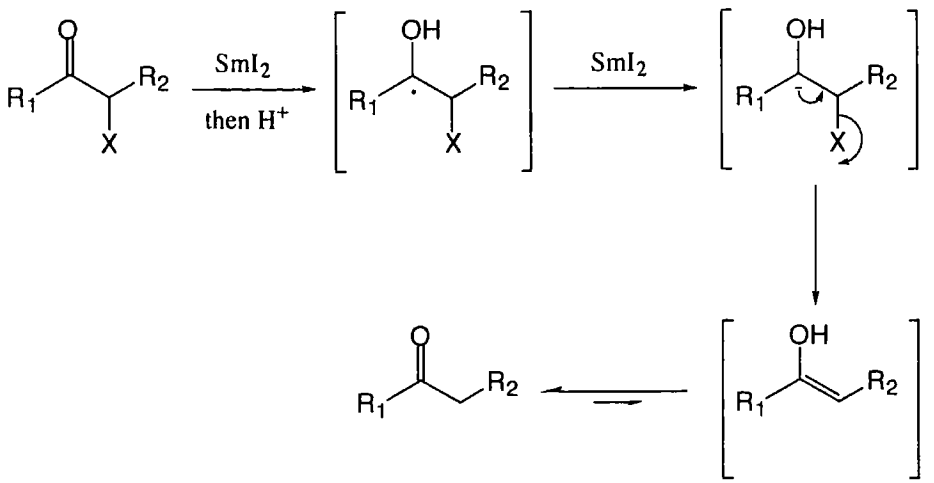
R	X	Conditions	Yield(%)
Me	Br	MeOH, -78°C	98
Me	OH	HMPA, pivalic acid, rt, 2-4h	71
Ph	OMe	HMPA, MeOH, rt, 12h	95
Me	OAc	HMPA, EtOH, rt, 5min	95

Scheme 1.12

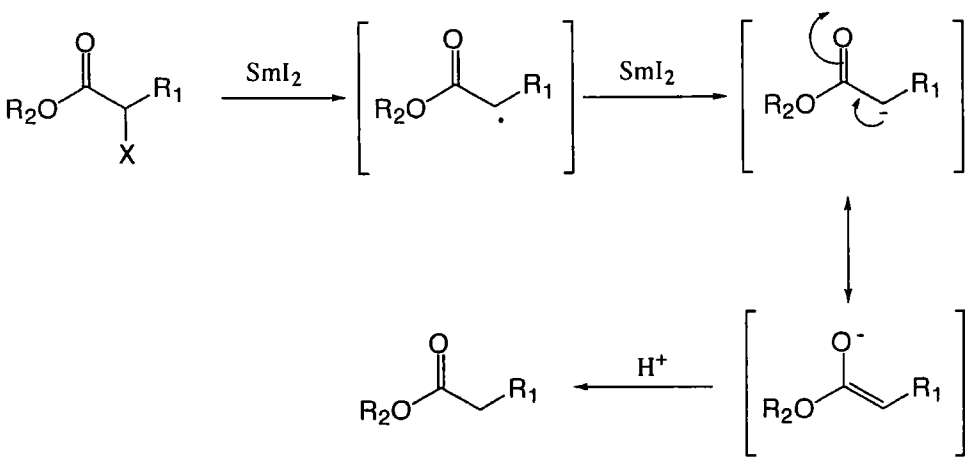
Two mechanisms can be envisaged:[27a]

(1) A ketyl radical generated *in situ* undergoes reduction to the enol, which then tautomerises to afford the carbonyl, Scheme 1.13.

(2) Preferential reduction of the heteroatom gives an enolate anion which is then protonated, Scheme 1.14.



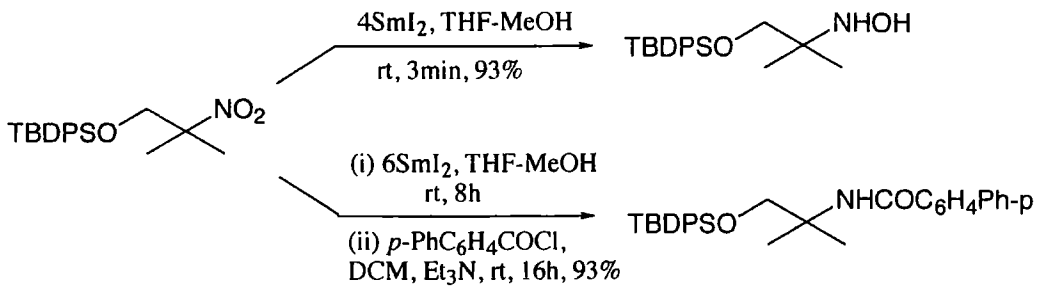
Scheme 1.13



Scheme 1.14

1.3.2.vi Nitrogen Based Substrates

Aromatic and aliphatic nitro compounds are reduced to hydroxylamines or amines. This is a stepwise process and selectivity is possible on the basis of careful adjustment of the reaction conditions, Scheme 1.15.[28]



Scheme 1.15

Nitriles are generally inert, although aromatic nitriles may be reduced to aromatic amines in either strongly acidic (H_3PO_4) or basic (NaOH) conditions.[28]

1.3.2.vii Summary

SmI_2 may become the preferred reagent for the selective reduction of α-heterosubstituted carbonyl compounds.

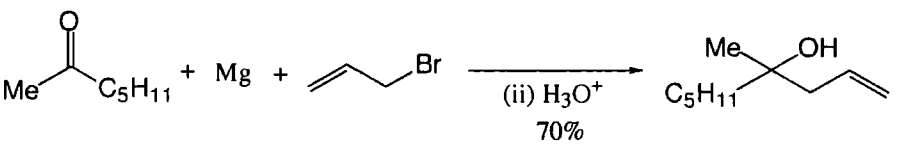
Alkyl and aromatic halides can be efficiently reduced using SmI_2. A range of functional groups are tolerated under the reaction conditions–alcohols, aromatic rings, ethers and esters, providing a basis for the chemoselective reduction of halides in the presence of these groups. Problems may arise if alternative electron acceptors are present such as aldehydes/ketones, α,β-unsaturated carbonyl groups and alkenes, when alternative radical processes can compete.

Although the reduction of simple carbonyl compounds is efficient, SmI_2 offers no significant advantage over established reductants.

1.3.3 Carbon-Carbon Bond Forming Reactions Mediated by SmI_2

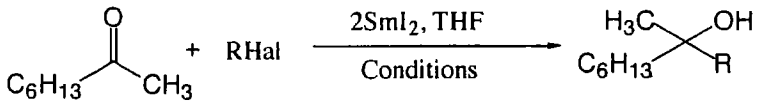
1.3.3.i Carbonyl Addition Reactions: The Barbier Reaction

The Barbier reaction is a one-step procedure which permits the construction of functionalised alcohols, from the corresponding aldehydes or ketones, Scheme 1.16.[29] It can be a useful alternative to the Grignard reaction and is preferentially employed in the synthesis of homoallylic alcohols, where discrete allylmagnesium/lithium reagents are unstable and frequently give low yields.[29]



Scheme 1.16

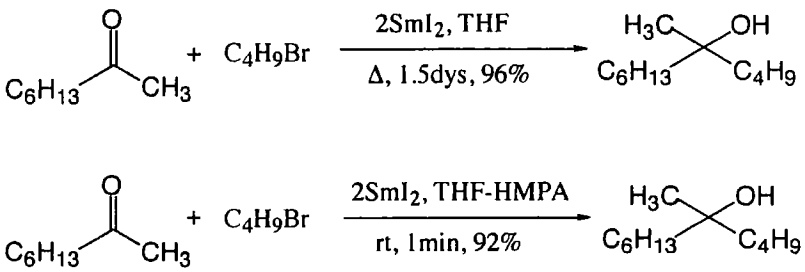
Yields in the Sm-based Barbier reaction are strongly influenced by the nature of the reactants and the precise reaction conditions. Primary alkyl iodides and tosylates, for example, undergo Barbier reactions with ketones in refluxing THF. Alkyl bromides are less reactive and alkyl chlorides are virtually inert, Scheme 1.17.[5] Unfortunately, aldehydes generate a mixture of products arising from competing Meerwein-Ponndorf reactions (promoted by secondary Sm alkoxides generated *in situ*.)[30] Aryl halides are generally incompatible with the reaction conditions (undergoing preferential reduction), although a recent report by Tani *et al.* indicates that switching to a benzene-HMPA solvent system may promote coupling.[31] Allylic and benzylic halides undergo reaction with ketones *and* aldehydes at room temperature.[5] Reactivity follows the order I>Br»Cl.



R	Conditions	Yield(%)
C_4H_9I	Reflux, 12h	97
C_4H_9Br	Reflux, 1.5dys	96
C_4H_9Cl	Reflux, 6dys	8
	rt, 15min	71
	rt, 25min	66
BnBr	rt, 30min	69

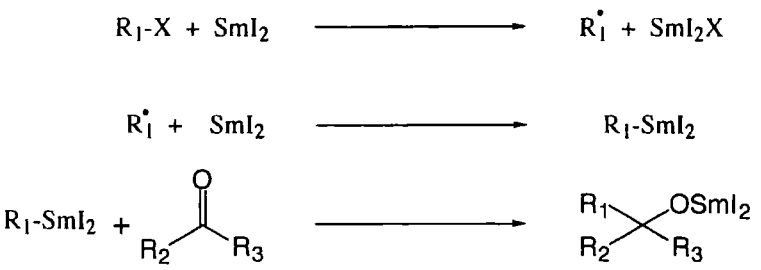
Scheme 1.17

Milder reaction conditions are possible when HMPA is used as a co-solvent, Scheme 1.18.[32]



Scheme 1.18

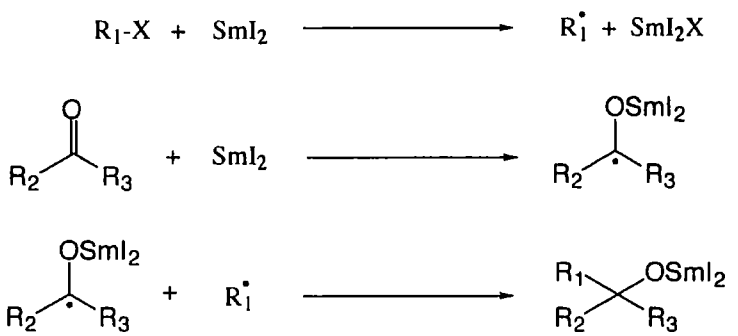
The exact mechanism of these intermolecular samarium Barbier reactions has yet to be established. Curran and co-workers have suggested that the reaction between alkyl halides and ketones, catalysed by HMPA, proceeds *via* an organometallic coupling mechanism, Scheme 1.19.[19]



Scheme 1.19

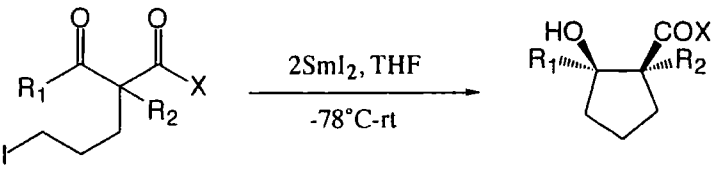
Two distinct experimental procedures were suggested by these workers: a samarium Grignard procedure (the alkyl halide is added first to the SmI_2 solution, followed by the ketone) and a samarium Barbier procedure (the ketone is added first, followed by the halide, or, the ketone and halide are added simultaneously). Reactions which follow the organometallic addition mechanism outlined above usually give better yields when conducted under the former, rather than the latter, conditions.

Kagan has proposed an equally plausible mechanism involving the generation of ketyl radicals, Scheme 1.20.[14a]

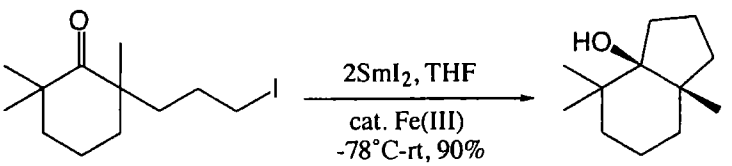


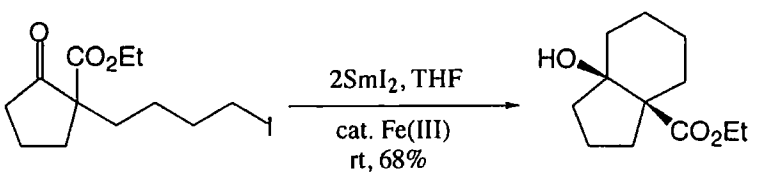
Scheme 1.20

A particular advantage of this methodology is in the extension to intramolecular processes, as this permits the construction of carbocyclic systems with yields and selectivities unattainable by traditional reagents (typically organolithium reagents), Scheme 1.21.[33]



R_1	R_2	X	Yield(%)
^iPr	H	NMe_2	87
Et	H	NMe_2	79
Pr	Me	OEt	87

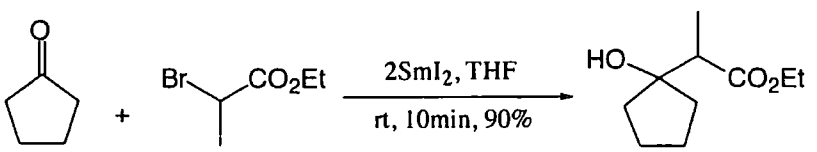




Scheme 1.21

1.3.3.ii Carbonyl Addition Reactions: The Reformatsky Reaction

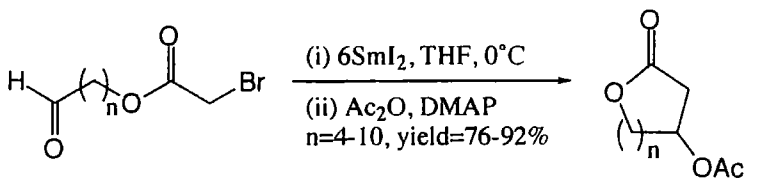
The coupling of aldehydes and ketones with α-halo esters to afford β-hydroxyesters, is known as the Reformatsky reaction. It is efficiently achieved with SmI_2, Scheme 1.22.[14a]



Scheme 1.22

The intramolecular version has been successfully applied to the synthesis of medium and large ring lactones, Scheme 1.23.[34] This provides a useful alternative to traditional

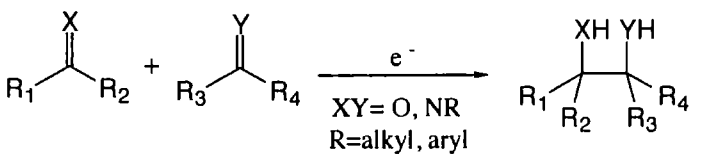
methods, such as the Baeyer-Villager oxidation of cyclic ketones, which often produces a range of yields and selectivities.



Scheme 1.23

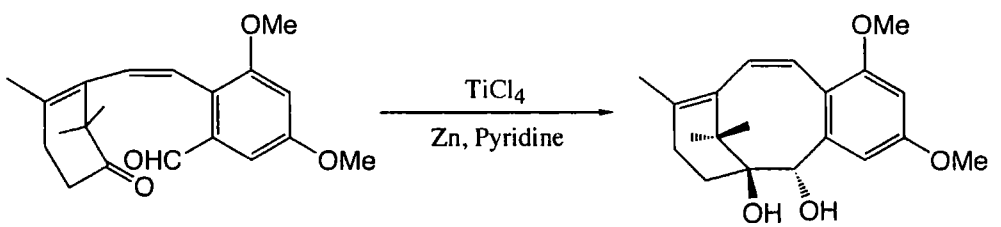
1.3.3.iii Reductive Coupling Reactions: The Pinacol Reaction

In the absence of a proton source, the pinacol reaction permits the facile construction of 1,2-diols, diamines and amino alcohols *via* reductive coupling of carbonyl compounds and imines, Scheme 1.24.[35]



Scheme 1.24

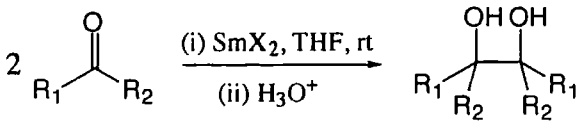
This reaction occupies a central role within organic synthesis– for example, the key step in the construction of the Taxane skeleton by Swindell *et al.*, Scheme 1.25.[36]



Scheme 1.25

Although *in situ* generated transition metal complexes are the most commonly used initiator the strongly reducing conditions of the reaction limits the range of functionality that can be

present in the molecule. Alternatively, various lanthanide compounds (in particular samarium(II)iodide and samarium(II)bromide) may be utilised. This milder, more selective process permits a range of coupling reactions, Scheme 1.26.[37]



R_1	R_2	X	Rxn Time	Yield(%)
Ph	H	I	30s	95
C_7H_{15}	H	I	3h	85
Ph	CH_3	I	30s	95
C_6H_{13}	CH_3	I	24h	80%
C_6H_{13}	CH_3	Br	5min	70%

Scheme 1.26

Whilst the intermolecular pinacol reaction proceeds with limited stereoselectivity, good stereocontrol can be realised with the intramolecular version. This selectivity arises from prior coordination of the carbonyl oxygen with the intermediate ketyl radical, Figure 1.2. One such example is reported by Hanessian and co-workers, who investigated the formation of *cis*-diols from several 1,5-and 1,6-dicarbonyls, Scheme 1.27.[38]

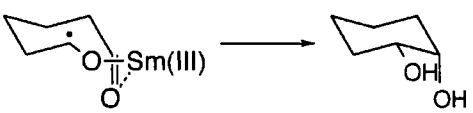
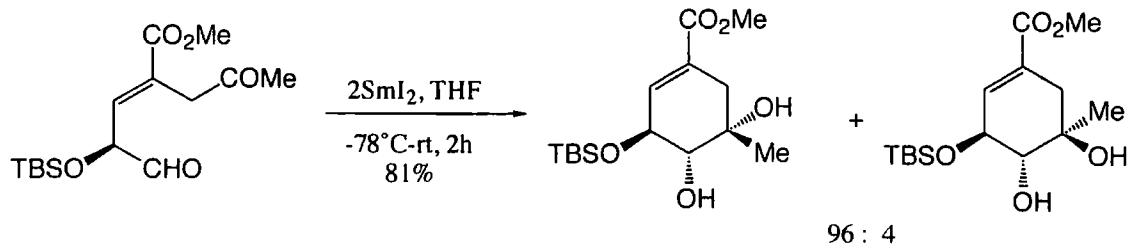


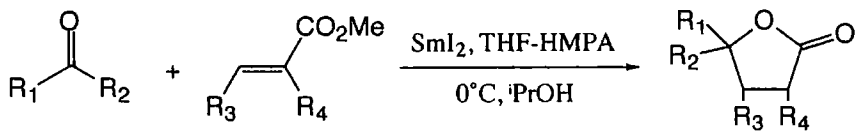
Figure 1.2



Scheme 1.27

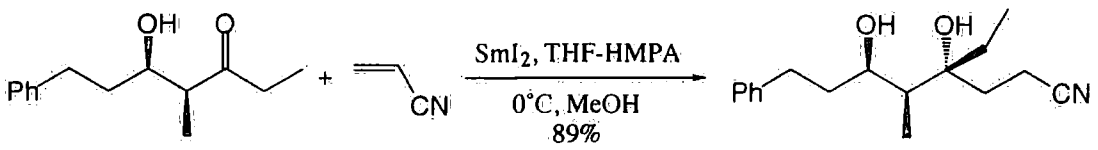
1.3.3.iv Reductive Coupling Reactions: Ketyl-olefin coupling

The ketyl radicals generated by carbonyl reduction may be trapped by a variety of radical processes. Coupling to activated alkenes and alkynes has been used to generate substituted butyrolactones, Scheme 1.28.[39] The role of the Sm-ketyl is supported by the fact that chelating hydroxyl groups generally produce high levels of stereocontrol in intermolecular coupling, in which the Sm(III) ions serve as a template for the reaction, Scheme 1.29 and Figure 1.3.[40]



R_1	R_2	R_3	R_4	Yield(%) [dr]
H	H	H	CH_3	45
PhC_2H_4	H	H	CH_3	78 [2.3:1]
$-(CH_2)_5-$		CH_3	CH_3	89 [4.9:1]

Scheme 1.28



Scheme 1.29

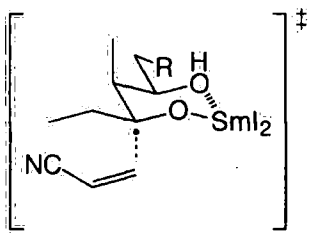
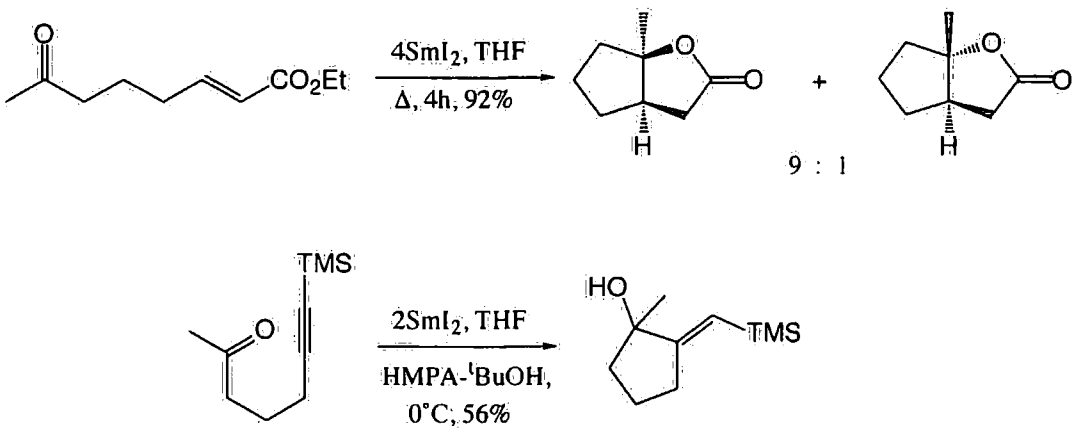


Figure 1.3

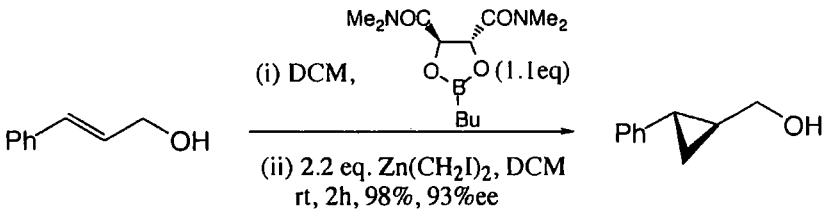
Activated alkenes and alkynes can participate in intramolecular ketyl-olefin cyclisations, Scheme 1.30.[41] High levels of diastereoselectivity are observed for alkene substrates.



Scheme 1.30

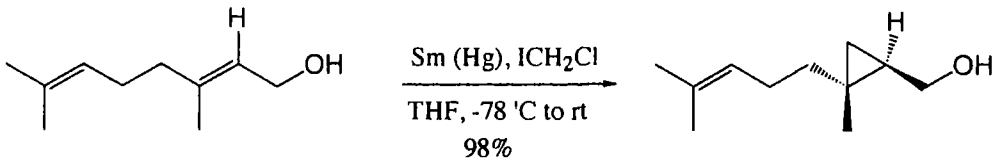
1.3.3.v Cyclopropanation Reactions

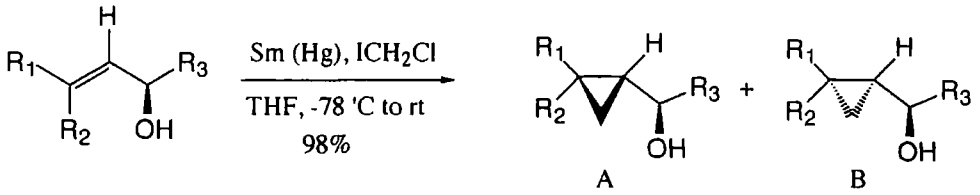
Classically the Simmons-Smith procedure (utilising methylene iodide and a Zn-Cu couple) and the transition-metal catalysed reactions of diazocarbonyl compounds provide two routes to cyclopropanes directly from alkenes.[42,43] High levels of stereocontrol are achieved through the use of chiral ligands, Scheme 1.31.[44,45]



Scheme 1.31

The Sm-mediated reaction provides a mild alternative, exhibiting high chemoselectivity and diastereoselectivity in the cyclopropanation of acyclic allylic alcohols, Scheme 1.32.[46] This is attributed to initial coordination of the samarium, prior to reaction with the metal-bound carbenoid, Figure 1.4.[46a]





R_1	R_2	R_3	Yield(%)	A : B
Ph	H	n-Bu	99	1 : 1.4
Ph	H	t-Bu	76	>200 : 1

Scheme 1.32

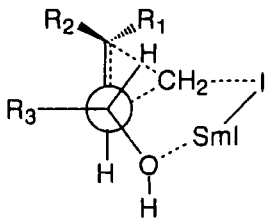
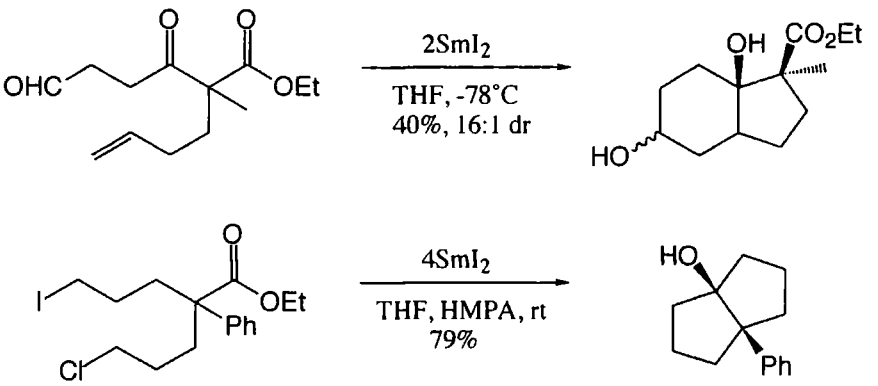


Figure 1.4

1.3.3.vi Summary

The use of SmI_2 in organic synthesis is continually increasing and few reductants are comparable to this reagent in terms of selectivity and yield. HMPA has greatly enhanced the power of this reagent and other electron-donating ligands may prove equally useful.

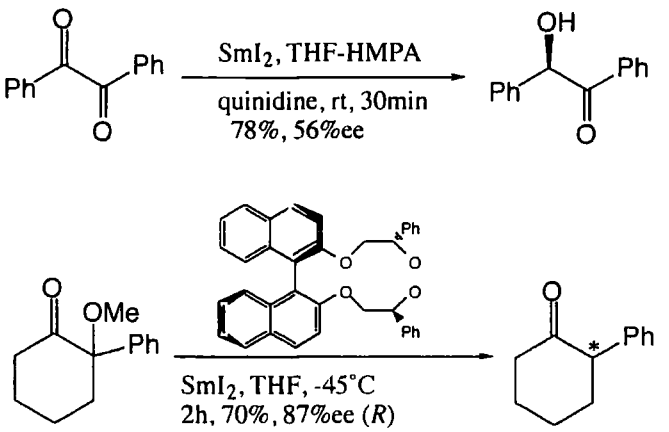
While true atom economy has yet to be realised, the recent applications of SmI_2 in sequential reactions represents an exciting development in this area of organolanthanide chemistry, Scheme 1.33.[47]



Scheme 1.33

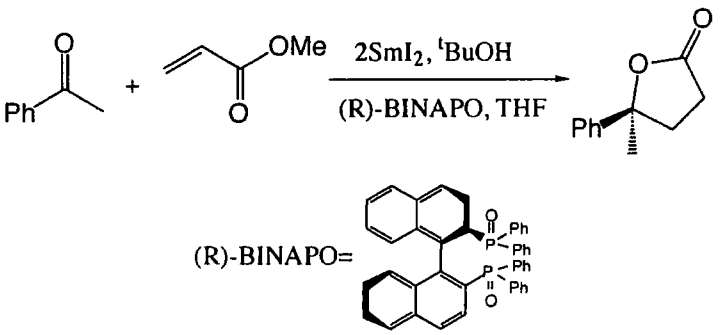
1.3.3.vii Enantioselective Reactions Employing SmI_2

As outlined in the preceeding sections, high distereoselectivity can be achieved in reactions utilising Ln(II) reagents *via* substrate-based stereocontrol. Conversely, the potential for enantioselective reactions by employing asymmetric Ln(II) reagents has yet to be realised. At the outset of this work inter-ligand asymmetric induction had only been achieved in reactions involving enantioselective protonation of samarium enolates, using chiral proton sources, Scheme 1.34.[48]



Scheme 1.34

Concurrent with our results, the first example of the use of chiral ligands in enantioselective SmI_2-mediated carbon-carbon bond forming reactions has recently emerged. Mikami and Yamaoka have reported the use of a chiral phosphine oxide ligand, (*R*)-BINAPO, to induce moderate enantioselectivity in the synthesis of substituted butyrolactones from aryl ketones and α,β-unsaturated esters, Scheme 1.35.[49] However, stoichiometric quantities of (*R*)-BINAPO are required and yields are generally low in this process.



Temp.(°C)	Yield(%)	ee(%)	Config.
-78	46	67	S
-105	26	74	S

Scheme 1.35

1.3.3.viii Summary

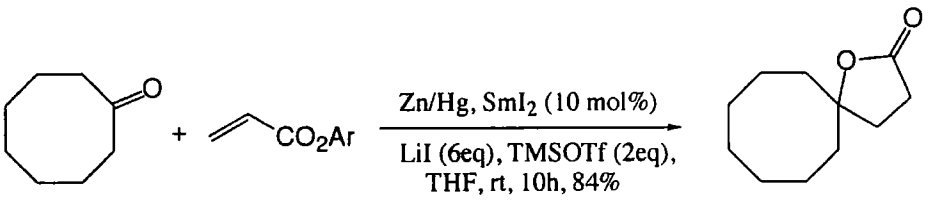
In conclusion, the potential for reagent-based stereocontrol in Sm(II)-mediated processes remains largely unexplored and this area is the fundamental goal of this project.

1.4 Regeneration of lanthanide(II) species

To date, lanthanide reagents have almost invariably been used in stoichiometric quantities. As valuable chemoselective reagents they are relatively expensive and more cost effective approaches are sought. Three strategies for recycling of Ln(II) species to provide an

effective catalytic cycle involve either chemical, electrochemical or photochemical reduction. There are precedents for all three methods in the literature and these are briefly discussed below.

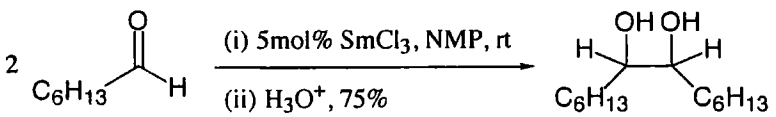
Although a number of chemical reagents exist for chemical reduction *in situ* e.g. BuLi and lithium naphthalenide, most of these have limited use in terms of substrate compatibility. Corey, for example, has reported the use of a Zn/Hg amalgam for the recycling of SmI_2 from SmI_3.[50] This procedure was facilitated by the addition of LiI and TMSOTf, Scheme 1.36.



Scheme 1.36

This section will focus on the two more convenient strategies which enable the clean recycling of Ln(II) species, namely, electrochemical and photochemical reduction.

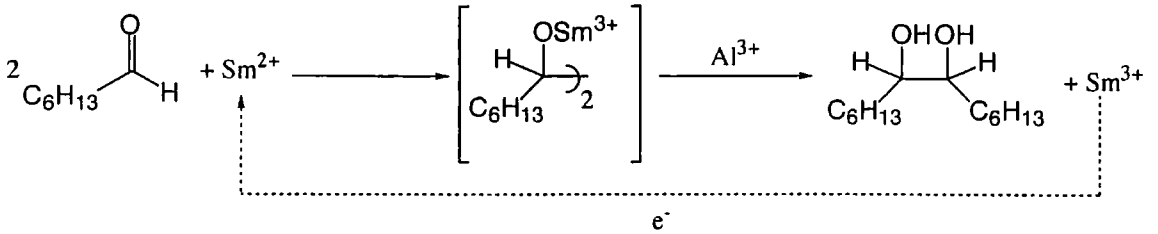
The first applications of electrochemical mediated regeneration of Ln(II) reagents was reported by Dunach *et al.*[51] They described the use of samarium(II) compounds to promote the electrochemical pinacolisation of aldehydes and ketones, Scheme 1.37.



Scheme 1.37

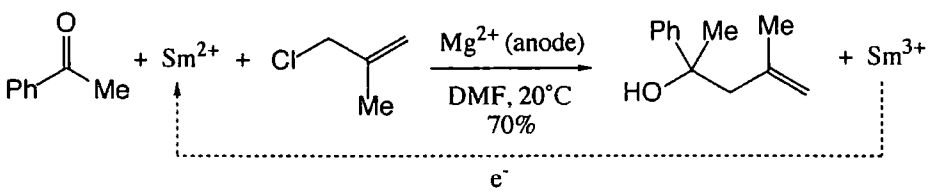
In this, samarium(III) chloride was employed as the catalytic precursor to Sm(II) and the intermediate Sm(III) pinacolate undergoes transmetallation with Al(III), produced at the

anode. Subsequent reduction yields free Sm(II) ions, which are capable of re-entering the catalytic pathway, Scheme 1.38.



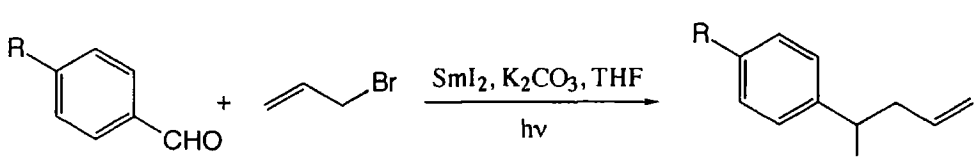
Scheme 1.38

In a related process, $SmCl_3$ has also been used in the electrochemical Barbier reaction of ketones and allyl chlorides, Scheme 1.39.[52]



Scheme 1.39

An alternative to the use of electrochemical recycling is provided by photochemical reduction. For example, Watanabe has reported the use of samarium diiodide and ytterbium diiodide in the preparation of a range of homoallylic alcohols, Scheme 1.40.[53] Photochemical regeneration of the lanthanide(II) catalysts was successful although continuous irradiation was required.



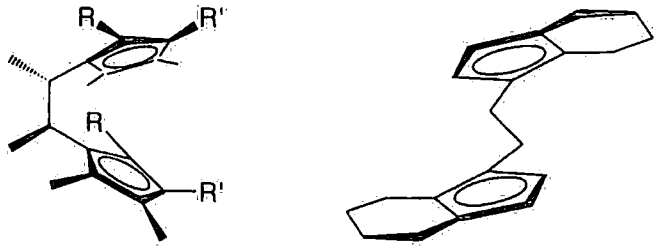
R	M	Yield
H	Sm	51%
H	Yb	43%
Me	Sm	19%

Scheme 1.40

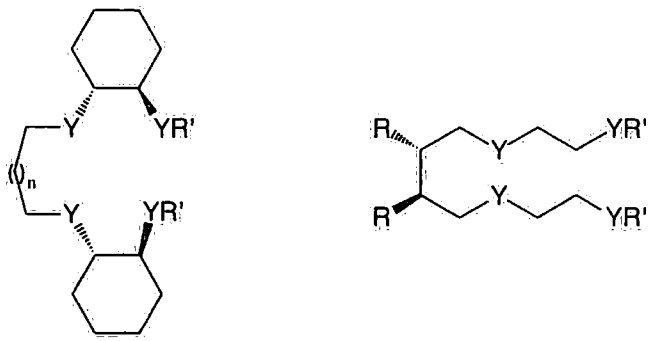
1.5 Proposed Work

The aim of this project was the investigation of ligand-promoted enantioselectivity in Ln(II)-mediated processes, as opposed to diastereoselectivity through substrate-based stereocontrol, which is well established. An ultimate goal is the development of catalytic schemes (Section 1.4).

Two series of ligands for the exploration of these objectives are outlined in Figure 1.5. These are comprised of substituted cyclopentadienyl ligands (series one) which are discussed in the following chapter and polyoxo/aza ligands (series two) which are discussed in Chapter 3.



Series One: R,R'=H, alkyl



Series Two: Y=NH, NR'', O; R'=H, alkyl.

Figure 1.5

SECTION B

RESULTS AND DISCUSSION

SECTION B: RESULTS AND DISCUSSION

CHAPTER 2

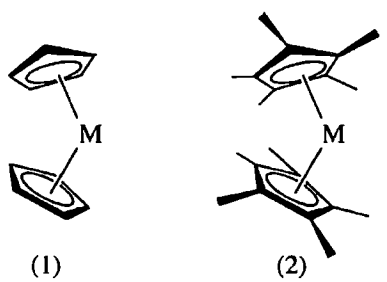
Synthesis of Bis-Pentaalkylcyclopentadienyl Systems

2.1 Introduction

This chapter is concerned with the synthesis of chiral bis-pentaalkylcyclopentadienyl ligands and their potential application in Ln(II)-mediated asymmetric synthesis. However, a brief review of cyclopentadienylmetal reagents will be given initially.

2.2 Cyclopentadienylmetal Complexes in Organic Chemistry

Dicyclopentadienyl (C_5H_5, Cp) (1) and bis-(pentamethylcyclopentadienyl) (C_5Me_5, Cp*) (2) ligands, Figure 2.1, have found widespread use in organometallic chemistry.[54] This area of chemistry is too large to be discussed in detail and the following sections are intended to give only a brief overview of these cyclopentadienyl systems, with emphasis on features of particular relevance to this project.



(1) (2)

Figure 2.1

2.2.1 Dicyclopentadienyl and Bis-(pentamethylcyclopentadienyl)samarium(II) Reagents

Although less well investigated than SmI_2, dicyclopentadienylsamarium(II) [Cp_2Sm] and bis-(pentamethylcyclopentadienyl)samarium(II) [Cp^*_2Sm] exhibit an enhanced reactivity relative to SmI_2. This is attributed to the electron-donating properties of the cyclopentadienyl ligands.

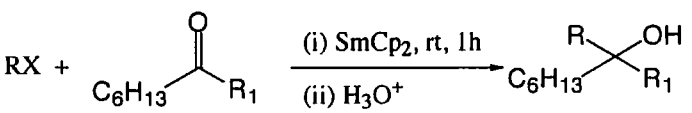
Dicyclopentadienyl and bis-(pentamethylcyclopentadienyl)samarium(II) are prepared by the reaction of SmI_2 with sodium cyclopentadiene (NaCp) and potassium pentamethylcyclopentadienyl (KCp^*) respectively, Scheme 2.1.[55]

$$SmI_2 + 2NaCp \xrightarrow{THF} SmCp_2 + 2NaI$$

$$SmI_2 + 2KCp^* \xrightarrow{THF} SmCp^*_2 + 2KI$$

Scheme 2.1

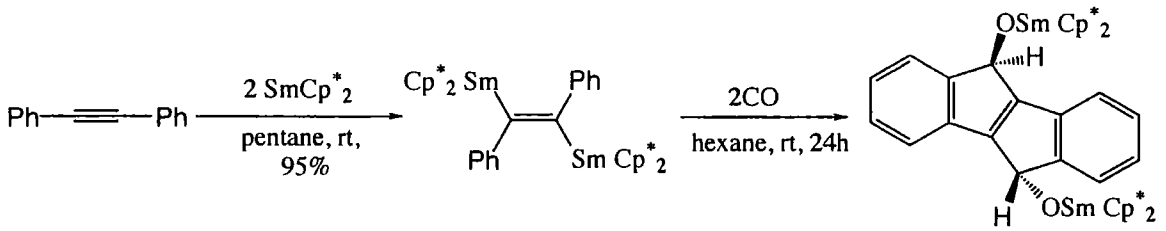
Kagan first reported the use of Cp_2Sm in pinacol reactions between acetophenone and benzaldehyde.[56] This reagent promoted Barbier reactions between aliphatic ketones and various halides under milder conditions than SmI_2 (room temperature as opposed to boiling THF), Scheme 2.2.[56] Yields were comparable to those obtained using SmI_2 and the relatively more difficult preparation of Cp_2Sm, coupled with the low solubility of this reagent, precluded its use in these processes. Cp_2Sm, however, is preferred over SmI_2 in Barbier reactions between aliphatic aldehydes and halides, in which competing Meerwein-Ponndorf-Verley reduction is supressed, Scheme 2.2.[30]



R	R_1	Cp_2Sm (Eq)	Yield (%)
C_4H_9I	CH_3	2	69
C_4H_9I	H	4	59
	H	3	86
BnBr	H	2	60

Scheme 2.2

In contrast to Cp_2Sm, Sm(II) complexes of pentamethylcyclopentadienyl (Cp^*) are readily soluble in a range of solvents. Cp^* confers even higher levels of stability, reactivity and crystallinity to metal complexes, than the corresponding Cp ligand. These factors are attributed both to the increased bulk of this ligand (which prevents oligomerisation and inhibits solvent coordination at the metal centre) and alkylation about the ring (which further increases electron donation to the metal). Evans has prepared a range of novel organometallic compounds using Cp_2^*Sm, for example, Scheme 2.3.[57] The use of these reagents in organic synthesis remains largely unexplored.



Scheme 2.3

2.2.2 Chiral *ansa*-Metallocenes

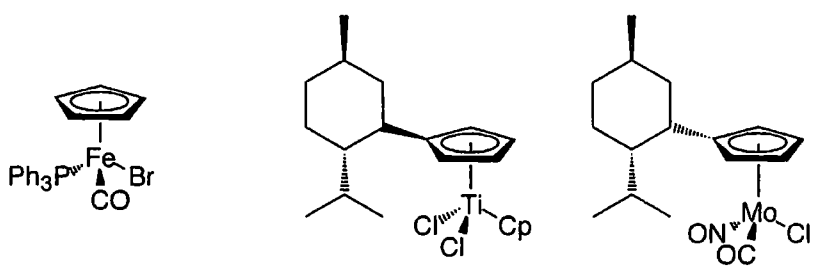
2.2.2.i Chirality in Cyclopentadienylmetal Complexes

Chirality in cyclopentadienylmetal complexes can arise in three ways:[58]

(i) metal-centred chirality, (3),

(ii) ligand-centred chirality, (4) and

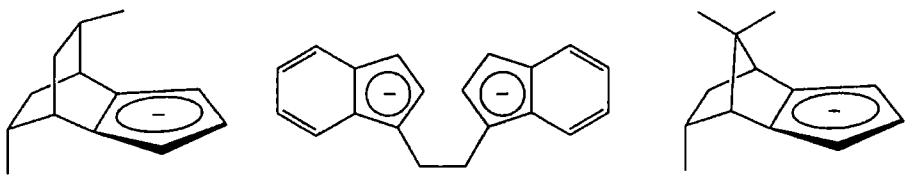
(iii) a combination of (i) and (ii), (5), Figure 2.2.



(3) (4) (5)

Figure 2.2

The relationship between the two faces of the cyclopentadienyl ligand gives rise to further sub-classes of chirality, Figure 2.3. If the faces are equivalent (homotopic) by virtue of a C_2-axis of symmetry or free rotation about a substituent on the ring, then a single stereoisomer results upon metallation. If the faces are related by a mirror plane the ligand is enantiotopic and will give a mixture of enantiomers when metallated. Conversely, faces not related by symmetry are diastereotopic and give rise to diastereoisomers upon metallation.

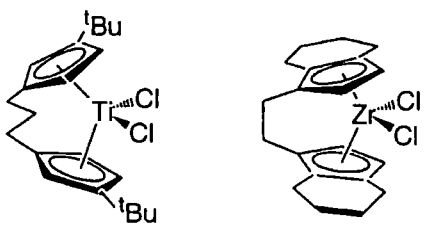


Homotopic Enantiotopic Diastereotopic

Figure 2.3

2.2.2.ii Development and Synthetic Applications

Brintzinger's seminal work on the synthesis of chiral C_2-symmetric *ansa* (or bridged)-trimethylenebis-[1-(3-*tert*-butylcyclopentadienyl)]titanium dichloride (6) and ethylene bridged bis-(tetrahydroindenyl) metallocenes (7), revolutionised the use of cyclopentadienyl-based ligands in organic/organometallic chemistry, Figure 2.4.[59]



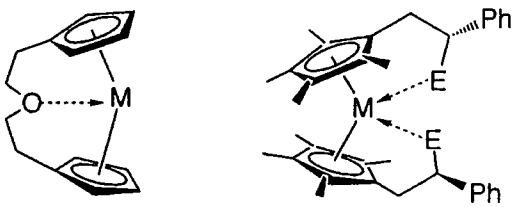
(6) (7)

Figure 2.4

These systems combined the favourable properties of free cyclopentadienyl and pentaalkylcyclopentadienyl ligands (solubility, reactivity and stability) with tethering

which prevents rotation about the cyclopentadienyl ring and permitted a more rational approach to the design of chiral cyclopentadienylmetal complexes.

Donor functionalisation, that is, the introduction of Lewis-basic atoms into the side chain could provide further stability and coordinative saturation at the metal centre, (8) and (9), Figure 2.5.[60] Stereochemistry could be incorporated into these ancilliary ligands, Figure 2.5.[60] Both features could play an important role in catalytic processes employing these complexes.



(8) (9)

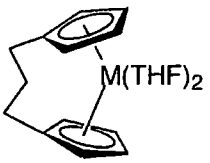
Figure 2.5

Most notably, *ansa*-metallocenes have been utilised in the catalytic stereoregular polymerization of alkenes and enantioselective hydrogenations.

Brintzinger and co-workers, for example, have employed an ethylene-bridged bisindenyl zirconium dichloride ligand in the stereoregular polymerization of propene to form isotactic poly(propylene).[61] This class of polymerization reactions has been extensively investigated.[62]

2.2.2.iii Lanthanide Complexes

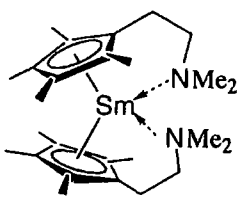
Kagan's use of dicyclopentadienyl and bis-(pentamethylcyclopentadienyl) samarium(II) reagents in organic synthesis and the development of *ansa*-metallocenes, prompted several groups to investigate the incorporation of Ln(III) and Ln(II) ions into related complexes. In fact, Schumann *et al.* prepared ring bridged-dicyclopentadienyl complexes of Sm(II) (10a) and Yb (II) (10b), Figure 2.6.[63]



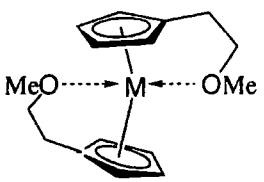
(10a) M=Sm
(10b) M=Yb

Figure 2.6

Jutzi[64] and Qian[65] have exploited the concept of donor functionalisation to stabilise Ln(II) complexes, (11) and (12a, b), Figure 2.7.



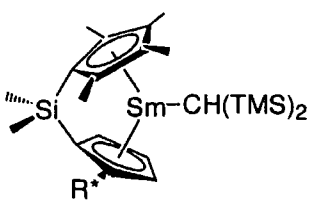
(11)



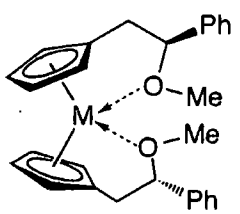
(12a) M=Sm
(12b) M=Yb

Figure 2.7

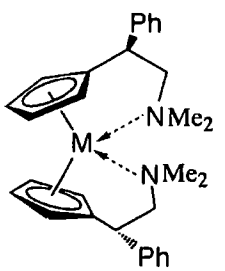
To date, the trivalent *ansa*-samarium complex (13), used by Marks in the enantioselective hydrogenation of styrene and 2-phenyl-1-butene, and the donor functionalised Ln(II) complexes reported by Molander, are the only examples of enantiomerically pure lanthocenes, Figure 2.8.[66,67]



(13) R*=(-)-Menthyl



(14) M=Sm
(15) M=Yb



(16) M=Sm
(17) M=Yb

Figure 2.8

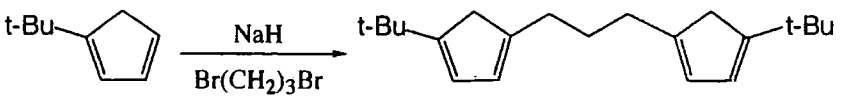
2.3 Previous Synthetic Approaches to Chiral Cyclopentadienyls

2.3.1 Introduction

There is a wealth of synthetic approaches to bridged bis-cyclopentadienes and the subject has been reviewed recently.[58] Consequently, the aim of this section is to give a brief overview of existing synthetic strategies.

2.3.2 Synthesis of Bis-cyclopentadiene Ligands

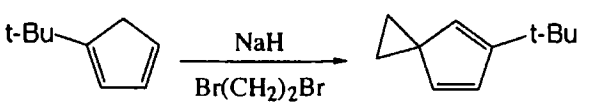
The first example of a bis-cyclopentadiene system (19), reported by Brintzinger, was prepared by the selective alkylation of substituted cyclopentadienes with 1,3-dibromopropane, Scheme 2.4.[68] Alkyl substituents smaller than isopropyl lead to competing 1,2-alkylation.



(18) (19)

Scheme 2.4

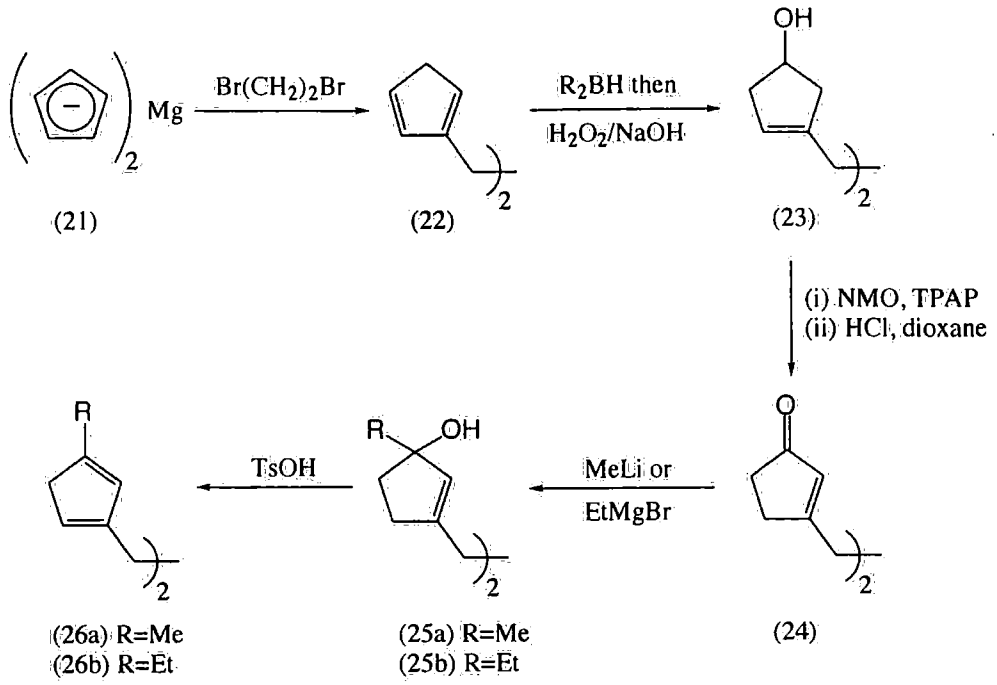
The use of NaCp as a nucleophile in the preparation of ethylene-bridged cyclopentadienes may cause problems due to preferential formation of spiro-cyclopropanes, *via* intramolecular cyclisation, Scheme 2.5.[69]



(18) (20)

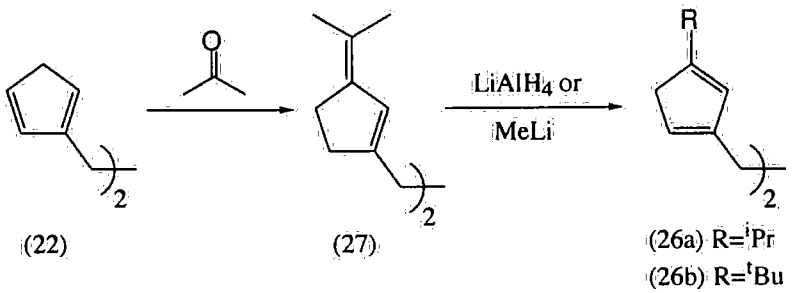
Scheme 2.5

This problem was circumvented by the use of Cp_2Mg in an elegant route to substituted *ansa*-metallocenes described by Collins and co-workers, Scheme 2.6.[70]



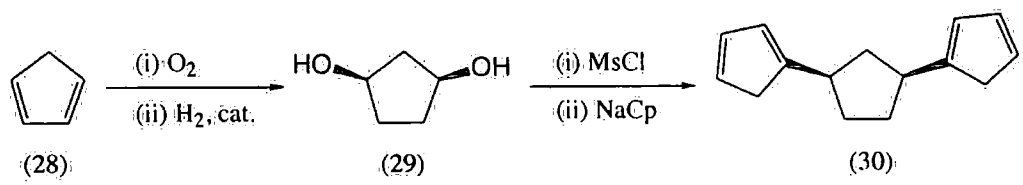
Scheme 2.6

Treatment with $LiAlH_4$ or MeLi affords the *iso*-butyl or *tert*-butyl derivatives respectively, Scheme 2.7.[70]



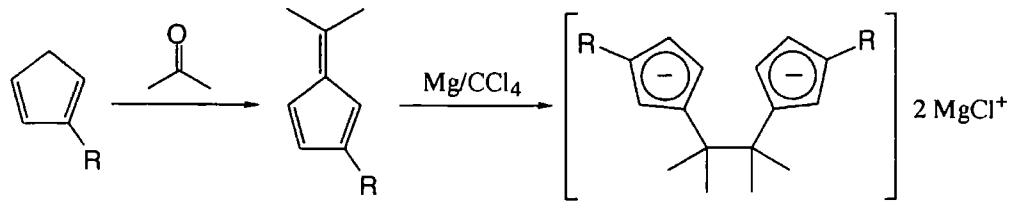
Scheme 2.7

Alternatively a more rigid backbone may be used to limit side chain mobility, Scheme 2.8.[71]



Scheme 2.8

A more general approach to ethylene bridged bis-cyclopentadienes is via the reductive coupling of substituted 6,6-dimethylfulvenes, Scheme 2.9.[72]



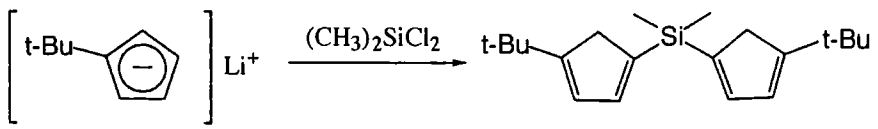
(31a) R=t-Bu
(31b) R=i-Pr

(32a) R=t-Bu
(32b) R=i-Pr

(33a) R=t-Bu
(33b) R=i-Pr

Scheme 2.9

The dimethylsilyl group has been used to bridge substituted cyclopentadienes by the addition of two equivalents of the cyclopentadienyl anion to dichlorodimethylsilane, Scheme 2.10.[73] This linking method is particularly effective for sterically demanding analogues, such as pentamethylcyclopentadienyl ligand (13) (see Figure 2.8).

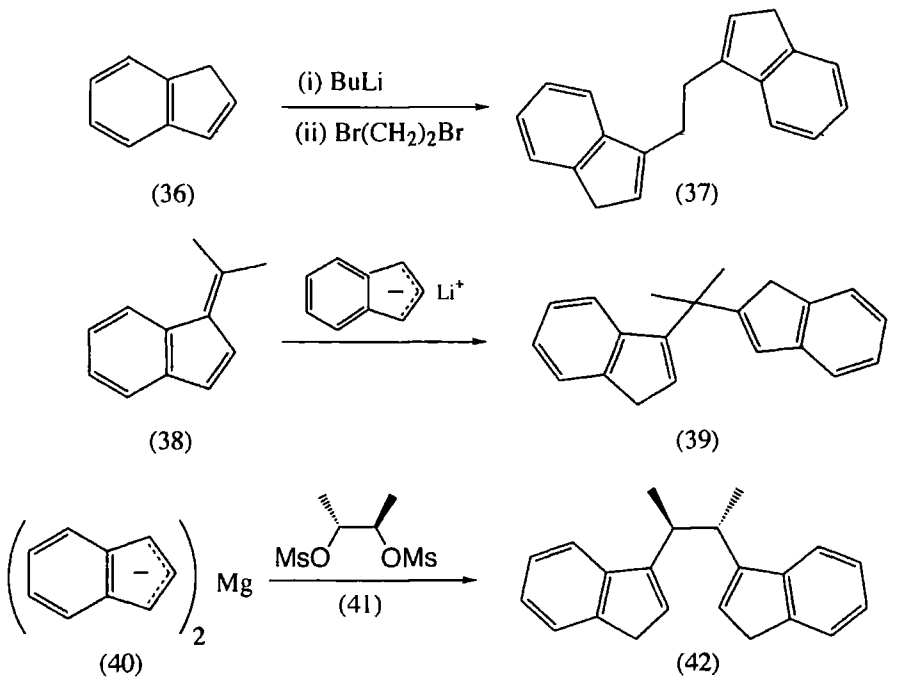


(34)

(35)

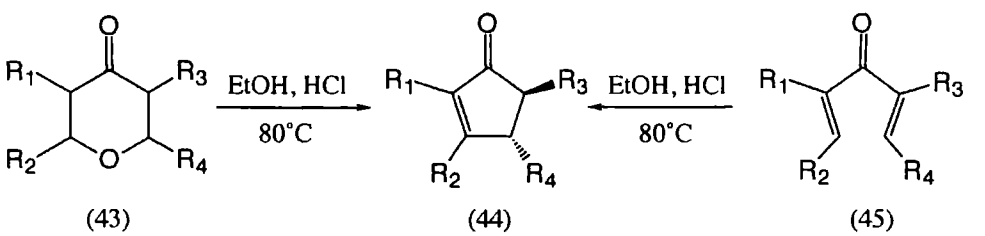
Scheme 2.10

Substituted indenyl derivatives are simply prepared by application of the above methodology, for example, Scheme 2.11.[74] Particularly noteworthy is the incorporation of an asymmetric backbone (42).[75]



Scheme 2.11

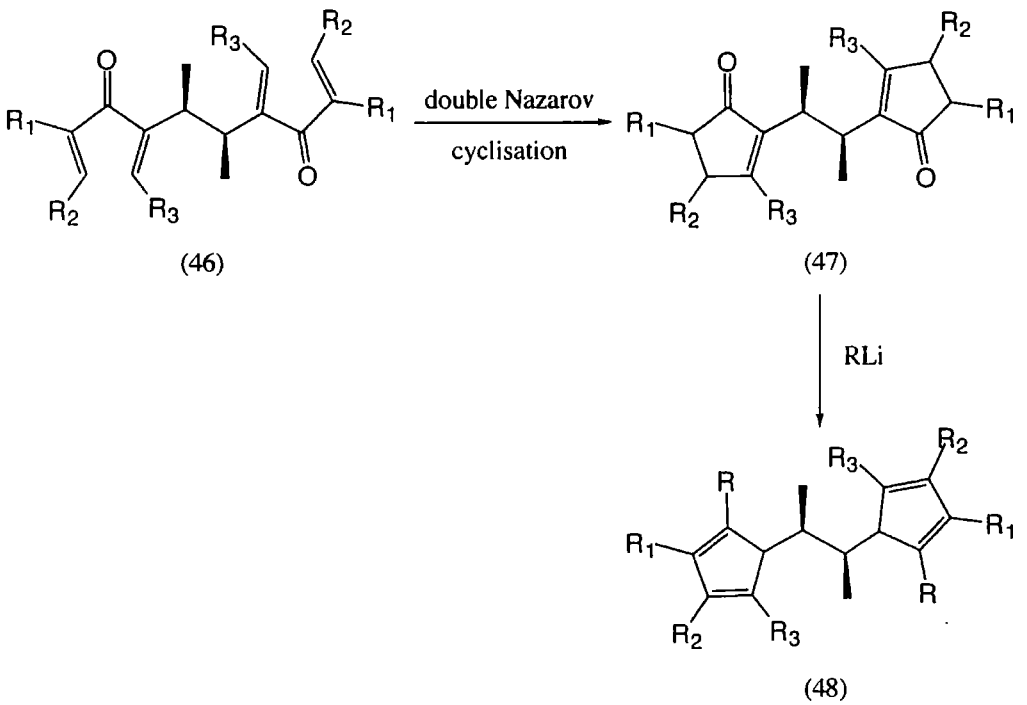
An alternative approach to *ansa*-cyclopentadienes involves the linking of non-cyclic precursors prior to cyclopentannulation. The most common cycloannulation process is the Nazarov cyclisation, Scheme 2.12.[76] This provides a versatile route to a range of substituted cyclopentadienes via the facile functionalisation of 2-cyclopentenones (44). In addition, preparative methods for the construction of the prerequisite divinyl ketones (45) and their synthetic equivalents (43) are well established.



Scheme 2.12

The linking of two divinyl synthons would generate a double-Nazarov system, which could potentially undergo double cyclisation to afford a bridged bis-cyclopentadiene,

Scheme 2.13. This concept is unprecedented and is central to our synthetic strategy, which is discussed in the following section.

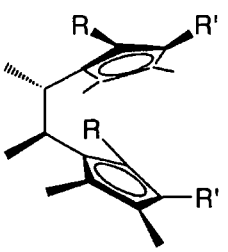


Scheme 2.13

2.4 Nazarov Cyclisation Approach

2.4.1 Introduction

After consideration of the work outlined above we elected to commence this project with the synthesis of the ethano-bridged peralkylated cyclopentadienyl (49) ligand, Figure 2.9.



(49)

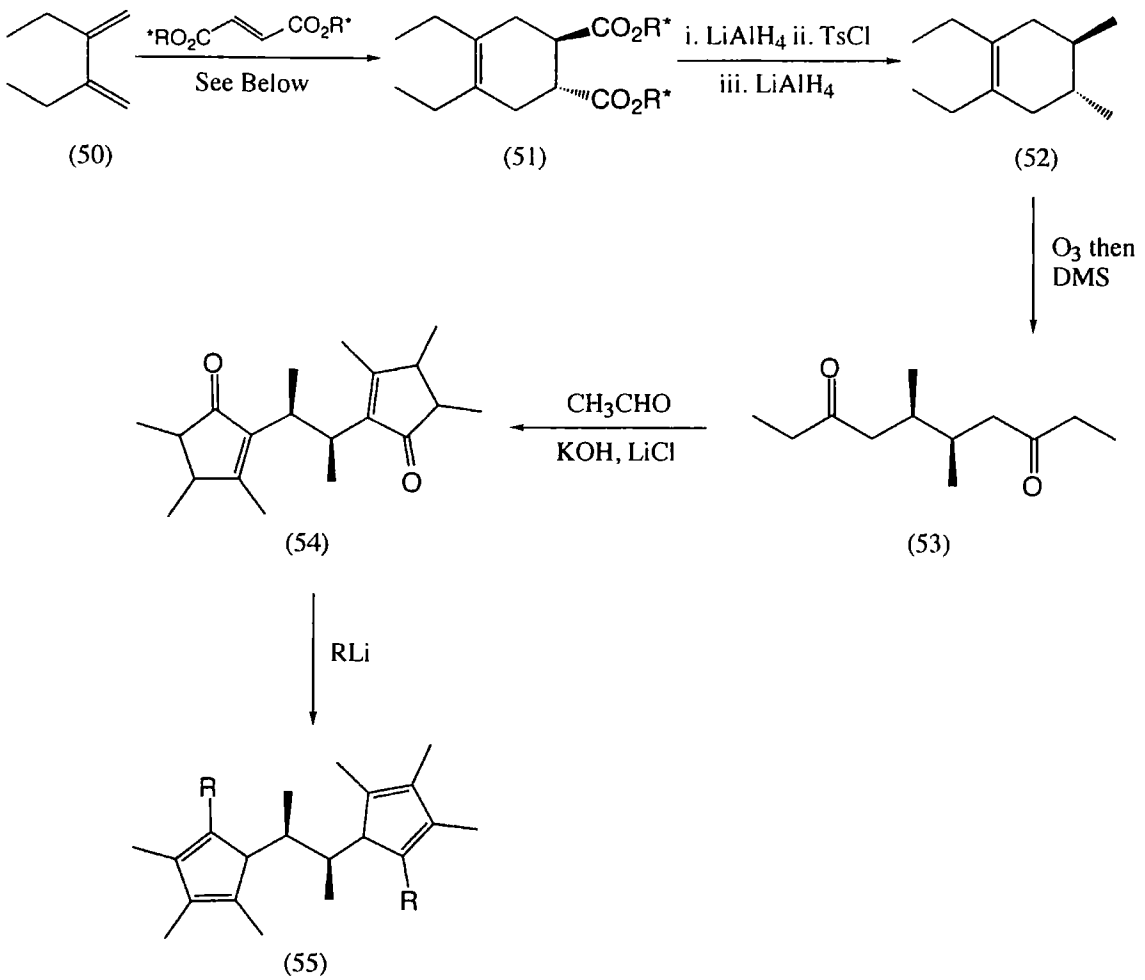
R, R'=alkyl

Figure 2.9

This system combines the favourable properties of *ansa*-bis-pentamethylcyclopentadienyl ligands (solubility, stability, reactivity and rigidity) with C_2-symmetry, which prevents diastereoisomer formation upon complexation. The enhanced reducing power of this pentaalkyl-substituted ligand may permit the use of Eu and Yb for which the divalent state is not normally of sufficient reducing power to be considered. This, in turn, may lead to differing chemoselectivities in subsequent reactions employing these complexes.

By shortening or lengthening the tether the steric influence that the chiral ligands exert on the active (free) face of the complex should be reduced or increased respectively. This effect may increase stereoselectivity in reactions utilising these complexes. In order to extend this section of our work into the area of enantioselective synthesis, we will examine a number of chiral ligands containing suitable alkyl or indenyl substituents.

The silicon-linked unit (13) used by Marks[4], Figure 2.8, presented difficulties due to the formation of diastereomeric complexes on binding to samarium. To avoid this problem we have opted to use enantiomerically pure bis pentaalkylcyclopentadienyl ligands, accessed via an established enantioselective Diels-Alder reaction, Scheme 2.14.[77]



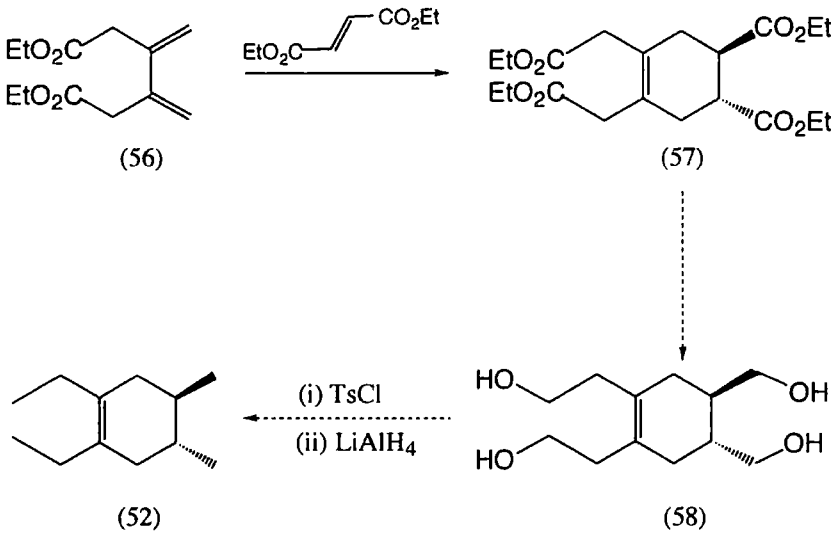
Scheme 2.14

A double cross aldol reaction and Nazarov cyclisation (*vide supra*), on the key 1,6-dicarbonyl compound (53) would produce the desired bis-cyclopentenone (54). Treatment with a suitable organometallic reagent would produce the bis-pentaalkylcyclopentadienyl ligand (55). Thus a series of related ligands can be prepared by simply varying the nature of the organometallic reagent. In this way the possibilities for attaining enhanced selectivity through the use of bulkier and/or chelating groups on the cyclopentadienyl ligands can be explored.

Synthesis of the key 1,6-dicarbonyl compound (53) will be discussed in the following section.

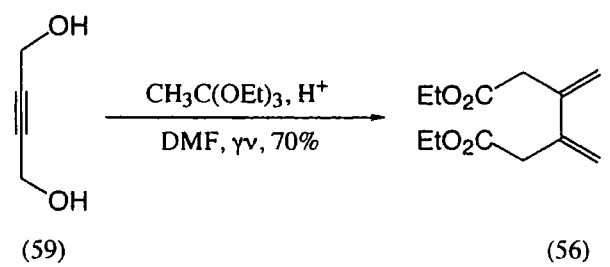
2.4.2 Synthesis of Dicarbonyl Compound (53)

The diene (50), Scheme 2.14, is not commercially available. We chose to verify the synthesis in a racemic series, Scheme 2.15.



Scheme 2.15

Preparation of the diene diester (56) was undertaken by heating 2-butyne-1,4-diol with an excess of triethyl orthoacetate at 110°C, in the presence of an acid catalyst.[78] Ethanol formed during the course of the reaction was collected using a Dean-Stark apparatus. This approach, however, was unsatisfactory and methodology recently reported by Srikrishna and co-workers was adopted.[79] In this, a mixture of 2-butyne-1,4-diol, triethyl orthoacetate and propionic acid in DMF (in an open conical flask) was irradiated in a domestic microwave oven at high power (750W), Scheme 2.16, with monitoring by ^{1}H NMR.

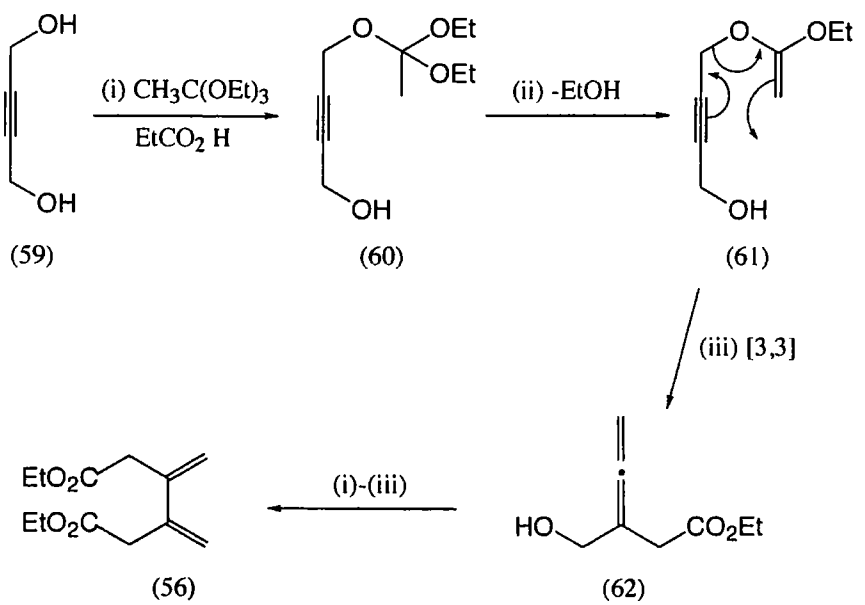


Scheme 2.16

In microwave-promoted reactions energy transfer operates through dielectric loss rather than conduction or convection.[80] Heating efficiency is largely dependent upon the nature of the solvent. Therefore, polar solvents such as DMF and acetonitrile, in which there is a significant dipole moment, produce greater heat transfer when compared to solvents such as toluene and pentane.

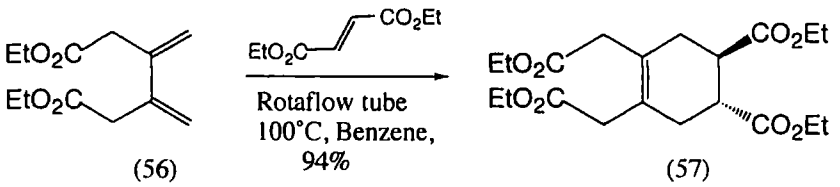
The use of a domestic microwave oven, rather than a commercial "continuous microwave reactor" (CMR), which would have allowed more efficient cooling and a greater control of heating temperature, presented some difficulties.[80] For example, the sample had to be removed periodically and cooled to prevent excessive loss of solvent, whilst when rapid heating was followed by long periods of cooling, decomposition (dimerisation or polymerisation) occurred! This balance, between rapid heating and satisfactory cooling times, is not fully understood within the field of microwave-assisted reactions.

The formation of small quantities of allene (62) was observed by ^{1}H NMR, consistent with the proposed mechanism, Scheme 2.17.



Scheme 2.17

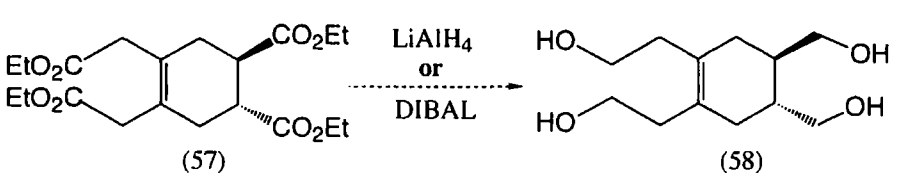
Conversion of the diene diester (56) to the Diels-Alder adduct (57) was achieved by reaction with diethyl fumarate, Scheme 2.18.



Scheme 2.18

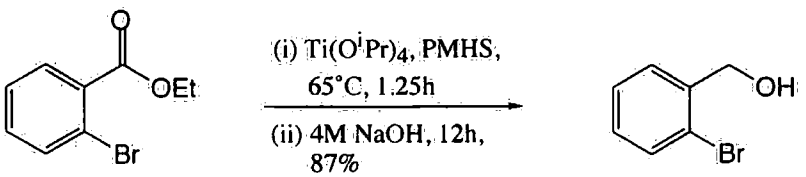
Cycloadditions are accompanied by a decrease in the volume of the system, so may be subjected to rate acceleration with increasing pressure. This feature was exploited by conducting the thermally promoted Diels-Alder reaction in a sealed tube "Rotaflow tube". A preliminary investigation was performed on an NMR scale, in order to monitor the progress and rate of reaction. Subsequently, the reaction was repeated using a "Rotaflow tube", producing the desired adduct in 94%, after heating for 24 hours. Formation of the ester (57) was confirmed by a molecular ion peak at *m/z* 398 and ion peaks were observed at *m/z* 353 and *m/z* 279 corresponding to the loss of EtO and $EtCO_2$ fragments respectively. Further evidence was provided by the ^1H NMR with a triplet at δ2.80 and a mutiplet at δ2.42 corresponding to the ring CH and CH_2 groups. Loss of the methylene protons associated with the dienophile was also observed (^1H NMR).

Reduction to the corresponding alcohol (58), Scheme 2.19, was attempted with $LiAlH_4$ and DIBAL using standard procedures. Whilst the reaction appeared to proceed, it proved impossible to isolate any of the desired product.



Scheme 2.19

Recently, Reading and Buchwald reported the use of a titanium siloxane reagent in the thermal conversion of esters to primary alcohols, Scheme 2.20.[81] This procedure provides a mild, chemoselective method for the reduction of esters.

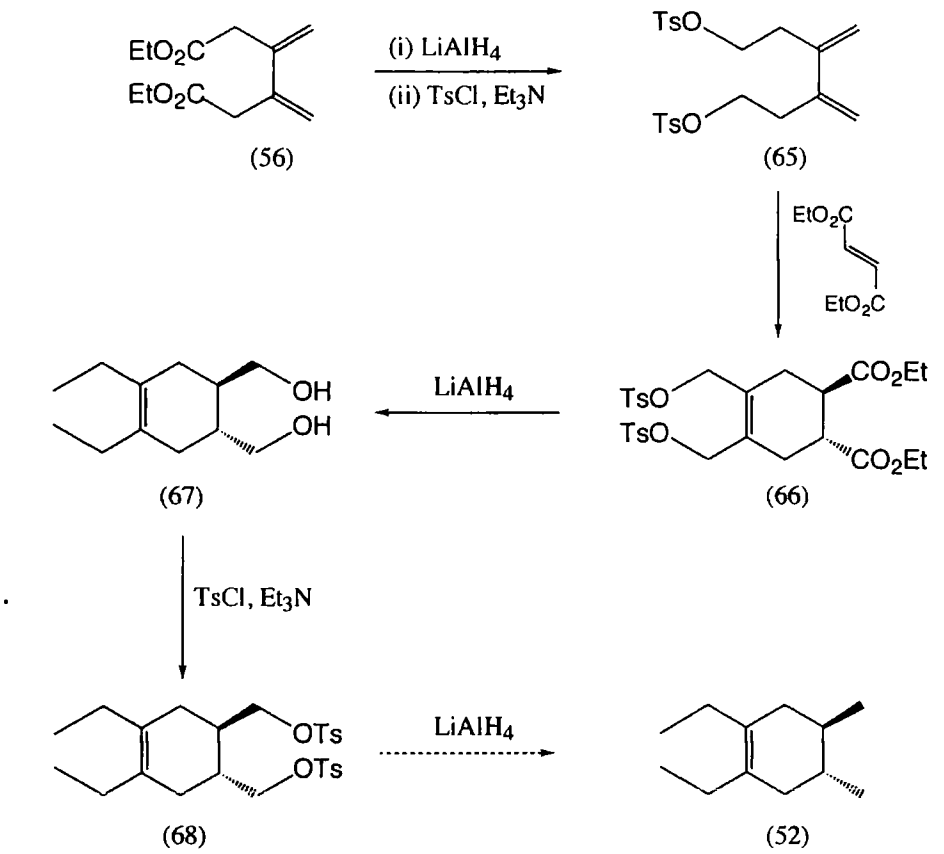


(63) (64)

PMHS=polymethylhydrosiloxane

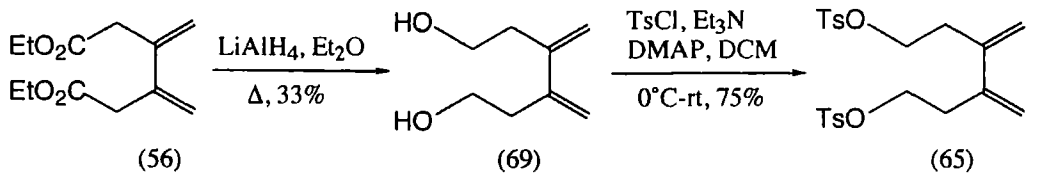
Scheme 2.20

Following this precedent titanium isopropoxide was added to a solution of the ester (57) and diphenylsilane in THF. Work-up afforded a polymeric siloxane impurity but none of the alcohol (58). In a final attempt to isolate the alcohol (58), the $LiAlH_4$ reduction was repeated, the reaction was quenched in the usual way and then a solution of *p*-toluenesulfonyl chloride in dichloromethane was added. Unfortunately, the protected alcohol was not produced and an alternative route to the cyclohexene (52), Scheme 2.21, was therefore pursued. This follows a longer stepwise strategy which avoids the formation of tetra-ols.



Scheme 2.21

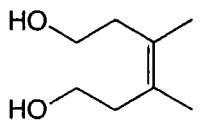
Following Scheme 2.21, a solution of the diene diester (56) in ether was added to a $LiAH_4$ slurry and the mixture heated at reflux for 12 hours to afford the diol (69) in 33% yield, after purification by flash column chromatography, Scheme 2.22.



Scheme 2.22

A characteristically weak molecular ion peak was observed at *m/z* 142. A broad singlet at δ1.76 in the ^1H NMR and an O-H stretch at 3500-3200 cm^{-1} corresponded to the presence of the alcohol functionality. Additionally, loss of the ethyl protons in the ^1H NMR further substantiated formation of the diol (69). The desired reduction was

accompanied by the formation of a by-product (70) arising from 1,4-reduction of the diene (56), Figure 2.10. This could be prevented by conducting the reduction at room temperature. The analogous DIBAL reduction produced the diol (69) in similar yield.



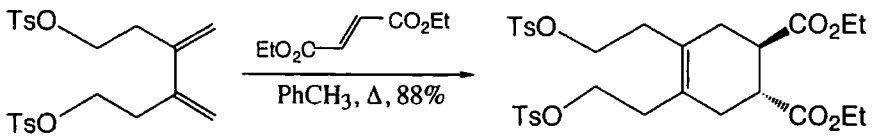
(70)

Figure 2.10

Conversion of the diol (69) to the ditosylate (65) was achieved, in 75% yield, by the addition of *p*-TsCl to a solution of the diol (69), triethylamine and DMAP in dichloromethane, Scheme 2.22. The ditosylate (65) was identified by characteristic tosyl signals at δ7.52, 7.32 and 2.40 in the ^{1}H NMR. Consumption of the diol (69) was confirmed by the loss of the O-H stretching vibration at 3500-3200 cm^{-1} in the IR spectrum.

The low yields encountered in the preparation of the diester (56) were thought to arise from decomposition of the diol (69) during purification and a "one pot" reduction and tosylation of the diester (56) was undertaken. This involved the reduction and extraction of the diester (56) in the usual manner, followed by tosylation as described above. Thus, the tosylate (65) was obtained in 78% overall yield under $LiAlH_4$ reduction. A similar procedure using DIBAL proceeded in lower yield (55%).

Preparation of the Diels-Alder adduct (66) was effected through the addition of diethyl fumarate to a solution of the tosylate (65), in toluene, which was then heated at reflux overnight. Purification by flash column chromatography afforded the desired compound in 88% yield, Scheme 2.23.



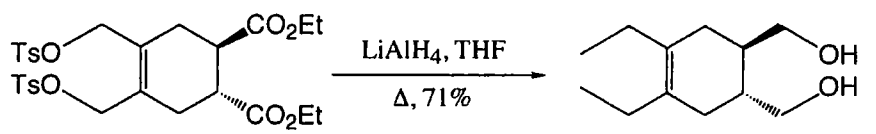
(65) (66)

Conditions	Time (h)	Yield (%)
PhMe, Reflux	12	88
1,2-DCE, Rotaflow tube	2.5	97

Scheme 2.23

Synthesis was confirmed, in part, by the appearance of a multiplet at δ2.15 corresponding to the diastereotopic CH_2 protons in the cyclohexene ring, with associated loss of the methylene protons of the diene. Further enhancement in reaction rate and yield was subsequently achieved by conducting the reaction in a Rotaflow tube, using 1,2-dichloroethane as the solvent.

Reduction to the diol (67) was achieved using $LiAlH_4$, Scheme 2.24. The slurry was heated at reflux for 1.5 hours. Flash chromatography of the combined crude extracts gave the diol (67) in 71% yield.



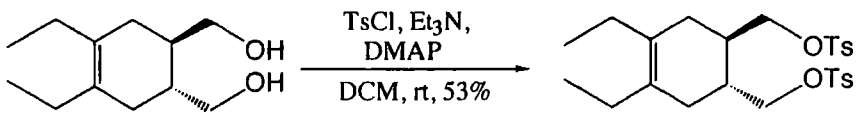
(66) (67)

Scheme 2.24

A weak molecular ion peak was observed at *m/z* 198. Further confirmation of the structure was obtained from a broad singlet at δ3.90 in the ^1H NMR and an O-H stretch at 3566-3214 cm^{-1}.

Conversion of the diol (67) to the ditosylate (68) was then achieved using standard methodology, Scheme 2.25.[82] Purification by column chromatography afforded the

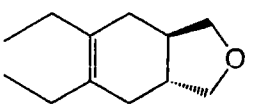
desired tosylate (68) in 53%, which was identified by characteristic tosyl signals in the ^{1}H NMR and loss of the O-H stretching vibration in the IR spectrum.



(67) (68)

Scheme 2.25

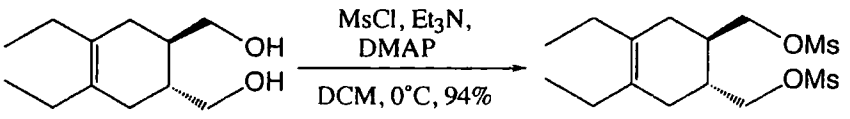
Interestingly, a by-product was also generated and analysis of the ^{13}C NMR spectrum suggested that a cyclic species (71) was formed, Figure 2.11, *via* intramolecular elimination of a tosyl moiety (*vide infra*).



(71)

Figure 2.11

Initial studies towards the cyclohexene hydrocarbon (52), through reaction of the ditosylate (68) with $LiAlH_4$ were unsatisfactory (poor yield). It was hoped that the dimesylate (72) might be more readily reduced and this substrate was prepared using a standard procedure,[83] Scheme 2.26.

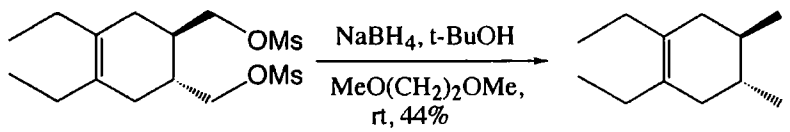


(67) (72)

Scheme 2.26

A molecular ion peak was observed at *m/z* 354. A 6H singlet at δ2.97 in the ^{1}H NMR corresponded to the presence of the mesylate functionality, with concomitant loss of the O-H stretching vibration in the IR spectrum.

A range of procedures for the reduction of methanesulfonyloxy groups to alkanes have been reported in the literature. For example, Theodore and Nelson have reported a mild, efficient method for the cleavage of methanesulfonyloxy groups to afford alkanes with sodium borohydride in *tert*-butyl alcohol.[84] Application of this methodology to the dimesylate (72) generated the desired cyclohexene (52) in 44% yield, Scheme 2.27, with recovery of both monomesylate and starting material.

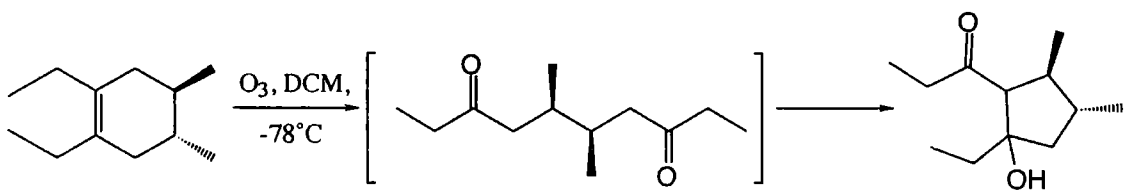


(72) (52)

Scheme 2.27

A modification using sodium cyanoborohydride in HMPA, as proposed by Hutchins,[85] was less successful, yielding the cyclohexene (52) in only 10% yield. However, reduction to the cyclohexene (52) was achieved in good yield (79%) using $LiAlH_4$ in THF.

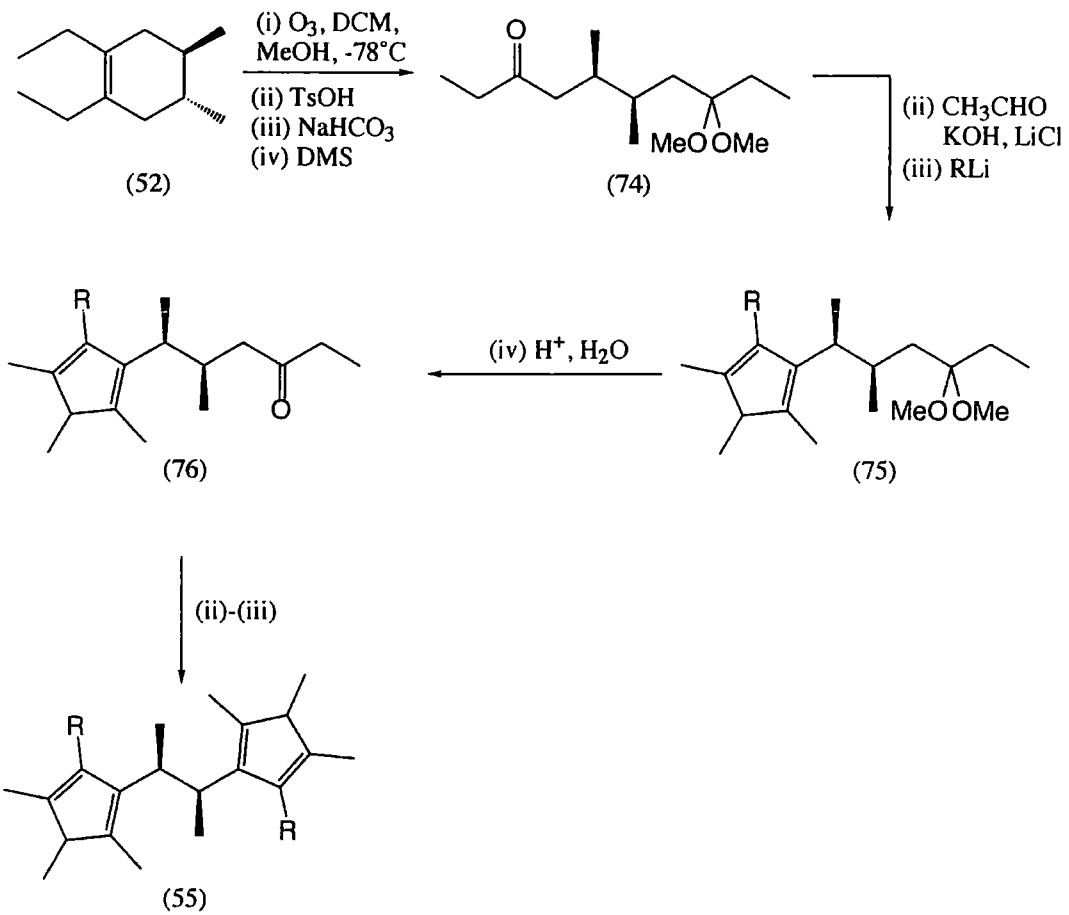
Ozonolysis of the cyclohexene (52) under standard conditions[86] (O_3 then DMS) led to preferential formation of the five-membered ring (73), Scheme 2.28. This is attributed to an intramolecular aldol reaction of the 1,6-dicarbonyl compound (53), formed *in situ*.



(52) (53) (73)

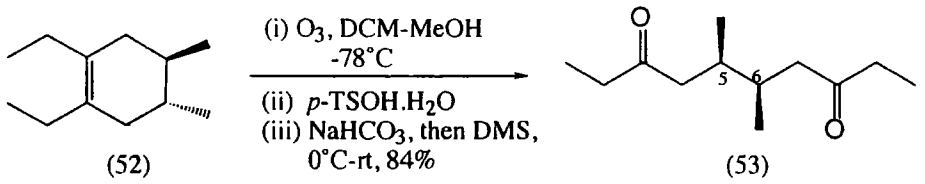
Scheme 2.28

A possible solution to this problem was thought to lie in the generation of a ketal (74), using an established modification of the ozonolysis conditions, Scheme 2.29.[87] Unable to undergo cyclisation, this product could be manipulated to afford a monocyclopentadiene (75), using the cross aldol/Nazarov cyclisation approach. This could then be deprotected and the resulting ketone (76) converted into the second cyclopentadiene ring.



Scheme 2.29

Surprisingly, these conditions led to generation of the diketone (53) in 84% yield, with no observable formation of the ketal (74), Scheme 2.30. Presumably *p*-TsOH and sodium bicarbonate function as a buffer, inhibiting enolisation and thus the aldol reaction.



(52) (53)

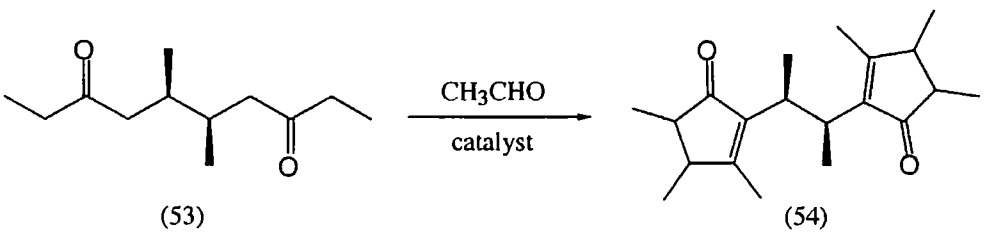
Scheme 2.30

Confirmation of this key intermediate was obtained by a molecular ion at *m/z* 198, with a base peak at *m/z* 99 corresponding to cleavage of the C-5/C-6 bond. Further evidence was provided by a total of six signals in the ^{13}C NMR, which indicated the symmetry of the product, with a C=O absorption at δ211.2. A characteristic absorption at 1709 cm^{-1} (C=O) appeared in the IR, with concomitant loss of the alkene C=C stretch.

Having overcome initial problems concerning synthesis of the cyclohexene substrate (52) and subsequent oxidative cleavage to afford the desired diketone (53), an efficient cyclisation procedure was sought. This is the subject of the following section.

2.4.3 Attempted Synthesis of Bis-cyclopentenone (54): Nazarov Cyclisation

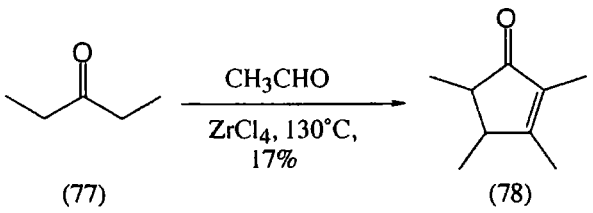
With the 1,6-dicarbonyl compound (53) in hand, attention was directed towards the synthesis of the bis-cyclopentenone (54), Scheme 2.31.



(53) (54)

Scheme 2.31

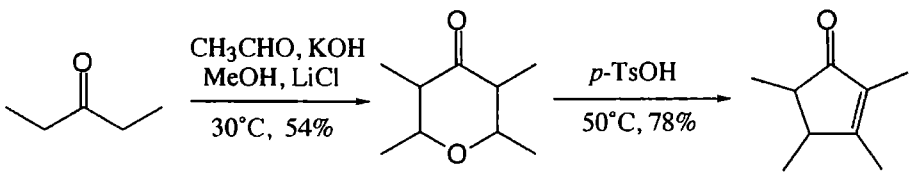
Two approaches were considered to effect cyclisation. The first, reported by Ishii and co-workers comprises a novel "one pot" double cross aldol reaction followed by a Nazarov cyclisation, Scheme 2.32.[88] The process is promoted by a range of zirconium catalysts ($ZrCl_4$, $ZrCp_2Cl_2$ and $ZrOCl_2.8H_2O$).



(77) (78)

Scheme 2.32

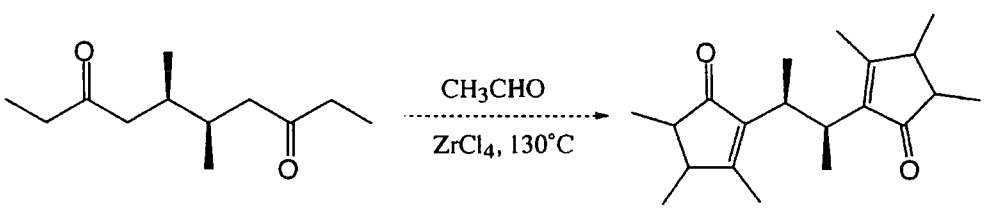
The second method, published by Kohl and Jutzi,[89] involves the generation of pyrone (79) *via* a double cross aldol reaction between 3-propanone (77) and acetaldehyde, Scheme 2.33. Acid-catalysed dehydration then affords the cyclopentenone (78).



(77) (79) (78)

Scheme 2.33

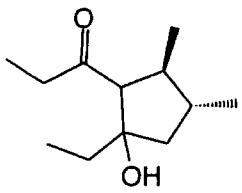
Ishii's methodology was initially investigated on an NMR scale as this provided a convenient method for monitoring the reaction, Scheme 2.34. The ketone (53) was added to a solution of the catalyst in acetaldehyde and the mixture was heated to 130°C. Subsequent runs involved variation of the catalyst ($ZrCl_4$, $ZrCp_2Cl_2$ and $ZrOCl_2.8H_2O$ were employed successively) and altering both temperature and order of addition of the reagents.



(53) (54)

Scheme 2.34

However, all attempts to generate the desired cyclopentanone species (54) were unsuccessful and in the majority of cases the only non-polymeric material which could be isolated was the β-hydroxyketone (73), arising from intramolecular cyclisation, Figure 2.11.

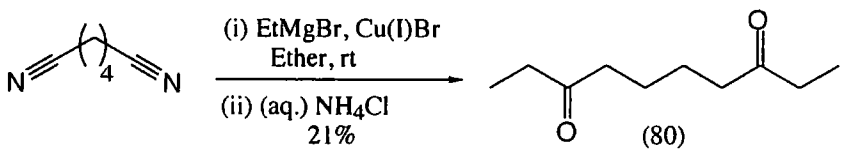


(73)

Figure 2.11

Application of Jutzi's methodology was then attempted but proved to be equally problematic, affording an intractible mixture of products, with little evidence of formation of the intermediate pyrone (NMR or GC-MS).

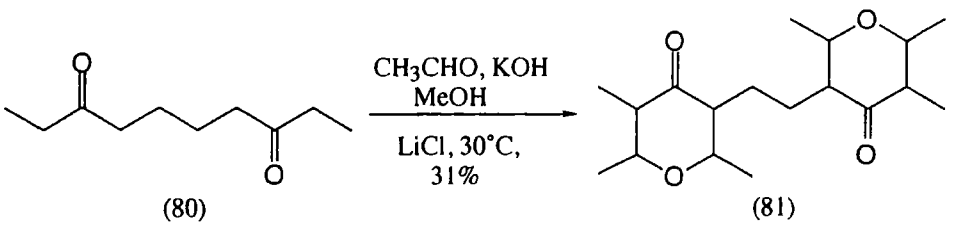
In order to conserve valuable diketone (53), decan-3,8-dione (80) was prepared as a model compound for further studies of this cyclisation reaction, Scheme 2.35.[90] Synthesis was confirmed by comparison of the spectral data with published results.[91]



(80)

Scheme 2.35

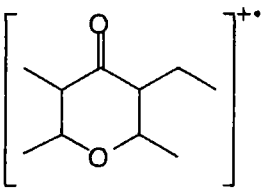
Application of Jutzi's methodology using this substrate led to generation of the intermediate pyrone (81) in 31% yield, as a mixture of stereoisomers, Scheme 2.36.



(80) (81)

Scheme 2.36

Evidence to support the proposed structure was provided by ^{1}H NMR data (multiplets at δ2.70 and 3.90 are characteristic of the CH protons of the pyrone ring). Although a molecular ion was not obtained using GC-MS (CI or EI), a peak observed at *m/z* 170 corresponded to fragmentation of the ethano-bridge, Figure 2.12.

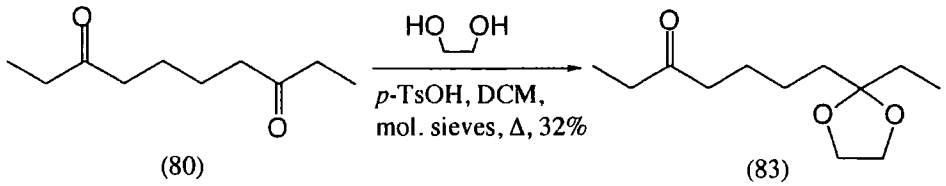


(82)

Figure 2.12

Unfortunately, substrate (81) failed to undergo acid-catalysed dehydration and afforded a polymeric material upon treatment with *p*-TsOH or H_2SO_4/HCO_2H at 50°C, 30°C and 0°C.

In a final attempt to functionalise the carbonyl moieties, the corresponding monoketal (83) was prepared, Scheme 2.37, with the idea that this compound would resist competing aldol reaction and would permit synthesis of the bis-cyclopentadienyl ligand (55) in a stepwise fashion. Treatment with one equivalent of ethylene glycol gave a statistical mixture of the diketal, monoketal and starting material (80), which could be separated by flash column chromatography.



(80) (83)

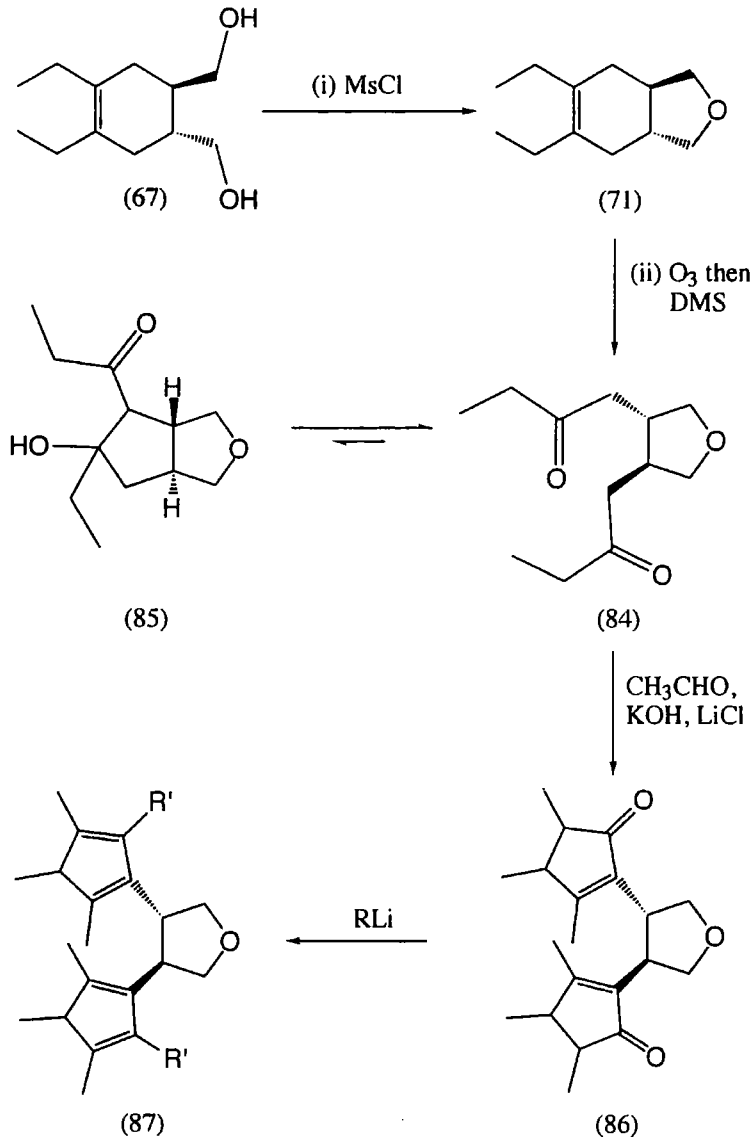
Scheme 2.37

A 4H singlet was observed at δ3.87 in the ^{1}H NMR spectrum, corresponding to the dioxolane protons. The presence of a C=O stretch in the IR spectrum and an absorption at δ211.0 in the ^{13}C spectrum indicated that monoprotection had occurred, leaving the second carbonyl group intact, as required.

Unfortunately this compound also produced unsatisfactory results when subjected to Ishii's conditions. Again the order of reagent addition was varied, with no evidence of cyclopentenone formation by NMR, IR and GC-MS data.

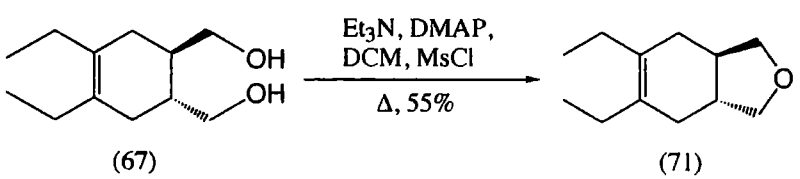
2.4.4 Alternative Strategy: Cyclic Tether

The aldol reaction is reversible and in order to inhibit this process a cyclic backbone tether system (87) was then investigated, Scheme 2.38. Intramolecular aldol reaction would produce a strained *trans*-fused 5,5-ring system (85), which would be disfavoured with respect to the desired acyclic structure (84). This precursor could then be manipulated to afford the bis-pentaalkyl cyclopentadienyl ligand (87).



Scheme 2.38

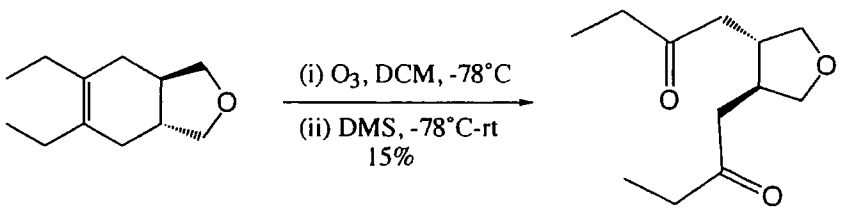
Treament of diol (67) with *one* equivalent of methanesulfonylchloride afforded the cyclic ether (71) in 55% yield, Scheme 2.39. Starting material (67) and monomesylated product were recovered and could be recycled to afford the desired ether (71).



Scheme 2.39

As expected, ^{13}C NMR data showed only six carbon environments, signals at δ130.9 and 72.7 corresponding to the C=C and C–O groups respectively. Loss of the O-H stretching vibration was also observed in the IR spectrum.

Oxidation to the diketone (84) was achieved using standard methodology, Scheme 2.40.[86] Ozone was passed through a solution of the cyclic ether (71) in dichloromethane for 15 minutes. Dimethyl sulfide was added and the solution was stirred for 6 hours. Flash chromatography afforded the cyclic ether in 15% yield, although the process remains unoptimised.



(71) (84)

Scheme 2.40

A characteristic C=O absorption was observed at 1712 cm^{-1} in the IR spectrum, with concomitant loss of the C=C stretch. Successful oxidation of the double bond was further supported by a C=O signal at δ210.3 in the ^{13}C NMR spectrum.

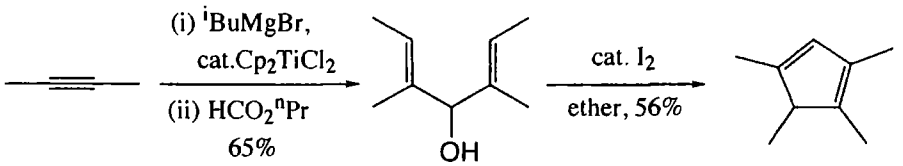
Importantly, there was no evidence (IR, ^{1}H, ^{13}C) of the cyclic aldol product (85) or the corresponding α,β-unsaturated ketone, which would have arisen from dehydration of (85). Time constraints prevented elaboration of this substrate into the bis-pentaalkylcyclopentadienyl system (87).

During the synthesis of the diketone (84) an efficient route to tetramethylcyclopentadienyl ligands was also developed and this is discussed in the following section.

2.5 Synthesis of Bis(tetramethylcyclopentadienyl) Ligands

2.5.1 Introduction

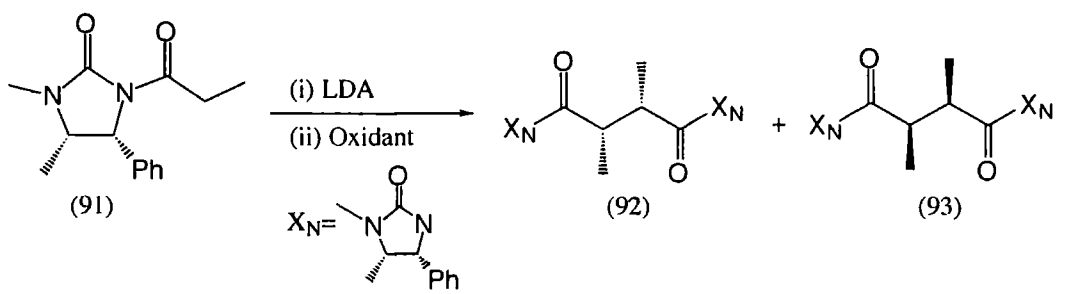
This approach is based on two recent reports, the first of which, published by Garner and Prince, described the use of a cyclodehydration process in the synthesis of tetramethylcyclopentadiene (90), Scheme 2.41.[92]



(88) (89) (90)

Scheme 2.41

The second report concerned Helmchen's work on the stereoselective synthesis of succinic acid derivatives using chiral imidazolidinones, Scheme 2.42.[93] Iodine and Cu(II) salts were used as mild oxidants.



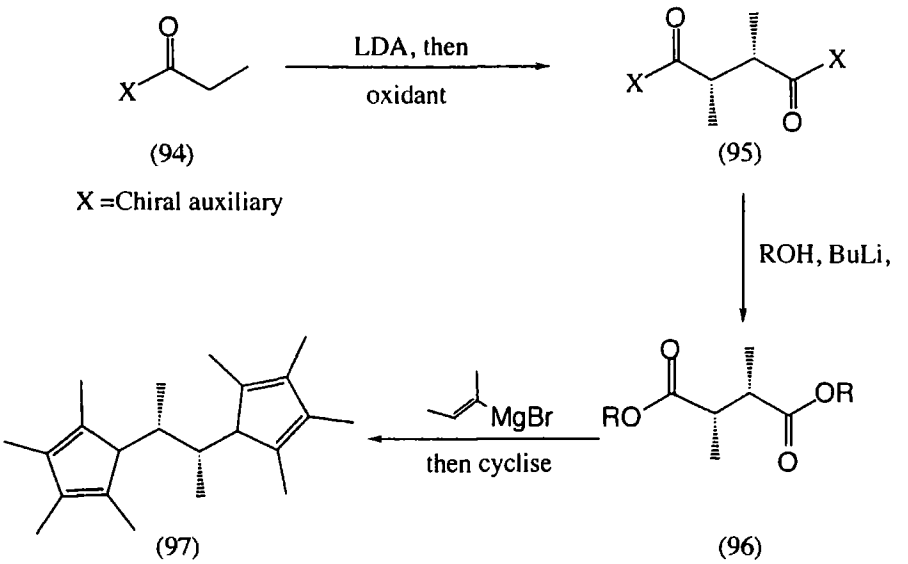
(91) (92) (93)

Oxidant	Diastereoselectivity	Yield (%)
I_2	92: 93 = >99 : 1	70
Cu(II)	92: 93 = >99 : 1	66

Scheme 2.42

Thus, a combination of these reactions formed the basis of an efficient route to a bis-tetraalkylcyclopentadiene ligand (97) from the succinate (95), Scheme 2.43. Either the

(*S,S*))-diasteroisomer (92) or the analogous (*R,R*)-diastereoisomer (93) could be employed as both would generate a *trans* methyl relationship in the asymmetric backbone.

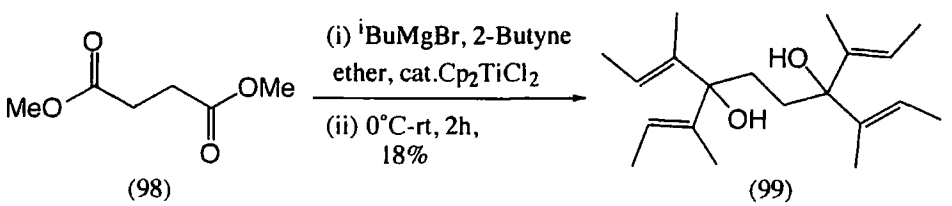


Scheme 2.43

2.5.2 Cyclodehydration Reaction: A Model Study

Garner's procedure provided an attractive means by which to convert ester (96) into the bis-cyclopentadiene (97). In a model study of this cyclodehydration approach, we elected to use comercially available dimethyl succinate in place of a chiral ester.

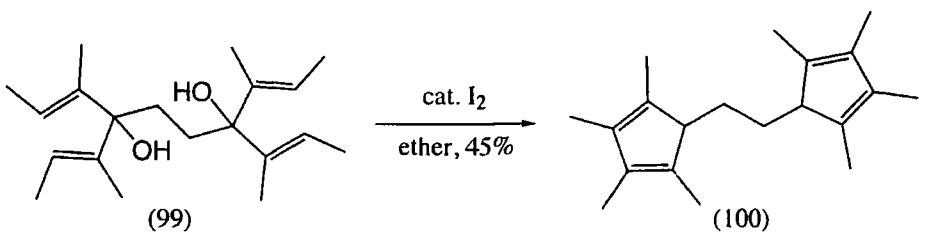
(*E*)-2-butenylmagnesium bromide was prepared *in situ* using a titanium-mediated hydromagnesiation reaction between 2-butyne and *iso*-butylmagnesium bromide, Scheme 2.44.[94] A solution of dimethyl succinate in ether was then added to give the tertiary alcohol (99) in 18% yield (as the only non-polymeric material). To date, modifications to the reaction, in terms of dilution and altering the rate of addition have failed to improve the yield.



Scheme 2.44

Evidence for the formation of this bis-tertiary alcohol (99) was obtained from a characteristically weak molecular ion peak at *m/z* 306. A total of six signals in the ^{13}C NMR confirmed the symmetry of the product, with alkenic absorptions at δ138.2 and δ118.9.

Cyclisation of the alcohol (99) to the cyclopentadiene (100) was achieved using Garner's methodology, Scheme 2.45. Initial attempts were complicated by polymerisation. However, this could be avoided by slow addition of the alcohol (99) to a solution of iodine in ether, to afford the bis-cyclopentadiene (100) in 45% yield after flash chromatography.

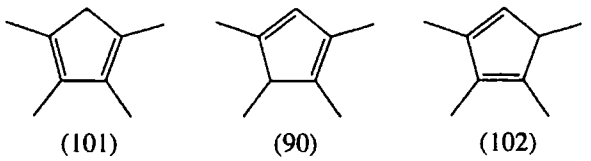


(99) (100)

Scheme 2.45

EI and CI (NH_3) caused fragmentation of the bis-cyclopentadiene (100) before a molecular ion could be observed. A satisfactory mass spectrum was eventually obtained using CI (CH_4). An intense molecular ion was observed at *m/z* 271 and a fragment ion at *m/z* 135 corresponded to symmetrical cleavage of the ethano-bridge, generating a pentamethylcyclopentadiene radical cation.

In contrast to Garner's original work, Figure 2.13, the bis-cyclopentadiene (100) was isolated as a mixture of isomers (^{1}H and ^{13}C), indicating that there was a lower barrier to equilibration than in the tetramethylcyclopentadiene system.[92] This is due to additional substitution about the ring and formation of tetra-substituted olefins in all instances.



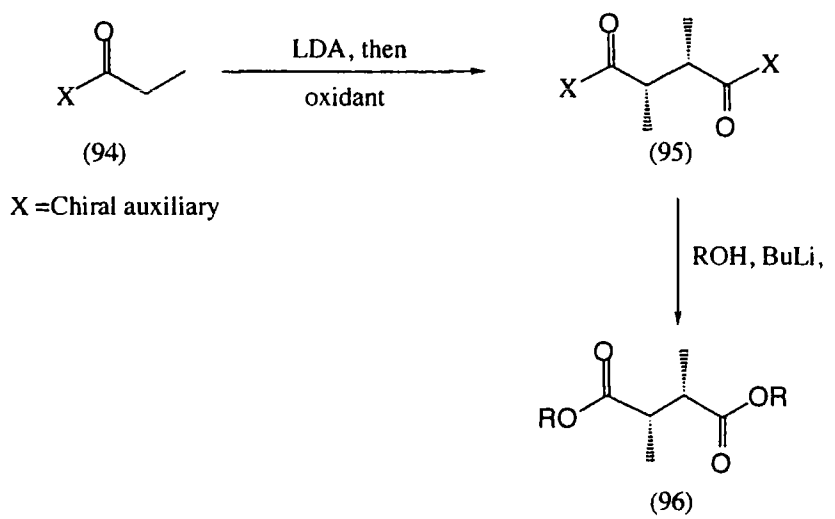
(101) (90) (102)

Major Product

Figure 2.13

The cyclodehydration methodology was deemed viable, albeit in low yield and synthesis of the chiral ester moiety (96) was then pursued.

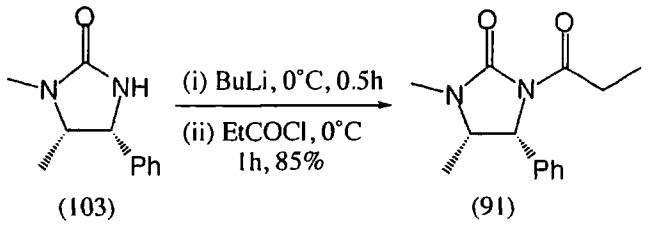
2.5.3 Stereoselective Enolate Coupling: Synthesis of A Succinic Acid Derivative



Scheme 2.46

Initial approaches to enolate oxidative coupling (94-95) followed the approach of Helmchen (*vide supra*), Scheme 2.46.

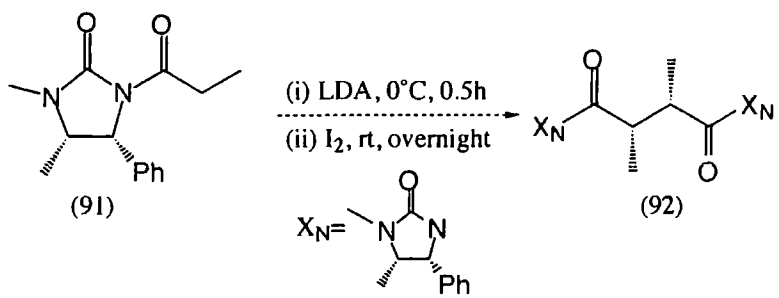
(4*R*, 5*S*)-(-)-1,5-Dimethyl-4-phenyl-imidazolidin-2-one (103) was prepared according to an established procedure,[95] Scheme 2.47, and subsequently acylated with propionyl chloride. All stages of the synthesis were verified by comparison with the literature data.



(103) (91)

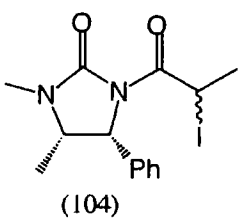
Scheme 2.47

Initial attempts to achieve enolate coupling were undertaken using iodine as the oxidant, Scheme 2.48. Despite the literature precedent the only products of this reaction were the iodide (104), Figure 2.14, and starting material (91).



(91) (92)

Scheme 2.48



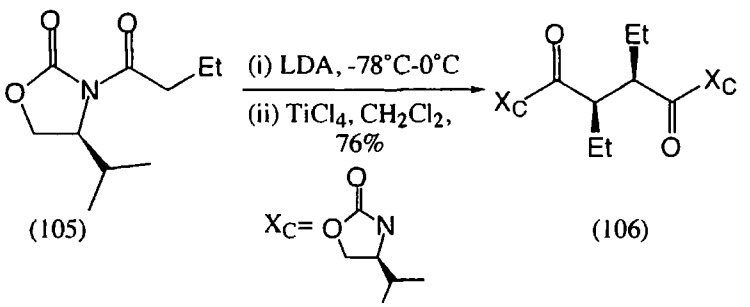
(104)

Figure 2.14

Helmchen and co-workers have also employed this iodide in subsequent coupling reactions by the addition of a solution of the iodide (104) in THF to a pre-formed solution of the enolate.[96] However, in our hands this approach also proved unsuccessful.

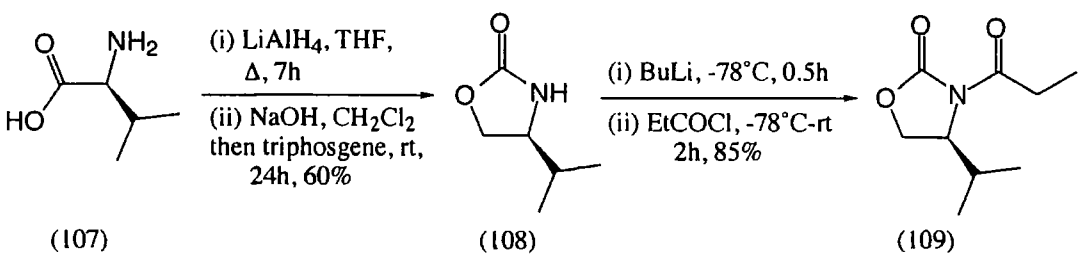
The use of a range of oxidants led to complete recovery of the imidazolidinone (91) in all cases.

Owing to the failure of imidazolidinones to exhibit the desired reactivity, we then examined the use of other auxiliaries in this process. Kise *et al.*[97] have reported the use of chiral oxazolidinones in a related titanium-mediated coupling reaction, Scheme 2.49.



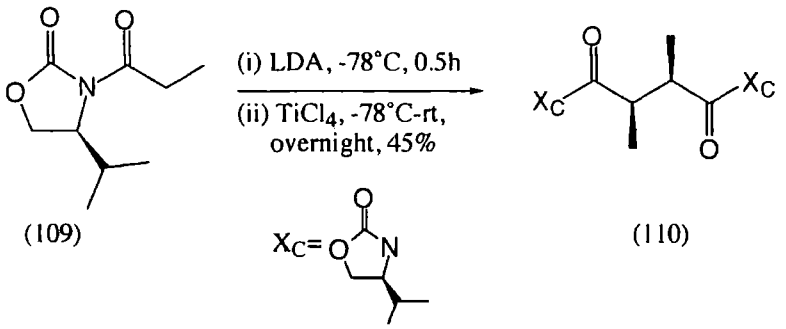
Scheme 2.49

Adopting this precedent, 4-(*S*)-isopropyl-oxazolidin-2-one (108) was prepared from L-valine in a "one pot" procedure described by Greene and co-workers.[98] This substrate was then converted into 4-(*S*)-isopropyl-3-propionyl-oxazolidin-2-one (109) in 85% yield by reaction with propionyl chloride, Scheme 2.50.



Scheme 2.50

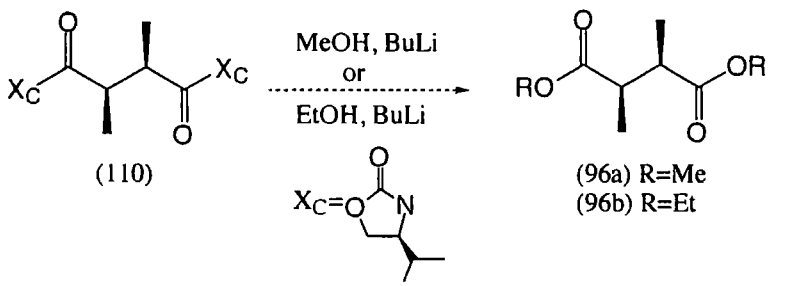
The procedure described by Kise was then employed, Scheme 2.51, which afforded the coupling product (110) in 45% yield after purification by column chromatography. Diastereomeric excess (82%) could be increased (to 88%) by a single recrystallisation from petrol/ethyl acetate.



Scheme 2.51

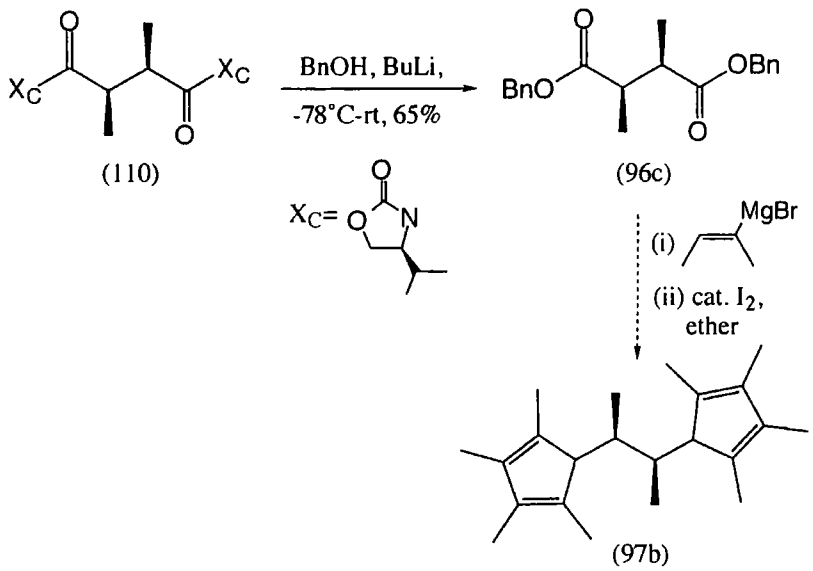
The IR spectrum showed the presence of two carbonyl environments corresponding to the oxazolidinone C=O, and the bridging chain C=O stretches. Loss of the signal due to the CH_2 protons in the propionyl moiety of the oxazolidinone precursor (109) and an absorption at δ4.05 ($CH_3C\underline{H}CO$) provided further evidence for the synthesis of (110). Final confirmation of the structure was obtained from a weak molecular ion at *m/z* 369, with a base peak at *m/z* 128 corresponding to the 4-(*S*)-isopropyl-oxazolidin-2-one (109) fragment.

Attempted conversion into the ester (96) using MeOLi or EtOLi, Scheme 2.52, generated a complex product mixture.[99] This presumably occurred due to competing nucleophilic attack at the oxazolidinone carbonyl and the acyl moiety (endocyclic versus exocyclic cleavage).[99b]



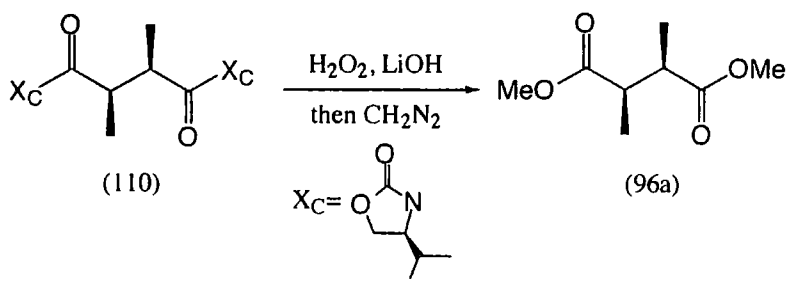
Scheme 2.52

This problem was overcome using BnOLi, Scheme 2.53, but attempts to convert this substrate into the desired bis(tetramethylcyclopentadienyl) ligand (97b) were complicated by the formation of benzyl alcohol.



Scheme 2.53

In accordance with the route discussed in Section 2.52, future approaches would involve cleavage to afford the carboxylic acid and conversion into the methyl ester (96a), prior to cyclisation, Scheme 2.54.



Scheme 2.54

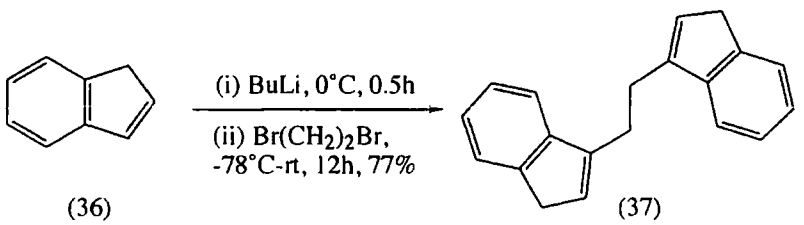
2.6 Indenyl Systems

2.6.1 Introduction

To the best of our knowledge, there are no examples of indenyl complexes incorporating lanthanide cations. Consequently we sought to exploit this area of organolanthanide chemistry by the preparation of trivalent and divalent complexes.

2.6.2 Synthesis of Indenyl Ligands

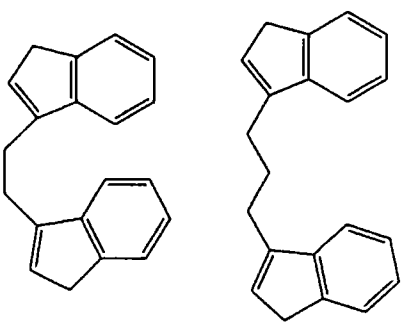
Jensen has reported the convenient synthesis of *rac*-bis(3-indenyl)ethane (37) through the addition of indenyllithium to 1,2-dibromoethane, Scheme 2.55.[100]



(36) (37)

Scheme 2.55

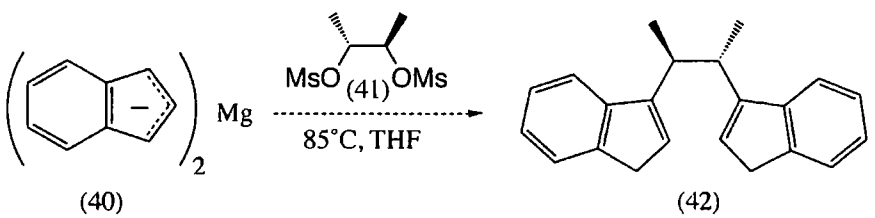
Following this protocol, we were able to produce the ethano-bridged system (37) in 79% and the propano-bridged system (111) in 56% yield, Figure 2.15. Synthesis was verified by comparison with the literature data.



(37) (111)

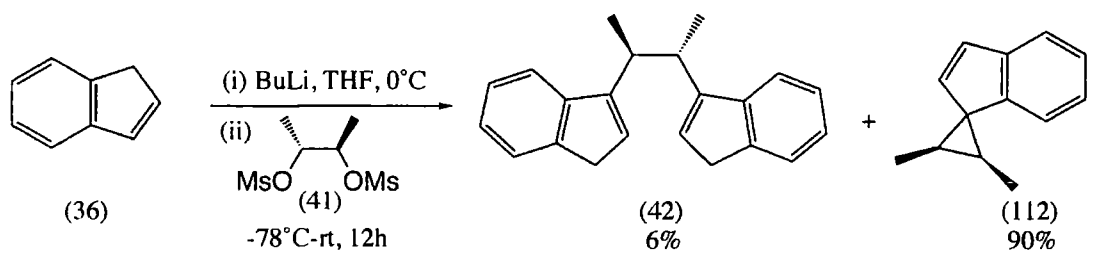
Figure 2.15

Synthesis of a chiral butylene-bridged indenyl system (42), Scheme 2.56, was undertaken using the approach reported by Bosnich and co-workers.[75] In this, diindenylmagnesium (40) was utilised to circumvent spirocycle (112) formation, which occurred when more conventional BuLi/indene methodology was employed, Scheme 2.57. Despite the literature precedent, in our hands Bosnich's methodology only led to recovery of the starting material (41), presumably due to the high instability of the intermediate organomagnesium reagent. The desired ligand was then prepared (6%) using indenyllithium, Scheme 2.57, and the major by-product was the spirocycle (112) (90%).



(40) (42)

Scheme 2.56



(36) (42) 6% (112) 90%

Scheme 2.57

2.6.3 Attempted Complexation of Indenyl Ligands (37) and (111)

Complexations were initially attempted using lanthanide(III) salts, rather than unstable Ln(II) species.

BuLi was added to a solution of the indenyl ligand in THF, at -78°C, and the resulting indenyl anion was added to a solution of $SmCl_3$ or $YbCl_3$ in dry, degassed THF. After stirring for several hours at room temperature the volume of the solution was reduced

and a thin layer of pentane allowed to diffuse through the solution, in an attempt to induce crystallisation.[63] Unfortunately, this, and subsequent attempts to recrystallise the *ansa*-metallocene from a range of solvents, proved unsuccessful. In view of the difficulties encountered in the complexation of the indenyl systems (37) and (111), this work was not pursued further.

2.7 Conclusion

The key dicarbonyl compound (53) was produced in good yield. Unfortunately subsequent attempts to cyclise this substrate were complicated by an intramolecular aldol reaction, although initial studies indicate that the use of a cyclic ether backbone may inhibit this competing reaction.

In retrospect, model studies of the double Nazarov cyclisation reaction using 3,8-decanedione (80) would have permitted a more rapid evaluation of this methodology.

An efficient route for bis(tetramethylcyclopentadienyl) ligands was developed using the oxidative coupling of N-acyl oxazolidinones, and it is hoped that future work will afford the corresponding *ansa*-lanthocenes.

CHAPTER 3

Synthesis and Applications of Polyaza/oxo Ligands

3.1 Introduction

This chapter is concerned with the preparation of polyaza/oxo lanthanide complexes and their subsequent application in enantioselective synthesis.

The synthesis of nitrogen and oxygen ligand systems for lanthanide complexation has been reviewed recently[101] and the following section is intended to give a brief overview of related complexes in organolanthanide chemistry. It should be stressed that the majority of reports have focused on the use of Ln(III) species as Lewis acid catalysts, rather than the use of Ln(II) reagents as one-electron reductants.

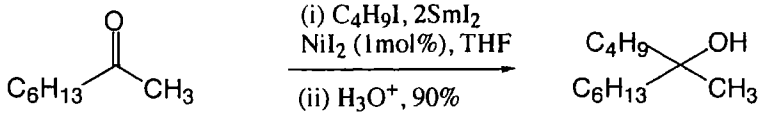
3.2 Nitrogen and Oxygen Ligand Systems in Organolanthanide Chemistry

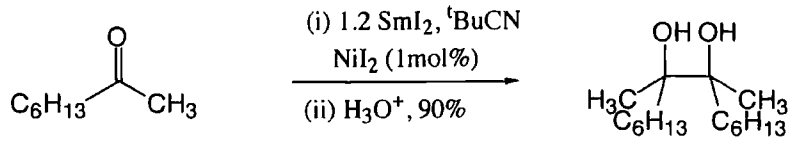
3.2.1 Introduction

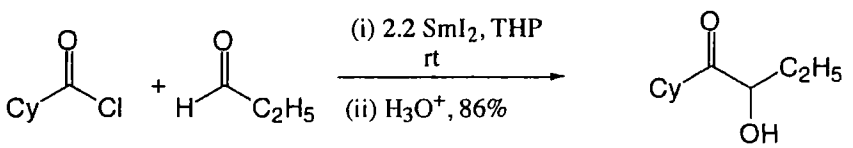
The use of nitrogen/oxygen-based additives and solvents such as HMPA, DMPU, CH_3CN and THP represents the simplest case of N/O ligand systems in organolanthanide chemistry. The following sections discuss this chemistry and also the use of more elaborate polyaza/oxo ligands in organic synthesis.

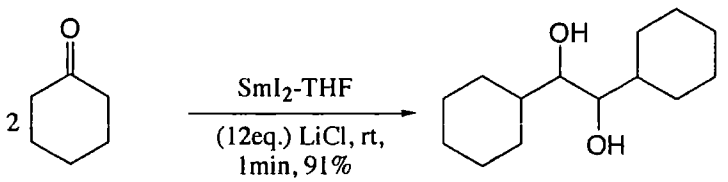
3.2.2 The Effect of Additives in SmI_2-Mediated Reactions

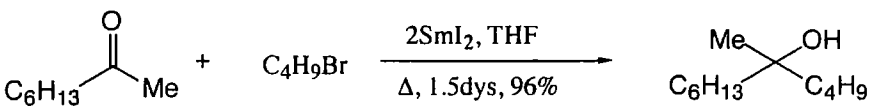
A range of additives and solvents have been employed in SmI_2-promoted reactions, Scheme 3.1.[102]

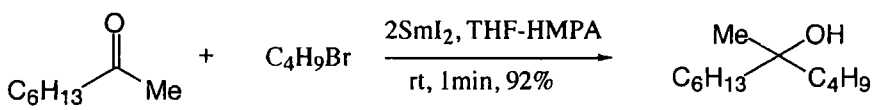


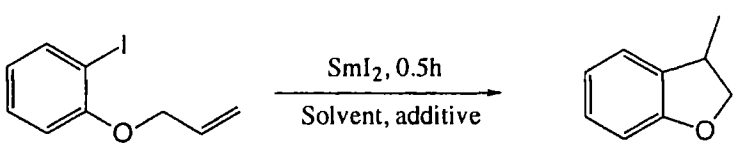








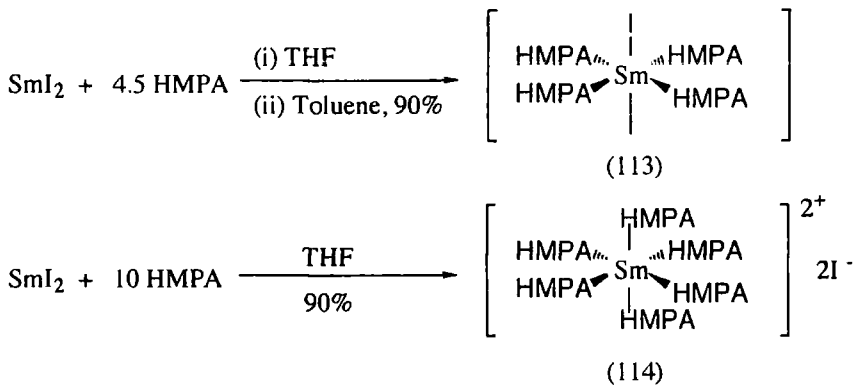




Additive	Solvent	Yield (%)
none	CH_3CN	0
DMPU	CH_3CN	100
DMPU	THF	5

Scheme 3.1

To date, the most general additive is HMPA, which substantially enhances the reducing power of SmI_2-THF systems [E^o=-1.33V; (4 equivalents of HMPA) E^o=-2.05V].[103] Crystallographic data reported by Wakatsuki *et al*[104], Scheme 3.2, revealed that the Sm-O(HMPA) bonds were shorter than those found in most Sm(II)-O systems, reflecting the unusually strong electron-donating capability of this ligand which, in turn, is responsible for the high reactivity of SmI_2-THF/HMPA mixtures. Interestingly, excess HMPA lead to the formation of sterically hindered $[Sm(HMPA)_6]I_2$ complexes (114). Thus, the extent of complexation of SmI_2 with HMPA can alter the environment about the Sm(II) ion both electronically and sterically; resulting in subtle changes in regio-and stereoselectivity upon altering the HMPA concentration.



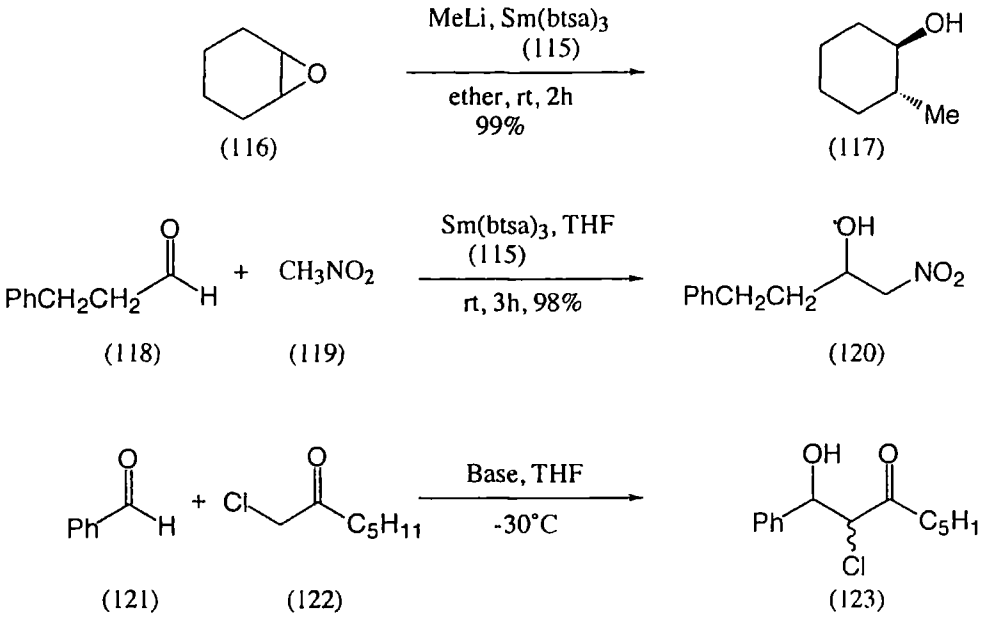
Scheme 3.2

In addition, the choice of solvent can alter the efficiency of the additive; the use of DMPU in THF produces a marked reduction in reactivity when compared to the reaction in acetonitrile (see Scheme 3.1).

3.2.3 Aza Lanthanides

The most commonly employed aza lanthanide (or lanthanide amide) is the bis(trimethylsilyl)amide (btsa) complex (115), readily obtained *via* reaction between lanthanide halides and lithiated btsa compounds. A range of transformations are possible using this reagent, Scheme 3.3.[105] $Sm(btsa)_3$ has been employed in the alkylation of epoxides, and as a base in catalytic aldol reactions between aldehydes and

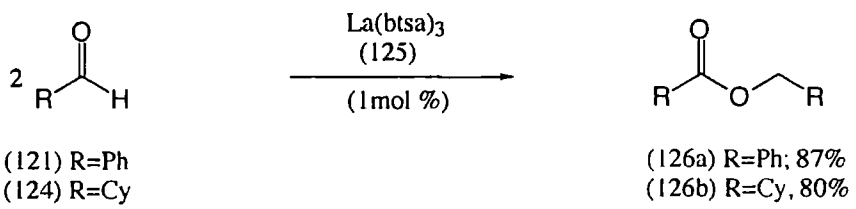
either α-chloro ketones or nitromethane.[105b,c] In the latter case this monomeric catalyst exhibited higher reactivity than the corresponding samarium alkoxide.



Base	Time (h)	Yield (%)
$Sm(btsa)_3$	18	90
$Sm(O^iPr)_3$	24	56

Scheme 3.3

$La(btsa)_3$ has been used recently as a highly durable homogeneous catalyst in Tishchenko reactions, Scheme 3.4.[106]



Scheme 3.4

3.2.4 Oxo Lanthanides

The synthesis of oxo lanthanide complexes is significantly more difficult as there is a tendency to form aggregates in solution, the extent of which is dependent upon the steric bulk of the ligand. Recent work has shown that mononuclearity and rigidity can be imparted to alkoxide and aryloxide ligands with careful design, Figure 3.1.[107]

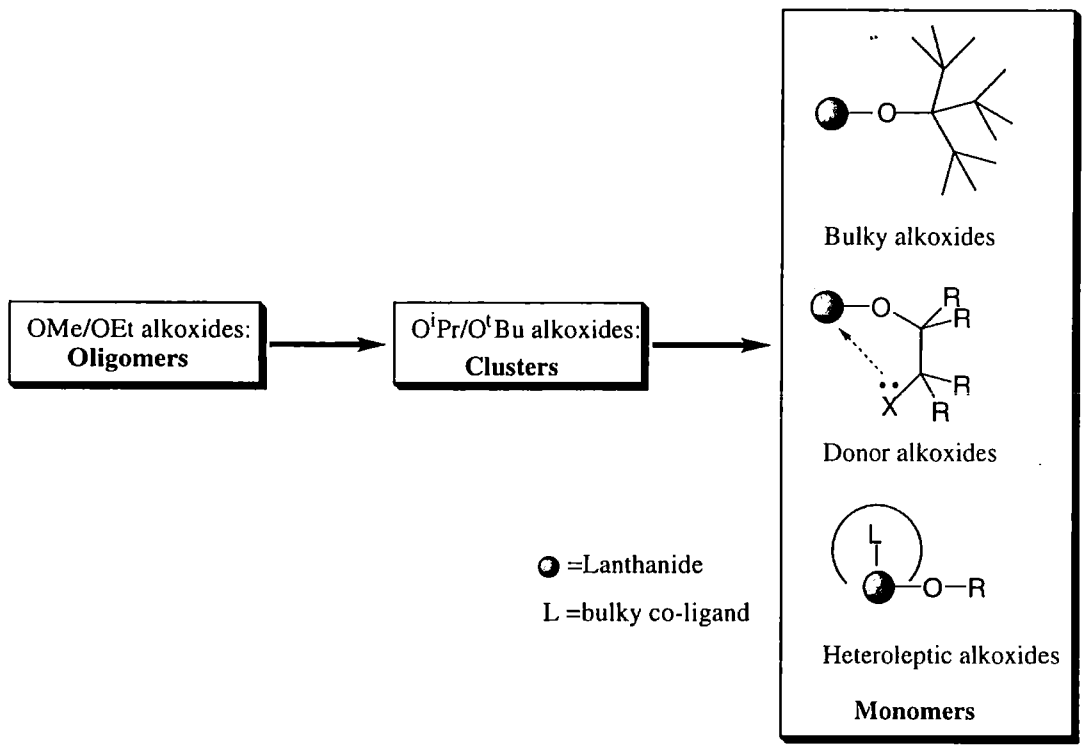
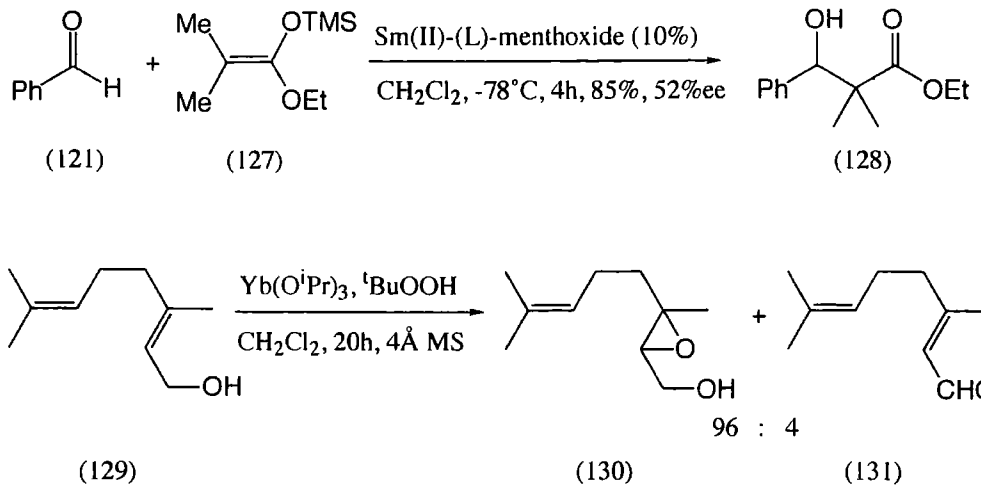


Figure 3.1

Simple lanthanide alkoxides, however, have been employed in organic synthesis with some success. For example, Sm(II) menthoxide catalyses the reaction of silyl ketene acetals with aldehydes and Yb(O^{i}Pr)$_3$ promotes the *tert*-butyl-peroxide-assisted oxidation of allylic alcohols, Scheme 3.5.[108]

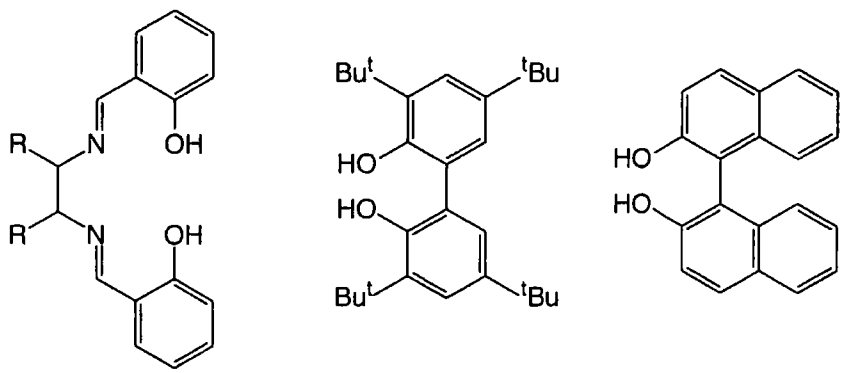


(121) (127) (128)

(129) (130) (131)

Scheme 3.5

Aryloxide complexes have attracted considerable attention in organolanthanide chemistry due to their high activity as catalysts in stereoselective organic transformations (*vide infra*). Chelating Schiff-base (132), biphenol (133) and binaphthol (134) ligands have been reported to impart stability to both Ln(III) and Ln(II) complexes, Figure 3.2.[109]

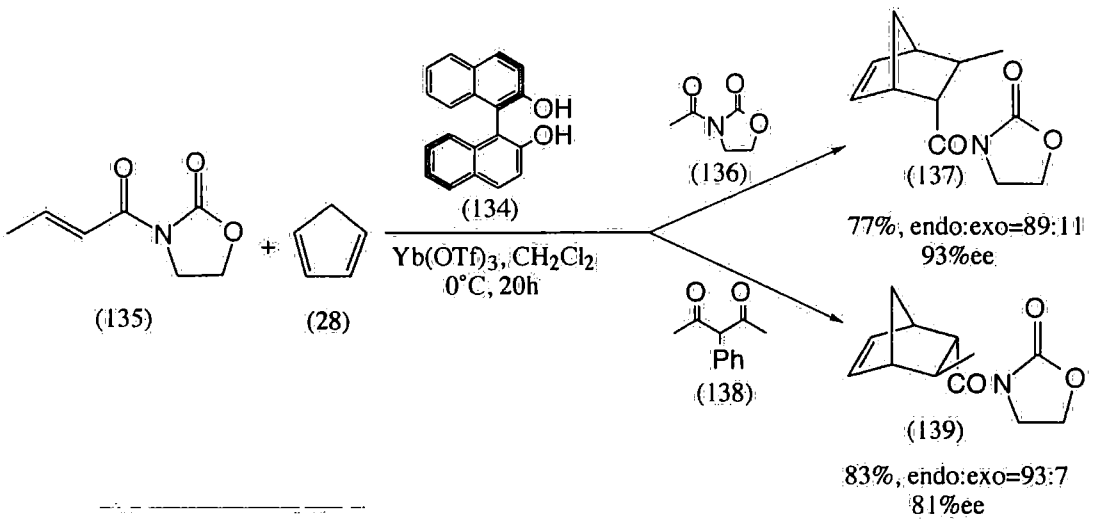


(132a) R=H; salen
(132b) Me; hapen

(133) (134)

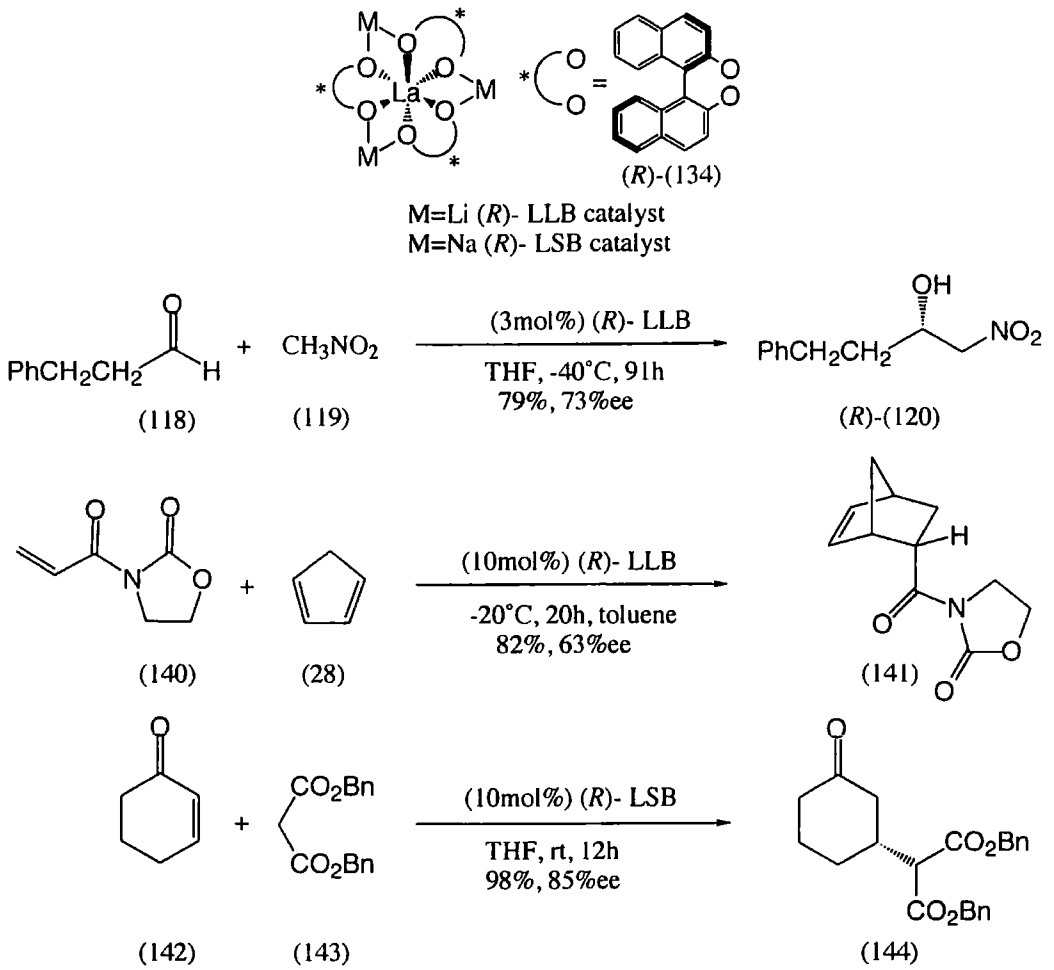
Figure 3.2

The sterically rigid binaphthol (BINOL) ligand (134) was used by Kobayashi and co-workers in enantioselective Diels-Alder reactions employing achiral additives, Scheme 3.6.[110]



Scheme 3.6

A significant advance in the use of BINOL-based systems in organolanthanide chemistry was achieved by the preparation of heterobimetallic complexes, which exhibited enhanced moisture stability. The utilisation of lithium-lanthanum-BINOL (LLB) and sodium-lanthanum-BINOL (LSB) complexes in catalytic asymmetric synthesis is now well established, largely due to the work of Shibasaki, Scheme 3.7.[9]



(118) (119) (140) (28) (141) (142) (143) (144)

Scheme 3.7

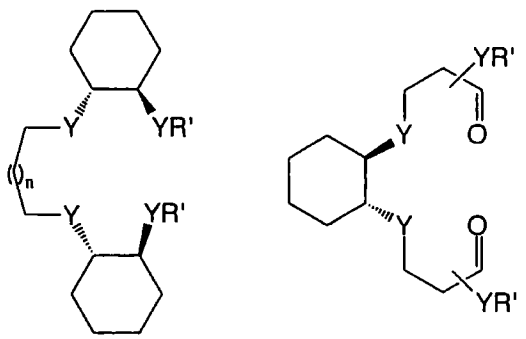
3.3 Summary

The use of nitrogen and oxygen ligand sets in organolanthanide chemistry is well precedented and it is now possible to produce ancilliary ligands with stability, solubility and reactivity comparable to cyclopentadienyl-based systems. Furthermore, the use of suitable additives can greatly enhance the reducing power of SmI_2. However, the application of strongly activating (electron-donating) chiral polyaza/oxo ligands in Sm(II)-mediated enantioselective synthesis has yet to be explored (*vide infra*).

3.4 Proposed Work

3.4.1 Introduction

At the outset of this project, we intended to exploit the enhanced reactivity associated with donor co-solvents, such as HMPA, and couple this with the potential for asymmetric induction achieved by the incorporation of sterically rigid polyaza/oxo ligands at the Sm(II) centre. In order to probe the validity of this approach we sought to prepare C_2–symmetric polyaza/oxo ligands, based on a simple *trans*-cyclohexanediamine backbone, (145) and (146), Figure 3.3. This would enable us to examine their propensity for interligand asymmetric induction and permit structural revision on an iterative basis. As this would be a stoichiometric process an ultimate goal would be the development of catalytic cycles.



(145) (146)

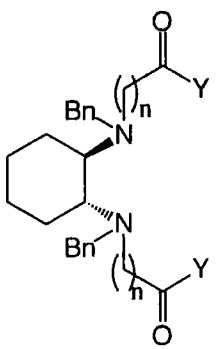
Y=NR', O; R'=H, alkyl.

Figure 3.3

In addition, these strongly electron-donating ligands would increase the redox potential of these systems and could allow the use of ytterbium and europium reagents, for which the divalent oxidation state is not normally of sufficient reducing power to be considered. Since Yb(II) and Eu(II) cations are somewhat smaller than Sm(II), the steric environment created by the sterically hindered polydentate ligands would be more pronounced. Consequently, reagents incorporating these elements could exhibit differing chemoselectivities to samarium-based reagents.

3.4.2 Synthesis of Polydentate Ligands

In all cases racemic ligands were prepared initially to verify the methodology and suitable protecting groups (benzyl or *p*-TsCl derivatives) were employed to prevent over-reaction. Aza/oxo ancilliary ligands incorporating both five-and-six ring chelate systems have been prepared bearing a range of functionalities, (147), Figure 3.4.



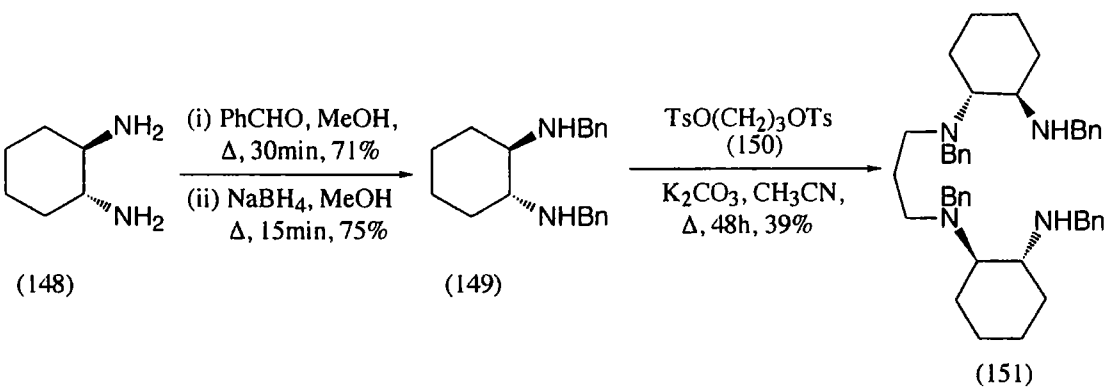
(147)

Y=NR', O; R'=H, alkyl
n=1,2

Figure 3.4

3.4.2.i Tetra-Aza Ligands

A possible route to the tetra-amine ligand (151) was envisaged from (±)-*trans*-cyclohexanediamine (148), Scheme 3.8.



(148) (149) (151)

Scheme 3.8

Preparation of the bisbenzylamine (149) was achieved using a procedure reported by Denmark *et al.*[111] Conversion to the polyamine (151) was then undertaken through reaction with the bistosylate (150), using established methodology.[112] A solution of the tosylate (150) and benzylamine (149) in acetonitrile was heated to reflux and afforded the desired polyamine (151) in only 39% yield after purification by flash chromatography. Modifications in base and metal ion ultimately afforded the tetra-amine (151) in 63% yield, Table 3.1.

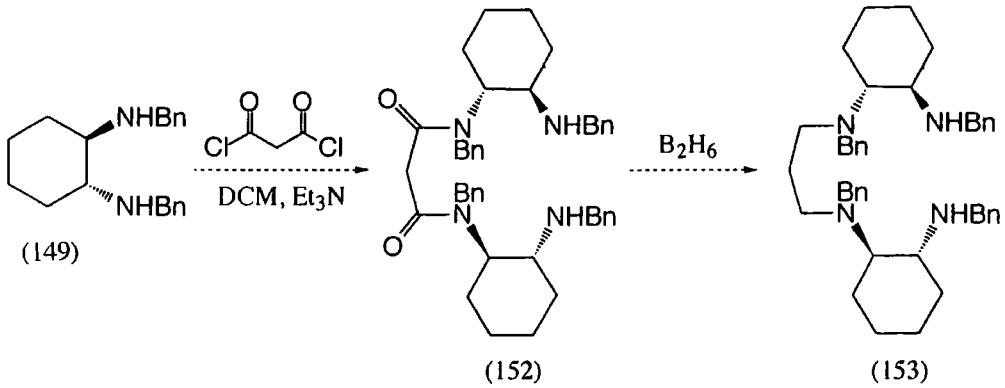
Base	Yield (%)
Na_2CO_3	63
K_2CO_3	39
NaH	0
Cs_2CO_3	43

Table 3.1

Appearance of multiplets at δ2.52 (4H) and δ1.45 (2H), in the ^{1}H NMR, are attributed to the CH_2 groups of the three-carbon tether. A molecular ion was observed at *m/z* 628 and ions produced at *m/z* 322 and *m/z* 91 corresponded, respectively, to C-C bond fragmentation at the aliphatic side chain and the formation of the characteristic tropylium ion.

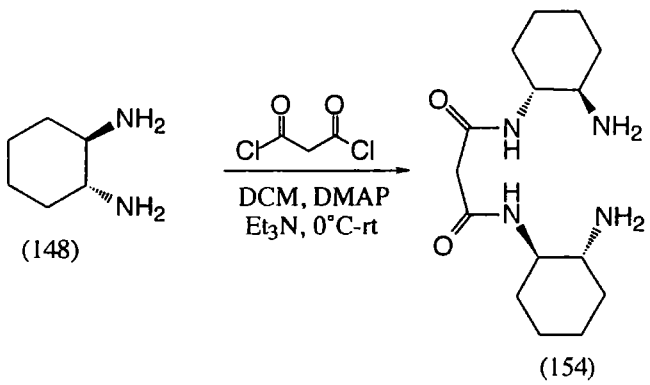
Theoretically, when employing racemic bisbenzyl amine (149), two diastereoisomers (*R*R*R*R**) and (R*R*S*S*) may be produced. However, ^{1}H NMR data showed the presence of a single isomer. Confirmation that this was the (*dl*)-form was provided by the use of (*R,R*)-benzyl amine, (*R,R*)-(149), which gave identical NMR data. This "molecular recognition" may have arisen from pronounced steric effects in the transition state, hindering formation of the *meso* isomer.

An alternative method for the synthesis of the polyamine (151) was explored through the preparation of the analogous amide (153), Scheme 3.9.[122]



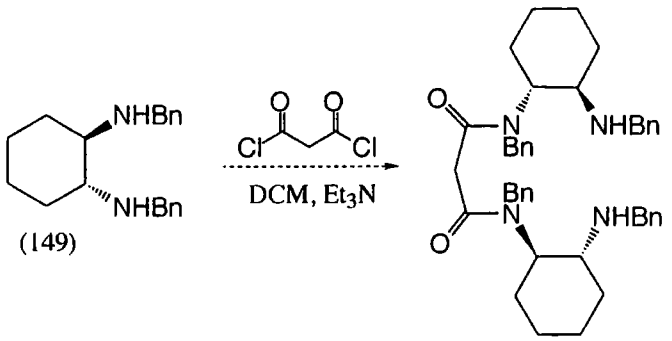
Scheme 3.9

A model study employing (±)-*trans*-cyclohexanediamine (148), gave the desired diamide (154) as evidenced by ^{1}H and ^{13}C NMR data, Scheme 3.10.



Scheme 3.10

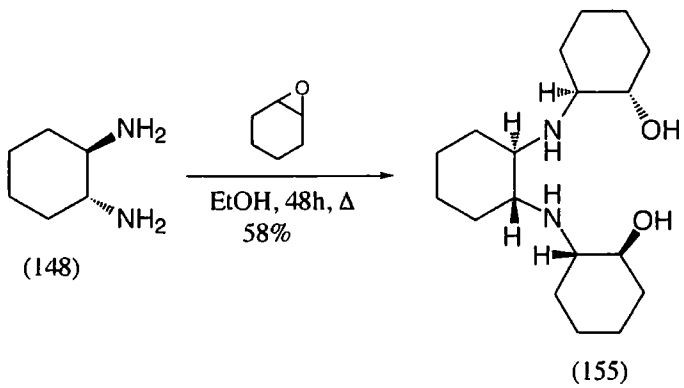
The reaction was attempted using the bisbenzylamine (149) although this failed to generate diamide (152), Scheme 3.11, and led to complete recovery of starting materials. This lack of reactivity has been attributed to the increased steric bulk of this amine (149) and the route was not pursued further.



Scheme 3.11

3.4.2.ii Mixed Aza/Oxo Ligands

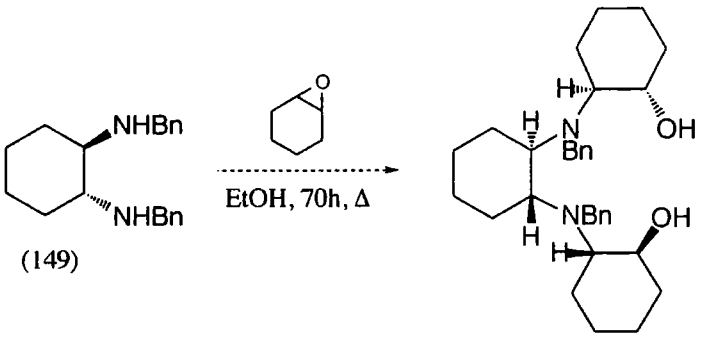
In addition to the tetra-amine system mentioned above, work has also been directed towards the synthesis of mixed nitrogen and oxygen systems, Scheme 3.12.



Scheme 3.12

Hancock and DeSousa have prepared the cyclohexane ligand (155) *via* a simple condensation reaction between cyclohexene oxide and (±)-*trans*-cyclohexanediamine (148), Scheme 3.12.[113] Following this procedure and recrystallising from hexane afforded the polyaza/oxo ligand (155) in 58% yield. Successful formation of the ligand was supported by a molecular ion at *m/z* 311 (MH^+) and a total of nine carbon environments in the ^{13}C NMR indicated that the ligand had been produced with high diastereoselectivity. Signals at δ77.9 and δ66.0 are characteristic of C-OH and C-NH moieties.

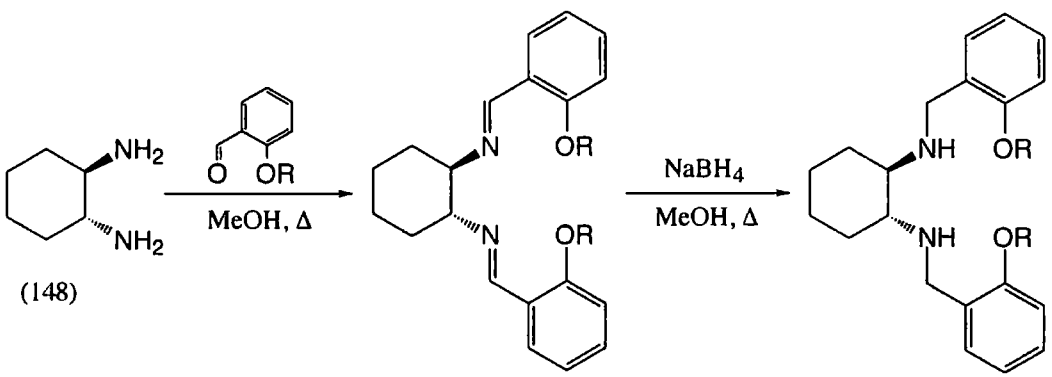
Attempted preparation of the bisbenzyl analogue (156) led to complete recovery of the starting material (149), Scheme 3.13.



(149) (156)

Scheme 3.13

Alternative polyaza/oxo systems, precedented in the work of Jacobsen, were also prepared, Scheme 3.14.[114]

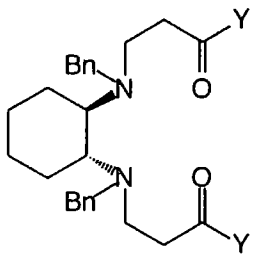


(148) (157) (158)

Compound	R	Yield (%)
(157a)	Me	66
(157b)	H	72
(158a)	Me	80
(158b)	H	49

Scheme 3.14

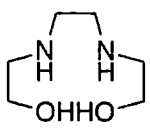
All ligands reported thus far have relatively little degree of freedom and work was also directed towards ligand systems with more flexible chelating arms, as typified by (159), Figure 3.5. These may facilitate metal ion complexation and, in addition, may generate systems which exhibit enhanced selectivity for the larger lanthanide ions in contrast to rigid cyclohexyl frameworks which promote selectivity for smaller metal ions, Figure 3.6.[113] This would enable us to explore size effects in subsequent reactions employing these complexes.



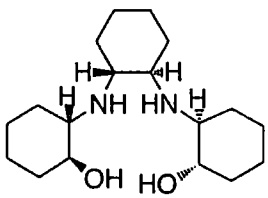
(159)

Y=NR'_2, OR'
R'=H, alkyl

Figure 3.5



(160)



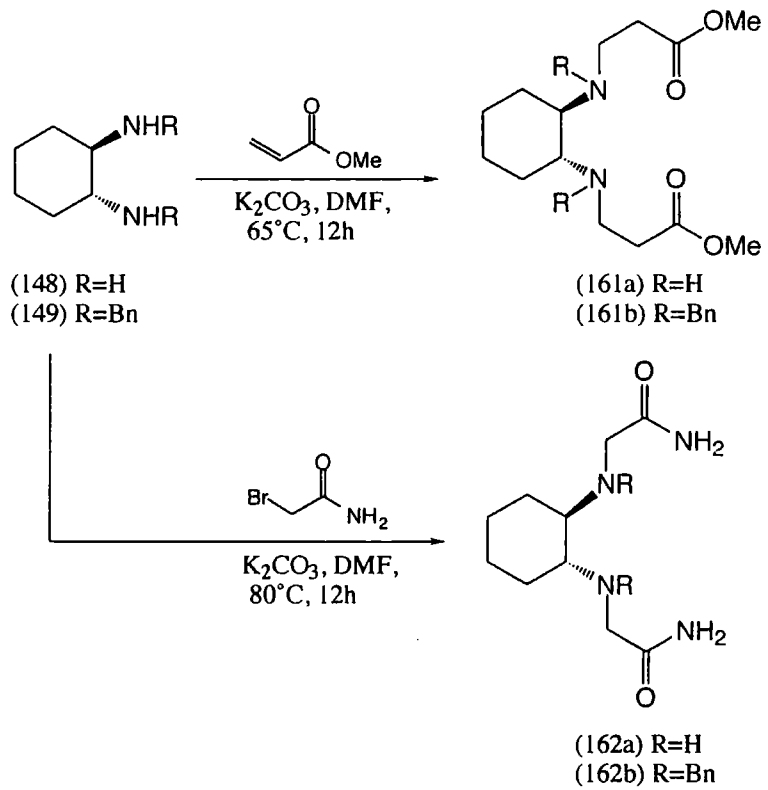
(155)

	Ionic Radius (Å)	(160)	(155)
log K_1 Cu^{2+}	0.57	11.5	9.68
log K_1 Zn^{2+}	0.74	4.77	4.79
log K_1 Pb^{2+}	1.18	4.8	6.12

Figure 3.6

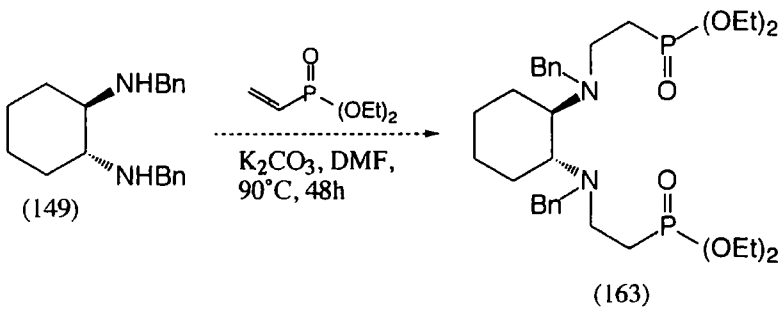
Preliminary work focused upon the addition of (±)-*trans*-cyclohexanediamine (148) to methyl acrylate and 2-bromoacetamide, Scheme 3.15.[112] Data available from the ^1H

and ^{13}C NMR spectra indicated that synthesis of these ligands had been successful. However, satisfactory purification of these compounds could not be effected by column chromatography or distillation. This problem may have been circumvented by the preparation of benzyl or *p*-Ts derivatives *in situ*. This remains to be investigated.



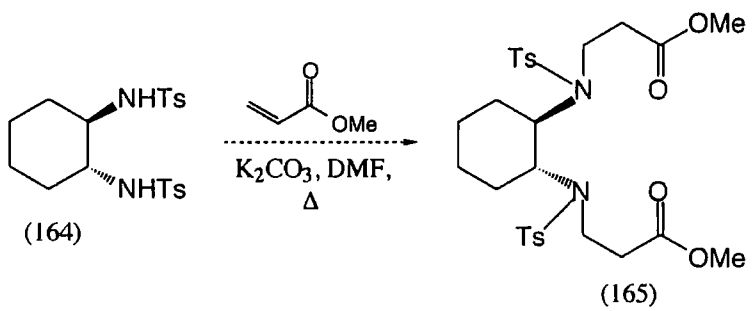
Scheme 3.15

Preparation of the benzylamine analogues (161b) and (162b), Scheme 3.15, was unsuccessful (80°C, 72 hours), undoubtedly due to the increased steric hindrance of these systems. Prolonged heating (96 hours) and altering both solution concentration and base (Na_2CO_3, Cs_2CO_3) failed to generate the desired ligands. Synthesis of the phosphonate (163), Scheme 3.16, was equally problematic and more forcing conditions (reflux, 12 hours) led to substantial decomposition of the starting materials.

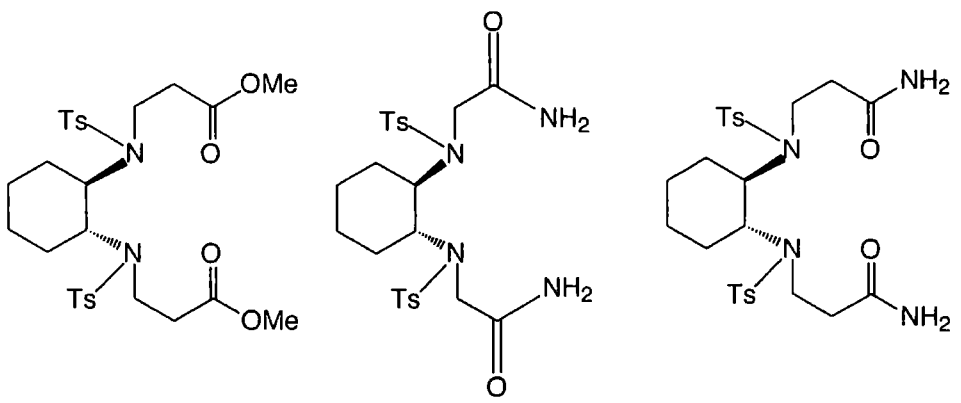


Scheme 3.16

Preparation of the sulphonated amine (164) was undertaken in an attempt to increase the acidity of the NH proton, facilitating anion formation and promoting the synthesis of dialkylated systems,[112] as typified by (165), Scheme 3.17. In addition, it was thought that this would produce crystalline derivatives which could be readily purified. Thus, differences in stability and/or reactivity using ester (165) and amide (166) based auxiliaries could then be investigated, Figure 3.7. The analogous 6-ring chelate amide (167) could be prepared in order to probe the effects of chelate size on reactivity, Figure 3.7.



Scheme 3.17

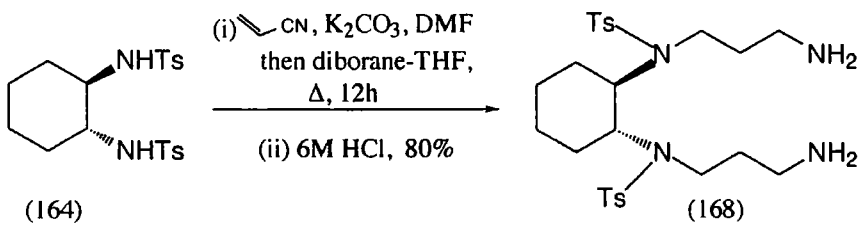


(165) (166) (167)

Figure 3.7

Unfortunately, neither system (165 or 166) could be prepared, in each case the monoalkylated adduct was observed by ^{1}H NMR and it seems that steric factors again inhibit double alkylation. Subsequent runs involved variation of the base (Cs_2CO_3) and concentration, with no evidence of polyaza/oxo ligand formation by NMR. Consequently, synthesis of ligand (167) was not attempted.

However, the bisamine (168), Scheme 3.18, was prepared *via* the condensation reaction between acrylonitrile and the sulfonated amine (164), followed by diborane reduction.[115] Presumably bisalkylation occurred as a result of the higher reactivity of acrylonitrile compared to methyl acrylate or 2-bromoacetamide used in the attempted synthesis of (165) and (166), respectively.



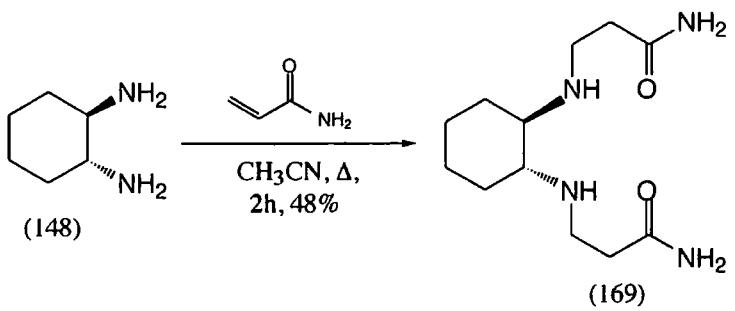
(164) (168)

Scheme 3.18

Synthesis was confirmed by a molecular ion at *m/z* 537 (MH^+). An N-H stretch was observed at 3156 cm^{-1} in the IR spectrum, with concomitant loss of the C=N stretching vibration attributed to the intermediate nitrile. Signals at δ2.95 (2H), δ2.80 (2H) and

δ1.90 (2H) in the ^{1}H NMR spectrum corresponded to the CH_2 groups of the propyl moiety.

The preparation of the bisamide ligand (169), Scheme 3.19, was readily achieved by the reaction between acrylamide and (±)-*trans*-cyclohexanediamine (148).[116] This may provide a route to benzyl and tosyl analogues in future studies.



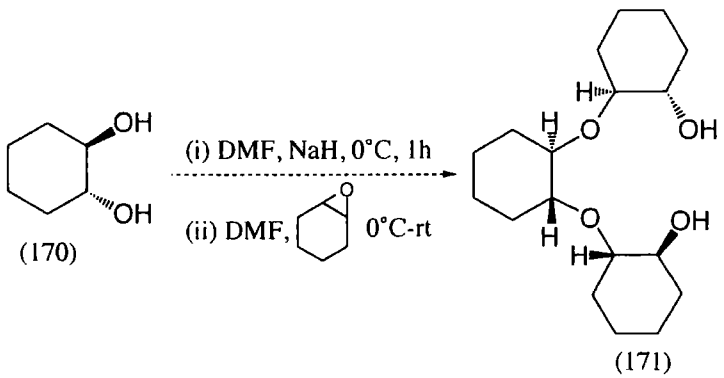
(148) (169)

Scheme 3.19

Formation of the bisamide (169) was supported by a molecular ion at *m/z* 257 (MH^+). A total of six carbon environments, by ^{13}C NMR, confirmed the symmetry of the product, with a C=O absorption at δ175.6. Further evidence was provided by a C=O stretching vibration at 1652 cm^{-1} in the IR spectrum.

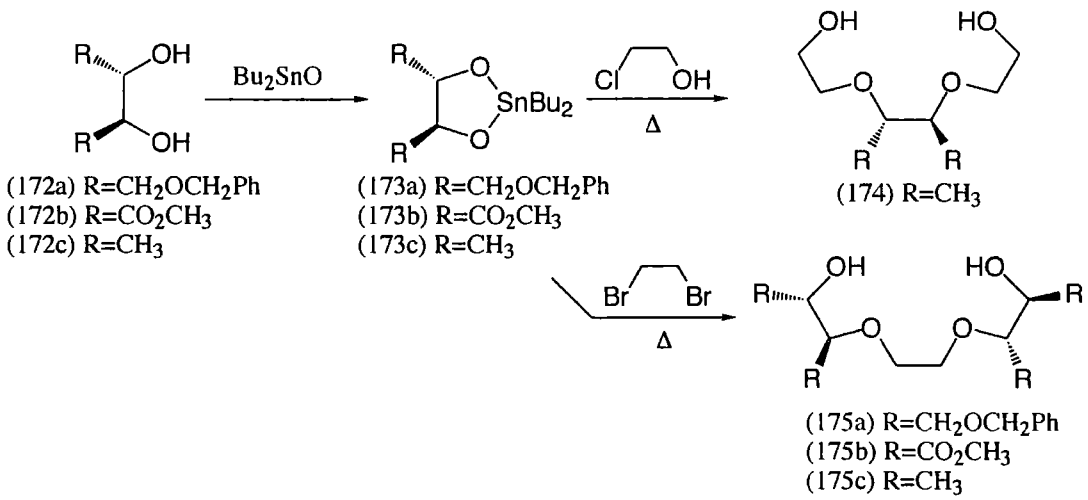
3.4.2.iii Tetra-Oxo Ligands

Synthesis of the polyoxo ligand (171) was attempted, Scheme 3.20, using a standard procedure reported by Gokel,[117] in which a solution of the cyclohexane diol (170) in DMF or THF was added to NaH at 0°C, the mixture stirred for 1 hour and cyclohexene oxide subsequently added. Unfortunately, in our hands significant polymerisation occurred and formation of the tetra-ol (171) was not observed.



Scheme 3.20

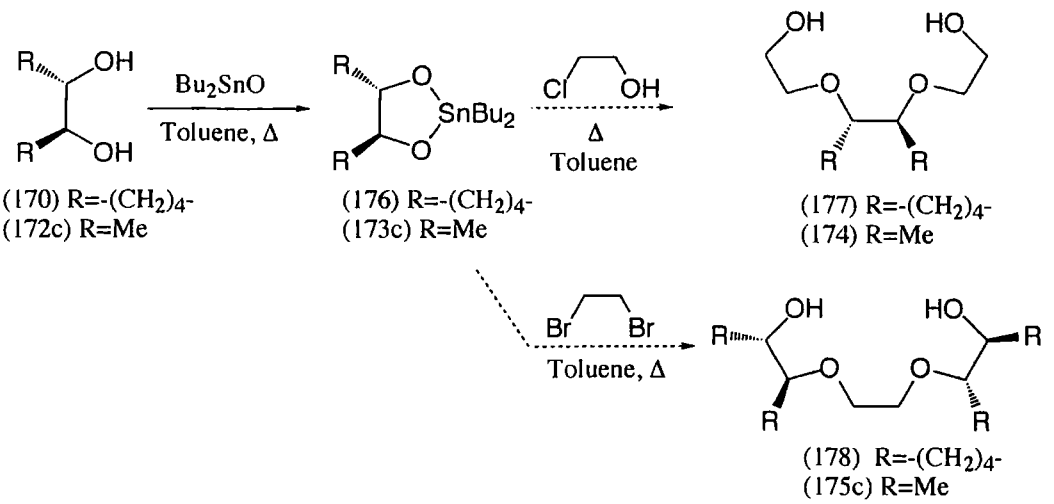
Gutiérrez and co-workers[118] have reported the facile synthesis of di-and-tetrasubstituted triethylene glycols (174, 175) by the reaction of stannylene acetals (173) with 2-chloroethanol and dibromoethane, Scheme 3.21.



Compound	R	Yield (%)
(174)	CH_3	84
(175a)	CH_2OCH_2Ph	71
(175b)	CO_2CH_3	82
(175c)	CH_3	84

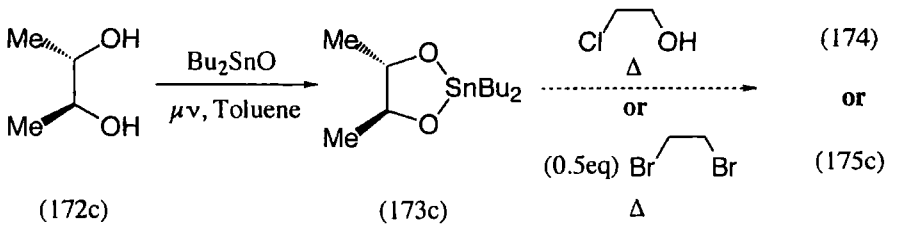
Scheme 3.21

Adopting this methodology we attempted to prepare cyclohexanediol (177, 178) and 2,3-butanediol (174, 175c) analogues, Scheme 3.22. This procedure afforded starting materials (170) and (172c), with no evidence of polyoxo ligand formation.



Scheme 3.22

The stannylene acetal (173c) of 2,3-butanediol was subsequently obtained [mp 130-131.5°C lit.[119] (134°C)] using microwave irradiation, Scheme 3.23,[119] however this intermediate failed to undergo alkylation using either 2-chloroethanol or dibromoethane. The stannylene acetal of cyclohexanediol could not be isolated.



Scheme 3.23

During the synthesis of the ligand systems described above (and several others outlined in the final section of this chapter) the application of these substrates in enantioselective carbon-carbon bond-forming reactions was investigated. This is the subject of the following section.

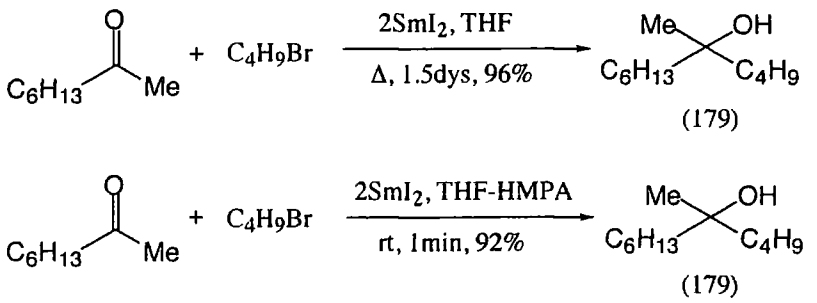
3.5 Application of Polyaza/oxo Ligands in the Barbier Reaction

3.5.1 Introduction

At this stage we sought to test the efficiency of these polyaza/oxo ligands in SmI_2-promoted carbon-carbon bond-forming reactions. Based on the observed results suitable structural modifications could be made to these ligand systems.

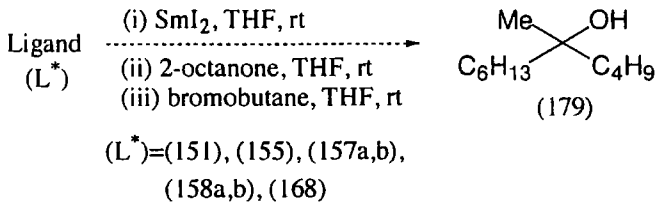
The comparison of yields and reaction rates, with uncatalysed and catalysed (HMPA) reactions was intended to give a qualitative measure of the efficacy of the polyaza/oxo ligands in SmI_2-mediated processes. Additionally, if these ligands served to provide reagent-based stereocontrol, one would expect to observe asymmetry in the process.

The Barbier reaction depicted in Scheme 3.24[532] between 2-octanone and bromobutane was chosen as a model reaction because a substantial increase in rate was achieved upon the addition of HMPA. A reaction which proceeded rapidly in the absence of additives would complicate any assessment of the rate increase resulting from the use of the polyaza/oxo ligands.



Scheme 3.24

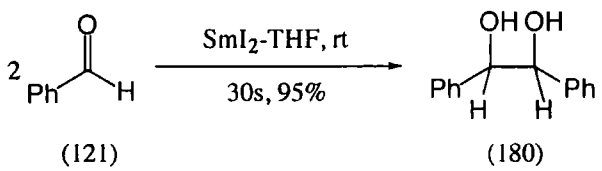
As outlined in Chapter 1 (Section 1.3.3.i), the Barbier reaction is typically conducted by the addition of the ketone to the SmI_2-THF-HMPA solution, followed rapidly by the halide. Adopting this protocol, we attempted to prepare SmI_2-THF-ligand mixtures, to which we could add THF solutions of the carbonyl compound and halide, Scheme 3.25.



(L*)=(151), (155), (157a,b), (158a,b), (168)

Scheme 3.25

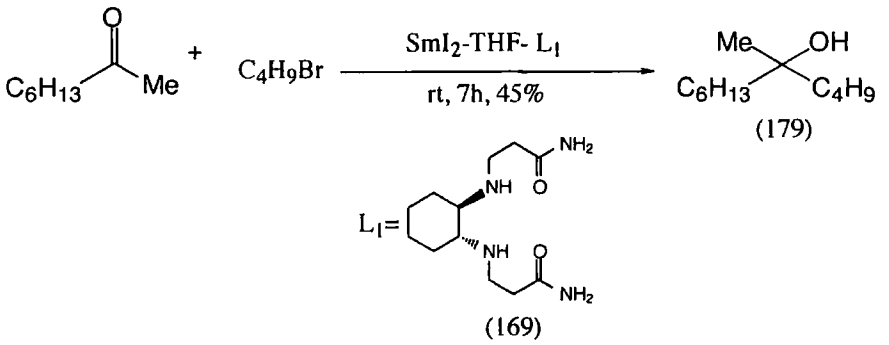
Unfortunately, with the ligands listed above, attempted preparation of prerequisite SmI_2-THF-ligand mixtures caused immediate 'quenching' of the SmI_2 solution, generally within minutes. Conversion into the inactive Sm^{3+} form was indicated by the characteristic colour change of the reagent from blue-green (Sm^{2+}) to yellow-orange (Sm^{3+}). Subsequently, 2-octanone was recovered in quantitative yield. Whilst Ln^{2+} complexes are intensely coloured and Ln^{3+} complexes generally pale in colour, it was thought necessary to verify that the observed colour change was due to the formation of Sm^{3+} ions. Benzaldehyde is known to undergo rapid pinacol coupling giving dihydrobenzoin (180) in the presence of Sm^{2+} without an added catalyst, Scheme 3.26.[37] Consequently, a solution of benzaldehyde was added to the yellow-orange SmI_2-THF-ligand mixtures. However, in no case was the diol (180) detected, substantiating oxidation of Sm^{2+} to Sm^{3+} ions in the presence of the polyaza/oxo ligands occurred.



Scheme 3.26

However, when SmI_2-THF-bisamide ligand (169) solutions were prepared the blue-green colour of the solution persisted. On addition of 2-octanone and bromobutane the formation of the alcohol (179) was observed after 7 hours, Scheme 3.27. Flash chromatography afforded the alcohol in 45% yield. A molecular ion was observed at

m/z 187 (MH^+), with a base peak at *m/z* 186 (M^+). A total of 12 carbon environments were observed by ^{13}C, with a signal at δ72.4 corresponding to the C-OH moiety; a 3H singlet at δ1.14 in the ^1H spectrum was attributed to the neighbouring methyl group, Scheme 3.27. Unfortunately, extended reaction times failed to improve the yield and the process remains to be fully optimised.



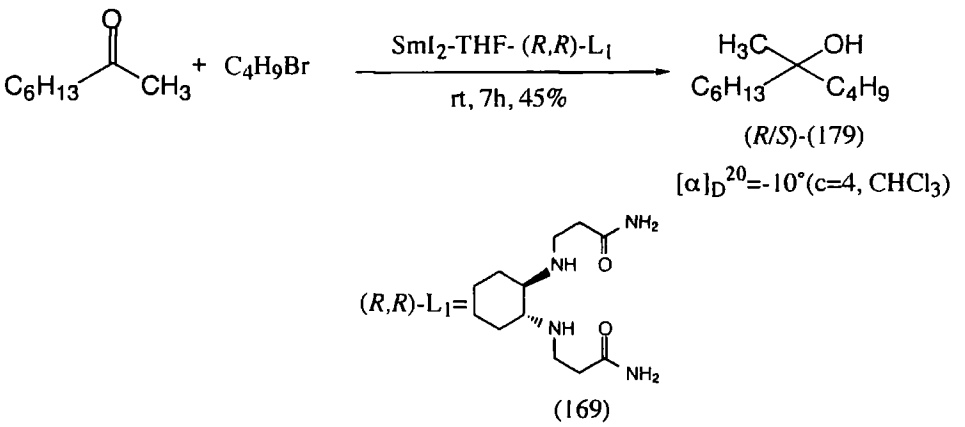
(179)

(169)

Scheme 3.27

A control reaction using a standard SmI_2-THF solution, without additives, failed to generate the alcohol (179). Thus, an increase in reaction rate was achieved by employing stoichiometric quantities of the bisamide (169).

After this promising result, the chiral ligand (*R,R*)-(169) was prepared using (*R,R*)-*trans*-cyclohexanediamine (148) and the Barbier reaction was repeated to give the alcohol (179) with non-zero optical rotation, Scheme 3.28. This represents the first example of an enantioselective Ln(II)-mediated Barbier reaction.



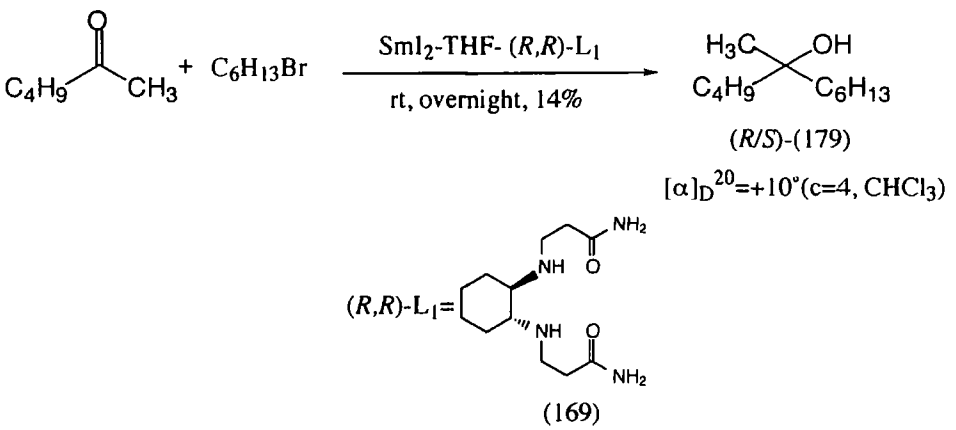
(*R/S*)-(179)

$[\alpha]_D^{20}$=-10°(c=4, $CHCl_3$)

(169)

Scheme 3.28

Trace impurities of the ligand {$[\alpha]_D^{21}$=-105° (c=8, $CHCl_3$)} could account for the minor rotation and in order to confirm that the ligand was directing the reaction we undertook the synthesis in a reverse sense, which would give the enantiomeric alcohol, Scheme 3.29. In this case the opposite enantiomer was generated (albeit in lower yield) with similar rotation, confirming that the reaction proceeds in an enantioselective manner. Further work is needed to establish a possible transition structure for the reaction and to explain the differences in yield when utilising 2-hexanone and bromohexane compared to 2-octanone and bromobutane.



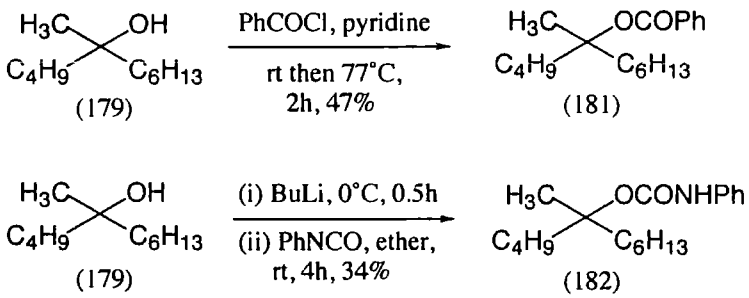
Scheme 3.29

3.5.2 Determination of Enantiomeric Purity

The next step was to determine the enantiomeric purity of the alcohol (*R/S*)-(179) in a satisfactory manner. Optical rotations for the individual enantiomers have not been reported so this precluded a simple estimation of enantiomeric excess by this method. Three methods exist for the determination of enantiomeric composition: GC, HPLC and NMR, all of which were initially investigated using racemic samples of the alcohol (179).

Analysis by chiral GC (cyclodextrin column) was attempted and a 'shoulder' was observed corresponding to the second enantiomer but complete separation could not be achieved.

One of the most commonly employed methods used to calculate the enantiomeric composition of various racemates is chiral HPLC. Many alcohols can be resolved directly using a Chiralcel OD column in conjunction with a UV detector.[120] However, the alcohol under investigation possessed no chromophores and this approach would have required the use of a Refractive Index detector, which presents significant practical difficulties. Okamoto *et al.* [120] have successfully resolved a range of phenylcarbamate and benzoate derivatives of aliphatic alcohols, using a Chiralcel OD column. In view of this report, we prepared the benzoate (181) and carbamate (182) derivatives of the alcohol (179) *via* reaction with benzoyl chloride and phenyl isocyanate respectively, Scheme 3.30.[121]



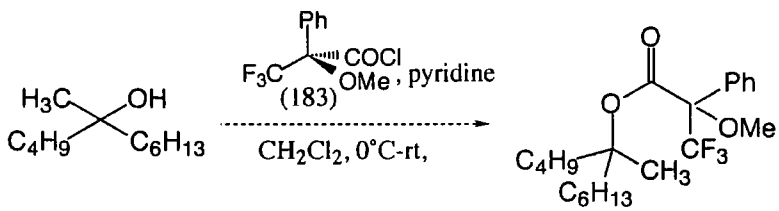
Scheme 3.30

Synthesis of the benzoate derivative (181) was confirmed by a molecular ion peak at *m/z* 290. A C=O stretch was observed at 1791 cm^{-1} in the IR spectrum and an absorption at δ165.5 in the ^{13}C spectrum was attributed to the C=O functionality. The presence of a phenyl unit was indicated by a characteristic 5H multiplet at δ7.5 in the proton spectrum. The carbamate derivative (182) gave rise to an absorption at 1728cm^{-1} in the IR with concomitant loss of the O-H stretch of the alcohol (179). A C=O signal was observed at δ154.6 in the ^{13}C spectrum, and ^{1}H NMR data confirmed the presence of the NH proton (broad singlet, δ11.05) and the phenyl group (5H multiplet centred at δ7.4).

Both derivatives were analysed by chiral HPLC, without success. Adequate enantiomer separation could not be achieved, even after varying the flow rate and

composition of the hexane/IPA eluant (99:1 to 9:1). Interestingly, Okamoto and co-workers[120] have advocated the use of Chiralpak AD columns in cases where OD columns fail to resolve enantiomers. They have noted that OD and AD columns produce a reversed order of elution of enantiomers, which suggests that these solid supports have "complementary enantiomer recognition". This approach may provide a convenient means for the determination of the enantiomeric composition of alcohols prepared in future studies using the bisamide (*R*/*R*)-(169). Unfortunately, an AD column was not available during the course of this project.

An obvious alternative was the preparation of a suitable diastereomeric derivative and subsequent NMR analysis.[122] Perhaps the most widely employed reagent for this means is Mosher's acid or acid chloride (183), Scheme 3.31. The resultant disatereoisomers can be analysed by ^{1}H or ^{19}F NMR and additionally by GC or HPLC, providing a method by which to verify enantioselectivity. However, as indicated, attempts to form the ester (184) failed and led to complete recovery of the alcohol (179).



(179) (184)

Scheme 3.31

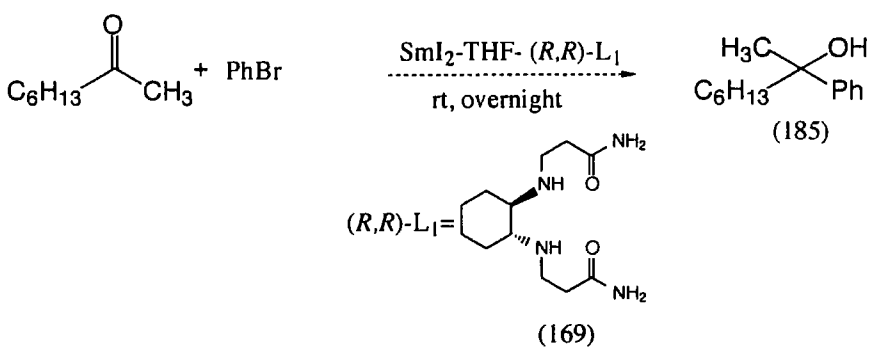
The use of chiral lanthanide shift reagents in the determination of enantiomeric composition is well established.[122] This is typically achieved by the addition of a suitable lanthanide salt to a solution of the chiral compound in a deuterated solvent. In this way an upfield or downfield shift–depending on the lanthanide employed–is induced by complexation of basic atoms in the substrate to the lanthanide ions. Adopting this methodology, we chose to use a praseodymium shift reagent, $Pr(hfc)_3$, known to be advantageous in the analysis of diastereotopic methyl groups (which

would be generated by the alcohol (179) upon complexation). Unfortunately, whilst the entire spectrum was 'shifted' to lower frequency as expected, significant overlapping of the signals from the neighbouring CH_2 groups with the diastereomeric methyl unit inhibited resolution. A broadening of the signals occurred upon addition of further shift reagent. In retrospect, application of the benzoate derivative (181) might have provided more substantial complexation to the shift reagent, *via* the less sterically hindered ester carbonyl, and produced satisfactory resolution. This remains to be explored.

A range of substrates was then investigated to correlate enantiomers with known species or provide compounds with 'in-built' chromophores and substantially different functionalities to facilitate resolution by HPLC or NMR. This is discussed in the following section.

3.5.3 Additional Barbier Reactions

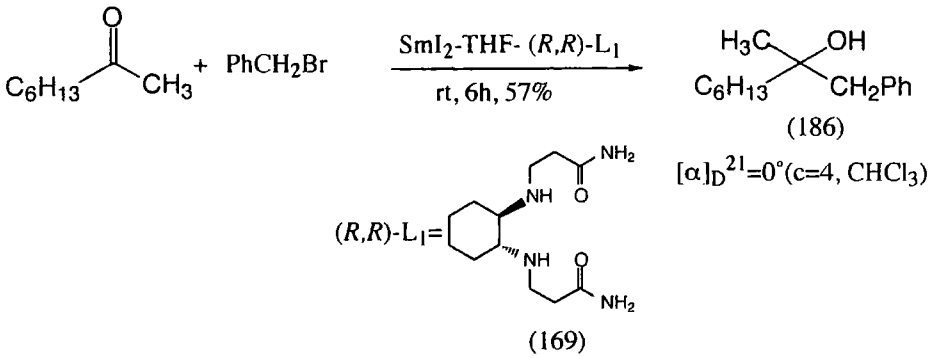
Initial attempts to generate aromatic alcohols[123] using bromobenzene failed, possibly due to preferential reduction of the aromatic halide (H-abstraction from the solvent, see Section 1.3.3.i), Scheme 3.32.



Scheme 3.32

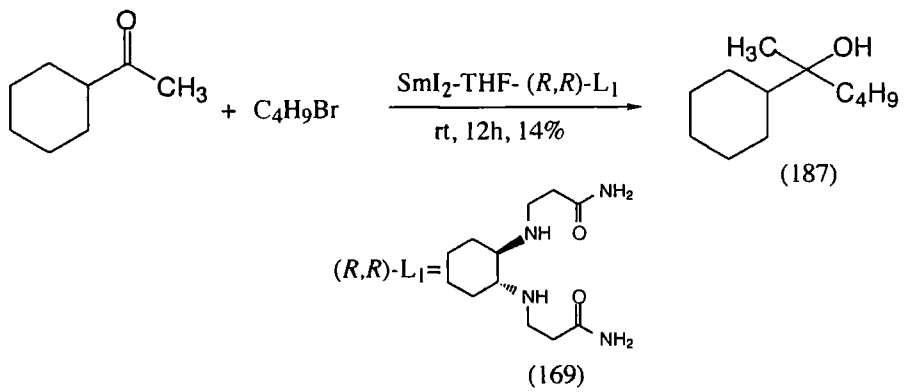
The reaction between 2-octanone and benzyl bromide, Scheme 3.33, highlights an important concept, namely the competition between uncatalysed and catalysed [bisamide (*R*/*R*)-(169)] reaction pathways; evidently, the uncatalysed pathway

predominates due to the lack of optical activity of the product. Indeed, Barbier reactions employing benzylic halides are significantly faster than those involving simple alkyl halides (Section 1.3.3.i).



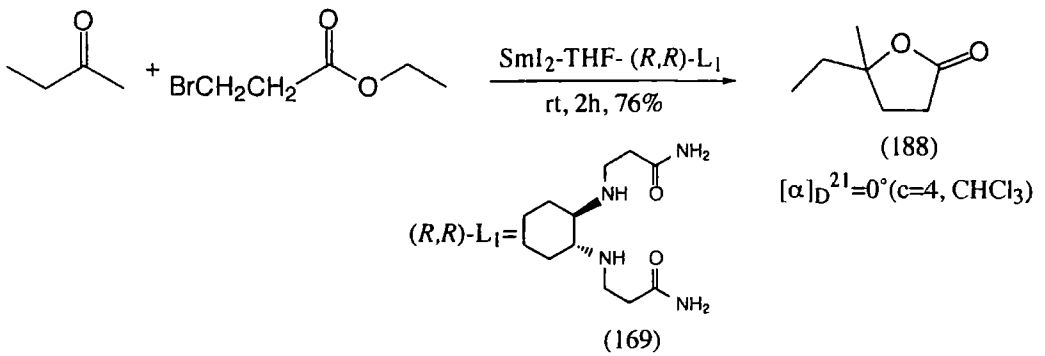
Scheme 3.33

Finally, the synthesis of alcohols of known optical rotation was then undertaken to permit the rapid assessment of enantiomeric excess. In all cases synthesis was verified by comparison with the literature data. The use of cyclohexyl methyl ketone afforded the corresponding tertiary alcohol (187) in 14% yield, Scheme 3.34, although the optical rotation[123] was inconclusive (a reproducible reading could not be obtained).



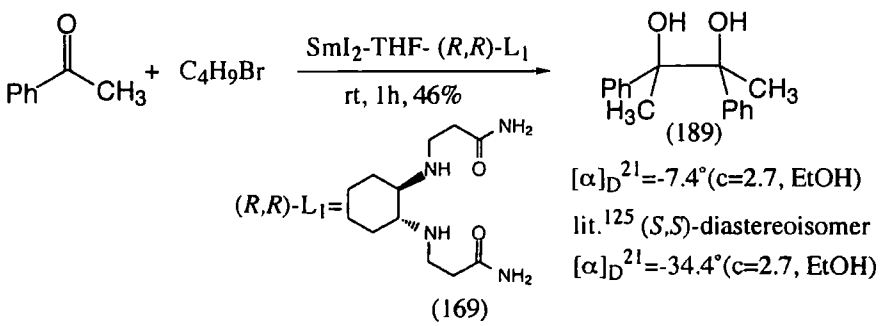
Scheme 3.34

The Barbier reaction between 2-butanone and 3-bromopropionate, Scheme 3.35,[124] was complete within the same timescale as the simple SmI_2-THF reaction. A zero optical rotation implies that the uncatalysed reaction was predominant, although this remains to be verified.



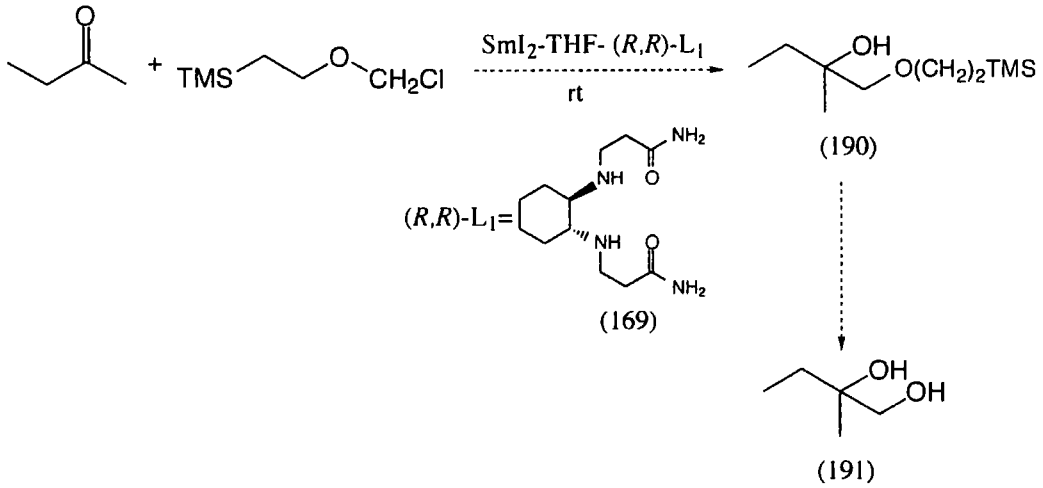
Scheme 3.35

Acetophenone failed to undergo Barbier reaction with bromobutane but afforded the pinacol (189) as a mixture of diastereoisomers (*dl*:*meso* 2:1), Scheme 3.36. Although not the desired process, the product was optically active indicating that the coupling proceeded in an enantioselective manner (estimated ee=32%).



Scheme 3.36

The Barbier reaction between 2-butanone and trimethylsilylchloromethylether [SEM-Cl], in an attempt to make the diol (191), was unsuccessful and simply lead to recovery of the 2-butanone, Scheme 3.37.[126]



Scheme 3.37

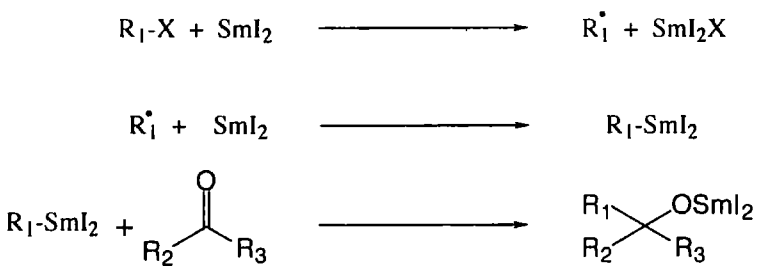
Unfortunately, time constraints prevented further investigation of bisamide-(169) promoted Barbier reactions and the enantioselectivity of the process has yet to be determined.

3.6 Mechanism of the Barbier Reaction

Regarding the mechanism of the HMPA-promoted Barbier reaction (Section 1.3.3.i), the underlying question concerns the nature of the carbon-carbon bond forming step. Recently, Curran has reviewed existing mechanistic information available on the HMPA-SmI_2-mediated Barbier reaction and obtained evidence in favour of an organometallic-addition mechanism in reactions employing simple alkyl ketones, Scheme 3.38.[19] It is conceivable that the use of similar electron-donating ligands, such as the bisamide (169), will give rise to analogous mechanistic pathways.

Curran noted that reductions under samarium Grignard conditions (see Section 1.3.3.i) could generate stable organosamarium intermediates. He then compared the reactions of prochiral ketones with organosamarium reagents under samarium Grignard and samarium Barbier conditions, with the idea that identical degrees of asymmetric induction would only be observed if identical mechanistic pathways (and hence similar organosamarium intermediates) were operating. 4-*tert*-Butylcyclohexanone afforded the same ratio of isomers under both conditions, substantiating an organometallic-

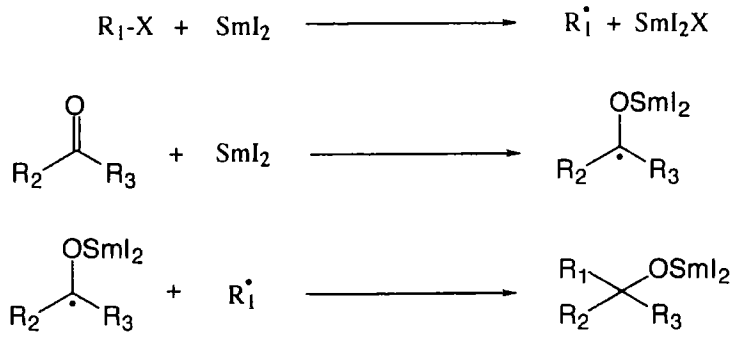
addition mechanism. On a cautionary note, reactions which follow the organometallic-addition mechanism outlined above usually give better yields when conducted under the samarium Grignard procedure. However, samarium Barbier conditions produced better yields with methyl, ethyl and isopropyl iodide.[19] Thus, the mechanism of these intermolecular samarium Barbier reactions has yet to be conclusively established.



Scheme 3.38

Such a mechanism, however, can be used to rationalise the enantioselectivity observed in the production of alcohol (179). Both the bisamide ligand (169) and the alkyl group would contribute to the steric environment at the metal centre, influencing the rate of complexation of 2-octanone prior to reaction. In addition, the carbonyl group would be orientated in such a way as to minimise steric interactions with the bound ligand, which would enforce a diastereomeric transition state, resulting in an overall enantioselective process. The increased size of hexyl bromide relative to bromobutane would lead to increased steric hindrance at the metal centre, inhibiting coordination of 2-butanone; resulting in a slower reaction and consequently reduced yield. This may be substantiated in future work by repeating the reaction using homologous aliphatic ketones and halides.

Alternative mechanisms have been proposed for the Barbier reaction, most notably a ketyl-radical coupling, Scheme 3.39.[14a]

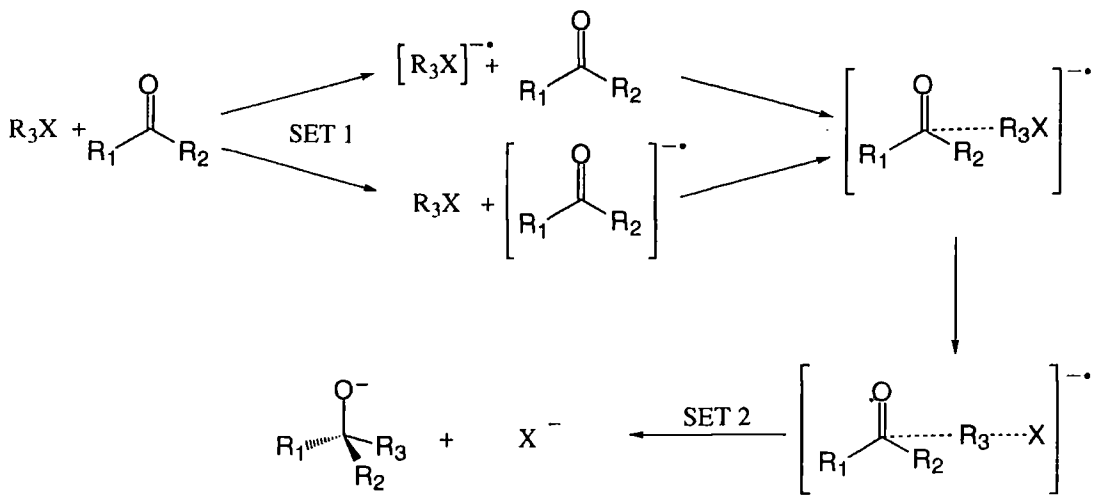


Scheme 3.39

The enantioselectivity observed using the bisamide (169) in the preparation of alcohol (179), Scheme 3.28, is consistent with a ketyl-radical coupling mechanism if one envisages a transition structure in which an alkyl radical preferentially attacks one face of the ketyl radical. The direction of attack is presumably dictated by steric interactions. However, this mechanism would require the simultaneous formation of an alkyl radical and ketyl radical at the metal surface or sufficiently long-lived radicals.

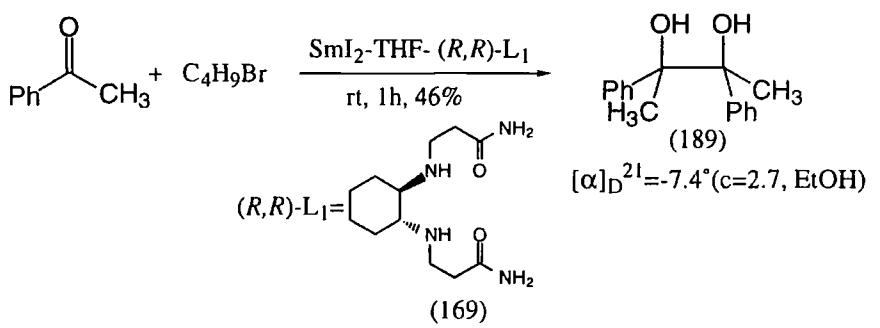
An S_N2 mechanism in which a ketyl radical attacks the alkyl halide would produce complete inversion of stereochemistry when employing chiral alkyl halides. This does not occur in practice and the S_N2 mechanism has been largely dismissed as a plausible pathway.

Interestingly, comparison with the mechanism of lithium-promoted Barbier reactions indicate that the nature of the key intermediate–ketyl or organosamarium–is influenced by the relative electron affinities of the halide and ketone, Scheme 3.40.[127] Consequently, aromatic ketones preferentially form ketyl radicals, whereas alkyl ketones are reduced less rapidly compared to the alkyl halide, so organosamarium intermediates predominate in this case.



Scheme 3.40

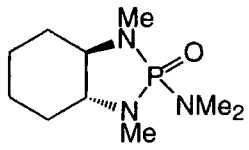
The Sm-Barbier mechanism may be similar and this is supported by attempts to prepare a tertiary alcohol *via* reaction between acetophenone and bromobutane, Scheme 3.36. The fact that the pinacol (189) was the only product isolated suggests that the aromatic ketyl radical, initially formed, undergoes preferential dimerisation.



Scheme 3.36

3.7 Future Work: Chiral HMPA and Cyclen Derivatives

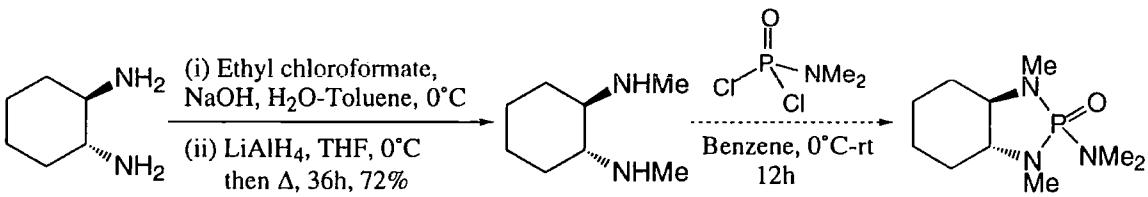
Future work will focus on the use of chiral HMPA analogues, as typified by (192) Figure 3.8. It is likely that these complexes will impart similar stability and reactivity to that found in SmI_2-HMPA based systems.



(192)

Figure 3.8

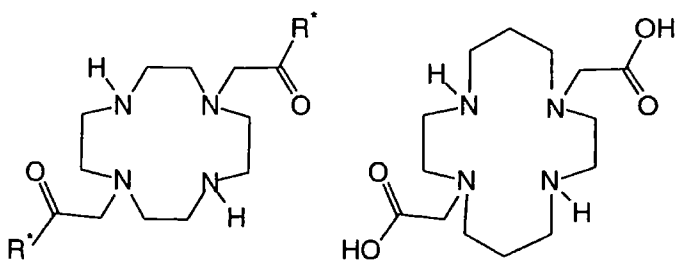
Preparation of the bismethylcyclohexanediamine (193) was achieved using the procedure reported by Alexakis *et al*, Scheme 3.41.[128] Conversion of (193) into the cyclic ligand (192) was unsuccessful although heating or modification of the concentration and/or solvent may subsequently afford the phosphoramide (192).



(148) (193) (192)

Scheme 3.41

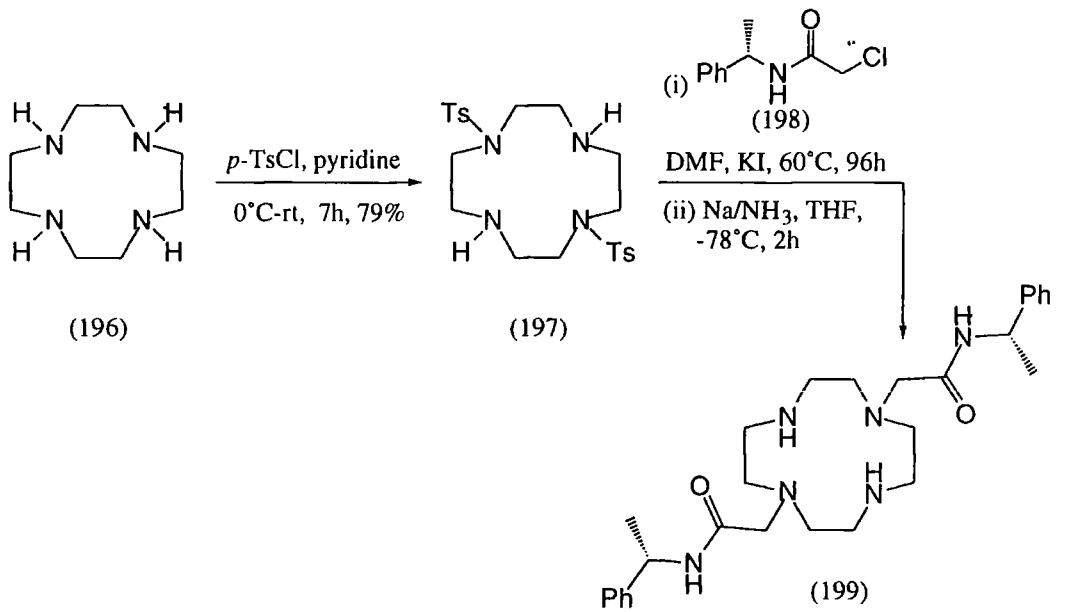
Cyclen-(194) and cyclam-(195) based ligands, Figure 3.9, were considered[129] in order to provide a more stable six-coordinate environment (complexation occurring *via* the four ring nitrogen atoms and the pendant carbonyl oxygen atoms), with quasi-C_2 symmetry about the metal.



(194) (195)

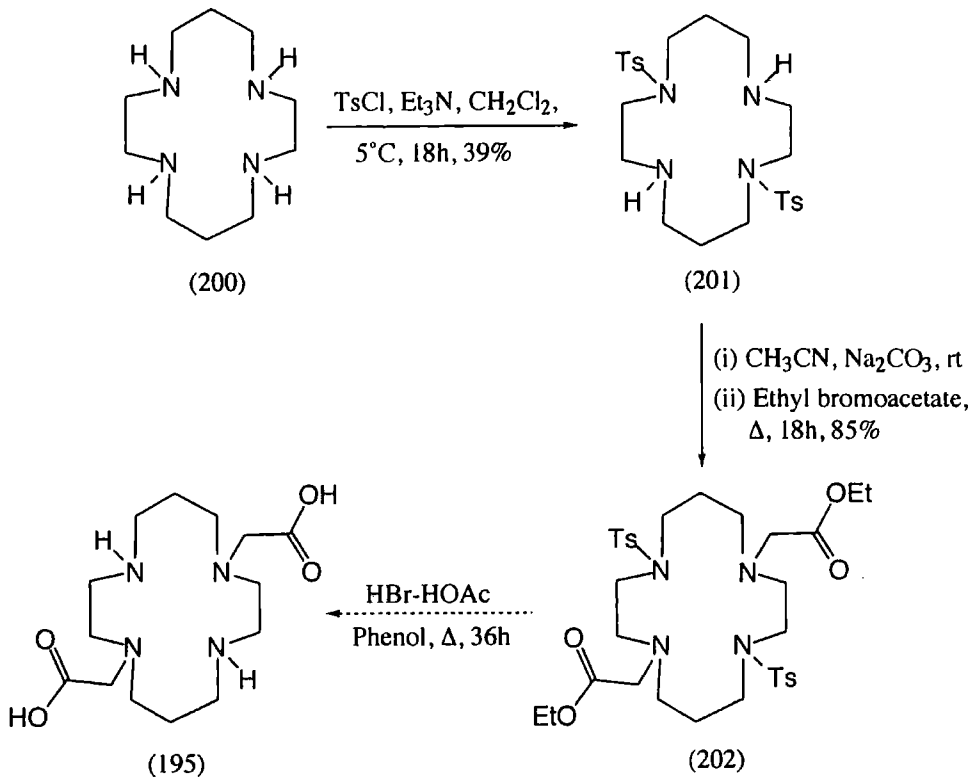
Figure 3.9

Synthesis of the cyclen (199) was achieved using established methodology, Scheme 3.42.[130] Evidence was provided by the appearance of a 10H multiplet in the ^{1}H NMR corresponding to the phenyl moieties; with concomitant loss of signals attributed to the tosyl groups. It should be noted that a suitable mass spectrum could not be obtained on this compound.



Scheme 3.42

Alternatively, cyclam (195) serves as a model compound and synthesis was attempted using the procedure reported by Parker *et al*, Scheme 3.43.[131] All stages of the synthesis were verified by comparison with the literature data. Unfortunately, deprotection using hydrogen bromide in acetic acid was unsuccessful and afforded a complex mixture of products.



Scheme 3.43

Work was suspended in both areas, the development of chiral HMPA analogues and cyclen derivatives, in order to investigate the bisamide ligand (169) discussed in the previous section. However, the complexation of Ln^{3+} ions by cyclen ligands is well established,[130] and were it possible to reduce these complexes to the reactive Ln^{2+} species *in situ* (electrochemically or photochemically), then catalytic cycles employing these Ln^{3+} complexes could be developed, realising a major goal of this project.

3.8 Conclusion

A large number of ligands have been prepared and tested for enantioselectivity in Sm-Barbier reactions; of these the bis-amide ligand (169) has allowed the first enantioselective Ln(II)-mediated Barbier reaction between 2-octanone and bromobutane. In addition, initial results suggest that this ligand may also be effective in enantioselective pinacol couplings of aryl ketones. The enantiomeric excess of these processes remains to be determined.

However, yields and reaction rates were poor compared to HMPA-promoted reactions and consequently the investigation of second generation ligands based on phosphonates and macrocyclic amines has been initiated.

SECTION C

EXPERIMENTAL

CHAPTER 4

Experimental Detail

4.1 Introduction

All reactions were carried out under a nitrogen or argon atmosphere in pre-dried glassware. Commercially available reagents were used as received. Yields refer to isolated yields of products of greater than 95% purity as determined by ^{1}H + ^{13}C NMR spectroscopy or elemental analysis (Durham University Microanalytical Laboratory). Infra Red (IR) spectra were recorded on a Perkin Elmer FT-IR 1720X spectrometer, fitted with a Graseby Specac Single Reflection Diamond ATR (10500 Series) "Golden Gate" accessory. Intensities are reported as strong (s), medium (m) or weak (w). Nuclear Magnetic Resonance (NMR) spectra were obtained on a Varian Gemini 200 (^{1}H at 199.973MHz, ^{13}C at 50.289MHz), Varian VXR-400 (^{1}H at 399.958MHz, ^{13}C at 100.581MHz), Varian Oxford 200 (^{1}H at 199.990MHz, ^{13}C at 50.293MHz), Varian Oxford 300 (^{1}H at 299.908MHz, ^{13}C at 75.411MHz) and Bruker AMX 250 (^{1}H at 250.133MHz, ^{13}C at 62.903MHz) spectrometers with $CDCl_3$ as solvent, unless otherwise stated. Chemical shifts are recorded in *ppm* (δ units) relative to residual non-deuterated solvent (^{1}H= 7.26, ^{13}C = 77.0 centre of triplet). Splitting patterns are reported as singlet (s), doublet (d), triplet (t), quartet (q) and multiplet (m). Low resolution mass spectra (EI or CI) were recorded on a VG Analytical 7070E Organic Mass Spectrometer, and gas chromatography-mass spectra (GC-MS) were recorded using a Hewlett Packard 5890 Series II gas chromatograph (25m SE30 column) connected to a VG mass Lab trio 1000. High resolution mass spectra were performed by the EPSRC service at Swansea. Electrospray Mass spectra were recorded on a

Fisons VG Platform. Optical rotations were measured on an Optical Activity LTD AA-10 Automatic Polarimeter. Melting points were conducted on a Gallenkamp melting point apparatus and are uncorrected.

Reactions were monitored by gas chromatography (GC) using a Perkin Elmer 8410 GC (SA50 column) gas chromatograph or by thin layer chromatography (tlc). Flash column chromatography was performed according to the method published by Still *et al.*[132] using Kieselgel 300-400 mesh silica.

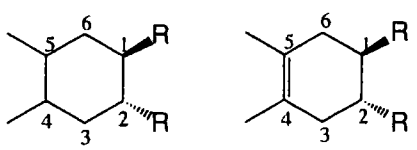
All solvents were distilled prior to use. Petroleum ethers refer to the fraction boiling in the 40-60°C range. Ether refers to diethyl ether. Solvents were dried in the following manner, under nitrogen: tetrahydrofuran and ether (sodium benzophenone ketyl); acetonitrile (potassium benzophenone ketyl); benzene, dichloromethane and N,N-dimethylformamide (calcium hydride); chloroform (phosphorous pentoxide); methanol (magnesium methoxide); ethanol (magnesium ethoxide). Other solvents were reagent grade and used as received, unless otherwise stated.

Magnesium turnings used in Grignard reactions were "activated" by flame-drying under vacuum, then stirring overnight in an inert atmosphere. In all instances the magnesium was judged to be activated by the deposition of a silver black mirror on the flask.[133]

CAUTION: HMPA is used in several procedures and this reagent is HIGHLY TOXIC.

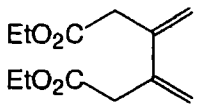
4.2 Experimental Detail

The following convention is used throughout to simplify the naming and characterisation of cyclohexane based systems (exceptions are indicted):



In general, compounds reported below are racemic, unless otherwise indicated.

1,6-Diethyl-3,4-dimethylidene-1,6-hexanedioate (56)[79]

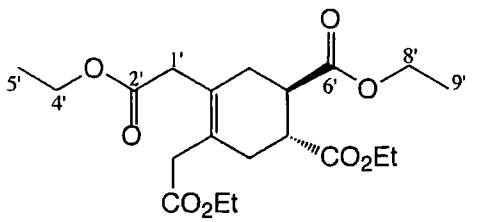


(56)

A conical flask was charged with 2-butyne-1,4-diol (0.25g, 2.90mmol), DMF (5ml), triethyl orthoacetate (5ml, 27.00mmol) and propionic acid (0.05ml, 0.29mmol). A glass funnel was placed in the neck of the flask and this homogeneous mixture was irradiated at high power in a microwave oven (700W) for 1 minute. A cooling period of 30 seconds was allowed in order to avoid excessive evaporation of the solvent. This procedure was repeated until complete consumption of the diol was observed by ^{1}H NMR (typically 10-15 minutes of heating). The crude product was allowed to cool to room temperature, then ether (20ml) was added. The solution was washed with 0.5M HCl and brine. The ether layer was removed and the aqueous phase re-extracted with a 2:1 mixture of ether and petrol (4 x 10ml). The organic layers were combined and dried ($MgSO_4$). Kugelrohr distillation (105-110°C, 0.07mbar) gave the title diene diester (56) as a colourless oil (0.43g, 66%): ν_{max} ($CHCl_3$ solution) 3250m, 2986s, 2937s, 2905s, 2876m, 1736 (C=O)s, 1672 (C=C)s, 1600 (C=C)s, 1476m, 1445m, 1369m, 1154m, 1124m, 1104m, 1032s cm^{-1}; δ_H (200MHz, $CDCl_3$) 5.19 (2H, s, C=CHH), 5.07 (2H, s, C=CHH), 4.05 (4H, q, J=7.5Hz, O-CH_2CH_3), 3.20 (4H, s, CH_2CO_2Et), 1.15 (6H, t, J=7.5Hz, O-CH_2CH_3); δ_C (50MHz, $CDCl_3$) 171.09 (C=O), 139.3 (C=CHH), 116.9 (C=CHH), 60.5 (O-CH_2CH_3), 40.2 (CH_2CO_2Et), 13.9 (O-CH_2CH_3); *m/z* (EI) 226 (M^+, 16%), 181 (19), 153 (56), 135 (30), 125 (52), 110 (30), 108 (29), 81 (61), 77 (34), 53 (100).

NB: This procedure has been carried out on larger scales using more concentrated solutions (1M) with extended overall heating times; the crude product was purified using a "short-path" distillation kit (rather than Kugelrohr apparatus) and yields were comparable to the small-scale reaction reported above.

1,2-Di(ethoxycarbonyl)-4,5-di(ethoxycarbonylmethyl)-cyclohex-4-ene (57)



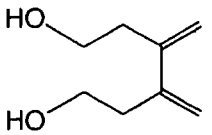
(57)

Two methods of preparation:

A) Rotaflow tube: A solution of diethyl fumarate (1.16g, 6.70mmol) in benzene (3.30ml) was added dropwise, with stirring, to a solution of the diene diester (56) (1.50g, 6.60mmol) in benzene (3.30ml). The resultant mixture was transferred to a "Rotaflow tube", which was then sealed and heated at 100°C for 23 hours. The solution was cooled, concentrated *in vacuo* and purified by flash column chromatography (2:1 petrol:ethyl acetate) to yield the tetraethyl ester (57) as a colourless oil (2.47g, 94%): ν_{max} ($CDCl_3$) 2983m, 1728 (C=O)s, 1368m, 1317m, 1178s, 1147s, 1095w, 1057w, 1026s cm^{-1}; δ_H (400MHz, $CDCl_3$) 4.05 (8H, q, J=7.2Hz, 4'-H, 8'-H), 3.00 (4H, AB system, J_{AB}=16.8Hz, 1'-H), 2.80 (2H, m, 2-H), 2.30-2.20 (4H, m, 3-H), 1.20 (12H, t, J=7.2Hz, 5'-H, 9'-H); δ_C (100MHz, $CDCl_3$) 174.3 (C=O), 170.6 (C=O), 126.2 (C=C), 60.6 (4'-C), 60.5 (8'-C), 41.5 (1'-C), 38.4 (2-C), 32.9 (3-C), 14.05 (9'-C) 14.01 (5'-C); *m/z* (EI) 398 (M^+, 5%), 278 (28), 251 (67), 205 (87), 177 (80), 149 (100), 133 (27), 105 (87), 91 (34).

B) A solution of diethyl fumarate (0.76g, 4.40mmol) in toluene (2.20ml) was added, dropwise, with stirring, to a solution of the diene diester (56) (1.01g, 4.40mmol) in toluene (2.20ml). The resulting mixture was heated at reflux for 24 hours, then cooled and concentrated. Flash column chromatography (2:1 petrol:ethyl acetate) yielded the tetraethyl ester (57) as a colourless oil (1.49g, 84%), with identical spectroscopic data to that described above.

2,3-Bis(2'-hydroxyethyl)-1,3-butadiene (69)



(69)

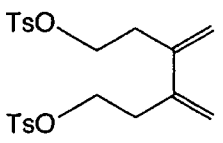
Two methods of preparation:

A) Using $LiAlH_4$: A solution of the diene diester (56) (1.77g, 7.83mmol) in ether (10ml) was added to a stirred slurry of $LiAlH_4$ (0.89g, 23.50mmol) in ether (12ml) at 0°C. The mixture was heated at reflux overnight. After cooling to 0°C, water (0.89ml) was added, followed by 15% NaOH (0.80ml) to afford a white, granular precipitate. Celite and ethyl acetate were then added and the reaction filtered. The celite residues were washed (ethyl acetate) and the combined filtrate concentrated. The celite residues were continuously extracted (ethyl acetate). Flash column chromatography (2:1 petrol:ethyl acetate) of the combined crude products afforded the title compound (69) as a colourless oil (0.37g, 33%): ν_{max} ($CDCl_3$) 3500-3200 (O-H)s, 3024s, 2984m, 1522 (C=C)m, 1476m, 1423m, 1226s, 1046s cm^{-1}; δ_H (200MHz, $CDCl_3$) 5.20 (2H, s, C=CHH), 5.10 (2H, s, C=CHH), 3.74 (4H, t, J=6Hz, HO-CH_2CH_2), 2.56 (4H, t, J=6Hz, HO-CH_2CH_2), 1.76 (2H, br s, OH); δ_C (50MHz, $CDCl_3$) 143.4 (C=CHH), 114.7 (C=CHH), 61.2 (HOCH_2CH_2), 37.6 (HOCH_2CH_2); *m/z* (EI) 143 (MH^+, 100%), 142 (M^+, 2), 141 (10).

B) Using DIBAL: DIBAL (2.20ml, 2.20mmol) was added to a solution of the diene ester (56) (0.10g, 0.44mmol) in THF (5ml) at -78°C. After 1 hour the reaction mixture was allowed to warm to room temperature, whereupon it was stirred for an additional hour. The mixture was then cooled to -78°C and methanol (0.25ml, 6.16mmol) added. Upon warming to room temperature, water (0.11ml, 6.16mmol) was added, followed by celite. The slurry was filtered, washed (ethyl acetate) and concentrated *in vacuo*. Flash column chromatography (2:1 petrol:ethyl acetate) yielded the title compound (69)

as a colourless oil (10mg, 31%), with identical spectroscopic data to that described above.

2,3-Bis-(2'-toluenesulfonyloxyethyl)-1,3-butadiene (65)



(65)

A solution of *p*-TsCl (0.39g, 2.06mmol) in dichloromethane (5ml) was added dropwise to a solution of the diol (69) (0.13g, 0.94mmol), triethylamine (0.22g, 2.06mmol) and DMAP (0.01g, 0.09mmol) in dichloromethane (5ml) at 0°C. The mixture was stirred at room temperature for 84 hours, then water (10ml) was added and the organic layer separated. The aqueous layer was re-extracted (ether) and the combined organics washed (brine), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was recrystallised (petrol/ethyl acetate) to afford the ditosylate (65) as white needles (0.31g, 75%): m.p.103.9-104.4°C; ν_{max} (KBr disc) 3030s, 3018s, 2978w, 1520w, 1480w, 1430w, 1360m, 1230s, 1202s, 1175s, 1100w, 1045w cm^{-1}; δ_H (200MHz, $CDCl_3$) 7.75 (4H, d, J=8.8Hz, Ar), 7.32 (4H, d, J=8.8Hz, Ar), 5.05 (2H, s, C=CHH), 4.95 (2H, s, C=CHH), 4.05 (4H, t, J=7.5Hz, TsO-CH_2CH_2), 2.55 (4H, t, J=7.5Hz, TsO-CH_2CH_2), 2.45 (6H, s, CH_3Ar); δ_C (50MHz, $CDCl_3$) 144.8 (Ar), 140.6 (Ar), 133.0 (C=CHH), 129.8 (Ar), 127.8 (Ar), 115.3 (C=CHH), 68.7 ($TsOCH_2CH_2$), 33.3 ($TsOCH_2CH_2$), 21.6 (CH_3Ar); *m/z* (CI, NH_3) 468 ($M(NH_4)^+$, 17%), 173 (21), 166 (100), 108 (28), 102 (23), 52 (31); Analysis Found: C, 58.70%; H, 5.85%. $C_{22}H_{26}O_6S_2$ requires C, 58.65%; H, 5.82%.

Alternative preparation of 2,3-bis-(2'-toluenesulfonyloxyethyl)-1,3-butadiene (65)

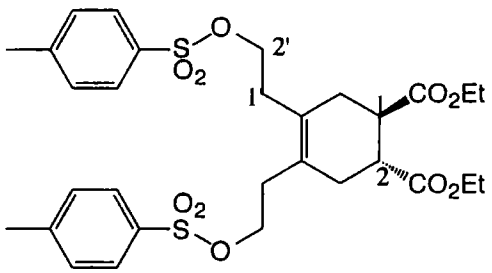
Two methods of preparation:

A) Using $LiAlH_4$: A solution of diene diester (56) (0.50g, 2.12mmol) in ether (10ml) was added to a stirred slurry of $LiAlH_4$ (0.24g, 6.86mmol) in ether (12ml) at 0°C. The mixture was stirred at room temperature for 3.3 hours, then cooled (0°C). Water (0.50ml) added, followed by 15% NaOH (0.40ml). Celite and ethyl acetate were added and the mixture filtered. The celite residue was extracted overnight (ethyl acetate). The crude products (0.47g, 3.33mmol) were taken up in dichloromethane (5ml) and then triethylamine (0.74g, 7.34mmol) and DMAP (0.04g, 0.31mmol) were added, followed by a solution of *p*-TsCl (1.41g, 7.42mmol) in dichloromethane (10ml). The resulting mixture was stirred for 12 hours then washed (water). The aqueous layer was re-extracted (ether) and the combined organics washed (brine), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography (4:1 petrol:ethyl acetate) of the "dry loaded" crude material afforded the ditosylate (65) (0.78g, 78%), with identical spectroscopic data to that described above.

B) Using DIBAL: DIBAL (22.0ml, 22.12mmol) was added to a solution of the diene diester (56) (1.00g, 4.43mmol) in THF (45ml) at -78°C. After 1 hour the reaction mixture was allowed to warm to room temperature, whereupon it was stirred for a further hour. The mixture was then cooled (-78°C) and methanol (2.50ml, 61.95mmol) added. Upon warming to room temperature, water (1.1ml, 61.95mmol) was added, followed by celite. The slurry was filtered, washed (ethyl acetate) and concentrated *in vacuo*. Continuous extraction (ethyl acetate) of the celite residues yielded additional crude product. A solution of *p*-TsCl (1.96g, 10.31mmol) in dichloromethane (7.5ml) was added dropwise to a solution of the crude diene diol (69) (0.66g, 4.68mmol), triethylamine (1.04g, 10.31mmol) and DMAP (0.05g, 0.45mmol) in dichloromethane (7.5ml) at 0°C. The mixture was stirred at room temperature for 48 hours, then water (10ml) was added and the organic layer separated. The aqueous layer was re-extracted (ether) and the combined organics washed (brine), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography (2:1 petrol:ethyl

acetate) yielded the ditosylate (65) (1.09g, 55%), with identical spectroscopic data to that described above.

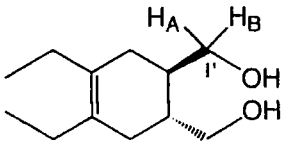
1,2-Di(ethoxycarbonyl)-4,5-di(2'-toluenesulfonyloxyethyl)cyclohex-4-ene (66)



(66)

A solution of diethyl fumarate (0.15g, 0.89mmol) in toluene (2.0ml) was added dropwise with stirring, to a solution of the ditosylate (65) (0.20g, 0.45mmol) in toluene (2.5ml). The resultant mixture was heated at reflux overnight. Concentration and flash column chromatography (2:1 petrol:ethyl acetate) gave the title ester (66) (0.24g, 88%): ν_{max} (KBr disc) 3018s, 2980s, 1728 (C=O)s, 1598m, 1521m, 1495m, 1306s, 1222s, 1096s, cm^{-1}; δ_H (200MHz, $CDCl_3$) 7.52 (4H, d, J=8.7Hz, Ar), 7.32 (4H, d, J=8.7Hz, Ar), 4.05 (4H, q, J=7.5Hz, $CH_3C\underline{H}_2O$), 3.95 (4H, t, J=6.5Hz, 2'-H), 2.50 (2H, m, 2-H), 2.40 (6H, s, $C\underline{H}_3Ar$), 2.25 (4H, t, J=6.5Hz, 1'-H), 2.15-1.85 (4H, m, 3-H), 1.20 (6H, t, J=7.5Hz, $C\underline{H}_3CH_2O$); δ_C (100MHz, $CDCl_3$) 173.8 (C=O), 144.9 (Ar), 132.6 (C=C), 129.8 (Ar), 127.6 (Ar), 127.0 (Ar), 67.8 (2'-C), 60.5 ($CH_3\underline{C}H_2O$), 41.1 (2-C), 31.9 (1'-C), 31.6 (3-C), 21.4 ($\underline{C}H_3Ar$), 14.0 ($\underline{C}H_3CH_2O$); *m/z* (EI) 622 (M^+, 0.01%), 331 (32), 330 (45), 131 (68), 107 (50), 205 (42), 91 (100).

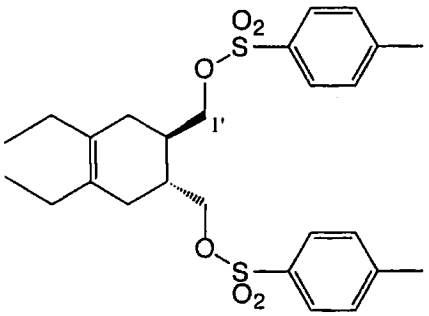
1,2-Di(1'-hydroxymethyl)-4,5-diethylcyclohex-4-ene (67)



(67)

A solution of the ester (66) (0.34g, 0.54mmol) in THF (5ml) was added to a slurry of $LiAlH_4$ (0.10g, 2.73mmol) in THF (5ml) at 0°C. The mixture was heated at reflux for 1.5 hours, then cooled (0°C) and water added (0.10ml), followed by 15% NaOH (0.10ml). Upon the formation of a white, granular precipitate, celite and ethyl acetate were added. Filtration through a celite plug, then continuous extraction of the celite residue (ethyl acetate) yielded the crude diol. Flash column chromatography (1:1 petrol:ethyl acetate) of the combined crude extracts gave (67) as a white, waxy solid (0.07g, 71%): m.p.50.5-51.1°C; ν_{max} ($CHCl_3$ solution) 3566-3214 (O-H)m, 3079s, 2891w, 1524m, 1480m, 1362s, 1224s, 1176s, 1045m cm^{-1}; δ_H (400MHz, $CDCl_3$) 3.90 (2H, br s, OH), 3.68 (2H, dd, J=2.5, 11Hz, H_A), 3.52 (2H, dd, J=5, 11Hz, H_B), 1.95 (4H, m, 3-H), 1.85 (4H, m, CH_3CH_2), 1.60 (2H, br s, 2-H), 0.90 (6H, t, J=7.5Hz, CH_3CH_2); δ_C (100MHz, $CDCl_3$) 130.2 (C=C), 66.4 (1'-C), 40.6 (2-C), 32.4 (3-C), 25.4 (CH_3CH_2), 13.2 (CH_3CH_2); *m/z* (EI) 198 (M^+, 9%), 180 (18), 149 (100), 107 (40), 93 (97), 84 (89), 79 (46), 55 (40), 41 (46); Analysis Found: C, 71.36%; H, 11.02%. $C_{12}H_{22}O_2$ requires C, 72.68%; H, 11.18%; HRMS (EI, M^+) $C_{12}H_{22}O_2$ *m/z* Calc. 198.1619; Found 198.1622.

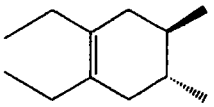
1,2-Di(1'-hydroxymethyltosylate)-4,5-diethylcyclohex-4-ene (68)



(68)

A solution of cyclohex-1-ene (67) (0.07g, 0.38mmol) in dichloromethane (2ml) was added dropwise to a solution of *p*-TsCl (0.18g, 0.96 mmol), triethylamine (0.09g, 0.96mmol) and DMAP (0.01g, 0.06mmol) in dichloromethane at 0°C. The mixture was stirred for 2.5 hours, at room temperature (under argon). Water (10ml) was added and the organic layer separated. The aqueous layer was re-extracted (ether) and the combined organics washed (brine), dried ($MgSO_4$) and concentrated *in vacuo*. The yellow oil obtained was purified by flash column chromatography (4:1 petrol:ethyl acetate) to yield the tosylate (68) as a colourless oil (0.10g, 53%): ν_{max} ($CHCl_3$ solution) 3019s, 2966s, 2930s, 2872s, 1598 (C=C)s, 1519m, 1495m, 1360s, 1223s, 1097s cm^{-1}; δ_H (400MHz, $CDCl_3$) 7.70 (4H, d, J= 8.4Hz, Ar), 7.35 (4H, d, J=8.4Hz, Ar), 3.88 (4H, d, J=4.4Hz, 1'-H), 2.40 (6H, s, CH_3Ar), 1.87 (10H, q, J=7.6Hz, 2-H, 3-H, CH_3CH_2), 0.82 (6H, t, J=7.5Hz, CH_3CH_2); δ_C (100MHz, $CDCl_3$) 144.8 (Ar), 132.6 (C=C), 129.8 (Ar), 128.8 (Ar), 127.8 (Ar), 71.4 (1'-C), 33.6 (2-C), 29.1 (3-C), 25.3 (CH_3CH_2), 21.6 (CH_3Ar), 13.0 (CH_3CH_2); *m/z* (EI) 506 (M^+, 0.1%), 81 (52), 69 (100).

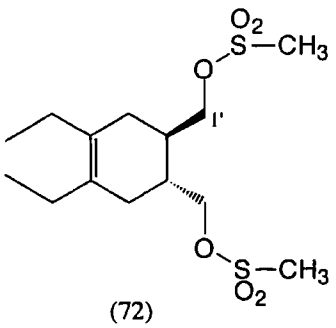
Attempted preparation of 1,2-dimethyl-4,5-diethylcyclohex-4-ene (52)



(52)

A solution of the tosylate (68) (0.18g, 0.35mmol) in THF (3ml) was added to a slurry of $LiAlH_4$ (0.04g, 1.07mmol) in refluxing THF (4ml). After 1.5 hours of heating, the solution was cooled (0°C) and water added, followed by 15% NaOH. Celite and ethyl acetate were added to the resulting precipitate. The celite residue was washed (ethyl acetate) and then continuously extracted (overnight). {In retrospect, petrol would have been a more suitable eluant}. Purification of the product using flash column chromatography (neat petrol) was unsuccessful.

1,2-Di(1'-methylsulfonyloxymethyl)-4,5-diethylcyclohex-4-ene (72)



(72)

Mesyl chloride (0.10ml, 1.29mmol) was added to a solution of the diol (67) (0.10g, 0.51mmol), triethylamine (0.15ml, 1.11mmol) and DMAP (0.10eq, 0.05mmol) in dichloromethane (5ml).[83] The mixture was stirred for 1 hour at 0°C, then for 30 minutes at room temperature. After washing (water), the dichloromethane layer was separated and the aqueous phase was then re-extracted (dichloromethane). The combined organics were washed with brine and 1M HCl, then dried ($MgSO_4$) and concentrated. Flash column chromatography (4:1 petrol:ethyl acetate) gave the title

mesylate (72) as a white solid (0.17g, 94%): m.p.94.4-95.2°C; ν_{max} ($CHCl_3$ solution) 3019s, 2967m, 2938w, 2873w, 1359s, 1338s, 1224s, 1205s, 1174s; δ_H (400MHz, $CDCl_3$) 4.16 (4H, m, 1'-H), 2.97 (6H, s, CH_3SO_2), 2.04 (4H, m, 3-H), 1.92 (6H, q, J=7.6Hz, CH_3CH_2, 2-H), 0.88 (6H, t, J=7.6Hz, CH_3CH_2); δ_C (100MHz, $CDCl_3$) 129.1 (C=C), 70.9 (1'-C), 37.3 (CH_3SO_2), 34.4 (2-C), 29.7 (3-C), 25.4 (CH_3CH_2), 13.1 (CH_3CH_2); *m/z* (EI) 354 (M^+, 2%), 162 (25), 149 (30), 133 (100), 105 (37), 93 (36); Analysis Found: C, 47.22%; H, 7.45%; $C_{14}H_{26}O_6S_2$ requires C, 47.43%; H, 7.39%.

1,2-Dimethyl-4,5-diethylcyclohex-4-ene (52)

Three methods:

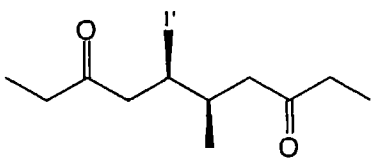
A)[85] The mesylate (72) (0.29g, 0.82mmol) and $NaBH_3CN$ (0.21g, 3.36mmol) were dissolved in HMPA (8.4ml) and the resulting solution stirred for 3.5 hours at room temperature. The mixture was then heated at 80°C for 96 hours. The reaction was quenched (water), extracted (petrol) and dried ($MgSO_4$). The crude residue was concentrated *in vacuo* and purified by flash column chromatography (neat petrol) to afford the title compound (52) as a colourless oil (14 mg, 10%): ν_{max} ($CDCl_3$ solution) 3019s, 2964m, 2928w, 2873w, 1260m, 1224s cm^{-1}; δ_H (200MHz, $CDCl_3$) 1.98 (4H, m, CH_3CH_2), 1.65 (2H, m, 3-H), 1.25 (4H, m, 3'-H, 2-H), 0.90 (12H, m, CH_3); δ_C (100MHz, $CDCl_3$) 130.6 (C=C), 38.3 (3-C), 35.3 (CH_3CH_2), 25.4 (2-C), 19.4 (CH_3CH_2), 13.3 (CH_3CH); *m/z* (EI) 166 (M^+, 24%), 137 (63), 95 (100), 81 (63), 67 (43), 55 (54), 41 (61), 29 (50); HRMS (EI, M^+) $C_{12}H_{22}$ *m/z* Calc. 166.1721; Found 166.1721.

B)[84] $NaBH_4$ (0.21g, 5.76mmol) was added to a stirred solution of the mesylate (72) (0.34g, 0.96mmol) and *t*-butyl alcohol (0.90ml, 9.60mmol) in monoglyme (10ml). The mixture was heated at reflux and stirred for 12 hours, then diluted with ether (10ml) and filtered through a celite pad. A 5% v/v solution of HCl was added to the

filtrate, which was then left to stir for 30 minutes. The layers were separated and the aqueous phase re-extracted (ether). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography (neat petrol) afforded the title compound (52) as a colourless oil (70mg, 44%) with identical spectroscopic data to that described above.

C) A solution of the mesylate (72) (0.21g, 0.61mmol) in THF (5ml) was added, *via* cannula, to a solution of $LiAlH_4$ (0.12g, 3.16mmol) in THF (5ml) at 0°C. After warming to room temperature, it was stirred for 2.5 hours. The solution was then cooled (0°C) and water was added (0.10ml), followed by 15% NaOH (0.10ml). Celite and petrol were added and the slurry was filtered. Flash column chromatography (neat petrol) afforded the title compound (52) as a colourless oil (80mg, 79%), with identical spectroscopic data to that described above.

5,6-Di-(methyl)-decane-3,8-dione (53)

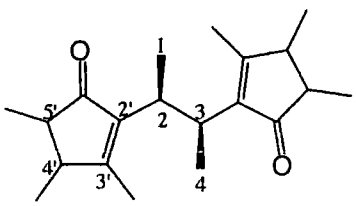


(53)

A solution of the cyclohexene (52) (0.50 g, 3.01mmol) in dichloromethane (10ml) and methanol (2ml), was stirred at -78°C under oxygen for 15 minutes. Then a stream of ozone (initially passed through a Dreschel bottle containing Drierite®) was allowed to bubble through the solution until generation of the blue ozonide was observed. The vessel was flushed with nitrogen, *p*-$TsOH.H_2O$ (56mg, 0.29mmol) added and the solution stirred at room temperature for 2 hours.[87] $NaHCO_3$ (1.01g, 12.04mmol) was added and the solution stirred for 15 minutes. Dimethyl sulfide (0.50ml, 6.62mmol) was added and the mixture then stirred overnight. The crude dione was concentrated *in vacuo* and flash column chromatography (neat petrol), afforded the title compound (53)

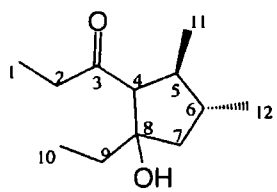
(0.50g, 84%) as a colourless oil: ν_{max} ($CHCl_3$ solution) 2966w, 1709 (C=O)s, 1460w, 1378w cm^{-1}; δ_H (400MHz, $CDCl_3$) 2.30 (6H, m, 2-H, 4-H), 2.16 (2H, dd, J=8.4Hz, 7.2Hz, 4'-H), 1.97 (2H, m, 5-H), 0.98 (6H, t, J=7.6Hz, 1-H), 0.73 (6H, d, J=6.8Hz, 1'-H); δ_C (100MHz, $CDCl_3$) 211.2 (C=O), 47.4 (2-C), 36.3 (4-C), 32.9 (5-C), 15.0 (1'-C), 7.8 (1-C); *m/z* (EI) 198 (M^+, 3%), 99 (100); HRMS (CI, MH^+) $C_{12}H_{22}O_2$ *m/z* Calc. 199.1698; Found 199.1698.

Attempted Synthesis of 2,3-Bis-(1'-oxo-3',4',5'-trimethylcyclopent-2'-enyl)butane (54): General Procedure[88] for Zirconium Catalysts



(54)

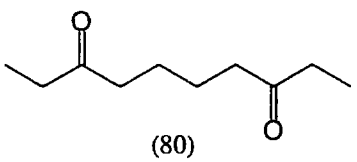
Dione (53) (0.40g, 2.02mmol), acetaldehyde (0.70ml, 12.12mmol) and zirconium catalyst (0.40mmol) were placed in a "Rotaflow tube" (under argon) and heated at 130°C for 1h. The resulting residue was extracted (ethyl acetate), filtered (celite), dried ($MgSO_4$) and concentrated *in vacuo*. Attempted purification of the crude product (0.18g) by flash column chromatography (15:1 petrol:ethyl acetate) was unsuccessful and led to isolation of the β-hydroxyketone (73):



(73)

ν_{max} ($CHCl_3$ solution) 3475 (O-H)m, 2957s, 1700 (C=O)s, 1457s, 1374s cm^{-1}; δ_H (200MHz, $CDCl_3$) 2.50-2.35 (4H, m, 2-H, 9-H), 2.2-2.30 (2H, m, 7-H), 2.20-2.15 (2H, m, 4-H, 5-H), 1.80-1.65 (2H, br s, OH, 6-H), 1.05-0.80 (12H, m, CH_3); δ_C (100MHz, $CDCl_3$) 211.3 (C=O), 60.4 (8-C), 47.29 (9-C), 47.26 (2-C), 36.4 (4-C), 33.9 (7-C), 29.7 (6-C), 21.0 (5-C), 14.8 (12-C), 14.1 (11-C), 11.5 (10-C), 7.8 (1-C); *m/z* (EI) 196 ((M^+-H_2O), 3%), 139 (0.12), 123 (12), 57 (100), 41 (15), 29 (44).

3,8-Decanedione (80)[90]

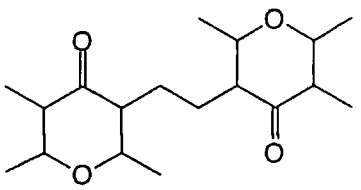


(80)

A two-necked 500ml round bottom flask was flushed with nitrogen, then charged with magnesium shavings (7.3g, 304.1mmol) and ether (100ml). Bromoethane (2ml, 26.81mmol) was added to the suspension to initiate reaction, whereupon the remaining bromoethane (13.2ml, 018mol) was added over 30 minutes, to maintain a gentle reflux. The mixture was stirred overnight; then titrated[134] at 0°C against a 1M solution of *sec*-butanol in xylene (9,10-phenanthroline indicator): calc. 1.75M EtMgBr in ether. EtMgBr (31.50ml, 55.47mmol, 1.75M in ether) was added, dropwise, to a solution of adiponitrile (2.10ml, 18.49mmol) in ether (40ml). Copper (I) bromide (0.10g, 0.73mmol) was added to the stirred solution and the mixture was heated at reflux overnight. The mixture was then cooled (0°C), and saturated NH_4Cl (20ml) added cautiously. The reaction was stirred for a further 2 hours, then extracted (ether), dried ($MgSO_4$) and concentrated *in vacuo* . Flash column chromatography (9:1 petrol:ethyl acetate), afforded the title compound (80) as a white solid (0.65g, 21%): m.p.58.2-58.9°C (lit.[91] 61°C); ν_{max} ($CHCl_3$ solution) 3016s, 2974s, 2948s, 1709 (C=O)s, 1521m, 1464s, 1418s, 1382m, 1223s, 1046s cm^{-1}; δ_H (200MHz, $CDCl_3$) 2.35 (8H,

m, 2-H, 4-H), 1.50 (4H, m, 5-H), 1.00 (6H, t, J=7.6Hz, 1-H); δ_C (50MHz, $CDCl_3$) 211.2 (C=O), 41.9 (2-C), 35.7 (4-C), 23.2 (5-C), 7.6 (1-C); *m/z* (EI) 171 (MH^+, 9%), 153 (11), 140 (100), 123 (23), 110 (73), 95 (21), 57 (57).

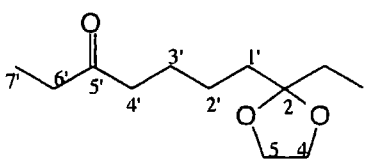
Bis-(2-oxo-3,4,6-trimethyltetrahydropyran-5-one)ethane (81)



(81)

A solution of the dione (80) (0.08g, 0.52mmol) in methanol (1ml) was added to a solution of KOH (0.02g, 0.37mmol) in MeOH (0.25ml) at 0°C.[89] LiCl was added (5mg, 0.1mmol), followed by acetaldehyde (0.46ml, 8.32mmol). The mixture was initially stirred for 6 hours at 0°C, before warming to room temperature and stirring overnight. 6M HCl (0.06ml) was then added and the solution stirred for 30 minutes, extracted (ether), washed (brine) and concentrated *in vacuo* to afford the crude pyrone (81) as a mixture of isomers.

2-Ethyl-2-(heptan-5'-one)-[1,3]-dioxolane (83)

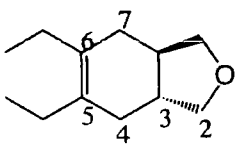


(83)

A solution of the dione (80) (0.20g, 1.17mmol), ethylene glycol (0.05ml, 0.73mmol) and *p*-TsOH.H_2O (8mg, 0.04mmol) in dichloromethane (30ml) was heated at reflux over molecular sieves for 24 hours. $NaHCO_3$ was then added and the crude product

extracted (chloroform), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography (8:1 petrol:ethyl acetate) afforded the title ketal (83) (80mg, 32%): ν_{max} (thin film) 2971m, 2876m, 1710 (C=O)s, 1459m, 1373m, 1202m, 1160m, 1068s cm^{-1}; δ_H (200MHz, $CDCl_3$) 3.87 (4H, s, 4-H), 2.39 (4H, m, 4'-H, 6'-H), 1.55 (6H, m, 1'-H, 2'-H, CH_3CH_2), 1.30 (2H, quintet, J= 6.5Hz, 3'-H), 1.00 (3H, t, 7.5Hz, 7'-H), 0.84 (3H, t, J=6.2Hz, CH_3CH_2); δ_C (50MHz, $CDCl_3$) 211.0 (C=O), 111.6 (2-C), 64.7 (4-C), 42.1 (6'-C), 41.8 (4'-C), 36.4 (CH_3CH_2), 35.6 (1'-C), 23.9 (2'-C), 23.2 (CH_3CH_2), 7.9 (3'-C), 7.6 (7'-C); *m/z* (CI, NH_3) 215 (MH^+, 18%), 185 (25), 171 (60), 153 (26), 101 (100), 95 (40), 57 (70).

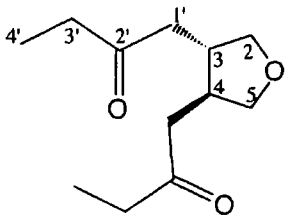
(*RR/SS*)-5,6-Diethyl-4,4a,7,7a-hexahydroisobenzofuran (71)



(71)

A solution of mesyl chloride (0.1ml, 1.29mmol) in dichloromethane (5ml) was added to a solution of the diol (67) (0.22g, 1.11mmol), triethylamine (0.4ml, 2.78mmol) and DMAP (13mg, 0.11mmol) in dichloromethane (5ml). The solution was heated at reflux overnight, then extracted (dichloromethane), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography (5:1 petrol:ethyl acetate) afforded the cyclic ether (71) as a colourless oil (0.11g, 55%): ν_{max} (thin film) 2933s, 1712 (C=C)m, 1459m, 1216m, 1012w cm^{-1}; δ_H (500MHz, $CDCl_3$) 4.01 (2H, dd, J=8.5, 2Hz, 2-H), 3.34 (2H, dd, J=8.5, 2Hz, 2'-H), 2.71 (2H, dd, J=16, 5.5Hz, 4-H), 2.42 (6H, m, 4'-H, CH_3CH_2), 2.15 (2H, m, 3-H), 0.94 (6H, t, J=7Hz, CH_3CH_2); δ_C (100MHz, $CDCl_3$) 130.9 (C=C), 72.7 (2-C), 42.4 (3-C), 31.3 (4-C), 25.9 (CH_3CH_2), 13.2 (CH_3CH_2); *m/z* (EI) 180 (M^+, 37%), 121 (36), 107 (22), 93 (58), 79 (59), 69 (29), 55 (64), 41 (100); HRMS (EI, M^+) $C_{12}H_{20}O$ *m/z* Calc. 180.1514; Found 180.1514.

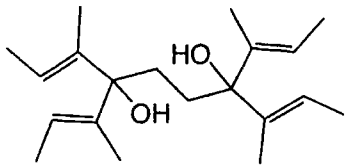
(3,4-*RR/SS*)-Bis(2'-oxobutyl)tetrahydrofuran (84)



(84)

A solution of the cyclic ether (71) (0.50 g, 2.77mmol) in dichloromethane (25ml) was stirred at -78°C under oxygen for 10 minutes. Then a stream of ozone (initially passed through a Dreschel bottle containing Drierite®) was allowed to bubble through the solution until generation of the blue ozonide was observed (15 minutes).[86] The vessel was flushed with nitrogen then DMS (2ml, 13.8mmol) was added and the mixture stirred at room temperature for 6 hours. Concentrating *in vacuo* removed residual DMS and flash column chromatography (neat petrol) afforded the title compound (84) as a colourless oil (70mg, 15%): ν_{max} (thin film) 2978m, 1712 (C=O)s, 1459m, 1411m, 1110m, 1045m cm^{-1}; δ_H (300MHz, $CDCl_3$) 3.96 (2H, dd, J=8.7, 6.6Hz, 2-H), 3.28 (2H, dd, J=8.7, 6Hz, 2-H), 2.67 (2H, dd, J=17, 5.4Hz, 1'-H), 2.40 (6H, m, 1'-H, 3'-H), 2.20 (2H, m, 3'-H), 0.98 (6H, t, J=7.5Hz, 4'-H); δ_C (75MHz, $CDCl_3$) 210.3 (C=O), 73.1 (2-C), 45.7 (3-C), 39.9 (3'-C), 35.9 (1'-C), 7.6 (4'-C); *m/z* (CI, NH_3) 230 ($M(NH_4)^+$, 72), 213 (MH^+, 100), 195 (43), 140 (22).

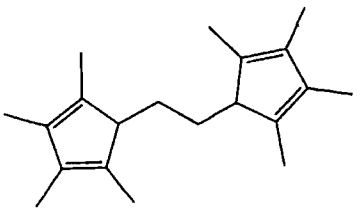
4,7-di(but-2'-en-2'-yl)-4,7-dihydroxy-3,8-dimethyldeca-2,8-diene (99)



(99)

Titanocene dichloride (0.59g, 2.41mmol) was added to a solution of 2-butyne (2.36ml, 30.11mmol) in ether (15ml) at 0°C, followed by dropwise addition of isobutyl magnesium bromide (15ml, 2M in ether, 30.0mmol).[92] The solution turned red/brown upon warming to room temperature and stirring for 2 hours. A solution of dimethyl succinate (0.84ml, 6.8mmol) in ether (3ml) was added and the reaction stirred overnight. The reaction was quenched (water), extracted (ether), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography (10:1 petrol:ethyl acetate) afforded the title diol (99) as the only non-polymeric material (40mg, 18%): m.p.134.4-135.6°C; ν_{max} ($CHCl_3$ solution) 3558-3230 (O-H)s, 3022s, 2978w, 1524m, 1230s, 1052m cm^{-1}; δ_H (200MHz, $CDCl_3$) 5.58 (4H, q, J=8Hz, $CH_3C\underline{H}$=C), 1.85 (2H, br s, OH), 1.64 (16H, m, $C\underline{H}_3$, $C\underline{H}_2$), 1.43 (12H, br s, $C\underline{H}_3$); δ_C (50MHz, $CDCl_3$) 138.18 (C=C), 118.9 (C=C), 80.3 ($\underline{C}OH$), 29.6 ($\underline{C}H_2COH$), 13.4 ($\underline{C}H_3$), 12.4 ($\underline{C}H_3$); *m/z* (EI) 311 (MH^+, 1%), 177 (18), 149 (79), 135 (100), 123 (39), 41 (37); Analysis Found: C, 78.42%; H, 11.34%. $C_{20}H_{34}O_2$ requires C, 78.37%; H, 11.18%.

Bis(2,3,4,5-tetramethylcyclopentadiene)ethane (100)

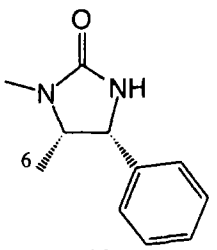


(100)

A solution of the diol (99) (50mg, 0.16mmol) in ether was added to a solution of iodine (12mg, 0.04mmol) in ether (2ml) at room temperature, then stirred for 2 hours.[92] Water was added and the residue extracted (ether), dried ($MgSO_4$) and concentrated. Flash column chromatography (neat petrol) afforded the cyclopentadiene (100) as the only non-polymeric material (19mg, 45%): ν_{max} ($CHCl_3$ solution) 2957s, 2928s, 2866s, 1443s, 1376s cm^{-1}; *m/z* (CI, CH_4) 271 (MH^+, 100%), 255 (19), 149 (31), 135 (52), 123 (15), 41 (50).

This product was comprised of a complex mixture of isomers. Consequently, ^1H and ^{13}C spectra were too complex to be reported.

(4*R*, 5*S*)-(-)-1,5-Dimethyl-4-phenyl-imidazolidin-2-one (103)[95]

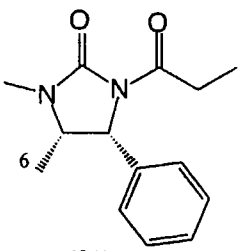


(103)

(1*R*, 2*S*)-(-)-Ephedrine hydrochloride (40g, 0.19mol) and urea (36g, 0.6mol) were placed in a round-bottomed flask and the mixture heated at 170-175°C for 1 hour (silicone oil bath), then at 190-200°C for 2.5 hours. After cooling, the reaction was treated with water and filtered. The residue was washed with water, 5% HCl and

water, then dried ($MgSO_4$). Recrystallisation (ethanol) afforded the title compound (103) as white needles (8.74g, 23%): m.p.174.1-175.1°C (lit.[95]175°C); $[\alpha]_D^{20}$= -46.6° (c=1, methanol) {lit.[95] $[\alpha]_D^{25}$= -44.3° (c=0.9, methanol)}; ν_{max} (KBr disc) 3373-3040 (N-H)s, 2973m, 2838s, 1732 (C=O)s, 1271m, 1123m, 1090m cm^{-1}; δ_H (200MHz, $CDCl_3$) 7.29-7.17 (5H, m, Ar), 5.00 (1H, s, NH), 4.70 (1H, d, J=8.4Hz, 4-H), 3.83 (1H, dq, J=8.4, 6.6Hz, 5-H), 2.69 (3H, s, CH_3N), 0.69 (3H, d, J=6.6Hz, 6-H); δ_C (50MHz, $CDCl_3$) 162.3 (C=O), 138.1 (Ar), 128.3 (Ar), 127.9 (Ar), 127.0 (Ar), 58.1 (4-C), 57.5 (5-C), 28.1 (CH_3N), 14.2 (6-C); *m/z* (EI) 190 (M^+, 54%), 175 (84), 132 (33), 104 (36), 91 (21), 58 (100).

(4*R*, 5*S*)-(-)-1,5-Dimethyl-4-phenyl-3-propionylimidazolidin-2-one (91)[95]

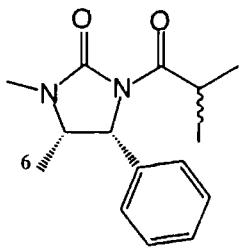


(91)

n-BuLi (21.0ml, 2.5M in hexane, 50.6mmol) was added to a solution of the imidazolidinone (103) (8.74g, 46.0mmol) in THF (92ml) at 0°C and the mixture was stirred for 30 minutes at 0°C. A solution of propionyl chloride (4.50ml, 50.6mmol) in THF (23ml) was added and the reaction was stirred for 1 hour at 0°C. The reaction was then quenched (NH_4Cl), extracted (dichloromethane), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography (2:1 petrol:ethyl acetate) afforded the acylated imidazolidinone (91) as a white solid (3.06g, 85%): m.p.91.8-93.1°C (lit.[95] 90°C); $[\alpha]_D$=-53.3° (c=1, dichloromethane) {lit.[95] $[\alpha]_D$=-54.7° (c=1, dichloromethane); ν_{max} (KBr disc) 3063w, 2990m, 1726 (C=O)s, 1685 (C=O)s, 1423s, 1373s, 1306s, 1238s cm^{-1}; δ_H (200MHz, $CDCl_3$) 7.32-7.12 (5H, m, Ar), 5.28 (1H, d, J=8.6Hz, 4-H), 3.90 (1H, dq, J=8.6, 6.8Hz, 5-H), 2.96 (2H, q, J=7.4Hz,

$CH_3C\underline{H}_2$), 2.82 (3H, s, $C\underline{H}_3N$), 1.09 (3H, t, J=7.4Hz, $C\underline{H}_3CH_2$), 0.80 (3H, d, J=6.8Hz, 6-H); δ_C (50MHz, $CDCl_3$) 173.4 (C=O), 155.9 (C=O), 136.6 (Ar), 128.3 (Ar), 127.9 (Ar), 126.8 (Ar), 59.2 (4-C), 53.9 (5-C), 29.2 ($CH_3\underline{C}H_2$), 28.0 ($\underline{C}H_3N$), 14.8 (6-C), 8.5 ($\underline{C}H_3CH_2$); *m/z* (CI, NH_3) 247 (MH^+, 100%), 246 (M^+, 86), 189 (77), 175 (49), 132 (80), 113 (37), 91 (20), 83 (39), 58 (80).

(4*R*, 5*S*)-1,5-Dimethyl-4-phenyl-3-(2'-iodo)-propionylimidazolidin-2-one (104)[96]



(104)

n-BuLi (17.88ml, 1.6M in hexanes, 44.71mmol) was added to a solution of diisopropylamine (6.28ml, 44.71mmol) in THF (40ml) at -10°C. After stirring for 30 minutes, the mixture was cooled to -78°C, whereupon a solution of the acylated imidazolidinone (91) (10g, 40.65mmol) in THF (31ml) was added, followed by DMPU (9.80ml, 81.30mmol). After 30 minutes, a solution of iodine (5.67g, 22.35mmol) in THF (67ml) was added and the reaction mixture was allowed to warm to room temperature overnight. The reaction was then quenched (NH_4Cl), extracted (dichloromethane) and the combined organics dried ($MgSO_4$), then concentrated *in vacuo*. Flash column chromatography (8:1 petrol:ethyl acetate) afforded the iodide (104) (3.5g, 24%): ν_{max} ($CHCl_3$ solution) 3436w, 3154w, 2982m, 1699 (C=O)s cm^{-1}; δ_H (200MHz, $CDCl_3$) 7.60-7.20 (5H, m, Ar), 5.40 (1H, d, J=9.1Hz, 4-H), 4.45 (1H, m, $CH_3C\underline{H}I$), 4.00 (1H, m, 5-H), 2.99 (3H, s, $C\underline{H}_3N$), 1.35 (3H, m, $C\underline{H}_3CHI$), 0.95 (3H, d, J=6.6Hz, 6-H); δ_C (50MHz, $CDCl_3$) 175.5 (C=O), 155.3 (C=O), 135.9 (Ar), 127.9 (Ar), 127.6 (Ar), 126.4 (Ar), 59.4 (4-C), 53.5 (5-C), 40.0 ($CH_3\underline{C}HI$), 28.1 ($\underline{C}H_3N$), 14.9 (6-C), 14.5 ($\underline{C}H_3CHI$).

Attempted Coupling of (4*R*, 5*S*)-(-)-1,5-Dimethyl-4-phenyl-3-propionylimidazolidin-2-one (91) with (4*R*, 5*S*)-1,5-Dimethyl-4-phenyl-3-(2'-iodo)-propionylimidazolidin-2-one (104)[96]

n-BuLi (0.60ml, 1.6M in hexanes, 0.88mmol) was added to a solution of diisopropylamine (0.12ml, 0.88mmol) in THF (2.0ml) at -10°C. After stirring for 30 minutes, the mixture was cooled to -78°C, then a solution of the imidazolidinone (91) (0.20g, 0.88mmol) in THF (4ml) was added and the solution was stirred for a further 30 minutes. A solution of the iodide (104) (0.29g, 0.80mmol) was then added and the reaction mixture was allowed to warm to room temperature overnight. The reaction was then quenched (NH_4Cl), extracted (dichloromethane) and the combined organics dried ($MgSO_4$), then concentrated *in vacuo*. Flash column chromatography (8:1 petrol:ethyl acetate) led to complete recovery of the imidazolidinone (91).

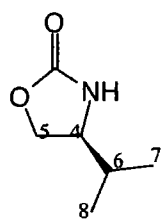
Attempted Coupling of (4*R*, 5*S*)-(-)-1,5-Dimethyl-4-phenyl-3-propionylimidazolidin-2-one (91): General Procedure for Copper Reagents[93]

n-BuLi (1.40ml, 1.6M in hexanes, 2.23mmol) was added to a solution of diisopropylamine (0.31ml, 2.23mmol) in THF (2.2ml) at -10°C. After stirring for 30 minutes, the mixture was cooled to -78°C, then a solution of the oxazolidinone (91) (0.50g, 2.03mmol) in THF (2.6ml) was added, followed by DMPU (0.50ml, 4.13mmol). After 1 hour, the copper (II) salt (2.23mmol, 1eq) was added and the reaction mixture was allowed to warm to room temperature overnight. The reaction was then quenched (NH_4Cl) extracted (dichloromethane and the combined organics dried ($MgSO_4$), then concentrated *in vacuo*. Flash column chromatography (8:1 petrol:ethyl acetate) led to complete recovery of the imidazolidinone (91).

Attempted Coupling of (4*R*, 5*S*)-(-)-1,5-Dimethyl-4-phenyl-3-propionylimidazolidin-2-one (91) using $TiCl_4$

A solution of the imidazolidinone (91) (0.20g, 0.80mmol) in THF (1.5 ml) was added to a solution of DMAP (0.11g, 0.88mmol) in THF (1.5ml) at -78°C. After stirring for 30 minutes, a solution of $TiCl_4$ (0.25ml, 10% in dichloromethane, 0.88mmol) was added and the solution was stirred overnight at room temperature. The reaction was then quenched (Na_2CO_3), filtered (celite), and the THF layer removed. The aqueous phase was re-extracted (ethyl acetate) and the combined organics were washed (brine) and dried ($MgSO_4$). Flash column chromatography (8:1 petrol: ethyl acetate) led to complete recovery of the imidazolidinone (91).

4-(*S*)-Isopropyloxazolidin-2-one (108)[98]

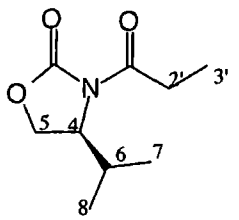


(108)

$LiAlH_4$ (7.11g, 0.18mol) was dried under vacuum (CAUTION) and then taken up in THF (200ml). A solution of L-valine (10.0g, 85.11mmol) in THF (140ml) was added to the $LiAlH_4$ slurry at 0°C. The resulting mixture was heated at reflux for 7 hours, then cooled (0°C) and quenched (10% NaOH, 13ml). Water (17ml) was added and the precipitate filtered (celite). After concentrating, the crude amino alcohol was dissolved in dichloromethane and 6M NaOH (64ml, 0.38mol) added. The solution was cooled (-5°C) and a solution of triphosgene (11.3g, 38.29mmol) in dichloromethane (68ml) added over 1 hour. The mixture was stirred at room temperature for 24 hours, then diluted (dichloromethane), filtered (celite) and washed (dichloromethane). After concentrating *in vacuo* , the residue was recrystallised (ethyl acetate/hexane) to afford the title compound (108) as white needles (6.58g, 60%): m.p.69.4-70.7°C (lit.[135] 71-

72°C); $[\alpha]_D^{21}$=+14.2° (c=7, $CHCl_3$) {lit.[135] $[\alpha]_D$=+14.8° (c=7, $CHCl_3$)}; ν_{max} (KBr disc) 3472 (N-H)m, 2974s, 2912s, 2876s, 1744 (C=O)s, 1472s, 1362s, 1178s, 1096s cm^{-1}; δ_H (300MHz, $CDCl_3$) 7.27 (1H, br s, NH), 4.39 (1H, t, J=8.7Hz, 5-H), 4.05 (1H, dd, J=8.7, 6.3Hz, 5'-H), 3.58 (1H, br dd, J=8.7, 6.3Hz, 4-H), 1.68 (1H, octet, J=6.6Hz, 6-H), 0.91 (3H, d, J=6.6Hz, 7-H), 0.85 (3H, d, J=6.6Hz, 8-H); δ_C (50MHz, $CDCl_3$) 160.6 (C=O), 68.4 (5-C), 58.2 (4-C), 32.5 (6-C), 17.7 (7-C), 17.4 (8-C); *m/z* (EI) 129 (M^+, 17%), 86 (100), 58 (26), 42 (62).

4-(*S*)-Isopropyl-3-propionyl-oxazolidin-2-one (109)[135]

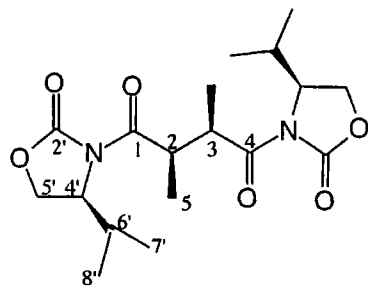


(109)

n-BuLi (8.5ml, 2.5M in hexane, 21.29mmol) was added to a solution of the oxazolidinone (108) (2.50g, 19.35mmol) in THF (40ml) at -78°C and the resulting mixture stirred for 30 minutes at -78 °C. A solution of propionyl chloride (1.85ml, 21.29mmol) in THF (10ml) was added dropwise over 20 minutes. The solution was then allowed to warm to room temperature and stirred for 2 hours. (Occasionally, a milky white solution formed which cleared on warming to room temperature). After cooling (0°C), the reaction was quenched (water), extracted (dichloromethane), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography (2:1 petrol: ethyl acetate) afforded the title compound (109) as a colourless oil (3.06g, 85%): $[\alpha]_D^{21}$=+95.3° (c=9, dichloromethane) {lit.[135] $[\alpha]_D^{20}$=+96.8° (c=8.7, dichloromethane)}; ν_{max} (thin film) 3026s, 2944s, 1785 (C=O)s, 1708 (C=O)s, 1462m, 1386s, 1234s cm^{-1}; δ_H (250MHz, $CDCl_3$) 4.35 (1H, m, 4-H), 4.17 (2H, m, 5-H), 2.85 (2H, m, 2'-H), 2.30 (1H, m, 6-H), 1.09 (3H, t, J=7.4Hz, 3'-H), 0.87 (3H, d, J=7Hz, 7-H), 0.83 (3H, d, J=7Hz, 8-H); δ_C (50MHz, $CDCl_3$) 200.0 (C=O), 173.8

(C=O), 63.2 (5-C), 58.2 (4-C), 28.9 (2'-C), 28.2 (6-C), 17.7 (7-C), 14.4 (8-C), 8.2 (3'-C); *m/z* (EI) 185 (M^+, 2%), 142 (12), 57 (100).

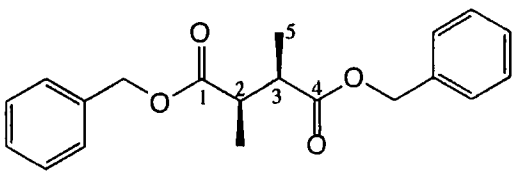
Di(4'(*S*)-Isopropyloxazolidinyl)-(2,3-*R,R*)-dimethyl succinate (110)



(110)

n-BuLi (1.40ml, 1.6M in hexanes, 2.20mmol) was added to a solution of diisopropylamine (0.30ml, 2.2mmol) in THF (2.2ml) at -10°C. The mixture was stirred for 30 minutes, then cooled (-78°C), whereupon a solution of the oxazolidinone (109) (0.37g, 2.0mmol) in THF (2.0ml) was added, dropwise. After stirring for a further 30 minutes, a solution of $TiCl_4$ (5.75 ml, 10% in dichloromethane, 20.24mmol) was added and the brown mixture was allowed to warm to room temperature overnight.[97] The reaction was quenched (Na_2CO_3), extracted (ethyl acetate), washed (brine) and dried ($MgSO_4$). After concentrating, the crude product was purified by flash column chromatography (8:1 petrol: ethyl acetate) to yield the title compound (110) (0.21g, 28%), as a mixture of diastereoisomers (82% de): m.p.243.6-244.9°C; $[\alpha]_D^{20}$=+50° (c=2, $CHCl_3$); ν_{max} (thin film) 2972m, 1770 (C=O)s, 1696 (C=O)s, 1383s, 1204s, 1106s cm^{-1}; δ_H (400MHz, $CDCl_3$) 4.35 (2H, m, 4'-H), 4.10 (4H, m, 5'-H), 4.05 (2H, m, 2-H), 2.35 (minor diastereoisomer, 0.17H, m, 6'-H), 2.24 (major diastereoisomer, 2H, m, 6'-H), 1.10 (6H, d, 6.4Hz, 5-H), 0.86 (12H, m, 7'-H, 8'-H); δ_C (75MHz, $CDCl_3$) 176.8 (C=O), 153.3 (C=O), 62.8 (5'-C), 58.5 (4'-C), 41.1 (2-C), 27.8 (6'-C), 17.8 (5-C), 14.9 (7'-C), 14.2 (8'-C); *m/z* (EI) 369 (MH^+, 2%), 240 (20), 211 (30), 154 (27), 140 (21), 128 (100); Analysis Found: C, 58.69%; H, 7.83%; N, 7.55%. $C_{18}H_{28}N_2O_6$ requires C, 58.68%; H, 7.66%; N, 7.60%.

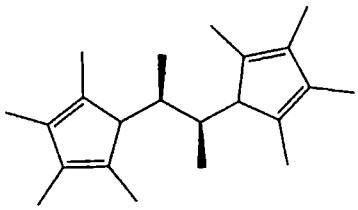
Dibenzyl-(2*R*,3*R*)-dimethylsuccinate (96c)



(96c)

n-BuLi (1.80ml, 1.6M in hexanes, 1.63mmol) was added to a solution of benzyl alcohol (0.22ml, 2.17mmol) in THF (8ml) at -78°C. After stirring for 5 minutes, a solution of the succinamide (110) (0.20g, 0.54mmol) in THF (2ml) was added and the mixture warmed to 0°C, then stirred overnight at this temperature.[99] The reaction was quenched (NH_4Cl), the THF layer removed and the aqueous phase re-extracted (dichloromethane). The combined organics were dried ($MgSO_4$), then concentrated *in vacuo*. Flash column chromatography (neat petrol), afforded the title ester (96c) as a white solid (0.58g, 65%): ν_{max} ($CHCl_3$ solution) 3033w, 2959s, 2875m, 1732 (C=O)s, 1455s, 1384w, 1265m, 1189s, 1160s, 1070s cm^{-1}; δ_H (200MHz, $CDCl_3$) 7.35-7.20 (10H, m, Ar), 5.05 (4H, AB system, J_{AB}=10Hz, $ArCH_2$), 2.80 (2H, m, 2-H), 1.10 (6H, d, J=6.2Hz, 5-H); δ_C (50MHz, $CDCl_3$) 174.1 (C=O), 135.8 (Ar), 128.4 (Ar), 128.1 (Ar), 128.0 (Ar), 66.3 ($ArCH_2$), 41.6 (2-C), 13.6 (5-C).

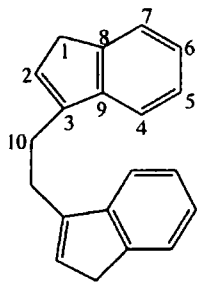
Attempted Synthesis of (2,3-*R*,*R*)-Butylene-1,1'-bis(2',3',4',5'-tetramethyl cyclopentadiene) (97b)



(97b)

Titanocene dichloride (0.16g, 6.42mmol) was added to a solution of 2-butyne (1.2ml, 7.76mmol) in ether (4.4ml) at 0°C, followed by the dropwise addition of isobutyl magnesium bromide (8ml, 2M in ether, 8mmol).[92] The solution turned red/brown upon warming to room temperature and stirring for 2 hours. A solution of the benzyl ester (96c) (0.58g, 1.78mmol) in ether (1ml) was added and the mixture was then stirred for a further 4 hours. The reaction was quenched (water), extracted (ether), dried ($MgSO_4$) and concentrated *in vacuo*. A solution of *p*-$TsOH.H_2O$ (0.02g, 0.15mmol) in chloroform (10ml) was added to the crude product and the reaction stirred for 30 minutes at room temperature. Removal of the solvent under reduced pressure and flash column chromatography (neat petrol) afforded the crude product (97b).

1,2-Bis(3-indenyl)ethane (37)[100]

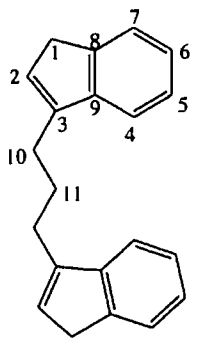


(37)

n-BuLi (10ml, 1.6M in hexane, 16mmol) was added to a solution of indene (1.28ml, 10mmol) in THF (15ml) at 0°C. This yellow suspension was warmed to room temperature and stirred for 40 minutes, whereupon a red-orange solution formed. This solution was added dropwise to a solution of 1,2-dibromoethane (0.43ml, 5mmol) in

THF (4ml) at -78°C, over 30 minutes. The reaction was allowed to warm to room temperature and then stirred overnight. After cooling (0°C), the reaction was quenched (0.1M HCl), extracted (ether), dried ($MgSO_4$) and concentrated *in vacuo*. The crude solid was recrystallised (acetone/ethanol) to afford the indene (37) as a pale yellow solid (0.77g, 77%): m.p.119.2-120.4°C (lit.[100] 120-122°C); ν_{max} (thin film) 3078m, 2895m, 1605 (C=C)s, 1461s, 1390s, 1231s cm^{-1}; δ_H (400MHz, $CDCl_3$) 7.52 (2H, d, J=7.2Hz, Ar), 7.44 (2H, d, J=7.6Hz, Ar), 7.35 (2H, dt, J=7.2, 0.8Hz, Ar), 7.25 (2H, dt, J=7.2, 1.2Hz, Ar), 6.28 (2H, br s, 2-H), 3.40 (4H, br s, 1-H), 3.00 (4H, br s, 10-H); δ_C (75MHz, $CDCl_3$) 145.3 (C-9), 144.4 (C-8), 144.1 (C-3), 127.9 (C-2), 126.0 (C-5), 124.5 (C-6), 123.7 (C-7), 118.8 (C-4), 37.7 (C-1), 26.2 (C-10); *m/z* (EI) 258 (M^+, 39%), 128 (100), 115 (17). Analysis Found: C, 93.12%; H, 7.10%. $C_{20}H_{18}$ requires C, 92.97%; H, 7.02%.

1,2-Bis(3-indenyl)propane (111)

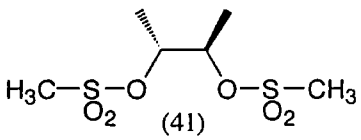


(111)

In an identical fashion 1,2-Bis(3-indenyl)propane (111) was prepared from 1,3-dibromopropane (0.72g, 72%): m.p.61.0-61.5°C; ν_{max} (thin film) 3061m, 2884m, 1605 (C=C)s, 1460s, 1390s cm^{-1}; δ_H (200MHz, $CDCl_3$) 7.52-7.24 (8H, m, Ar), 6.28 (2H, br s, 2-H), 3.38 (4H, br s, 1-H), 2.72 (4H, br s, 10-H), 2.19 (2H, quintet, J=7Hz, 11-H); δ_C (50MHz, $CDCl_3$) 145.5 (C-9), 144.5 (C-8), 144.2 (C-3), 127.9 (C-2), 126.0 (C-5), 124.5 (C-6), 123.7 (C-7), 119.0 (C-4), 37.7 (C-1), 27.6 (C-10),

26.2 (C-11); *m/z* (EI) 272 (M^+, 8%), 142 (100), 129 (41), 128 (74). Analysis Found: C, 92.45%; H, 7.43%. $C_{21}H_{20}$ requires C, 92.60%; H, 7.40%.

(2*R*,3*R*)-Di-(methanesulfonyl)-butane (41)[136]



(41)

Mesyl chloride (1.80ml, 23.30mmol) was added dropwise to a solution of (2*R*,3*R*)-butanediol (1.00g, 11.10mmol) and triethylamine (4.70ml, 35.40mmol) in dichloromethane, at 0°C. The solution was stirred at room temperature for 2.75 hours, then quenched (water), washed (brine), dried ($MgSO_4$) and concentrated *in vacuo* to afford the title dimesylate (41) (2.20g, 82%): m.p.110.6-113.1°C (lit.[136] 115-117°C); ν_{max} (thin film) 3034w, 1335s, 1317s, 1167s, 1062m cm^{-1}; δ_H (200MHz, $CDCl_3$) 4.76 (2H, m, CH_3CHO), 3.06 (6H, s, CH_3SO_2), 1.45 (6H, d, J=6.1Hz, CH_3CHO); δ_C (50MHz, $CDCl_3$) 78.7 (CH_3CHO), 38.8 (CH_3SO_2), 17.2 (CH_3CHO); *m/z* (EI) 247 (MH^+, 1%), 158 (35), 123 (100), 79 (89), 73 (40), 55 (37), 45 (42), 43 (49).

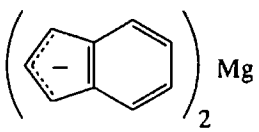
(0.76M) *n*-Butyl(*sec*-butyl)magnesium[137]

Caution: Safety shielding recommended. Petrol refers to the fraction boiling in the 95-120°C range.

sec-BuLi (0.9ml, 1.3M in cyclohexane, 1.17mmol) was added to a stirred solution of magnesium shavings (pre-activated, 4g, 0.16mol) in petrol (100ml). The mixture was heated until boiling, then the heat source was removed and the reaction allowed to cool just below the point of reflux. Then 2ml of a solution of n-butyl bromide-n-octyl bromide [made by the addition of n-butyl bromide (13.4ml, 0.12mol) to a solution of n-octyl bromide (2.4ml, 14mmol) in petrol (15.6ml)] was added to the suspension to

initiate reaction. The remainder of the solution was added added over 30 minutes, to maintain a gentle reflux. The mixture was then heated at reflux for 45 minutes, cooled (50°C) and a solution of *sec*-BuLi (100ml, 1.3M in cyclohexane, 0.13mol) in petrol (90ml) was added, over 30 minutes. The reaction was stirred at this temperature for an additional hour, then filtered (Schlenk, medium porosity), washed (petrol) and stored under argon, to afford a 0.76M solution of n-butyl(sec-butyl)magnesium in petrol.

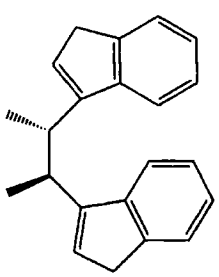
Diindenylmagnesium (40)[138]



(40)

A solution of *n*-butyl(*sec*-butyl)magnesium (50ml, 0.76M in petrol, 38.0mmol) was added *via* a pressure-equalising dropping funnel to freshly distilled, degassed indene (10.8g, 93.1mmol) over 2 hours at room temperature. The mixture was heated at reflux for 7 hours, then cooled. The pale orange solid was filtered (Schlenk, medium porosity) and washed (pentane) to afford diindenylmagnesium (40) (3.43g, 34%) as a cream-coloured solid, which was stored under argon.

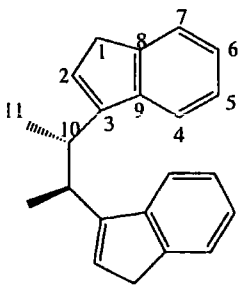
Attempted Synthesis of (*S*,*S*)-2,3-Butylene-1,1'-bis(indene) (42)[75]



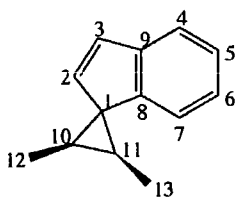
(42)

Dry, degassed THF (8ml) was added to diindenylmagnesium (40) (pre-weighed in a glove box: 0.51g, 1.99mmol) and the yellow suspension stirred at room temperature for 1 hour. The dimesylate (41) (0.39g, 1.58mmol) was added (in one portion) and the reaction was then heated at 85°C for 3.5 hours, to afford a deep red solution. The reaction was cooled (0°C), quenched (NH_4Cl), poured onto water and extracted with benzene/ether (1:2). The combined organics were then washed (brine), dried (Na_2SO_4) and concentrated *in vacuo* to yield recovered dimesylate (41) only.

(*S,S*)-2,3-Butylene-1,1'-bis (indene) (42)[100]



(42)



(112)

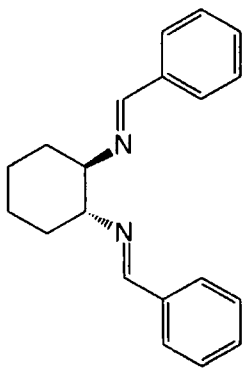
n-BuLi (7ml, 1.6M in hexane, 11.2mmol) was added to a solution of indene (1.28ml, 10mmol) in THF (20ml) at 0°C. This yellow suspension was warmed to room temperature and stirred for 40 minutes, whereupon a red-orange solution formed. This solution was added dropwise to a solution of the dimesylate (41) (1.23g, 5mmol) in THF (4ml) at -78°C, over 30 minutes. The reaction was allowed to warm to room temperature and then stirred overnight. After cooling (0°C), the reaction was quenched (0.1M HCl), extracted (ether), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography (petrol:ethyl acetate) afforded the title indene (42) as a white solid (84mg, 6%) and the spirocycle (112) as a yellow oil (1.26g, 90%).

Indene (42): m.p.135.7-136.4°C (lit.[75] 137-139°C); ν_{max} (thin film) 3062m, 2970m, 1600 (C=C)m, 1570m, 1460s, 1377s cm^{-1}; δ_H (200MHz, $CDCl_3$) 7.52 (2H, d, J=7.5Hz, Ar), 7.40 (2H, d, J=7.8Hz, Ar), 7.28 (2H, dt, J=7.8, 1.2Hz, Ar), 7.16 (2H, dt, J=7.3, 1.1Hz, Ar), 6.18 (2H, br s, 2-H), 3.30 (6H, m, 1-H, 10-H), 1.45

(6H, d, J=6.4Hz, 11-H); δ_C (50MHz, $CDCl_3$) 148.5 (C-9), 145.1 (C-8), 144.7 (C-3), 127.9 (C-2), 125.8 (C-5), 124.3 (C-6), 123.8 (C-7), 119.3 (C-4), 37.6 (C-1), 34.6 (10-C), 14.6 (11-C); *m/z* (EI) 286 (M^+, 15%), 143 (98), 128 (100), 115 (39).

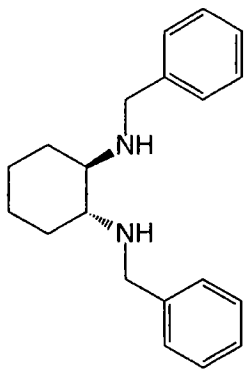
2,3-Dimethylspiro(cyclopropane-1,1'-indene) (112)[139]: δ_H (200MHz, $CDCl_3$) 7.59 (1H, d, J=7.1Hz, Ar), 7.35 (3H, m, Ar), 7.02 (1H, d, J=5.4Hz, 3-H), 6.49 (1H, d, J=5.4Hz, 2-H), 2.01 (2H, m, 10-H, 11-H), 1.50 (6H, m, 12-H, 13-H); δ_C (50MHz, $CDCl_3$) 144.5 (C-9), 143.8 (C-8), 138.0 (C-3), 127.4 (C-2), 124.3 (C-5), 122.6 (C-6), 120.8 (C-7), 119.7 (C-4), 43.2 (C-1), 31.0 (C-10), 29.4 (C-11), 16.4 (12-C), 12.9 (13-C); *m/z* (EI) 170 (M^+, 34%), 155 (100), 128 (24), 115 (35), 63 (24).

N,N'-Dibenzylidene-1,2-cyclohexanediimine[111]



To a solution of (±)-*trans*-cyclohexanediamine (148) (2.04g, 17.89mmol) in refluxing methanol (10ml) was added benzaldehyde (3.70g, 34.99mmol) in small portions. After 30 minutes the solution was allowed to cool. The precipitate was filtered and recrystallised (methanol) to afford (199) as yellow needles (3.68g, 71%): m.p.133.5-134.5°C (lit.[111] 134.0-135.0°C); ν_{max} (KBr disc) 3064w, 2934s, 2860s, 2948m, 2864m, 1642 (C=N)s, 1580m, 1449m, 1380w, 1308w, 1235s, 1205s, 1068w, 1028m cm^{-1}; δ_H (200MHz, $CDCl_3$) 8.20 (2H, s, N=CH), 7.57 (4H, m, Ar), 7.32 (6H, m, Ar), 3.41 (2H, m, 2-H), 1.86 (4H, m, 3-H), 1.60 (4H, br s, 4-H); δ_C (50MHz, $CDCl_3$) 162.0 (C=N), 137.3 (Ar), 131.1 (Ar), 129.3 (Ar), 128.1 (Ar), 74.7 (2-C), 33.9 (3-C), 25.4 (4-C); *m/z* (EI) 291 (MH^+, 100%), 187 (6), 106 (3).

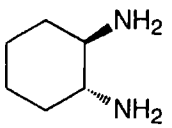
N,N'-Dibenzylcyclohexane-1,2-diamine (149)[111]



(149)

$NaBH_4$ (0.41g, 10.76mmol) was added to a solution of the diimine (199) (1.50g, 5.17mmol) in methanol (14ml) over 30 minutes. The mixture was heated at reflux for 15 minutes and then cooled. After the addition of water, the solution was extracted (dichloromethane), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was subjected to Kugelrohr distillation (200°C, 0.03mbar; lit.[111] 180°C, 0.01Torr) to give (149) as a colourless oil, which solidified upon standing (1.14g, 75%): ν_{max} ($CHCl_3$ solution) 3283 (N-H)m, 3086w, 3064w, 3020m, 2931s, 2857s, 1494m, 1453s, 1357w, 1216s, 1113m, 1052m, 1028w cm^{-1}; δ_H (200MHz, $CDCl_3$) 7.40-7.27 (10H, m, Ar), 3.80 (4H, AB system, J_{AB}=13.8Hz, CH_2Ar), 2.40-2.10 (4H, m, 2-H, 3-H), 1.95-1.80 (2H, br s, NH), 1.30-1.15 (2H, m, 3'-H), 1.15-0.95 (4H, m, 4-H); δ_C (50MHz, $CDCl_3$) 141.6 (Ar), 128.8 (Ar), 128.5 (Ar), 127.2 (Ar), 61.4 (CH_2Ar), 51.4 (2-C), 32.1 (3-C), 25.5 (4-C); *m/z* (EI) 294 (M^+, 4%), 203 (18), 189 (15), 146 (10), 108 (15), 107 (21), 106 (34), 96 (15), 91 (100).

Resolution of (±)-*trans*-1,2-cyclohexanediamine (148)[140]

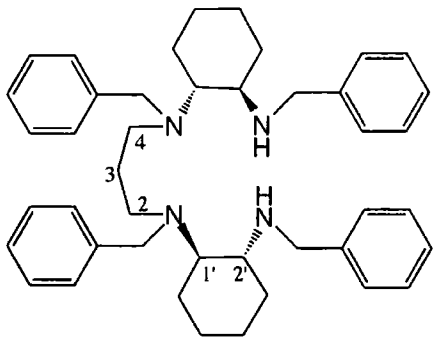


(*R,R*)-(148)

(±)-*trans*-Cyclohexanediamine (148) (50.0g, 438.6mmol) was dissolved in the minimum quantity of hot water. L-(+)-Tartaric acid (35.31g, 235.2mmol) was added in small batches, followed by heating on a steam bath for 10 minutes. Cooling the solution to 0°C, yielded the (*R,R*)-cyclohexanediamine tartrate salt (54.23g, 94%). To the hot filtrate was added L-(+)-Tartaric acid (35.12g, 233.9mmol) with enough water to dissolve all species. Ethanol was added, followed by cooling and scratching to induce crystallization to yield the (*S,S*)-cyclohexanediamine tartrate salt (39.61g, 68%). A solution of 3M NaOH (5ml, 15.15mmol), was added to the (*R,R*)-cyclohexanediamine tartrate salt (1.00g, 3.78mmol) and the resulting mixture heated for 2 hours. The aqueous residues were then subjected to continuous extraction (dichloromethane) for 96 hours. The (*R,R*)-*trans*-cyclohexanediamine was obtained as an oil (0.20g, 46%): $[\alpha]_D^{21}$=-25° (c=5, 1M HCl) {lit.[140] $[\alpha]_D^{21}$=-25° (c=5, 1M HCl)}; ν_{max} (Thin Film) 3318 (N-H)w, 2933m, 2856m, 1629m, 1477m, 1383m, 1354m, 1325m, 1290m, 1256m, 1239m, 1171m, 1042w cm^{-1}; δ_H (200MHz, D_2O) 2.25-2.10 (2H, m, 2-H), 1.75-1.45 (4H, m, 3-H), 1.20-0.80 (4H, m, 4-H); δ_C (50MHz, D_2O) 59.0 (2-C), 36.3 (3-C), 27.6 (4-C); *m/z* (EI) 114 (M^+, 14%), 97 (39), 70 (25), 69 (60), 56 (100), 44 (59), 43 (86).

The (*S,S*)-*trans*-cyclohexanediamine, (*S,S*)-(148), (oil) produced identical IR, ^1H, ^{13}C and MS data. Yield (0.17g, 40%): $[\alpha]_D^{21}$=+24.5° (c=5, 1M HCl).

1,5-Dibenzyl-1,5-di(2'-aminobenzylcyclohexyl)-1,5-diazapentane (151)



(151)

Anhydrous Na_2CO_3 (0.18g, 1.72mmol) was added to a solution of (±)-N,N'-dibenzylcyclohexane-1,2-diamine (149) (0.50g, 1.72mmol) in acetonitrile (15ml). Propane-1,3-diol ditosylate (150) (0.99g, 2.58mmol) was then added with stirring and the mixture was heated at reflux for 108 hours. After cooling, the mixture was filtered and the solid residue washed (acetonitrile). The filtrate was concentrated *in vacuo* and the resultant oil purified by flash column chromatography (4% methanol:dichloromethane) to afford the title tetramine (151) (0.34g, 63%): ν_{max} ($CHCl_3$ solution) 3450-3250 (N-H)w, 3027m, 2944s, 1604m, 1500m, 1451s, 1345m, 1254w, 1170m, 1080m cm^{-1}; δ_H (400MHz, $CDCl_3$) 7.39-7.16 (20H, m, Ar), 3.82 (8H, AB system, J_{AB}= 13.6Hz, CH_2Ar), 2.85 (4H, m, 2'-H), 2.65 (2H, m, NH), 2.52 (4H, m, 2-H), 1.90-1.65 (8H, m, 3'-H), 1.45 (2H, m, 3-H), 1.35-1.05 (8H, m, 4'-H); δ_C (100MHz, $CDCl_3$) 141.4 (Ar), 128.6 (Ar), 128.0 (Ar), 126.5 (Ar), 66.5 (CH_2Ar), 54.0 (2'-C), 49.2 (2-C), 31.3 (3'-C), 27.1 (3-C), 26.0 (4'-C); *m/z* (CI, NH_3) 435 (2), 322 (36), 243 (19), 134 (20), 105 (17), 91 (100), 69 (18), 55 (24).

(*R,R*)-N,N'-Dibenzylcyclohexane-1,2-diamine, (*R,R*)-(149)[5]

Benzaldehyde (3.80g, 35.85mmol) was added in small portions to a solution of (*R,R*)-*trans*-cyclohexanediamine (148) (2.04g, 17.96mmol) in refluxing methanol (10ml). After 30 minutes the solution was allowed to cool. A precipitate appeared upon

standing, which was filtered and washed with cold methanol. $NaBH_4$ (2.23g, 59.03mmol) was added to a solution of the crude imine (6.84g, 23.61mmol) in methanol (10ml). This mixture was heated at reflux for 24 hours, after which it was cooled, washed (water) and extracted (dichloromethane). Concentrating *in vacuo* afforded a yellow oil which was purified by Kugelrohr distillation (145-150°C, 0.04mbar) to give the title diamine, (*R,R*)-(149) as a colourless oil, which solidified upon standing (1.97g, 38%): $[\alpha]_D^{21}$=-70.7° (c=8, $CHCl_3$); ν_{max} ($CHCl_3$ solution) 3285 (N-H)m, 3085m, 3063s, 3028s, 2931s, 1602w, 1494s, 1452s, 1357m, 1215w, 1203w, 1113m, 1076m cm^{-1}; δ_H (200MHz, $CDCl_3$) 7.40-7.28 (10H, m, Ar), 3.85 (4H, AB system, J_{AB}=13.6Hz, CH_2Ar), 2.35-2.05 (4H, m, 2-H, 3-H), 1.95 (2H, br s, NH), 1.75-1.60 (2H, m, 3'-H), 1.15-0.95 (4H, m, 4-H); δ_C (50MHz, $CDCl_3$) 141.5 (Ar), 128.7 (Ar), 128.4 (Ar), 127.1 (Ar), 61.3 (CH_2Ar), 51.3 (2-C), 32.0 (3-C), 25.4 (4-C); *m/z* (EI) 295 (MH^+, 62%), 205 (12), 108 (10), 106 (16).

(*S,S*)-N,N'-Dibenzylcyclohexane-1,2-diamine, (*S,S*)-(149)[6]

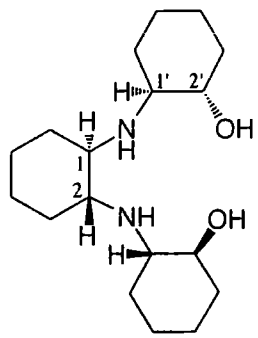
In an identical fashion the enantiomeric (*S,S*)-diamine (149) was prepared (2.29g, 61%): $[\alpha]_D^{21}$=+68.3° (c=8, $CHCl_3$); IR, ^1H, ^{13}C and MS data were identical to those of the (*R,R*)-enantiomer.

(*R*,R*,R*,R**)-1,5-dibenzyl-1,5-di(2-aminobenzylcyclohexyl)-1,5-diazapentane, (*R*,R*,R*,R**)-(151)

Anhydrous sodium carbonate (0.18g, 1.72mmol) was added to a solution of the diamine, (*R,R*)-(149) (0.50g, 1.72mmol) in acetonitrile (15ml). Propane-1,3-diol diosylate (150) (0.99g, 2.58mmol) was added, with stirring. The mixture was heated at reflux for 300 hours. After cooling, the mixture was filtered and the solid residue washed (acetonitrile). The filtrate was concentrated *in vacuo* and the resultant oil purified by flash column chromatography (4% methanol:dichloromethane) to afford the

title tetramine, (*R**,*R**,*R**,*R**)-(151) (0.28g, 52%): ν_{max} ($CHCl_3$ solution) 3450-3250 (N-H)w, 3062m, 2956s, 1604m, 1492m, 1362s, 1292m, 1174m, 1073w cm^{-1}; δ_H (400MHz, $CDCl_3$) 7.35-7.05 (20H, m, Ar), 3.75 (8H, AB system, J_{AB}=13.6Hz, CH_2Ar), 2.79 (4H, m, 2'-H), 2.55 (2H, m, NH), 2.50-2.35 (4H, m, 2-H), 1.85-1.06 (8H, m, 3'-H), 1.40 (2H, m, 3-H), 1.35-1.00 (8H, m, 4'-H); δ_C (100MHz, $CDCl_3$) 141.2 (Ar), 128.5 (Ar), 128.0 (Ar), 126.4 (Ar), 66.4 (CH_2Ar), 53.9 (2'-C), 49.1 (2-C), 31.1 (3'-C), 27.0 (3-C), 25.9 (4'-C); *m/z* (EI) 436 (4), 243 (22), 134 (30), 119 (11), 91 (100), 65 (11).

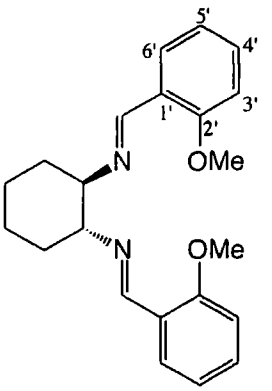
N,N'-Bis(2'-hydroxycyclohexyl)cyclohexane-1,2-diamine (155)[113]



(155)

Cyclohexene oxide (3.61g, 36.79mmol) was added to a solution of (±)-*trans*-cyclohexanediamine (148) (2.00g, 17.54mmol) in ethanol (90ml). The mixture was heated at reflux for 48 hours. Removal of the solvent and recrystallisation (hexane) afforded the diamine (155) as white needles (3.13 g, 58%): m.p.165.1-166.3°C; ν_{max} ($CHCl_3$ solution) 3200-3020 (O-H, N-H)s, 3015s, 2994s, 2940s, 2868s, 1452s, 1374m, 1202m, 1224s, 1098s, 1076m cm^{-1}; δ_H (200MHz, $CDCl_3$) 7.64 (2H, br s, NH), 3.41 (2H, m, 2'-H), 2.39-2.24 (4H, m, 1'-H, 2-H), 1.91 (4H, m, 3'-H), 1.70-1.50 (8H, m, 6'-H, 6-H, 3-H), 1.27-0.89 (12H, m, 4'-H, 5'-H, 4-H, 5-H), 0.75-0.50 (2H, br s, OH); δ_C (50MHz, $CDCl_3$) 77.9 (2'-C), 66.0 (1'-C), 65.9 (1-C), 35.7 (3'-C), 33.6 (6'-C), 33.0 (3-C), 26.0 (4'-C), 25.8 (5'-C), 21.8 (4-C); *m/z* (EI) 311 (MH^+, 100%), 196 (31), 195 (26), 177 (22), 98 (61), 81 (37), 56 (33), 41 (31).

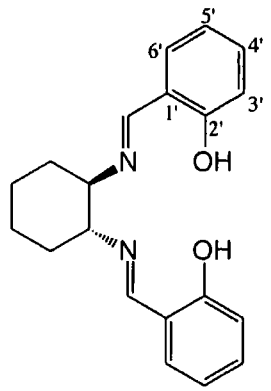
N,N'-Bis(2'-methoxybenzylidene)cyclohexane-1,2-diamine (157a)[141]



(157a)

A solution of (±)-*trans*-cyclohexanediamine (148) (1.05ml, 8.77mmol) in methanol (40ml) was heated at reflux, then *o*-anisaldehyde (2.1ml, 17.54mmol) was added, over 30 minutes. The solution was heated at reflux overnight, then concentrated *in vacuo* and the resulting yellow solid was recrystallised (methanol) to afford the title imine (157a) as yellow needles (2.02g, 66%): m.p.103.5-104.6°C (lit.[141] 105-106°C); ν_{max} ($CHCl_3$ solution) 3075m, 2919s, 1639 (C=N)s, 1580s, 1487s, 1373s, 1198s, 1080s cm^{-1}; δ_H (200MHz, $CDCl_3$) 8.60 (2H, s, N=C<u>H</u>), 7.79 (2H, d, J=7.6Hz, 6'-<u>H</u>), 7.24 (2H, dd, J=8.4, 7.4Hz, 4'-<u>H</u>), 6.86 (2H, dd, J=7.6, 7.4Hz, 5'-<u>H</u>), 6.77 (2H, d, 8.4Hz, 3'-<u>H</u>), 3.70 (6H, s, OC<u>H</u>$_3$), 3.41 (2H, m, 1-<u>H</u>), 1.83-1.50 (8H, m, 3-<u>H</u>, 4-<u>H</u>); δ_C (125MHz, $CDCl_3$) 158.5 (Ar), 157.4 (Ar), 131.2 (Ar), 127.4 (Ar), 125.1 (Ar), 120.4 (Ar), 110.6 (C=N), 73.9 (O<u>C</u>H$_3$), 55.2 (1-<u>C</u>), 33.0 (3-<u>C</u>), 24.5 (4-<u>C</u>); *m/z* (EI) 350 (M^+, 1%), 217 (100), 186 (20), 136 (63), 119 (24), 91 (36), 77 (10).

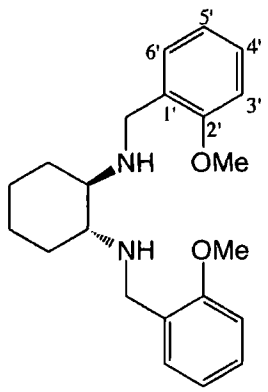
N,N'-Bis(2'-hydroxybenzylidene)cyclohexane-1,2-diamine (157b)[141]



(157b)

A solution of (±)-*trans*-cyclohexanediamine (148) (1.60ml, 13.15mmol) in methanol (40ml) was heated at reflux, then salicylaldehyde (2.95ml, 27.60mmol) was added over 30 minutes. The solution was heated at reflux overnight, then concentrated *in vacuo* and the resulting solid was recrystallised (methanol) to afford the imine (157b) as white prisms (3.04g, 72%): m.p.117.2-117.9°C (lit.[141] 119°C); ν_{max} ($CHCl_3$ solution) 3560 (O-H)w, 3044w, 2941m, 1632 (C=N)s, 1580s, 1460s, 1382s, 1278s, 1095s cm^{-1}; δ_H (200MHz, $CDCl_3$) 8.28 (2H, s, N=CH), 7.18 (4H, m, 6'-H, 4'-H), 6.86 (4H, m, 5'-H, 3'-H), 3.34 (2H, m, 1-H), 1.91-1.75 (8H, m, 3-H, 4-H); δ_C (75MHz, $CDCl_3$) 164.6 (Ar), 160.8 (Ar), 132.0 (Ar), 131.3 (Ar), 118.52 (Ar), 118.50 (Ar), 116.6 (C=N), 72.5 (1-C), 33.0 (3-C), 24.0 (4-C); *m/z* (EI) 322 (M^+, 61%), 201 (100), 184 (32), 159 (25), 122 (69), 107 (20), 77 (22).

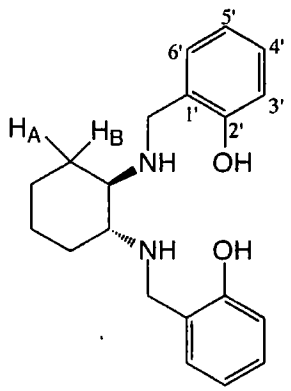
N,N'-Bis(2'-methoxybenzyl)cyclohexane-1,2-diamine (158a)



(158a)

$NaBH_4$ (0.23g, 6.0mmol) was added to a solution of the (±)-diimine (157a) (1.0g, 2.86mmol) in methanol (10ml), over 30 minutes. The mixture was heated at reflux for 4 hours, then stirred at room temperature overnight. The reaction was quenched (water), extracted (dichloromethane) and dried ($MgSO_4$), then concentrated *in vacuo* to afford the amine (158a) as a colourless oil (0.81g, 80%): ν_{max} (thin film) 3301 (N-H) m, 3063m, 2925s, 1600s, 1587s, 1491s, 1288s, 1104s, 1030s cm^{-1}; δ_H (200MHz, $CDCl_3$) 7.25 (4H, m, 6'-H, 4'-H), 6.86 (4H, m, 5'-H, 3'-H), 3.76 (4H, AB system, J_{AB}=13.2Hz, CH_2NH), 3.73 (6H, s, OCH_3), 2.20 (6H, m, 1-H, 3-H), 1.70 (2H, m, NH), 1.20 (4H, m, 4-H); δ_C (50MHz, $CDCl_3$) 157.4 (Ar), 129.26 (Ar), 129.23(Ar), 127.6 (Ar), 120.1 (Ar), 109.8 (Ar), 60.8 (OCH_3), 54.9 (1-C), 45.8 (CH_2NH), 31.5 (3-C), 25.0 (4-C); *m/z* (EI) 354 (M^+, 3%), 233 (72), 137 (55), 121 (88), 91 (100).

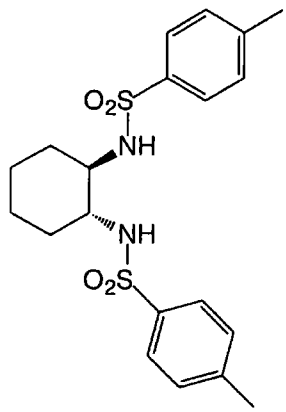
N,N'-Bis(2'-hydroxybenzyl)cyclohexane-1,2-diamine (158b)



(158b)

$NaBH_4$ (0.25g, 6.83mmol) was added to a solution of the (±)-diimine (157b) (1.0g, 3.10mmol) in methanol (10ml), over 30 minutes. The mixture was heated at reflux for 30 minutes, then stirred at room temperature overnight. The reaction was quenched (water), extracted (dichloromethane) and dried ($MgSO_4$). After concentrating *in vacuo*, the resultant solid was purified by recrystallisation (ethanol) to afford amine (158b) as white prisms (0.50g, 49%): m.p.135.6-136.1°C; ν_{max} (thin film) 3444-3264 (O-H/N-H)w, 3020s, 2940s, 1616w, 1589s, 1490s, 1255s, 1224s cm^{-1}; δ_H (200MHz, $CDCl_3$) 7.19 (2H, s, NH), 7.10 (2H, t, J=7.2Hz, 6'-H), 6.91 (2H, d, J=7.2Hz, 4'-H), 6.75 (4H, m, 5'-H, 3'-H), 3.93 (4H, AB system, J=12.9Hz, CH_2NH), 2.40 (2H, m, 1-H), 2.10 (2H, m, H_A), 1.65 (2H, m, H_B), 1.18 (4H, m, 4-H); δ_C (50MHz, $CDCl_3$) 157.8 (Ar), 128.8 (Ar), 128.3 (Ar), 122.7 (Ar), 119.1 (Ar), 116.4 (Ar), 59.6 (1'-C), 49.5 (1-C), 30.3 (3-C), 24.1 (4-C); *m/z* (EI) 326 (M^+, 20%), 219 (42), 107 (100), 98 (27), 96 (89), 56 (61).

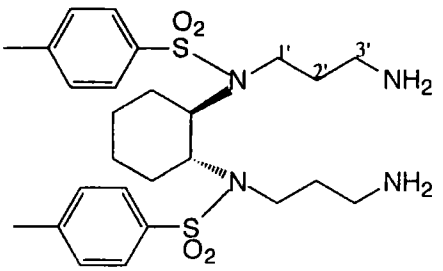
N,N'-Bis(p-toluenesulfonyl)cyclohexane-1,2-diamine (164)[142]



(164)

Diisopropylethylamine (32ml, 180mmol) was added to a solution of (±)-*trans*-cyclohexanediamine (148) (4.57g, 40mmol) in dichloromethane (90ml). The mixture was stirred for 10 minutes, then cooled to -50°C and *p*-TsCl (15.32g, 80mmol) added. After stirring for 30 minutes at room temperature, the slurry was poured onto 1M HCl (300ml), then extracted (ether), washed (brine), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was recrystallised (dichloromethane/hexane) to afford the title diamine (164) as white needles (13.67g, 81%): m.p.168.5-169.8°C (lit.[142] 168-170°C); ν_{max} (KBr disc) 3380-3288 (N-H)m, 3018s, 2978s, 2941s, 2862m, 1596m, 1522m, 1456s, 1426s, 1342s, 1224s, 1205s, 1160s, 1091s cm^{-1}; δ_H (200MHz, $CDCl_3$) 7.80 (4H, d, J=8.8Hz, Ar), 7.30 (4H, d, J=8.8Hz, Ar), 4.80 (2H, br s, NH), 2.75 (2H, m, 2-H), 2.45 (6H, s, CH_3Ar), 1.85 (2H, m, 3-H), 1.60 (2H, m, 3'-H), 1.10 (4H, m, 4-H); δ_C (100MHz, $CDCl_3$) 143.5 (Ar), 136.9 (Ar), 129.7 (Ar), 127.1 (Ar), 56.5 (CH_3Ar), 33.1 (2-C), 24.1 (3-C), 21.5 (4-C); *m/z* (CI, NH_3) 440 ($M(NH_4)^+$, 7%), 423 (MH^+, 5%), 269 (66), 189 (43), 139 (41), 113 (100).

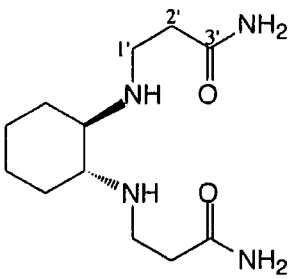
N,N'-Bis(p-toluenesulfonyl)-N,N'-bis(3-aminopropyl)cyclohexane-1,2-diamine (168)



(168)

Acrylonitrile (0.58ml, 8.87mmol) was added to a solution of the diamine (164) (1.50g, 3.55mmol) and anhydrous K_2CO_3 (1.57g, 8.37mmol) in DMF (7.10ml). The mixture was stirred at room temperature for 72 hours. Water was then added and the residue extracted (dichloromethane). After removal of the organic layer, the aqueous layer was re-extracted (dichloromethane). The combined organics were dried ($MgSO_4$), filtered through an alumina pad and concentrated *in vacuo*. A solution of diborane (1.0M in THF, 12ml, 11.58mmol) was then added to the crude mixture (0.89g, 1.81mmol) and the mixture heated at reflux overnight. Water (3ml) and THF (10ml) were then added, the solvent evaporated and 6M HCl added (20ml). The mixture was then heated at reflux for a further 2.5 hours, whereupon the solvent was evaporated. The residue was washed (2M NaOH) and then extracted (dichloromethane). The combined organics were dried ($MgSO_4$) and concentrated *in vacuo* to afford the title diamine (168) as a white solid (1.03, 80%): m.p.179.1-180.2°C; ν_{max} ($CHCl_3$ solution) 3156 (N-H)w, 2952s, 2866m, 1598m, 1460m, 1386s, 1348s, 1170s, 1158s, 1094s; δ_H (200MHz, $CDCl_3$) 7.60 (4H, d, J=8.8Hz, Ar), 7.30 (4H, d, J=8.8Hz, Ar), 3.70 (2H, br s, NH_2), 3.45 (2H, br s, NH_2), 2.95 (4H, m, 3'-H), 2.80 (4H, m, 1'-H), 2.25 (6H, s, CH_3Ar), 1.90 (4H, m, 2'-H), 1.40-0.90 (10H, m, cyclohexyl); δ_C (50MHz, $CDCl_3$) 144.4 (Ar), 135.9 (Ar), 130.1 (Ar), 127.2 (Ar), 59.7 (3'-C), 40.0 (2-C), 29.6 (1'-C), 24.8 (3'-C), 21.5 (2'-C), 21.4 (CH_3Ar), 19.2 (4-C); *m/z* (EI) 537 (MH^+, 1%), 381 (18), 364 (51), 307 (84), 153 (69), 91 (100); Analysis Found: C, 57.13%; H, 7.58%; N, 10.59%. $C_{26}H_{40}N_4O_4S_2$ requires C, 58.18%; H, 7.51%; N, 10.43%.

N,N'-Bis(3'-propionamide)cyclohexane-1,2-diamine (169)[116]



(169)

A solution of (±)-*trans*-cyclohexanediamine (148) (2.28g, 20.0mmol), acrylamide (2.84g, 39.9mmol) and acetonitrile (15ml) was heated at reflux for 2 hours. The mixture was then cooled, filtered and the residue recrystallised (acetonitrile/ether) to afford the amide (169) as white needles (2.45g, 48%): ν_{max} (thin film) 3396 (N-H)w, 3197w, 2928w, 2824w, 1652 (C=O)s, 1628s, 1406m, 1461m, 1206m, 1136s cm^{-1}; δ_H (200MHz, $CDCl_3$) 7.10 (2H, br s, $CONH_2$), 6.31 (2H, br s, $CONH_2$), 2.96-2.69 (2H, m, 1'-H), 2.33 (4H, m, 2'-H), 2.10-2.00 (6H, m, NH, 1-H, 3-H), 1.68 (4H, m, 3-H), 1.18-0.90 (4H, m, 4-H); δ_C (50MHz, $CDCl_3$) 175.6 (C=O), 61.4 (1'-C), 42.5 (2'-C), 36.3 (1-C), 31.5 (3-C), 24.9 (4-C); *m/z* (CI, NH_3) 257 (MH^+, 46%), 241 (18), 213 (100).

(*R,R*)-N,N'-Bis(3'-propionamide)cyclohexane-1,2-diamine, (*R,R*)-(169)

In an identical fashion, the chiral (*R,R*)-acrylamide (169) was prepared from (*R,R*)-(-)-*trans*-cyclohexanediamine (148) (2.75g, 54%): $[\alpha]_D^{21}$=-105° (c=8, $CHCl_3$). Analysis Found: C, 56.12%; H, 9.47%; N, 21.82%. $C_{12}H_{24}N_4O_2$ requires C, 56.22%; H, 9.43%; N, 21.85%.

IR, ^1H, ^{13}C and MS data were identical to those of the racemic ligand.

Samarium diiodide[11b]

Two methods:

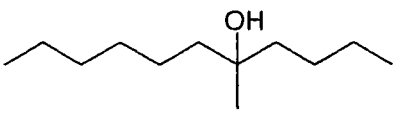
(A) Bulk solution (0.1M in THF):

Samarium powder (3.0g, 19.95mmol) was dried under vacuum (CAUTION) and 5ml of a solution of diiodomethane (0.89ml) in THF (100ml) was carefully added at room temperature, *via* a dropping funnel. The slurry was then cooled (0°C) and the remaining diiodomethane-THF solution was added over 1 hour (formation of a green-blue solution is common). The reaction mixture was allowed to warm to room temperature and was then stirred for 3-4 hours (stirring overnight is possible), whereupon a deep blue solution formed.

(B) *In situ* generation of SmI_2 (0.1M in THF):

Samarium powder (0.6g, 3.99mmol) was dried under vacuum (CAUTION) and then THF (20ml) was added. The slurry was cooled (0°C) and diiodomethane (0.18ml) added. After stirring for 1-2 hours at room temperature, the usual deep blue solution formed.

5-Methylundecan-5-ol (179)[32]



(179)

HMPA (1ml, 22.8mmol, CAUTION: HIGHLY TOXIC) was added to a solution of SmI_2 (20ml, 0.1M in THF) at room temperature and the solution immediately turned deep purple. A solution of 2-octanone (0.07ml, 0.50mmol) in THF (2.5ml) was added, followed by a solution of bromobutane (0.15ml, 2.0mmol) in THF (2.5ml). After stirring for 1 minute a yellow precipitate formed and the reaction was quenched by the addition of HCl (0.1 M). The mixture was extracted (ether), washed (sodium thiosulfate) and the combined organics dried ($MgSO_4$), then concentrated *in vacuo*. Flash column chromatography (neat petrol) afforded the tertiary alcohol (179) as a

colourless oil (87mg, 94%): ν_{max} ($CHCl_3$ solution) 3602-3118 (O-H)s, 2962s, 2930s, 1468s, 1382m, 1150m cm^{-1}; δ_H (300MHz, $CDCl_3$) 1.40 (4H, m, $C\underline{H}_2COH$), 1.28 (13H, m, $C\underline{H}_2$, OH), 1.14 (3H, s, $C\underline{H}_3C$), 0.90 (6H, m, $C\underline{H}_3CH_2$); δ_C (75MHz, $CDCl_3$) 72.7 ($\underline{C}OH$), 41.8 ($\underline{C}H_2$), 41.5 ($\underline{C}H_2COH$), 31.8 ($\underline{C}H_3COH$), 29.9 ($\underline{C}H_2$), 26.9 ($\underline{C}H_2$), 26.1 ($\underline{C}H_2$), 23.8 ($\underline{C}H_2$), 23.3 ($\underline{C}H_2$), 22.6 ($\underline{C}H_2$), 14.11 ($\underline{C}H_3CH_2$), 14.09 ($\underline{C}H_3CH_2$); *m/z* (CI, NH_3) 187 (MH^+, 13%), 186 (M^+, 100%), 180 (55), 168 (18).

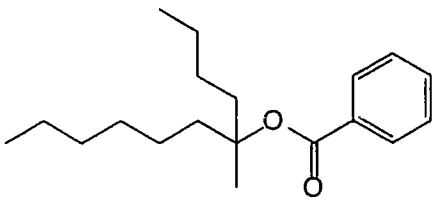
(*R/S*)-5-Methylundecan-5-ol, (*R/S*)-(179)

A) Using bis-amide ligand (*R,R*)-(169): Samarium powder (0.60g, 3.99mmol) was dried under vacuum (CAUTION) and then THF (20ml) was added. The slurry was cooled (0°C) and diiodomethane (0.18ml) added. After stirring for 1-2 hours at room temperature the usual deep blue solution formed. This solution was added to the bis-amide ligand (*R,R*)-(169) (0.51g, 2.0mmol) at room temperature. A solution of 2-octanone (0.07ml, 0.50mmol) in THF (2.5ml) was added to the mixture, followed by a solution of bromobutane (0.21ml, 3.0mmol) in THF (2.5ml). After stirring for 7 hours at room temperature, the reaction was quenched by the addition of 0.1M HCl. The mixture was extracted (ether), washed (sodium thiosulfate) and the combined organics dried ($MgSO_4$), then concentrated *in vacuo*. Flash column chromatography (neat petrol) afforded the tertiary alcohol (*R/S*)-(179) as a colourless oil (40mg, 45%): IR, ^1H, ^{13}C and MS data were identical to those of the HMPA-catalysed reaction; $[\alpha]_D^{20}$=-10° (c=4, $CHCl_3$).

B) Inverse addition: Samarium powder (0.60g, 3.99mmol) was dried under vacuum (CAUTION) and then THF (20ml) was added. The slurry was cooled to 0°C and diiodomethane (0.18ml) added. After stirring for 1-2 hours at room temperature the usual deep blue solution formed. This solution was added to the bis-amide ligand (*R,R*)-(169) (0.50g, 2.0mmol) at room temperature. A solution of 2-hexanone

(0.12ml, 1.0mmol) in THF (2.5ml) was added to the mixture, followed by a solution of bromobutane (0.56ml, 4.0mmol) in THF (2.5ml). After stirring overnight the reaction was quenched by the addition of 0.1M HCl. The mixture was extracted (ether), washed (sodium thiosulfate) and the combined organics dried ($MgSO_4$), then concentrated *in vacuo*. Flash column chromatography (neat petrol) afforded the tertiary alcohol (*R/S*)-(179) as a colourless oil (24mg, 14%): $[\alpha]_D^{20}$=+10° (c=4, $CHCl_3$); ^1H, and ^{13}C data were identical to those of the HMPA-catalysed reaction.

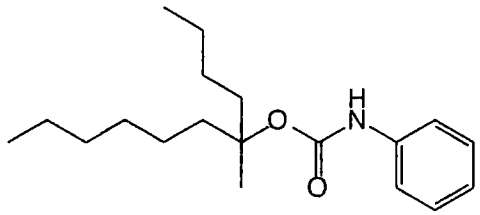
(*R/S*)-5-Benzoyloxy-5-methyl-undecane (*R/S*)-(181)



(*R/S*)-(181)

Benzoyl chloride (0.20ml, 0.59mmol) was added to a solution of the (*R/S*)-alcohol (179) (0.11g, 0.90mmol) in pyridine (6ml) at 0°C. The solution was allowed to warm to room temperature overnight, then heated at 77°C for 2 hours. The reaction was quenched (water), extracted (ether) and concentrated *in vacuo*. Flash column chromatography (10:1 petrol:ethyl acetate) afforded the ester (*R/S*)-(181) as a colourless oil (80mg, 47%): ν_{max} ($CHCl_3$ solution) 3070m, 2960s, 2934s, 1791 (C=O)s, 1456s, 1285s, 1122s, 1037m cm^{-1}; δ_H (200MHz, $CDCl_3$) 7.5 (5H, m, Ar), 1.95 (2H, m, CH_2C-O), 1.85 (2H, m, CH_2C-O), 1.54 (3H, s, CH_3C-O), 1.34 (12H, m, CH_2), 0.88 (6H, m, CH_3CH_2); δ_C (50MHz, $CDCl_3$) 165.5 (C=O), 132.3 (Ar), 132.0 (Ar), 130.5 (Ar), 129.3 (Ar), 128.8 (Ar), 128.1 (Ar), 85.7 (CH_2C-O), 38.5 (CH_2), 38.2 (CH_2), 31.7 (CH_3C-O), 29.6 (CH_2), 25.9 (CH_2), 23.9 (CH_2), 23.6 (CH_2), 23.0 (CH_2), 22.6 (CH_2), 14.08 (CH_3), 14.06 (CH_3); *m/z* (EI) 290 (M^+, 0.3%), 198 (5), 168 (34), 122 (66), 105 (100).

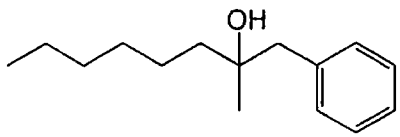
Octan-2-butyl-N-phenylundecylcarbamate (182)



(182)

n-BuLi (0.60ml, 1.6M in hexanes, 0.96mmol) was added to a solution of the (±)-alcohol (179) (0.10g, 0.53mmol) at 0°C. After 30 minutes a solution of phenyl isocyanate (0.07ml, 0.64mmol) in ether (2.5ml) was added and the mixture stirred at room temperature for 4 hours. The reaction was quenched (NH_4Cl), extracted (ethyl acetate), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography (10:1 petrol:ethyl acetate) gave the carbamate (182) as a colourless oil (55mg, 34%): ν_{max} ($CHCl_3$ solution) 3352 (N-H)s, 2944s, 2836s, 1728 (C=O)m, 1556m, 1452m, 1036s, cm^{-1}; δ_H (300MHz, $CDCl_3$) 11.05 (1H, br s, NHPh), 7.60-7.20 (5H, m, Ar), 1.80 (2H, m, CH_2COH), 1.57 (3H, s, CH_3CO), 1.37 (12H, m, CH_2), 1.20 (2H, m, CH_2), 1.06 (6H, m, CH_3CH_2); δ_C (75MHz, $CDCl_3$) 154.6 (C=O), 137.9 (Ar), 128.8 (Ar), 128.5 (Ar), 123.6 (Ar), 88.7 (CH_3CO), 38.3 (CH_2COH), 38.1 (CH_2COH), 31.6 (CH_3COH), 29.4 (CH_2), 25.5 (CH_2), 23.5 (CH_2), 23.3 (CH_2), 22.8 (CH_2), 22.5 (CH_2), 14.0 (CH_3CH_2), 13.9 (CH_3CH_2); *m/z* (EI) 305 (M^+, 0.4%), 212 (38), 168 (30), 93 (100), 56 (80), 41 (63), 55 (79), 70 (45).

1-Phenyl-2-methyloctan-2-ol (186)



(186)

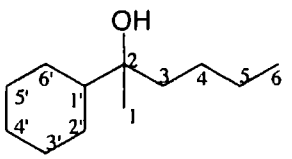
HMPA (1.4ml, 8mmol, CAUTION: HIGHLY TOXIC) was added to a solution of SmI_2 (20ml, 0.1M in THF) at room temperature and the solution immediately turned deep purple. A solution of 2-octanone (0.07ml, 0.50mmol) in THF (2.5ml) was added, followed by a solution of benzyl bromide (0.23ml, 2.0mmol) in THF (2.5ml). After stirring for 5 minutes, a yellow precipitate formed and the reaction was quenched by the addition of 0.1M HCl. The mixture was extracted (ether), washed (sodium thiosulfate) and the combined organics dried ($MgSO_4$), then concentrated *in vacuo*. Flash column chromatography (neat petrol) afforded the alcohol (186) as a colourless oil (80mg, 82%): ν_{max} ($CHCl_3$ solution) 3548-3184 (O-H)m, 3020s, 2966s, 2868s, 1228s, 1082m cm^{-1}; δ_H (300MHz, $CDCl_3$) 7.30-7.25 (5H, m, Ar), 2.78 (2H, AB system, J_{AB}=14.4Hz, $C\underline{H}_2Ph$), 1.46 (4H, m, $C\underline{H}_2COH$), 1.40-1.32 (7H, m, OH, $C\underline{H}_2$), 1.16 (3H, s, $C\underline{H}_3COH$), 0.92 (3H, t, J=7.9Hz, $C\underline{H}_3CH_2$); δ_C (50MHz, $CDCl_3$) 138.0 (Ar), 130.4 (Ar), 128.0 (Ar), 126.3 (Ar), 72.5 ($CH_3\underline{C}OH$), 47.9 (CH_2Ph), 41.8 (CH_2), 31.8 ($\underline{C}H_3CHO$), 29.8 (CH_2), 26.4 (CH_2), 23.9 (CH_2), 22.6 (CH_2), 14.0 ($\underline{C}H_3CH_2$); *m/z* (EI) 220 (M^+, 4%), 135 (38), 129 (82), 92 (100), 69 (57), 43 (65).

Attempted Synthesis of (*R/S*)- 1-Phenyl-2-methyl-2-octanol, (*R/S*)-(186)

Samarium powder (0.60g, 3.99mmol) was dried under vacuum (CAUTION) and then THF (20ml) was added. The slurry was cooled to 0°C and diiodomethane (0.18ml) added. After stirring for 1-2 hours at room temperature the usual deep blue solution formed. This solution was added to the bis-amide ligand (*R,R*)-(169) (0.51g,

2.0mmol) at room temperature. A solution of 2-octanone (0.07ml, 1.0mmol) in THF (2.5ml) was added to the mixture, followed by a solution of benzyl bromide (0.70ml, 6.0mmol) in THF (2.5ml). After stirring for 6 hours, a yellow precipitate formed and the reaction was quenched by the addition of 0.1M HCl. The mixture was extracted (ether), washed (sodium thiosulfate) and the combined organics dried ($MgSO_4$), then concentrated *in vacuo*. Flash column chromatography (neat petrol) afforded the tertiary alcohol (*R/S*)-(186) as a colourless oil (56mg, 57%): IR, ^1H, ^{13}C and MS data were identical to those of the HMPA-catalysed reaction; $[\alpha]_D$ data inconclusive (see Section 3.5.3).

Attempted Synthesis of (*R/S*)- 2-cyclohexyl-hexan-2-ol, (*R/S*)-(187)[123]

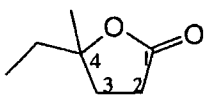


(*R/S*)-(187)

Samarium powder (0.60g, 3.99mmol) was dried under vacuum (CAUTION) and then THF (20ml) was added. The slurry was cooled (0°C) and diiodomethane (0.18ml) added. After stirring for 1-2 hours at room temperature the usual deep blue solution formed. This solution was added to the bis-amide ligand (*R,R*)-(169) (0.51g, 2.0mmol) at room temperature. A solution of cyclohexylmethyl ketone (0.13ml, 1.0mmol) in THF (2.5ml) was added to the mixture, followed by a solution of bromobutane (0.64ml, 6.0mmol) in THF (2.5ml). After stirring for 48 hours a yellow precipitate formed and the reaction was quenched by the addition of 0.1M HCl. The mixture was extracted (ether), washed (sodium thiosulfate) and the combined organics dried ($MgSO_4$), then concentrated *in vacuo*. Flash column chromatography (neat petrol) afforded the tertiary alcohol, (*R/S*)-(187) as a colourless oil (11mg, 5%): $[\alpha]_D$ data inconclusive (see Section 3.5.3); ν_{max} ($CHCl_3$ solution) 3620-3110 (O-H)s, 2934m, 2916w, 1214s cm^{-1}; δ_H (300MHz, $CDCl_3$) 1.85-1.60 (4H, m, 3-H, 1'-H,

OH), 1.55 (3H, s, CH_3COH), 1.40 (2H, m, 4-H), 1.30-1.10 (8H, m, 2'-H, 3'-H), 1.09-1.00 (4H, m, 4'-H, CH_3CH_2), 0.90 (3H, t, J=6Hz, CH_3CH_2); δ_C (100MHz, $CDCl_3$) 74.4 (COH), 47.1 (CH_3COH), 39.6 (3-C), 27.5 (1'-C), 26.8 (2'-C), 26.7 (3'-C), 25.4 (4'-C), 24.0 (4-C), 23.3 (5-C), 14.15 (CH_3CH_2); *m/z* (EI) 184 (M^+, 0.4%), 140 (23), 72 (20), 57 (70), 44 (100).

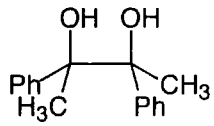
Attempted Synthesis of (*R/S*)- 4-hydroxy-4-methyl-hexanoic acid lactone, (*R/S*)-(188)[124]



(*R/S*)-(188)

Samarium powder (0.60g, 3.99mmol) was dried under vacuum (CAUTION) and then THF (20ml) was added. The slurry was cooled to 0°C and diiodomethane (0.18ml) added. After stirring for 1-2 hours at room temperature the usual deep blue solution formed. This solution was added to the bis-amide ligand (*R,R*)-(169) (0.51g, 2.0mmol) at room temperature. A solution of 2-butanone (0.08ml, 1.0mmol) in THF (2.5ml) was added to the mixture, followed by a solution of 3-bromopropionate (0.25ml, 2.0mmol) in THF (2.5ml). After stirring for 2 hours a yellow precipitate formed and the reaction was quenched by the addition of 0.1M HCl. The mixture was extracted (ether), washed (sodium thiosulfate) and the combined organics dried ($MgSO_4$), then concentrated *in vacuo*. Flash column chromatography (15:1 petrol:ethyl acetate) afforded the title lactone (*R/S*)-(188) as a colourless oil (55mg, 76%): ν_{max} (thin film) 3026s, 2982s, 1766 (C=O)s, 1464m, 1386m, 1234m cm^{-1}; δ_H (300MHz, $CDCl_3$) 2.57 (2H, m, 2-H), 2.04 (2H, m, 3-H), 1.67 (2H, m, CH_3CH_2), 1.35 (3H, s, CH_3CO), 0.94 (3H, t, J=7.5Hz, CH_3CH_2); δ_C (75MHz, $CDCl_3$) 176.8 (C=O), 87.1 (4-C), 33.5 (2-C), 32.3 (3-C), 29.1 (5-C), 25.0 (CH_3CO), 8.12 (6-C); *m/z* (EI) 129 (MH^+, 1%), 73 (16), 56 (16), 99 (100), 43 (43).

2,3-Diphenylbutane-2,3-diol (189)



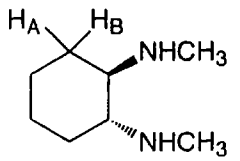
(189)

Samarium powder (0.60g, 3.99mmol) was dried under vacuum (CAUTION) and then THF (20ml) was added. The slurry was cooled (0°C) and diiodomethane (0.18ml) added. After stirring for 1-2 hours at room temperature the usual deep-blue solution formed. This solution was added to the bis-amide ligand (*R,R*)-(169) (0.51g, 2.0mmol) at room temperature. A solution of acetophenone (0.12ml, 1.0mmol) in THF (2.5ml) was added to the mixture, followed by a solution of bromobutane (0.64ml, 6.0mmol) in THF (2.5ml). After stirring for 1 hour a yellow precipitate formed and the reaction was quenched by the addition of 0.1M HCl. The mixture was extracted (ether), washed (sodium thiosulfate) and the combined organics dried ($MgSO_4$), then concentrated *in vacuo*. Flash column chromatography (neat petrol) afforded the pinacol (189) as a colourless oil (56mg, 46%), which was a mixture of diastereoisomers by NMR, (dl):(meso) ratio=2:1; $[\alpha]_D$=-7.4° (c=2.7, ethanol) {lit.[125] (S,S)-diastereoisomer $[\alpha]_D$=-34.4° (c=2.7 ethanol)}; ν_{max} ($CHCl_3$ solution) 3626-3106 (O-H)s, 2940w, 1450s, 1064s cm^{-1}; *m/z* (EI) 242 (M^+, 0.1%), 121 (100), 105 (28), 77 (40), 51 (22).

(dl): δ_H (300MHz, $CDCl_3$) 7.24 (10H, m, Ar), 2.64 (2H, br s, OH), 1.50 (6H, s, CH_3); δ_C (75MHz, $CDCl_3$) 143.6 (Ar), 127.3 (Ar), 127.0 (Ar), 126.9 (Ar), 78.8 (COH), 24.8 (CH_3).

(meso): δ_H (300MHz, $CDCl_3$) 7.24 (10H, m, Ar), 2.35 (2H, br s, OH), 1.59 (6H, s, CH_3); δ_C (75MHz, $CDCl_3$) 143.5 (Ar), 127.2 (Ar), 126.87 (Ar), 126.83 (Ar), 78.4 (COH), 25.2 (CH_3).

N,N'-Dimethylcyclohexane-1,2-diamine (193)[128]



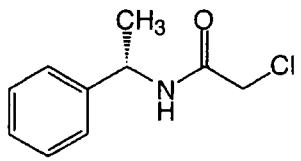
(193)

Ethyl chloroformate (35.0g, 0.32mol) and a solution of NaOH (14.4g, 0.36mol) in water (15ml) were added simultaneously (two pressure-equalising dropping funnels) to a solution of (±)-*trans*-cyclohexanediamine (148) (17.0g, 0.15mol) in toluene (225ml). The rate of addition was maintained to keep the reaction temperature at 0-10°C.

After the addition, the mixture was stirred at room temperature for 3 hours. The precipitate was filtered, rinsed (dichloromethane) and the filtrate was dried ($MgSO_4$) then concentrated *in vacuo* to afford the crude formamide, which was sufficiently pure to be used without further purification.

A solution of the carbamate (13.16g, 51.41mmol) in THF (100ml) was added to a slurry of $LiAlH_4$ (8.0g, 0.20mol) in THF (230ml) at 0°C. The solution was warmed to room temperature, then heated at reflux for 36 hours. After cooling (0°C), ethylenediamine (20ml) was added, then 15% NaOH (10ml), and finally water (20ml). The filtrate was concentrated and the resulting residue was extracted (ethyl acetate). The combined organics were dried ($MgSO_4$) and concentrated *in vacuo*. Distillation (65-68°C, 9mbar; lit.[128] 78-80°C, 18mm) afforded the diamine (193) as a pale yellow oil (5.19g, 72%): ν_{max} (thin film) 3298 (N-H)s, 2927s, 2852s, 2788s, 1473s, 1145s, 1104s, 1082s cm^{-1}; δ_H (200MHz, $CDCl_3$) 2.18 (6H, br s, $NHCH_3$), 1.85 (4H, m, 1-H, H_A), 1.50 (2H, m, H_B), 1.25 (2H, br s, $NHCH_3$), 1.10-0.80 (4H, m, 4-H); δ_C (50MHz, $CDCl_3$) 62.9 (1-C), 33.3 (3-C), 30.5 (4-C), 24.7 ($NHCH_3$); *m/z* (GC-MS, EI) 142 (M^+, 15%), 112 (31), 70 (100), 57 (79), 44 (55), 42 (48), 28 (24).

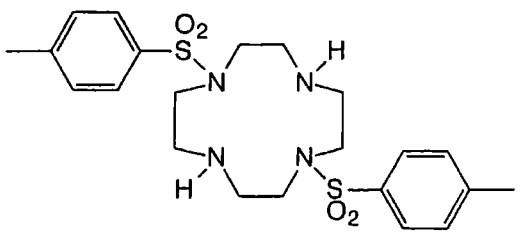
(*R*)-N-2-chloroethanoyl-2-phenylethylamine (198)[143]



(198)

A solution of chloroacetyl chloride (7.25ml, 112.94 mmol) in acetone (25ml) was added to a solution of (*R*)-(+)-α-methylbenzylamine (10.81g, 89.2mmol) and Na_2CO_3 (13.5g, 0.127mol) in water:acetone (1:1, 100ml) at 0°C. After 1.5 hours, the solvent was removed and the residue acidified with 6M HCl, then extracted (ethyl acetate). The organics were washed (brine) and concentrated *in vacuo*. Recrystallisation (ethyl acetate/ether) afforded the title amide (198) as white needles (13.04g, 74%): mp.94.2-95.4°C (lit.[143] 94°C); ν_{max} (thin film) 3261 (N-H)s, 2977w, 1648 (C=O)s, 1549s, 1233s, 1107m cm^{-1}; δ_H (200MHz, $CDCl_3$) 7.32 (5H, m, Ar), 6.85 (1H, br s, NH), 5.14 (1H, quintet, J=7.7Hz, CH_3CHAr), 4.08 (2H, s, CH_2Cl), 1.54 (3H, d, J=8Hz, CH_3CHAr); δ_C (50MHz, $CDCl_3$) 165.3 (C=O), 142.1 (Ar), 128.8 (Ar), 127.7 (Ar), 126.1 (Ar), 49.3 (CH_2Cl), 42.5 (CH_3CHAr), 21.6 (CH_3CHAr); *m/z* (EI) 197 (M^+, 12%), 162 (100), 120 (42).

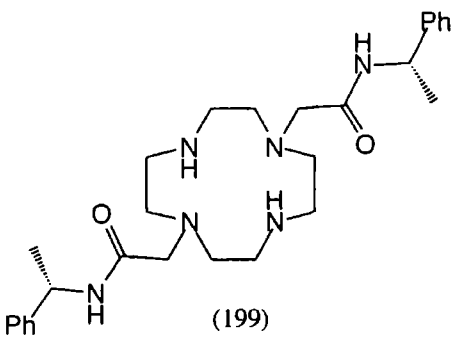
1,7-*p*-Toluenesulfonyl-1,4,7,10-tetraazacyclododecane (197)[144]



(197)

A solution of *p*-TsCl (2.68g, 14.08mmol) in pyridine (13.5ml) was added to a solution of 1,4,7,10-tetraazacyclododecane (1.21g, 7.04mmol) in pyridine (13.5ml) at 0°C. The solution was stirred at room temperature for 4 hours then the pyridine was removed *in vacuo* and the residue taken up in water, then the reaction stirred for a further 3 hours. The precipitate was filtered, washed successively with water, aqueous sodium carbonate and water. The title compound was isolated as a yellow powder (2.26g, 70%): mp.233.5-233.9°C (lit.[144] 232-234°C); ν_{max} (thin film) 3444 (N-H)s, 2974s, 2870s, 1600s, 1500s, 1449s, 1342s, 1158s, 1095s cm^{-1}; δ_H (200MHz, $CDCl_3$) 7.69 (4H, d, J=8.4Hz, Ar), 7.36 (4H, d, J=8.0Hz, Ar), 3.39 (8H, m, $C\underline{H}_2N$), 3.15 (8H, t, J=4.8Hz, $C\underline{H}_2N$), 2.44 (6H, s, $C\underline{H}_3Ar$); δ_C (50MHz, $CDCl_3$) 144.3 (Ar), 133.8 (Ar), 130.0 (Ar), 127.2 (Ar), 49.0 ($\underline{C}H_2N$), 48.8 ($\underline{C}H_2N$), 21.4 ($\underline{C}H_3Ar$); *m/z* (ESMS) 481 (MH^+, 100%).

Attempted Synthesis of 4,10-[(*R*)-N-2-ethanoyl-2-phenylethylamine]-1,4,7,10-tetraazacyclododecane (199)



(199)

A solution of cyclododecane (197) (0.25g, 0.52mmol) and K_2CO_3 (0.15g, 1.1mmol) in DMF (5ml) was stirred at room temperature for 0.5 hours. KI (0.19g, 1.19mmol) and (*R*)-N-2-chloroethanoyl-2-phenylethylamine (198) (0.22g, 1.14mmol) were then added and the mixture was heated to 60°C for 96 hours. After cooling, the residue was washed with de-ionised water, extracted (dichloromethane) and concentrated *in vacuo*. A solution of the crude product (0.17g, 0.21mmol) in THF (3.5ml) and ethanol (0.2ml) was cooled to -78°C, the vessel was charged with ammonia (50ml) and sodium (0.6g,

26.1 mmol) was added. The resulting blue solution was stirred for 2 hours, then quenched by the addition of ethanol and the reaction was allowed to warm to room temperature overnight. Water was added, the aqueous phase extracted (dichloromethane), then concentrated *in vacuo* to afford the crude product (as judged by NMR data).

SECTION D

APPENDIX

Appendix

The Board of Studies in Chemistry

Colloquia, Lectures and Seminars from Invited Speakers 1995-1998

1995

October 11 Prof. P. Lugar, Frei Univ. Berlin, FRG‡
Low Temperature Crystallography

October 13 Prof. R. Schmutzler, Univ. Braunschweig, FRG‡
Calixarene-Phosphorus Chemistry: A New Dimension in Phosphorus Chemistry

October 18¤ Prof. A. Alexakis, Univ. Pierre et Marie Curie, Paris‡
Synthetic and Analytical Uses of Chiral Diamines

October 25 Dr.D.Martin Davies, University of Northumbria‡
Chemical reactions in organised systems

November 1¤ Prof. W. Motherwell, UCL London‡
New Reactions for Organic Synthesis

November 3 Dr B. Langlois, University Claude Bernard-Lyon
Radical Anionic and Psuedo Cationic Trifluoromethylation

November 8¤ Dr. D. Craig, Imperial College, London‡
New Stategies for the Assembly of Heterocyclic Systems

November 15 Dr Andrea Sella, UCL, London‡
Chemistry of Lanthanides with Polypyrazoylborate Ligands

November 17 Prof. David Bergbreiter, Texas A&M, USA‡
Design of Smart Catalysts, Substrates and Surfaces from Simple Polymers

November 22 Prof. I Soutar, Lancaster University‡
A Water of Glass? Luminescence Studies of Water-Soluble Polymers

November 29 Prof. Dennis Tuck, University of Windsor, Ontario, Canada‡
New Indium Coordination Chemistry

December 8 Professor M.T. Reetz, Max Planck Institute, Mulheim
Perkin Regional Meeting

1996

January 10¤ Dr Bill Henderson, Waikato University, NZ‡
Electrospray Mass Spectrometry–a new sporting technique

January 17 Prof. J. W. Emsley, Southampton University‡
Liquid Crystals: More than Meets the Eye

January 24¤ Dr Alan Armstrong, Nottingham Univesity‡
Alkene Oxidation and Natural Product Synthesis

January 31 Dr J. Penfold, Rutherford Appleton Laboratory
Soft Soap and Surfaces

February 7 Dr R. B. Moody, Exeter University‡
Nitrosations, Nitrations and Oxidations with Nitrous Acid

February 12 Dr Paul Pringle, University of Bristol
Catalytic Self-Replication of Phosphines on Platinum(O)

February 14¤ Dr J. Rohr, University of Gottingen, FRG‡
Goals and Aspects of Biosynthetic Studies on Low Molecular Weight Natural Products

February 21 Dr C R Pulham , University of Edinburgh‡
Heavy Metal Hydrides–an exploration of the chemistry of stannanes and plumbanes

February 28 Prof. E. W. Randall, Queen Mary & Westfield College‡
New Perspectives in NMR Imaging

March 6¤ Dr Richard Whitby, University of Southampton‡
New approaches to chiral catalysts: Induction of planar and metal centred asymmetry

March 7 Dr D.S. Wright, University of Cambridge
Synthetic Applications of Me_2N-p-Block Metal Reagents

March 12 RSC Endowed Lecture–Prof. V. Balzani, University of Bologna‡
Supramolecular Photochemistry

March 13 Prof. Dave Garner, Manchester University‡
Mushrooming in Chemistry

April 30 Dr L.D.Pettit, Chairman, IUPAC Commission of Equilibrium Data
pH-metric studies using very small quantities of uncertain purity

October 9 Professor G. Bowmaker, University of Aukland, NZ‡
Coordination and Materials Chemistry of the Group 11 and Group 12 Metals: Some Recent Vibrational and Solid State NMR Studies

October 14° Professor A. R. Katritzky, University of Gainesville, Florida, USA
Recent Advances in Benzotriazole Mediated Synthetic Methodology

October 16° Professor Ojima, State University of New York at Stony Brook‡
Silylformylation and Silylcarbocyclisations in Organic Synthesis

October 22° Professor Lutz Gade, University of Wurzburg, Germany‡
Organic transformations with Early-Late Heterobimetallics: Synergism and Selectivity

October 22 Professor B. J. Tighe, Department of Molecular Sciences and Chemistry, University of Aston‡
Making Polymers for Biomedical Application–can we meet nature's challenge?

October 23° Professor H. Ringsdorf (Perkin Centenary Lecture), Johannes Gutenberg-Universitat, Mainz, Germany‡
Function Based on Organisation

October 29 Professor D. M. Knight, Department of Philosophy, University of Durham.
The Purpose of Experiment–A Look at Davy and Faraday

October 30 Dr Phillip Mountford, Nottingham University‡
Recent Developments in Group IV Imido Chemistry

November 6 Dr Melinda Duer, Chemistry Department, University of Cambridge‡
Solid-state NMR Studies of Organic Solid to Liquid-crystalline Phase Transitions

November 12 Professor R. J. Young, Manchester Materials Centre, UMIST

New Materials - Fact or Fantasy?

November 13[¤] Dr G. Resnati, Milan[‡]
Perfluorinated Oxaziridines: Mild Yet Powerful Oxidising Agents

November 18[¤] Professor G. A. Olah, University of Southern California, USA[‡]
Crossing Conventional Lines in my Chemistry of the Elements

November 19 Professor R. E. Grigg, University of Leeds
Assembly of Complex Molecules by Palladium-Catalysed Queueing Processes

November 20 Professor J. Earnshaw, Deptartment of Physics, Belfast University[‡]
Surface Light Scattering: Ripples and Relaxation

November 27 Dr Richard Templer, Imperial College, London[‡]
Molecular Tubes and Sponges

December 3 Professor D. Phillips, Imperial College, London
A Little Light Relief

December 4 Professor K. Muller-Dethlefs, York University[‡]
Chemical Applications of Very High Resolution ZEKE Photoelectron Spectroscopy

December 11[¤] Dr Chris Richards, Cardiff University[‡]
Sterochemical Games with Metallocenes

1997

January 15[¤] Dr V. K. Aggarwal, University of Sheffield[‡]
Sulfur Mediated Asymmetric Synthesis

January 16[¤] Dr Sally Brooker, University of Otago, NZ[‡]
Macrocycles: Exciting yet Controlled Thiolate Coordination Chemistry

January 21 Mr D. Rudge, Zeneca Pharmaceuticals
High Speed Automation of Chemical Reactions

January 22 Dr Neil Cooley, BP Chemicals, Sunbury[‡]
Synthesis and Properties of Alternating Polyketones

January 29 Dr Julian Clarke, UMIST‡
What can we learn about polymers and biopolymers from computer-generated nanosecond movie-clips?

February 4 Dr A. J. Banister, University of Durham
From Runways to Non-metallic Metals–A New Chemistry Based on Sulphur

February 5 Dr A. Haynes, University of Sheffield‡
Mechanism in Homogeneous Catalytic Carbonylation

February 12¤ Dr Geert-Jan Boons, University of Birmingham‡
New Developments in Carbohydrate Chemistry

February 18 Professor Sir James Black, Foundation/King's College London
My Dialogues with Medicinal Chemists

February 19 Professor Brian Hayden, University of Southampton‡
The Dynamics of Dissociation at Surfaces and Fuel Cell Catalysts

February 25 Professor A. G. Sykes, University of Newcastle
The Synthesis, Structures and Properties of Blue Copper Proteins

February 26 Dr Tony Ryan, UMIST‡
Making Hairpins from Rings and Chains

March 4¤ Professor C. W. Rees, Imperial College
Some Very Heterocyclic Chemistry

March 5¤ Dr J. Staunton FRS, Cambridge University‡
Tinkering with biosynthesis: towards a new generation of antibiotics

March 11 Dr A. D. Taylor, ISIS Facility, Rutherford Appleton Laboratory
Expanding the Frontiers of Neutron Scattering

March 19 Dr Katharine Reid, University of Nottingham‡
Probing Dynamical Processes with Photoelectrons

April 22¤ Dr G. B. Hammond.
Synthon approach to the selective formation of organic compounds using propargyl and vinyl phosphonates

October 8 Prof. E. Atkins, Department of Physics, University of Bristol
Advances in the control of architecture for polyamides: from nylons to genetically engineered silks to monodisperse oligoamides

October 15 Dr. R. Mark Ormerod, Department of Chemistry, Keele University‡
Studying catalysts in action

October 21 Prof. A. F. Johnson, IRC, University of Leeds
Reactive processing of polymers: science and technology

October 22ª Prof. R.J. Puddephatt (RSC Endowed Lecture), University of Western Ontario‡
Organoplatinum chemistry and catalysis

October 23ª Prof. M.R. Bryce, University of Durham, Inaugural Lecture‡
New Tetrathiafulvalene Derivatives in Molecular, Supramolecular and Macromolecular Chemistry: controlling the electronic properties of organic solids

October 28 Prof. A P de Silva, The Queen's University, Belfast
Luminescent signalling systems

October 29 Prof. Bob Peacock, University of Glasgow‡
Probing chirality with circular dichroism

November 5 Dr Mimi Hii, Oxford University‡
Studies of the Heck reaction

November 11ª Prof. V Gibson, Imperial College, London
Metallocene polymerisation

November 12 Dr Jeremy Frey, Department of Chemistry, Southampton University‡
Spectroscopy of liquid interfaces: from bio-organic chemistry to atmospheric chemistry

November 19ª Dr Gareth Morris, Department of Chemistry, Manchester University ‡
Pulsed field gradient NMR techniques: Good news for the Lazy and DOSY

November 20 Dr Leone Spiccia, Monash University, Melbourne, Australia
Polynuclear metal complexes

November 25 Dr R. Withnall, University of Greenwich
Illuminated molecules and manuscripts

November 26 Prof. R.W. Richards, University of Durham, Inaugural Lecture‡
A random walk in polymer science

December 2 Dr C.J. Ludman, University of Durham
Explosions

December 3 Prof. A.P. Davis, Department. of Chemistry, Trinity College Dublin‡
Steroid-based frameworks for supramolecular chemistry

December 10 Sir Gordon Higginson, former Professor of Engineering in Durham and retired Vice-Chancellor of Southampton University
1981 and all that

December 10 Prof. Mike Page, Department of Chemistry, University of Huddersfield‡
The mechanism and inhibition of beta-lactamases.

1998

January 14 Prof. David Andrews, University of East Anglia‡
Energy transfer and optical harmonics in molecular systems

January 20 Prof. J. Brooke, University of Lancaster
What's in a formula? Some chemical controversies of the 19th century

January 27 Prof. Richard Jordan, Dept. of Chemistry, University of Iowa, USA‡
Cationic transition metal and main group metal alkyl complexes in olefin polymerisation

January 28 Dr Steve Rannard, Courtaulds Coatings (Coventry)
The synthesis of dendrimers using highly selective chemical reactions

February 3ª Dr J. Beacham, ICI Technology
The chemical industry in the 21st century

February 4 Prof. P. Fowler, Department of Chemistry, Exeter University‡
Classical and non-classical fullerenes

February 11 Prof. J. Murphy, Dept of Chemistry, Strathclyde University‡

February 17 Dr S. Topham, ICI Chemicals and Polymers
Perception of environmental risk: The River Tees, two different rivers

February 18 Prof. Gus Hancock, Oxford University‡
Surprises in the photochemistry of tropospheric ozone

February 24° Prof. R. Ramage, University of Edinburgh
The synthesis and folding of proteins

February 25 Dr C. Jones, Swansea University‡
Low coordination arsenic and antimony chemistry

March 4 Prof. T.C.B. McLeish, IRC of Polymer Science Technology, Leeds University‡
The polymer physics of pyjama bottoms (or the novel rheological characterisation of long branching in entangled macromolecules.)

March 11 Prof. M.J. Cook, Dept of Chemistry, UEA‡
How to make phthalocyanine films and what to do with them

March 17 Prof. V. Rotello, University of Massachusetts, Amherst
The interplay of recognition & redox processes–from flavoenzymes to devices

March 18 Dr John Evans, Oxford University‡
Materials which contract on heating (from shrinking ceramics to bullet proof vests

(‡ Invited specially for the graduate training programme)

(° Those attended by the author)

First Year Induction Course

This course consists of a series of one hour lectures on the services available in the department.

Departmental Organisation –	Dr. E.J.F. Ross
Safety Matters –	Dr. G.M. Brooke

Electrical Appliances –	Mr. B.T. Barker
Chromatography and Microanalysis –	Mr. L.Lauchlin
Library Facilities –	Mrs. M. Hird
Mass Spectroscopy –	Dr. M. Jones
Nuclear Magnetic Resonance Spectroscopy –	Dr. R.S. Matthews and Dr A. Kenwright
Glass-blowing Techniques –	Mr. R. Hart and Mr. G. Haswell

Seminars, Colloquia and Presentations

October	1995	Perkin Annual Meeting, University of Durham
December	1995	Postgraduate Symposium, Sunderland
December	1995	Modern Aspects of Stereochemistry, Sheffield University
July	1996	Transition Metals in Organic Synthesis, Imperial College, London
December	1996	Postgraduate Symposium, Sunderland
December	1996	Modern Aspects of Stereochemistry, Sheffield University
July	1997	Modern aspects of organic synthesis, St. Catherine's College, Oxford†
August	1997	RSC Autumn Meeting, University of Aberdeen¥
September	1997	9th RSC-SCI Medicinal Chemistry Symposium, Churchill College, Cambridge
December	1997	Modern Aspects of Stereochemistry, Sheffield University
March	1998	RSC-SCI Annual meeting, University of Edinburgh¥
June	1998	University of Durham Graduate Colloquia¥
July	1998	BOSS-7, Louvain-la-Neuve, Belgium†

(† poster presentation by the author)

(¥ oral presentation by the author)

SECTION E

REFERENCES

References

1. (a) D. A. Johnson, *Dalton Trans.* 1974, 1671; (b) L. R. Morss, *Chem. Rev.*, 1976, **76**, 827.
2. F. Albert Cotton and G. Wilkinson in *Advanced Inorganic Chemistry: A Comprehensive Text*, Wiley Interscience, 4th Edition, 1980, pp 981-1004.
3. R. G. Pearson, *J. Am. Chem. Soc.* 1963, **85**, 3533; Strictly, cyclopentadienyl ligands are soft bases but they exhibit constant effective ligand radii, so comply with the criteria for ionic bonding reported by K. N. Raymond and C. W. Eigenbroth, *Acc. Chem. Res.* 1980, **13**, 276.
4. V. P. Conticello, L. Brard, M. A. Giardello, Y. Tsuji, M. L. Sabat, C. L. Stern and T. J. Marks, *J. Am. Chem. Soc.* 1992, **114**, 2761.
5. P. Girard, J. -L. Namy, H. B. Kagan, *J. Am. Chem. Soc.* 1980, **102**, 2693.
6. G. A. Molander and J. B. Etter, *J. Am. Chem. Soc.* 1987, **109**, 6556.
7. G. A. Molander and J. B. Etter, *J. Org. Chem.* 1987, **52**, 3942.
8. J. -L. Namy, J. Souppe, H. B. Kagan, *Tetrahedron Lett.* 1983, 765.
9. M. Shibasaki, H. Sasai and T. Arai, *Angew. Chem. Int. Ed. Engl.* 1997, **36**, 1236.
10. S. Kobayashi, H. Ishitani, M. Araki and I. Hachiya, *Tetrahedron Lett.* 1994, **35**, 6325.
11. (a) G. A. Molander, *Chem. Rev.* 1992, **92**, 29; (b) T. Imamoto in *Lanthanides in Organic Synthesis*, Best Synthetic Methods Series, Academic Press, London 1994; (c) F. A. Kahn and R. Zimmer, *J. Prakt. Chem.* 1997, **339**, 101.
12. G. A. Molander, *Org. React.* 1994, **46**, 211.
13. J. Inanaga, M. Ishikawa and M. Yamaguchi, *Chem. Lett.* 1987, 1485.
14. (a) H. B. Kagan, J. -L. Namy and P. Girard, *Tetrahedron*, 1981, **37**, Supplement 1 No. 1, 175; (b) P. Girard, J. -L. Namy, H. B. Kagan, *J. Am. Chem. Soc.* 1980, **102**, 2693.

15. T. Imamoto in *Lanthanides in Organic Synthesis*, Best Synthetic Methods Series, Academic Press, London 1994, Ch.4.3.1.

16. J. -L. Namy, P. Girard and H. B. Kagan, *Nouv.J. Chim.* 1981, **5**, 479; (b) J. -L. Namy, J. Collin, C. Bied and H. B. Kagan, *Synlett*, 1992, 733; (c) A.-M. Krief and H.B. Kagan, *Acros Organics Acta* 1996, **2**, 17; (d) D. P. Curran, M. J. Totleben, *J. Am. Chem. Soc.* 1992, **114**, 6050; (e) P. Girard, J. -L. Namy, H. B. Kagan, *J. Am. Chem. Soc.* 1980, **102**, 2693..

17. H. M. Walborsky and M. Topolsky, *J. Org. Chem.* 1992, **57**, 370.

18. J. Inanaga, M. Ishikawa and M. Yamaguchi, *Chem. Lett.* 1987, 1485.

19. D. P. Curran, T. L. Fevig, C. P. Jasperse and M. Totleben, *Synlett* 1992, 942.

20. G. A. Molander in *Comprehensive Organic Chemistry, Addition to C-X π-bonds*, B. M. Trost and I. Fleming, Eds., Pergammon Press, Oxford, 1991, **1**, 251; (b) See also P. Girard, J. -L. Namy, H. B. Kagan, *J. Am. Chem. Soc.* 1980, **102**, 2693; *idem.*, *Tetrahedron*, 1981, **37**, Supplement 1 No. 1, 175.

21. (a) H. Kunzer, M. Stahnke, G. Sauer and R. Wiechert, *Tetrahedron Lett.* 1991, **32**, 1949; (b) J. Belloch, M. Virgili, A. Moyano, M. A. Pericas and A. Riera, *Tetrahedron Lett.* 1991, **32**, 4579.

22. See P. Girard, J. -L. Namy, H. B. Kagan, *J. Am. Chem. Soc.* 1980, **102**, 2693 and G. A. Molander, *Org. React.* 1994, **46**, 211 and references therein.

23. S. Fukuzawa, M. Iida, A. Nakanishi, T. Fujinami and S. Sakai, *Chem. Comm.* 1987, 920; See also H. B. Kagan, J. -L. Namy and P. Girard, *Tetrahedron*, 1981, **37**, Supplement 1 No. 1, 175.

24. A. K. Singh, R. K. Bakshi and E. J. Corey, *J. Am. Chem. Soc.* 1987, **109**, 6187

25. Y. Kamochi and T. Kudo, *Rev. Heteroatom Chem.* 1994, **11**, 165.

26. J. Inanaga, S. Sakai, Y. Handa, M. Yamaguchi and Y. Yokoyama, *Chem. Lett.* 1991, 2117; (b) A. Cabrera and H. Alper, *Tetrahedron Lett.* 1992, **33**, 5007; (c) R. Yanada, K. Bessho and K. Yanada, *Synlett*, 1995, 443.

27. (a) Diagrams adapted from G. A. Molander and G. Hahn, *J. Org. Chem.* 1986, **51**, 1135; (b) K. Kusuda, J. Inanaga and M. Yamaguchi, *Tetrahedron Lett.* 1989, **30**, 2945; (c) N. Akane, Y. Kanagawa, Y. Nishiyama, Y. Ishii, *Chem. Lett.* 1992, 2431; (d) H. B. Kagan and J. L. Namy,*Tetrahedron* 1986, **42**, 6573; (e) K. Otsubo, J. Inanaga and M. Yamaguchi,*Tetrahedron Lett.* 1987, **28**, 4437; (f) M. T. Reetz and E. H. Lauterbach,*Tetrahedron Lett.* 1991, **32**, 4477; (g) G. A. Molander, B. E. LaBelle and G. Hahn,*J. Org. Chem.* 1986, **51**, 5259.

28. (a) A. S. Kende and J. S. Mendoza,*Tetrahedron Lett.* 1991, **32**, 1699; (b) T. Kudo and Y. Kamochi, *Tetrahedron*, 1992, **48**, 4301.

29. C. Blomberg in *The Barbier Reaction and Related One-Step Processes*, Reactivity and Structure Concepts in Organic Chemistry Vol. 31, Eds. K. Hafner, C. W. Rees, B. M. Trost, J. -M. Lehn, P. vonRague Schleyer and R. Zahradnik, Springer-Verlag Press, 1993.

30. J. -L. Namy, J. Souppe, J. Collin and H. B. Kagan, *J. Org. Chem.* 1984, **49**, 2045.

31. M. Kunishima, K. Hioki, K. Kono, T. Sakumo and S. Tani, *Chem. Pharm. Bull.* 1994, **42**, 2190.

32. J. Inanaga, M. Ishikawa and M. Yamaguchi, *Chem. Lett.* 1987, 1487.

33. G. A. Molander, J. B. Etter and P. W. Zinke, *J. Am. Chem. Soc.* 1987, **109**, 453.

34. T. Tabuchi, K. Kawamura, J. Inanaga and M. Yamaguchi, *Tetrahedron Lett.* 1986, **27**, 3889.

35. T. Wirth, *Angew. Chem. Int. Ed. Engl.* 1996, **35**, 61 and references therein.

36. C. S. Swindell and W. Fan, *Tetrahedron Lett.* 1996, **37**, 2321.

37. T. Imamoto and S. Nishimura, *Chem. Lett.* 1990, 1141; (b) A. Lebrun, J. -L. Namy and H. B. Kagan, *Tetrahedron Lett.* 1993, **34**, 2311; See also J. -L. Namy, J. Souppe, H. B. Kagan, *Tetrahedron Lett.* 1983, **24**, 765.

38. J. -L. Chiara, W. Cabri and S. Hanessian, *Tetrahedron Lett.* 1991, **32**, 1125.

39. K. Otsubo, J. Inanaga and M. Yamaguchi, *Tetrahedron Lett.* 1986, **27**, 5763.

40. M. Kawatsura, K. Hosaka, F. Matsuda and H. Shirahama, *Synlett* 1995, 729.

41. E. J. Enholm, H. Satici and A. Trivellas, *J. Org. Chem.* 1989, **54**, 5841; See also S. Fukuzawa, M. Iida, A. Nakanishi, T. Fujinami and S. Sakai, *Chem. Comm.* 1987, 920.

42. H. Simmons, *Org. React.* 1973, **20**, 1.

43 For a leading reference see H. M. L. Davis in *Comprehensive Organic Synthesis*, Vol.4, Ed. M. F. Semmelhack, Series Eds. B. M. Trost and I. M. Fleming, Pergammon Press, Oxford, 1991, Ch. 4.8.

44. D. A. Evans, K. A. Woerpel, M. M. Hinman and M. M. Faul, *J. Am. Chem. Soc.* 1991, **113**, 726.

45. A. B. Charette and J.-F. Marcoux, *Synlett* 1995, 1197.

46. (a) G. A. Molander and L. S. Harring, *J. Org. Chem.* 1989, **54**, 3525; See also G. A. Molander and J. B. Etter, *J. Org. Chem.* 1987, **52**, 3942.

47. G. A. Molander and C. R. Harris, *Tetrahedron*, 1998, **54**, 3321.

48. (a) S. Takeuchi and Y. Ohgo, *Chem. Lett.* 1988, 403; (b) Y. Nakamura, S. Takeuchi, Y. Ohgo, M. Yamaoka, A. Yoshida and K. Mikami, *Tetrahedron Lett.* 1997, **38**, 2709.

49. K. Mikami and M. Yamaoka, *Tetrahedron Lett.* 1998, **39**, 4501.

50. E. J. Corey and G. Z. Zheng, *Tetrahedron Lett.* 1997, **38**, 2045.

51. E. Leonard, E. Dunach and J. Pericon, *Chem. Comm.* 1989, 276.

52. H. Hebri, E. Dunach and J. Pericon, *Tetrahedron Lett.* 1993, **34**, 1475.

53. T. Kondo, M. Akazone and Y. Watanabe, *Chem. Comm.*, 1991, 757.

54. M. C. Johnson, *Acc. Chem. Res.* 1978, **11**, 57.

55. (a) W. J. Evans, J. W. Grate, H. W. Choi, I. Bloom, W. E. Hunter and J. L. Atwood, *J. Am. Chem. Soc.* 1985, **107**, 941; (b) W. J. Evans, L. A. Hughes and T. P. Hanusa, *J. Am. Chem. Soc.* 1984, **106**, 4271.

56. J. -L. Namy, J. Collin, J. Zhang and H. B. Kagan, *J. Organometallic Chem.* 1987, **328**, 81.

57. W. J. Evans, D. K. Drummond, L. R. Chamberlain, R. J. Doedens, S. G. Bott, H. Zhang and J. L. Atwood, *J. Am. Chem. Soc.* 1988, **110**, 4983.

58. Diagrams taken from R. L. Halterman, *Chem. Rev.* 1992, **92**, 965.

59. (a) H. Schnutenhaus and H. H. Brintzinger, *Angew. Chem. Int. Ed. Engl.* 1979, **18**, 777; (b) F. R. W. P. Wild, L. Zsolnai, G. Huttner and H. H. Brintzinger, *J. Organometallic Chem.* 1982, **232**, 233.

60. R. Anwander and W. A. Hermann in *Topics in Current Chemistry* , Ch.1, Volume 179, 1996.

61. W. Kaminsky, K. Kulper, H. H. Brintzinger and F. R. W. P. Wild, *Angew. Chem. Int. Ed. Engl.*, 1985, **24**, 507.

62. H. H. Brintzinger, D. Fischer, R. Mulhaupt, B. Rieger and R. M. Waymouth *Angew. Chem. Int. Ed. Engl.* 1995, **34**, 1143.

63. S. J. Swamy, J. Loebel and H. Schumann, *J. Organometallic Chem.* 1989, **379**, 51.

64. P. Jutzi, J. Dahlhaus and M. O. Kristen, *J. Organometallic Chem.* 1993, **450**, C1.

65. D. Deng, C. Qian, F. Song, Z. Wang, G. Wu and P. Zheng, *J. Organometallic Chem.* 1993, **443**, 79.

66. M. A. Giardello, V. P. Conticello, L. Brard, M. Sabat, A. L. Rheingold, C. L. Stern and T. J. Marks, *J. Am. Chem. Soc.* 1994, **116**, 10212; See also V. P. Conticello, L. Brard, M. A. Giardello, Y. Tsuji, M. Sabat, C. L. Stern and T. J. Marks, *J. Am. Chem. Soc.* 1992, **114**, 2761.

67. G. A. Molander, H. Schumann, E. C. E. Rosenthal and J. Demtschuk, *Organometallics* 1996, **15**, 3817.

68. S. McLean and P. Haynes, *Tetrahedron* 1965, **21**, 2343; See also H. Schnutenhaus and H. H. Brintzinger, *Angew. Chem. Int. Ed. Engl.* 1979, **18**, 777

69. (a) K. Hafner, G. F. Thiele, C. Mink, *Angew. Chem. Int. Ed. Engl.* 1988, **27**, 1191; (b) T. Kauffmann, J. Ennen, H. Lhotak, A. Rensing, F. Steinseifer and A. Wattermann, *Angew. Chem. Int. Ed. Engl.* 1980, **19**, 328.

70. S. Collins, Y. Hong and N. J. Taylor, *Organometallics* 1990, **9**, 2695; M. S. Erickson, F. R. Fronczek and M. L. McLaughlin, *J. Organometallic Chem.* 1991, **415**, 75.

71. R. L. Haltermann, unpublished results, *Chem. Rev.* 1992, **92**, 965.

72. (a) H. Schwemlein, H. H. Brintzinger, *J. Organometallic Chem.* 1983, **254**, 69; (b) S. Gutman, P. Burger, H. -U. Hund, J. Hofmann and H. H. Brintzinger *J. Organometallic Chem.* 1989, **369**, 343.

73. H. Wiesenfelt, A. Reinmuth, E. Barsties, K. Evertz and H. H. Brintzinger, *J. Organometallic Chem.* 1989, **369**, 359; T. Mise, S. Miya and H. Yamazaki, *Chem. Lett.* 1989, 1853.

74. (a) E. Marechal, A. Lapert, *Bull. Soc. Chim. Fr.* 1967, 2954; (b) W. Spaleck, M. Antberg, V. Dolle, R. Klein, J. Rohrmann and A. Winter, *Nouv. J. Chem.* 1990, **14**, 499; See also H. Wiesenfelt, A. Reinmuth, E. Barsties, K. Evertz and H. H. Brintzinger, *J. Organometallic Chem.* 1989, **369**, 359.

75. A. L. Rheingold, N. P. Robinson, J. Whelan and B. Bosnich *Organometallics* 1992, **11**, 1869.

76. For a leading review see: K. L. Habermas, S. E. Denmark, T. K. Jones, *Org. Reacts.* 1994, **45**, 1 and references therein.

77. P. N. Devine and T. Oh, *J. Org. Chem.* 1992, **57**, 397.

78. Y. Ishino, I. Nishiguchi, M. Kim and T. Harashima, *Synthesis* 1982, 740.

79. A. Srikrishna, S. Nagaraju and P. Kondaiah, *Tetrahedron* 1995, **51**, 1809.

80. C. R. Strauss and R. B. Trainor, *Aust. J. Chem.* 1995, **48**, 1665.

81. M. T. Reading and S. L. Buchwald, *J. Org. Chem.* 1995, **60**, 7884.

82. T. W. Greene in *Protective Groups in Organic Synthesis*, Wiley, 1981.

83. R. K. Crossland and K. L. Servis, *J. Org. Chem.* 1970, **35**, 3195.

84. L. J. Theodore and W. L. Nelson, *J. Org. Chem.* 1987, **52**, 1309.

85. R. O. Hutchins, D. Kandasamy, C. A. Maryanoff, D. Masilamani, B. E. Maryanoff, *J. Org. Chem.* 1977, **42**, 82.

86. M. E. Jung, K. Shishido and L. H Davis, *J. Org. Chem.* 1982, **47**, 891.

87. S. L. Schreiber, R. E. Claus and J. Reagan, *Tetrahedron Lett.* 1982, **23**, 3867.

88. T. Yuki, M. Hashimoto, Y. Nishiyama and Y. Ishii, *J. Org. Chem.* 1993, **58**, 4497.

89. F. X. Kohl and P. Jutzi, *J. Organometallic Chem.* 1983, **243**, 119.

90. F. J. Weiberth and S. S. Hall, *J. Org. Chem.* 1987, **52**, 3901.

91. A. Nishinaga, K. Rindo and T. Matsuura, *Synthesis* 1986, 1038.

92. C. M. Garner and M. E. Price, *Tetrahedron Lett.* 1994, **35**, 2463 and references therein.

93. T. Langer, M. Illich and G. Helmchen, *Tetrahedron Lett.* 1995, **36**, 4409.

94. F. Sato, H. Ishikawa and M. Sato, *Tetrahedron Lett.* 1981, **22**, 85.

95. G. Cardillo, A. D'Amico, M. Orena and S. Sandri, *J. Org. Chem.* 1988, **53**, 2354.

96. T. Langer, M. Illich and G. Helmchen, *Synlett* 1996, 1137.

97. N. Kise, K. Tokioka, Y. Aoyama and Y. Matsumura, *J. Org. Chem.* 1995, **60**, 1100.

98. A. Correa, J. -N. Denis and A. A. Greene, *Syn. Comm.* 1991, **21**, 1.

99. (a) D. A. Evans, T. C. Britton, J. A. Ellman and R. L. Dorow, *J. Am. Chem. Soc.* 1990, **112**, 4011; (b) D. J. Ager, I. Prakash and D. R. Schaad, *Aldrichimica Acta* 1997, **30**, 3 and references therein.

100. Q. Yang and M. D. Jensen, *Synlett* 1996, 147.

101. R. C. Mehrotra, A. Singh and U. M. Tripathi, *Chem. Rev.* 1991, **91**, 1287.

102. (a) F. Machrouhi, B. Hamann, J. -L. Namy and H. B. Kagan, *Synlett* 1996, 633; (b) B. Hamann, J. -L. Namy and H. B. Kagan, *Tetrahedron* 1996, **52**,

14225; (c) W. Cabri, I. Candiani, M. Colombo, L. Franzoi and A. Bedeschi, *Tetrahedron Lett.* 1995, **36**, 949; (d) J. R. Fuchs, M. L. Mitchell, M. Shibangi and R. A. Flowers, *ibid.* 1997, **38**, 8157; (e) J. -L. Namy, M. Colomb and H. B. Kagan, *ibid.* 1994, **35**, 1723; (f) E. Hasegawa and D. P. Curran, *J. Org. Chem.* 1993, **58**, 5008.

103. M. Shabangi and R. A. Flowers, *Tetrahedron Lett.* 1997, **38**, 1137.

104. Z. Hou, Y. Zhang and Y. Wakatsuki, *Bull. Chem. Soc. Jpn.* 1997, **70**, 149.

105. (a) W. J. Evans, D. K. Drummond, H. Zhang and J. L. Atwood, *Inorg. Chem.* 1988, **27**, 575; (b) I. Mukerji, A. Wayada, G. Dabbagh and S. H. Bertz, *Angew. Chem. Int. Ed. Engl.* 1986, **25**, 760; (c) H. Sasai, S. Arai and M. Shibasaki, *J. Org. Chem.* 1994, **59**, 2661.

106. H. Berberich and P. W. Roesky, *Angew. Chem. Int. Ed. Engl.* 1998, **37**, 1569.

107. Figure modified from R. Anwander in *Topics in Current Chemistry* , Ch.4, Volume 179, 1996.

108. (a) Y. Makioka, I. Nakagawa, Y. Taniguchi, K. Takaki and Y. Fujiwara, *J. Org. Chem.* 1993, **58**, 4771; (b) A. Lebrun, J. -L. Namy and H. B. Kagan, *Tetrahedron Lett.* 1991, **32**, 2355.

109. (a) L. -W. Yang, S. Liu, E. Wong, S. J. Rettig and C. Orvig, *Inorg. Chem.* 1995, **34**, 2164; (b) S. Afshar and J. I. Bullock, *Inorg. Chem Acta.* 1980, **38**, 145; (c) *ibid.* P. Guerriero, U. Casellato, S. Tamburini, P. A. Vigato and R. Graziani, 1987, **129**, 127; (d) G. B. Deacon, T. Feng, P. MacKinnon, R. H. Newnham, S. Nickel, B. W. Skelton and A. H. White, *Aust. J. Chem.* 1993, **46**, 387; (e) G. Qi, Y. Lin and J. Hu, *Polyhedron* 1995, **14**, 413; (f) G.-Z. Qi, Q. Shen and Y. -H. Lin, *Acta Cryst. C.* 1994, 1456; (g) C. J. Schaverien, N. Meijboom and A. Guy Orpen, *Chem. Comm.* 1992, 124.

110. S. Kobayashi, H. Ishitani, *J. Am. Chem. Soc.* 1994, **116**, 4083.

111. S. E. Denmark, H. Stadler, R. L. Dorow and J. -H. Kim, *J. Org. Chem.* 1991, **56**, 5063.

112. For leading references see *Macrocycle Synthesis: A Practical Approach*, Ed. D. Parker, Series Eds. L. M. Harwood and C. J. Moody, Oxford, 1996.

113. A. S. deSousa and R. B. Hancock, *Chem. Comm.* 1995, 415.

114. E. N. Jacobsen in *Catalytic Asymmetric Synthesis*, Ed. I. Ojima, VCH Publishers, 1993, Ch.4.2.

115. B. Dietrich, M. W. Hosseini, J. -M. Lehn and R. B. Sessions, *Helv. Chim. Acta* 1983, **66**, 1262.

116. Y. -K. Fu, C. -H. Len and C. -S. Chung, *J. Chem. Soc. Dalton Trans.* 1988, 2495.

117. *Crown Ethers and Cryptands,* G. Gokel, Monographs in Supramolecular Chemistry Series, Ed. J. Fraser Stoddart, RSC Press, 1991.

118. G. Godjoian, V. R. Wang, A. M. Ayala, R. V. Martinez, R. M. Bernhardt and C. G. Gutierrez, *Tetrahedron Lett.* 1996, **37**, 433.

119. A. Morcuenda, S. Valverde and B. Herradon, *Synlett* 1994, 89.

120. E. Yashima, C. Yamamoto and Y. Okamoto, *Synlett* 1998, 344.

121. W. J. Bailey and J. R. Griffith, *J. Org. Chem.* 1978, **43**, 2690.

122. D. Parker, *Chem. Rev.* 1991, **91**, 1441 and references therein.

123. B. Weber and D. Seebach, *Tetrahedron* 1994, **50**, 6117 and references therein.

124. K. Otsubo, K. Kawamura, J. Inanaga and M. Yamaguchi, *Chem. Lett.* 1987, 1487.

125. (a) D. J. Cram and K. R. Kopeky, *J. Am. Chem. Soc.* 1959, **81**, 2948; (b) D. Seebach, *Angew. Chem. Int. Ed. Engl.* 1975, **14**, 634.

126. T. Imamoto, T. Takeyama and M. Yokoyama, *Tetrahedron Lett.* 1984, **25**, 3225.

127. A. Moyano, M. A. Pericas, A. Riera and J. -L. Luche, *Tetrahedron Lett.* 1990, **31**, 7619.

128. A. Alexakis, S. Mutti and P. Mangeney, *J. Org. Chem.* 1992, **57**, 1224.

129. D. Parker, priv. comm.

130. R. S. Dickins, J. A. K. Howard, C. W. Lehmann, J. Moloney, D. Parker and R. D. Peacock, *Angew. Chem. Int. Ed. Engl.* 1997, **36**, 521.

131. I. M. Helps, D. Parker, J. R. Morphy and J. Chapman, *Tetrahedron* 1989, **45**, 219.

132. W. C. Still, M. Kahn and A. Mitra, *J. Org. Chem.* 1978, **43**, 2923.

133. A. Mendel, *J. Organometallic Chem.* 1966, **6**, 97.

134. S. C. Watson and J. F. Eastham, *J. Organometallic Chem.* 1967, **9**, 165.

135. D. A. Evans, J. Bartroli and T. L. Shih, *J. Am. Chem. Soc.* 1981, **103**, 2127.

136. N. C. Payne and D. W. Stephen, *J. Organometallic Chem.* 1981, **221**, 203; See also R. K. Crossland and K. L. Servis, *J. Org. Chem.* 1970, **35**, 3195.

137. C. W. Kaminski and B. J. McElroy, *Organometallic Synthesis*, Ed. R. B. King and J. J. Eisch, Academic Press, Vol. 3, 395.

138. J. J. Eisch and R. Sanchez, *J. Organometallic Chem.* 1985, **296**, C27.

139. R. A. Moss and C. M. Young, *J. Am. Chem. Soc.* 1983, **105**, 5859.

140. F. Gasbol, P. Steenbol and B. S. Sorensen, *Acta. Chem. Scand.* 1972, **26**, 3605; For recent resolution see: J. F. Larrow, E. N. Jacobsen, Y. Gao, Y. Hung, X. Nie and C. Zepp, *J. Org. Chem.* 1994, **59**, 1939.

141. P. Krasik and H. Alper, *Tetrahedron* 1994, **50**, 4347.

142. H. Takahashi, T. Kawakita, M. Yoshiokai and S. Kobayashi, *Tetrahedron* 1992, 5691.

143. M. Orena, G. Porzi and S. Sandri, *J. Org. Chem.* 1992, **57**, 6532.

144. A. Dumont, V. Jacques, P. Qixiu and J. F. Desreux, *Tetrahedron Lett.* 1994, **35**, 3707.