Studies in Enantioselective Catalysis using a Novel D-Mannitol based Titanium Trimer

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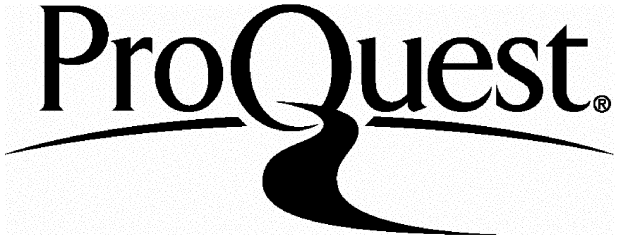

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ABSTRACT

The work presented in this thesis is divided into three parts. This research entails the discovery and development of a novel type of chiral titanium alkoxide, which acts as a Lewis acid for the reduction of prochiral ketones using catecholborane as the stoichiometric reductant.

In order to place this methodology in context, the first part is an overview highlighting the usefulness of such transition metal alkoxides in asymmetric organic synthesis. The review mainly revolves around the use of titanium and lanthanide alkoxides.

The second part is a discussion of the results obtained. It was discovered that reversible exchange reactions of a series of 3,4-di-*O*-benzyl-D-mannitol derivatives with titanium(IV) isopropoxide lead to the isolation of a novel trimeric Lewis acid complex which acts as an efficient precursor catalyst for the reduction of a range of prochiral ketones using catecholborane as reducing agent. The behaviour of this Lewis acid as a catalyst in a range of reactions was studied and the mechanism of the borane reduction was shown to involve boron-titanium exchange. The trimeric titanium alkoxide Lewis acid have also been used in a series of other asymmetric reactions and the results were a catalogue of failures. Other ligands derived from D-mannitol have been prepared and used for complexation with both titanium and lanthanum, but the structures of these complexes have so far not been characterised. Testing these unknown complexes on a number of asymmetric reactions proved to be unsuccessful.

The third part is an account of the experimental results and procedures employed throughout this work.

CONTENTS

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Finally, I would like to acknowledge the support given to me by my family throughout my academic years. This thesis is dedicated to them

ABBREVIATIONS

9-BBN	9-borabicyclo[3.3.1]nonane
^{11}B NMR	Boron Nuclear Magnetic Resonance
^{13}C NMR	Carbon Nuclear Magnetic Resonance
5-Cl-BIPOL	5,5'-dichloro-4,4',6,6'-tetramethyl-2,2'-biphenol
^{19}F NMR	Fluorine Nuclear Magnetic Resonance
^{1}H NMR	Proton Nuclear Magnetic Resonance
Abs.	Absorbance
Anal.	Microanalysis
aq.	Aqueous
Ar	Aryl
BINOL	1,1'-Bi-2,2'-naphthol
br	Broad
Bn	Benzyl
^{t}Bu	Tertiary Butyl
c	Concentration
cat.	Catalytic amount
Cat	Catechol
CatBH	Catecholborane
Conc.	Concentration
d	Doublet
Δ	Heating
dec.	Decomposed
DET	Diethyl tartrate
DCM	Dichloromethane
DIPT	Diisopropyl tartrate
DMF	Dimethylformamide
DMP	2,6-Dimethoxypyridine
DMSO	Dimethylsulfoxide

d.r.	diastereomeric ratio
ee	enantiomeric excess
EI	Electron Impact
equiv.	Molar equivalents
Et	Ethyl
Ether	diethyl ether
EtOAc	Ethyl acetate
EtOH	Ethanol
FAB	Fast Atom Bombardment
FG	Functional group
g	gram(s)
GC	Gas Chromatography
h	hour
HPLC	High Pressure Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
Hz	Hertz
IR	Infra Red
LA	Lewis Acid
lit.	literature value
LRMS	Low Resolution Mass Spectrometry
o	ortho
m	multiplet
m	meta
M	Molar
Me	Methyl
MeOH	Methanol
MHz	Megahertz
min.	minute
mM	millimolar

m.p.	Melting Point
MTPA	α-methoxy-α-trifluoromethylphenylacetyl
N	Normal
p	para
PE	Petroleum ether
Ph	Phenyl
ppm	Parts per million
^{i}Pr	Isopropyl
q	Quartet
s	Singlet
sat.	Saturated
SM	Starting Material
t	Triplet
TADDOL	α,α,α',α'-tetraaryl-1,3-dioxolane-4,5-dimethanol
TBDMS	^{t}Butyldimethylsilyl
TBHP	^{t}Butylhydroperoxide
TEA	Triethylamine
Temp.	Temperature
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl
Ts	*p*-Toluenesulfonyl
UV	Ultra Violet
UV-Vis	Ultra Violet to Visible
Xs.	Excess

Part 1. Introduction

INTRODUCTION

1.1 Recent Developments in the use of Transition Metal alkoxide mediated Lewis acid catalysts for Organic Synthesis

The work presented in this thesis entails the discovery and development of a novel type of chiral titanium alkoxide, which acts as a Lewis acid for the reduction of prochiral ketones using catecholborane as the stoichiometric reductant. In order to place this methodology in context, it is therefore appropriate to provide an overview highlighting the usefulness of such transition metal alkoxides in organic synthesis.

Enantioselective catalysis is both an economical and an environmentally friendly process. The idea of using a very small amount of chiral catalyst to achieve 'multiplication of chirality'[1] is a very attractive one, and the development of an enantioselective catalyst is a most challenging and formidable task for synthetic organic chemists.[2,3]

Metal complexes bearing chiral ligands have shown to be excellent enantioselective catalysts. Therefore, the development of enantioselective catalysts is greatly influenced by the selection of the central metal and the molecular design of the chiral organic ligand. The magnitude of asymmetric induction is very much governed by the metal–ligand bond lengths, particularly metal–oxygen and –nitrogen in the case of metal alkoxide and amide complexes (**Table 1**),[4,5] as well as the steric demands of the organic ligands. In principle, the shorter the bond length the greater the enantioselectivity, because the asymmetric environment created by the chiral ligand is closer to the reaction centre. Therefore as **Table 1** reveals, boron and aluminium are the ideal main group elements, and titanium is one of the best early transition metals.

Metal	M–O bond length (Å)	M–N bond length (Å)
Li	1.92-2.00	2.12
Mg	2.01-2.13	2.22
Zn	1.92-2.16	2.16
Sn	2.70	2.25
Al	1.92	1.95
B	1.36-1.47	1.40
Ti	1.62-1.73	2.30
Zr	2.15	2.30

Table 1

Both electron donating and sterically demanding ligands decrease the Lewis acidity but increase the configurational stability of titanium complexes in the order: Cp (cyclopentadienyl) > NR_2 > OR > X (halides).[4,6,7] Therefore, the Lewis acidity of titanium complexes decreases on going from titanium halides to titanium alkoxides to titanium amides and then to titanocenes. The Lewis acidity can be "fine-tuned" by mixing ligands such as in dialkoxytitanium dihalide complexes. By contrast, bond strengths with titanium decrease in the order: M–O > M–Cl > M–N > M–C.[4] The M–C bond strengths in Ti(IV) compounds are comparable with those of other metal–carbon bonds. However, the Ti–O bond is exceptionally strong.

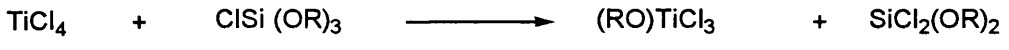
Although a vast number of reactions have been reported using metal complexes of increased Lewis acidity which contain both alkoxide and halide ligands, the present introductory review has been restricted to those which possess only alkoxide partners since these are most germane to the context of the present thesis. Emphasis has also been placed on the use of titanium since this has been our principal metal of choice throughout. Nevertheless, since very exciting developments in the use of lanthanide alkoxide complexes have taken place in recent years, and potential exists for incorporation of these in further continuation of this work, they have also been discussed.

Some of the more general preparative procedures for the preparation of chiral titanium alkoxide complexes are shown below.[8,9,10,11,12]

(1) Halide displacement using main group alkoxides *via* formal transmetallation (**Scheme 1**).

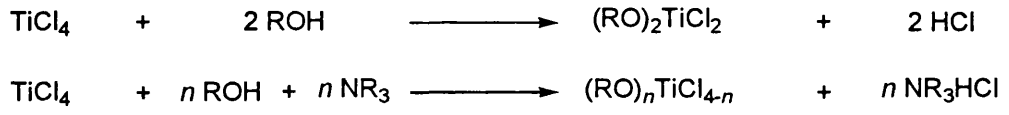
Scheme 1

(2) A halide can be replaced by metathesis of a silylated ligand with accompanying generation of silicon halide removed as a thermodynamic driving force (**Scheme 2**).



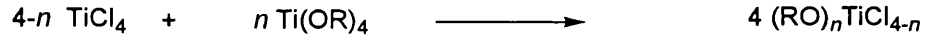
Scheme 2

(3) Evolution of HCl occurs with protic ligands, and hence must be removed or neutralised with a base (**Scheme 3**).



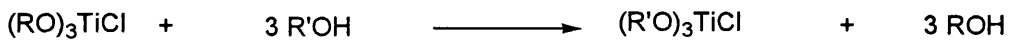
Scheme 3

(4) Ligand redistribution results in disproportionation (**Scheme 4**).



Scheme 4

(5) A chiral titanate ester can be prepared using transesterification with a free chiral alcohol (**Scheme 5**). In such reactions, the equilibrium is shifted towards the chiral titanium complex by azeotropic removal of the volatile achiral alcohol.



Scheme 5

(6) Alkyl (methyl, in particular) titanium complexes can be used for deprotonation of the chiral ligands with concomitant generation of an alkane (methane) (**Scheme 6**).

$$CH_3TiCl_3 + ROH \longrightarrow (RO)TiCl_3 + CH_4$$

Scheme 6

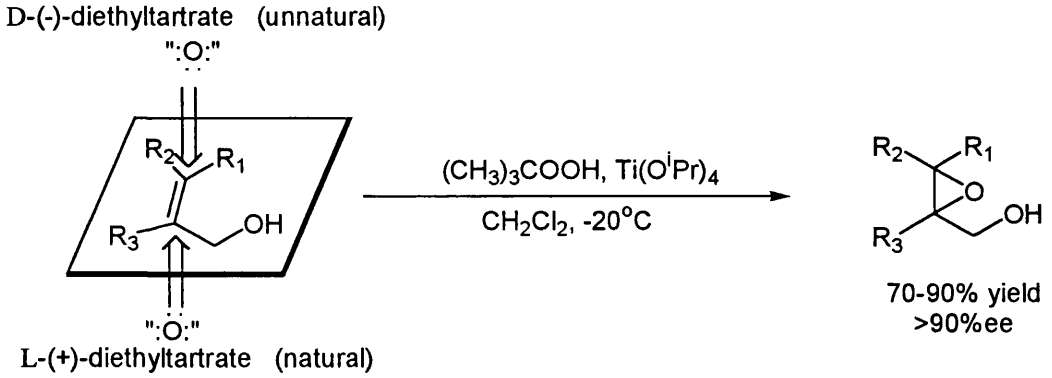
The introduction of this thesis has been divided into two parts, titanium alkoxides and rare-earth metal alkoxides. For simplicity, titanium alkoxides have been classed into four types of ligands and rare-earth metal alkoxides have been classed into three types of catalysts. The asymmetric reactions involved are discussed in the relevant classes of metal alkoxides.

The first class of chiral titanium alkoxides utilises the C_2 symmetric and readily available optically active tartrate esters as the chiral ligands.

1.2 Titanium alkoxide Lewis acids

1.2.1 The Sharpless-Katsuki asymmetric epoxidation of allylic alcohols

In 1980, Katsuki and Sharpless have reported that the combination of a titanium(IV) alkoxide, an optically active tartrate ester and *t*-butyl hydroperoxide constituted an excellent catalyst for asymmetric epoxidation of a wide range of allylic alcohols in good yield and with an enantiomeric excess of usually greater than 90%.[13] Most reactive allylic alcohols can be epoxidised with only 5-10mol% of the titanium-tartrate complex, and the level of asymmetric induction obtained under these catalytic conditions was within 1 or 2% of that obtained from using a stoichiometric amount of the catalyst. However, it was difficult to achieve complete epoxidation with many of the slower reacting allylic alcohols under catalytic conditions and, as a consequence, a stoichiometric quantity of the catalyst was employed for most asymmetric epoxidations. This problem was later solved by the addition of activated molecular sieves to the reaction and now all epoxidations are completed with only 5-10mol% of the catalyst.[14,15]



Scheme 7

The essence of titanium catalysed asymmetric epoxidation is encapsulated in **Scheme 7**, which involves all of the four essential components for the reaction, *viz*., the allylic alcohol substrate, a titanium(IV) alkoxide, a chiral tartrate ester, and an alkyl hydroperoxide. The asymmetric complex formed from these reagents delivers the peroxy oxygen to either the *Si*- face or the *Re*- face of the allylic alcohol depending on the absolute configuration of

the tartrate used. If D-(–)-tartrate is used, oxygen atom delivery will be from the top face of the allylic alcohol when drawn in the orientation shown in **Scheme 7**, and if L-(+)-tartrate is used, oxygen atom delivery will be from the bottom face. This rule is used to assign the absolute configuration of the epoxy alcohols prepared by this method. However the epoxidation of substrates with chiral R_2, R_3, and/or R_1 substituents does not always follow the rule and care must then be taken to assign the configuration of the product.[16]

Another feature of this reaction is its high chemoselectivity. The titanium tartrate system is compatible with many functional groups such as acetal, acetylene, amide, ether, epoxide, ester, isolated olefin, ketone, nitro, sulfone, and urethane. However, sulfides and phosphines are oxidised under the reaction conditions.[16]

Rapid exchange of titanium ligands in solution is crucial to the understanding of the reaction and its mechanism.[17,18,19] Thus, when mixing equimolar amounts of a titanium alkoxide and a dialkyl tartrate, the equilibrium presented by **Scheme 8** will quickly be reached with all but the most sterically demanding alkoxides.

$$Ti(O^iPr)_4 + \text{tartrate} \rightleftharpoons Ti(\text{tartrate})(O^iPr)_2 + 2\ {}^iPrOH$$

Scheme 8

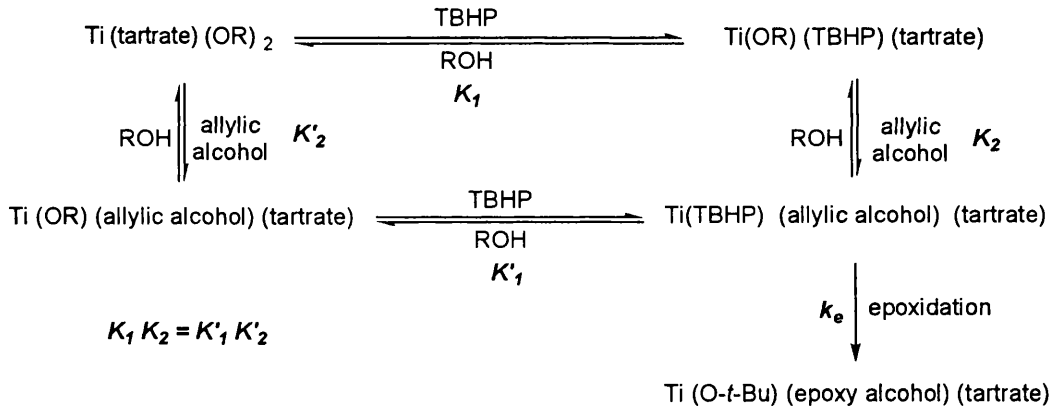
This equilibrium lies far to the right because the bidentate diol of the tartrate has a much higher binding constant for titanium than do simple alcohols. The binding of tartrate is also enhanced by the increased acidity of its hydroxyl groups due to the inductive effect of the esters. Rapid ligand exchange processes continue as the hydroperoxide oxidant and the allylic alcohol substrates are added to the reaction. Pseudo-first-order kinetic experiments were conducted and showed a first-order rate dependence on the titanium-tartrate complex, the hydroperoxide, and the allylic alcohol and an inverse second-order dependence on the non-olefinic alcohol ligands (i.e., isopropanol). The rate law derived from these results is expressed in **Scheme 9**. The mechanistic pathway outlined in

Scheme 10 is consistent with **Scheme 9** and clearly illustrates that ligand exchange processes are essential for successful catalytic epoxidation.

$$\text{Rate} = k\frac{[\text{Ti(tartrate)(OR)}_2][\text{TBHP}][\text{allylic alcohol}]}{[\text{ROH}]^2}$$

Scheme 9

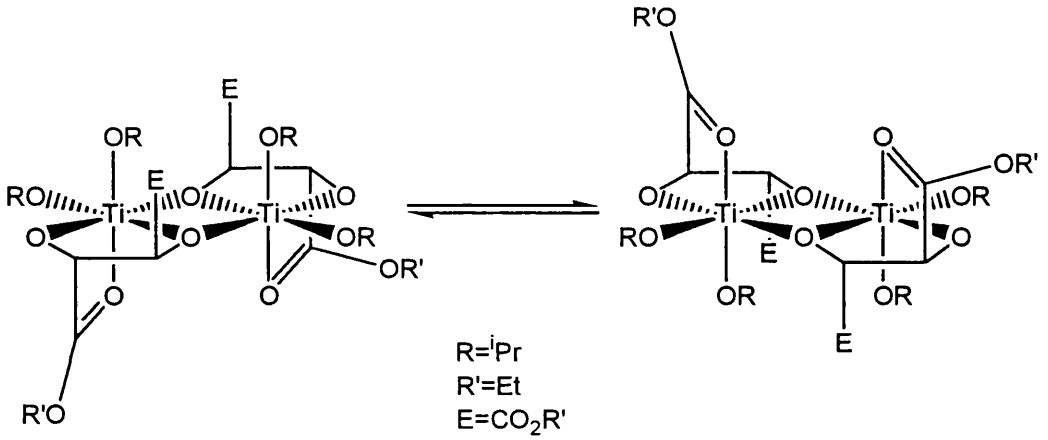
The two remaining alkoxide ligands in the Ti(tartrate)$(OR)_2$ complex are replaced with the hydroperoxide (TBHP) oxidant and the allylic alcohol substrate in a reversible exchange reaction to give the "active catalyst" Ti(tartrate)(TBHP)(allylic alcohol). In the rate determining step of the process, the oxygen delivery from the coordinated hydroperoxide to the allylic alcohol gives the Ti(tartrate)(*t*-BuO)(epoxy alcohol) complex. The product alkoxides are then replaced by more allylic alcohol and TBHP to regenerate the "active" intermediate and complete the catalytic cycle.



Scheme 10

The characterisation of the catalyst structure was shown to be extremely difficult due to the rapid ligand exchange reaction, which is so crucial to the success of the reaction. Some reliable structural information has been obtained from spectroscopic measurements on the complex in solution.[17,19b] These data clearly support the conclusion that the major molecular species formed in the solution is the dimeric composite, $Ti_2(tartrate)_2(OR)_4$. Isolation of this complex, as a crystalline solid, has not yet been achieved. Therefore, characterisation of the dimeric complex has been dependent on the X-ray data provided by the closely related complex, $Ti_2(dibenzyltartramide)_2(OR)_4$.[20] Interestingly, both complexes catalyse the epoxidation of

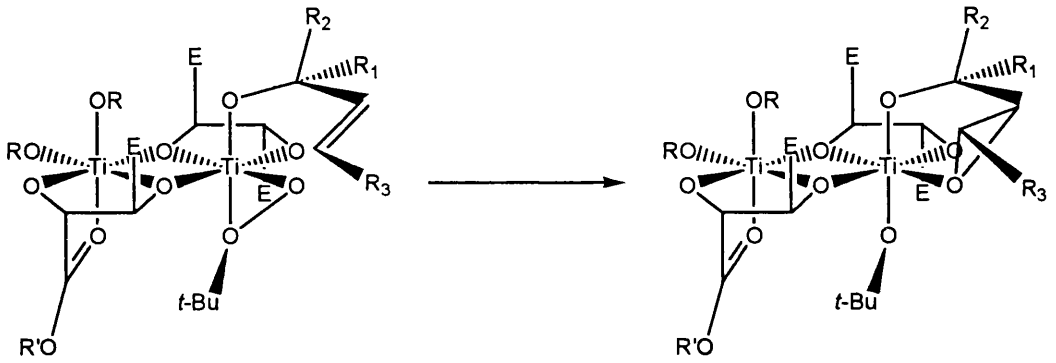
α-phenylcinnamyl alcohol with the same enantiofacial selectivity. From this analogy, the structure shown in **Scheme 11** has been proposed for the $Ti_2(tartrate)_2(OR)_4$ complex. This structure has a C_2 axis of symmetry with the two titanium atoms in identical stereochemical environments. To account for the "sameness" of all the tartrate ester groups in the room temperature NMR spectrum, a fluxional equilibrium between the two structurally degenerate complexes shown in **Scheme 11** has been proposed. Catalysis of the epoxidation process is thought to involve only one of the two titanium atoms, but the possibility that both are required has not been ruled out.



Scheme 11

A structure for the "loaded" catalyst, with the alkyl hydroperoxide and the allylic alcohol present, has been proposed (**Scheme 12**).[17] Orientation of the two compounds on the catalyst is now an important problem. Three coordination sites, two axial and one equatorial, become available by exchange of two isopropoxides and dissociation of the coordinated ester carbonyl group. These processes can occur with minimal perturbation of the remaining catalyst structure. The three coordination sites are in a semicircular (i.e., meridional) array around one edge of the catalyst face. In the reactive mode, coordination of the hydroperoxide is assumed to be bidentate by analogy to the precedent of bidentate TBHP coordination to vanadium.[17,21] The hydroperoxide must occupy the equatorial and one of the two available axial coordination sites, with the allylic alcohol in the remaining axial site. To achieve the necessary proximity for transfer of oxygen (the distal peroxide oxygen is assumed to be transferred) to the olefin, the distal

oxygen is placed on the equatorial site (**Scheme 12**) and the proximal oxygen is placed on the axial site. The axial site on the lower face of the complex (as drawn in **Scheme 12**) is chosen for the peroxide because of the larger steric requirements of the *t*-butyl group, or especially the trityl group when trityl hydroperoxide is used, in comparison to the allylic alcohol.



Scheme 12

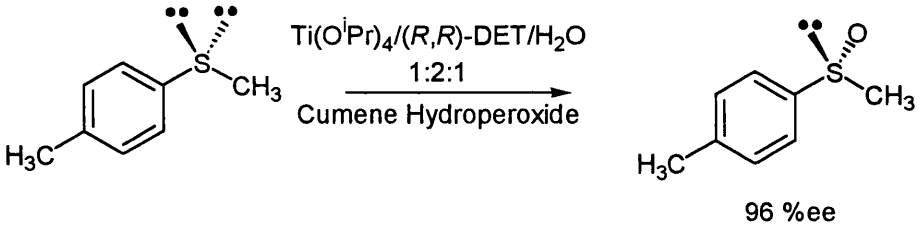
The allylic alcohol binds to the remaining axial coordination site, where stereochemical and stereoelectronic effects dictate the conformation shown in **Scheme 12**.[17] The structural model of the catalyst, oxidant, and substrate shown in **Scheme 12** illustrates a detailed version of the formalised rule presented in **Scheme 7**. Ideally, all observed stereochemistry of epoxy alcohol and kinetic resolution products can be rationalised according to the compatibility of their binding with the stereochemistry and stereoelectronic requirements imposed by this site.[17] A transition state model for the asymmetric epoxidation complex has been calculated by a frontier orbital approach and is also consistent with the formulation shown in **Scheme 12**.[22]

1.2.2 Asymmetric Oxidation of Sulfides

Chiral sulfoxides, which have an asymmetric center at sulfur are an important class of compounds which are finding increasing use as chiral auxiliaries in asymmetric synthesis[23,24,25,26,27,28]. Enantiopure sulfoxides can be prepared by several methods based on resolution, transformation of a chiral sulfinate into a sulfoxide and oxidation of a sulfide. Asymmetric oxidation of achiral R^1–S–R^2 sulfides is of course in principle the most straightforward route to prepare chiral sulfoxides.

The success of the Sharpless asymmetric epoxidation of allylic alcohols,[13,29] (see **Section 1.2.1)** attracted much attention to the titanium-chiral alcoholate combinations as potential mediators or catalysts in various reactions. In 1984, Kagan[30,31a] reported that the 'Sharpless catalyst' with the addition of one mole equivalent of water can oxidise simple thio ethers with *t*-butyl hydroperoxide to provide sulfoxides with quite high enantiomeric purity. Interestingly, under these conditions, the epoxidation of allylic alcohols is completely blocked. Modena and co-workers[32] also found the same beneficial effect of using a large excess of diethyl tartrate (4mol equiv.) with respect to $Ti(O^iPr)_4$. This stoichiometry also blocks epoxidation of allylic alcohols.[30] Although titanium complexes were originally used in stoichiometric amounts.[30,31,32,33,34,35,36] A later procedure was devised which features catalytic titanium complexes.[37,38]

Thus, as shown in **Scheme 13**, methyl *p*-tolyl sulfide is oxidised to methyl *p*-tolyl sulfoxide of high enantiomeric purity (80-90 %ee) when the Sharpless reagent is modified by the addition of one mole equivalent of water.[30,31,39] Under the 'Sharpless' conditions the sulfoxidation gave mixtures of racemic sulfoxide and sulfone. The optimised stoichiometry of the titanium complex is a 1:2:1 combination of $Ti(O^iPr)_4$/(*R*,*R*)-DET/H_2O, known as the Orsay reagent, and this is now used as a standard system for the oxidation of prochiral sulfides to chiral sulfoxides.[31a]



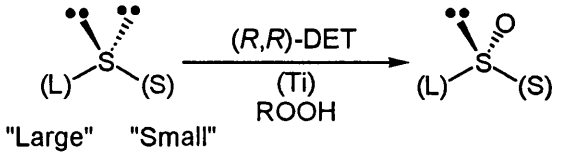
Scheme 13

The enantioselectivity is very much dependent on both the solvent[35] and the hydroperoxide[36,37,38] employed. The best solvents reported are dichloromethane and 1,2-dichloroethane and the best hydroperoxide is readily available cumyl hydroperoxide. The optimum temperature for performing this reaction is in the range of –20°C to –25°C. Diethyl tartrate was found to be the best ligand for enantioselective oxidation of thio ethers.

A decrease of the amount of Orsay reagent results in the reduction of enantioselectivity. However it was found that methyl *p*-tolyl sulfoxide of 85%ee could be obtained with only 20mol% of the titanium complex in the oxidation by cumyl hydroperoxide. This moderate but significant catalytic sulfoxidation has been obtained in the presence of molecular sieves.[33]

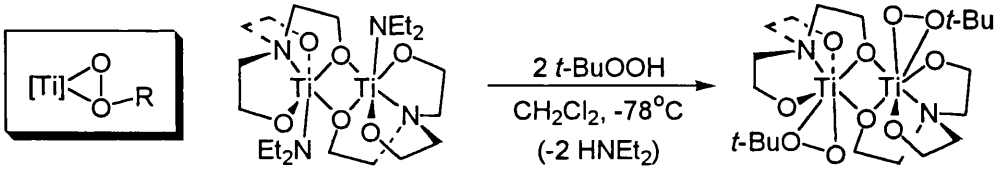
Recently it was reported that the combination Ti(O^{i}Pr)$_4$/(*R*,*R*)-DET/^{i}PrOH =1:4:4 may be used under acceptable catalytic conditions (10mol%) in the presence of 4A molecular sieves.[34,35] Enantiomeric excesses of up to 95% were observed for methyl *p*-tolyl sulfoxide and various aryl methyl sulfoxides and these are presently among the best in catalytic sulfoxidations.

A very good correlation exists between the absolute configuration of the tartrate used and the sulfoxide produced. **Scheme 14** provides excellent predictions, by taking (L) and (S) groups (on steric grounds), as large and small, respectively.



Scheme 14

The mechanisms of the asymmetric sulfoxidations involving the various combinations $Ti(O^iPr)_4$/(*R*,*R*)-DET and some additives are not yet well understood. It is necessary to take into account the diversity of titanium complexes produced by tartrates and which may inter-convert in solution.[40] In all asymmetric sulfoxidations promoted or catalysed by various chiral titanium complexes it is very reasonable to assume that the hydroperoxide reacts to give a peroxytitanium species (**1**) (**Scheme 15**). This is well supported by the X-ray crystal structure of (**3**) produced from the reaction of (diethylamino)-titanatrane (**2**) with *t*-butyl hydroperoxide.[41] Interestingly, the peroxo complex (**3**) cleanly oxidises benzyl methyl sulfide into benzyl methyl sulfoxide at 0°C in dichloromethane.



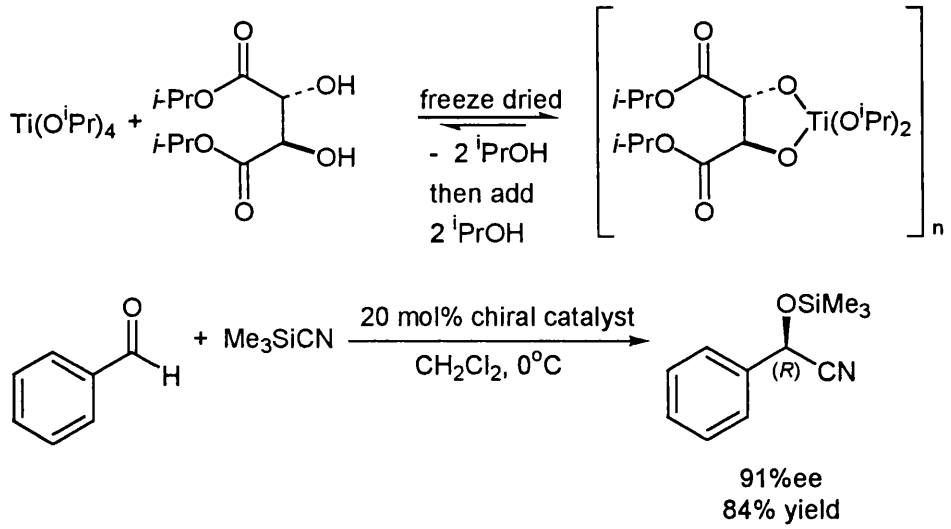
(**1**) (**2**) (**3**)

Scheme 15

1.2.3 Enantioselective Trimethylsilylcyanation of aldehydes

Enantiopure cyanohydrins are valuable building blocks for chemical syntheses giving rise to important classes of compounds such as α-hydroxy acids, α-hydroxy ketones and β-amino alcohols. The Oguni group[42] have reported an efficient procedure for the enantioselective addition of trimethylsilyl cyanide to aldehydes promoted by catalytic amounts of a modified Sharpless catalyst, which consists of titanium(IV) isopropoxide and an optically pure enantiomer of diisopropyltartrate (DIPT).

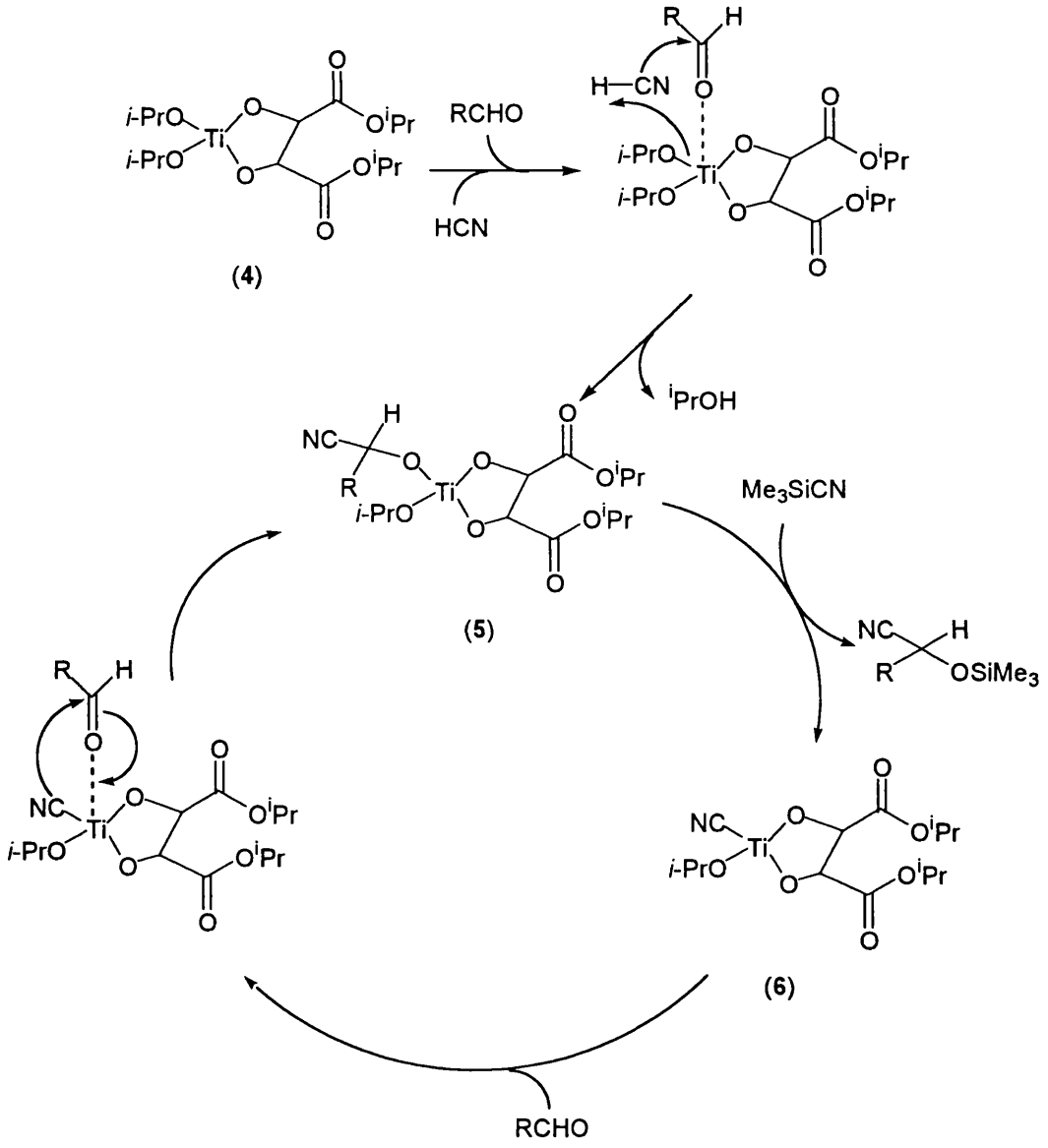
Highly enantioselective silylcyanation through the use of a freeze dried catalyst, prepared by the alkoxy exchange reaction between a 1:1.1 ratio of $Ti(O^iPr)_4$ and L-(+)-DIPT followed by complete removal of the liberated isopropanol and subsequent addition of 2 equivalents of isopropanol. The reaction of benzaldehyde with trimethylsilyl cyanide was catalysed by 20mol% of this catalyst to provide the product with 91%ee in 84% yield (**Scheme 16**). The enantioselectivity of this reaction is very much influenced by the concentration of the reactants. The substrate concentration of 0.05mol dm^{-3} and a catalyst concentration of 0.01mol dm^{-3} were reported to provide the best conditions.



Scheme 16

The proposed mechanism for this catalytic asymmetric trimethylsilylcyanation of aldehydes proceeds as outlined in **Scheme 17**. The first step is initial formation of the chiral titanium species (**4**) by an alkoxy exchange reaction (**Scheme 16**), between

$Ti(O^iPr)_4$ and L-(+)-DIPT. The hydrogen cyanide produced from reaction of trimethylsilyl cyanide with isopropanol then reacts with the aldehyde coordinated to the titanium in intermediate (**4**) to form the titanium species (**5**) and, from the stereochemical point of view, this step is considered to be the most important. The key process to accomplish the catalytic cycle is then the cleavage of the newly produced Ti–O bond in species (**5**) by trimethylsilyl cyanide to produce the trimethylsilyl ether of the cyanohydrin and the chiral titanium species (**6**). The chiral titanium species (**6**) can then catalyse the silylcyanation of another aldehyde and regenerate titanium species (**5**) to complete the catalytic cycle.

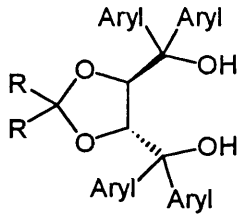


Scheme 17

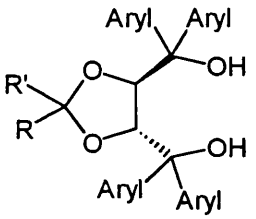
The second class of titanium alkoxide also utilises optically active C_2 symmetric dialkyl tartrate derivatives as the precursor for the synthesis of a new type of chiral ligand.

1.3 Titanium TADDOLates

Titanates derived from chiral diols (**7**) and (**8**)[43,44,45,46,47] (**Scheme 18**) have been demonstrated to be useful in both stoichiometric and catalytic asymmetric reactions: TADDOL being proposed[46] as a generic abbreviation of their systematic name – α,α,α',α'-tetraaryl-1,3-dioxolane-4,5-dimethanols. Ti-TADDOLate complexes has been shown to catalyse a wide variety of reactions such as additions of dialkylzinc reagents to aliphatic and aromatic aldehydes,[48] [2+2][49] and [4+2][50] cycloadditions, ene reactions,[51] cyanohydrin formation,[52] (for review articles[53]).



(**7**) (C_2-symmetrical)



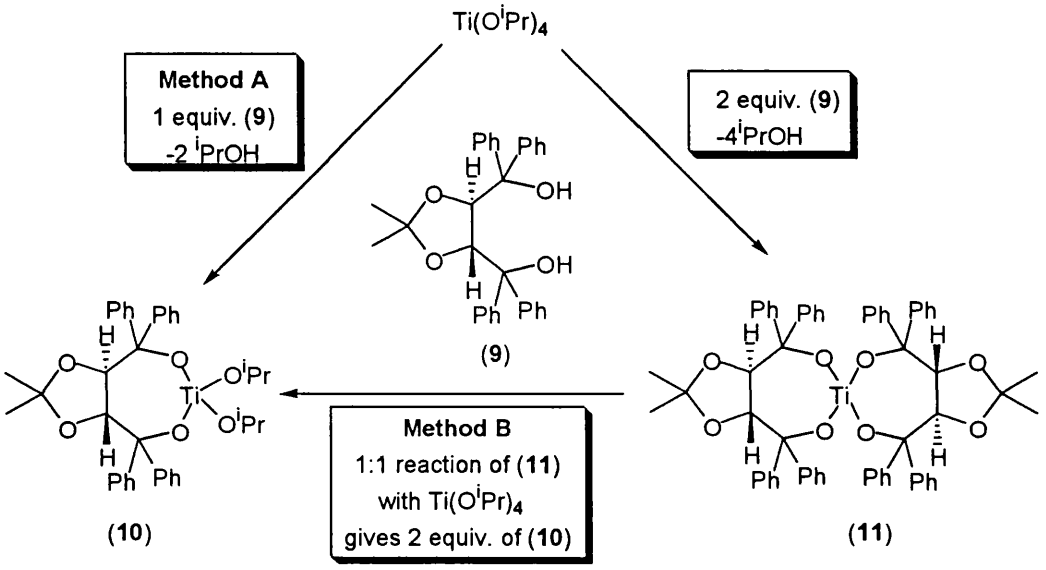
(**8**) (C_1-symmetrical)

Scheme 18

The chiral ligands (**7**) and (**8**) are readily prepared from the corresponding tartrate ester acetals and aryl Grignard reagents. These ligands have C_2 or C_1 symmetry, depending upon the aldehyde or ketone from which the tartrate acetal precursors are formed.

There are two practical procedures to synthesise Ti-(TADDOLate)(O^iPr)$_2$ (**10**) from Ti(O^iPr)$_4$, (see **Scheme 19**). A direct method to prepare Ti-(TADDOLate)(O^iPr)$_2$ (**10**) is from a 1:1 reaction of Ti(O^iPr)$_4$ and TADDOL (**9**), with azeotropic removal of two equivalents of isopropanol (**Method A** in **Scheme 19**).[48b,,54] The second method involves the synthesis of the spirotitanate Ti-(TADDOLate)$_2$ (**11**), which is used as an intermediate. This is also prepared by azeotropic removal of isopropanol from a 1:2 mixture of Ti(O^iPr)$_4$ and the TADDOL (**9**) in toluene, and is a crystalline solid which is stable to air and moisture. In solution however, Ti-(TADDOLate)$_2$ (**11**) is moisture sensitive and should be

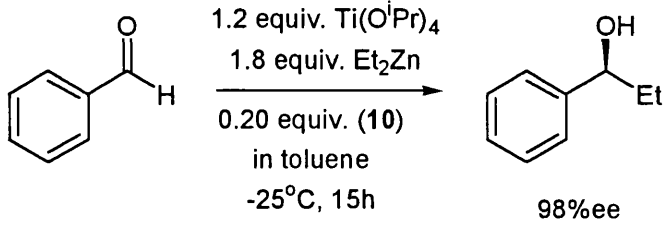
handled under inert atmosphere. Mixing the spirotitanate (**11**) with $Ti(O^iPr)_4$ in a 1:1 ratio provides titanate (**10**) quantitatively and instantaneously (**Method B** in **Scheme 19**). The solutions of (**10**) thus obtained are used directly.



Scheme 19

1.3.1 Addition of Et_2Zn to aldehydes in the presence of TADDOL-Titanates

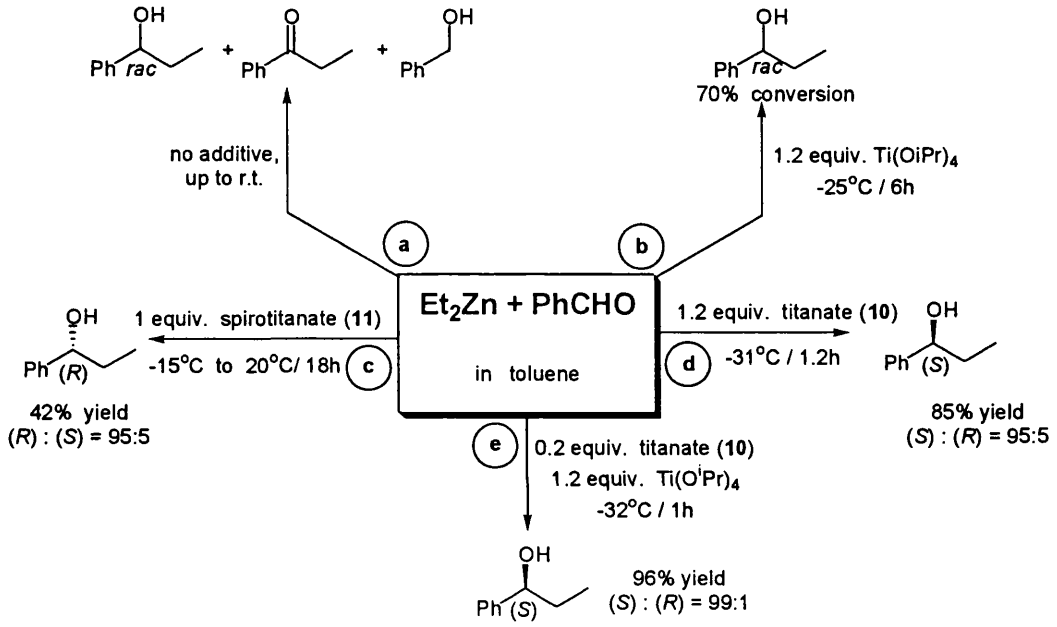
Seebach[48] have reported the Ti-(TADDOLate)$(O^iPr)_2$ catalysed additions of dialkylzinc reagents to aliphatic and aromatic aldehydes with enantioselectivities generally >98%ee (**Scheme 20**).



Scheme 20

To explain the mechanism of this reaction, the results from Seebach's earlier studies have to be discussed (**Scheme 21**). Diethylzinc does not react with benzaldehyde to any appreciable extent in toluene at temperatures around –30°C, whereas **(a)** at room temperature, benzyl alcohol, 1-phenyl-1-propanol, and propiophenone are isolated[55]. As expected however, **(b)** the nucleophilic transfer of an ethyl group to benzaldehyde from Et_2Zn occurs at *ca.* –25°C in the presence of 1.2 equiv. of the Lewis acid, $Ti(O^iPr)_4$. The

corresponding experiment with the spirotitanate (**11**) **(c)** led to a 95:5 mixture of (*R*)-enriched product in a slow reaction requiring temperaures above 0°C. **(d)** In contrast, the titanate (**10**) led to the formation of a 95:5 mixture, with the (*S*)-enantiomer predominant under identical conditions. **(e)** Surprisingly, an improvement of the enantioselectivity from 95:5 to 99:1 for the formation of the (*S*)-enantiomer, is achieved with the addition of 1.2 equiv. of the achiral $Ti(O^iPr)_4$ along with 0.2 equiv. of the chiral titanate (**10**).

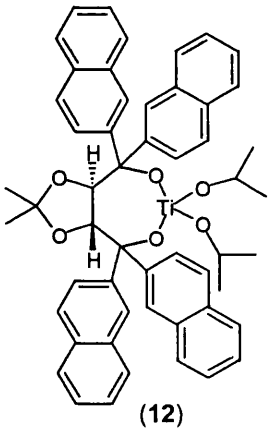


Scheme 21

The conclusions drawn from the results obtained by Seebach are very interesting and can be summarised as follows:

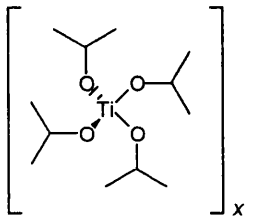
1. Highly hindered chiral titanates are more active catalysts than $Ti(O^iPr)_4$.
2. With increasing bulk of the α-substituents in the dioxolane dimethanols, the efficiency of the chiral catalyst increases in the order alkyl<Ph<β-naphthyl.
3. The rate and the enantioselectivity of the reaction decreases when the steric hindrance becomes too large, i.e. α-naphthyl derivatives.
4. Chiral titanates with less hindering groups such as tetramethyl, do not successfully compete as catalysts relative to $Ti(O^iPr)_4$.

5. Higher enantioselectivity is observed with substoichiometric amounts of the Ti-(TADDOLate)(O^iPr)$_2$ complex in the presence of excess Ti(O^iPr)$_4$ than it is with equimolar amounts of the chiral complex alone.

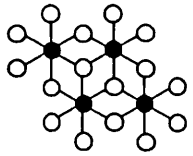


(**12**)

-steric hindrace to coordination
-fast dynamics of ligand exchange



-aggregates or solvated, higher coordinated Ti
-slow ligand exchange



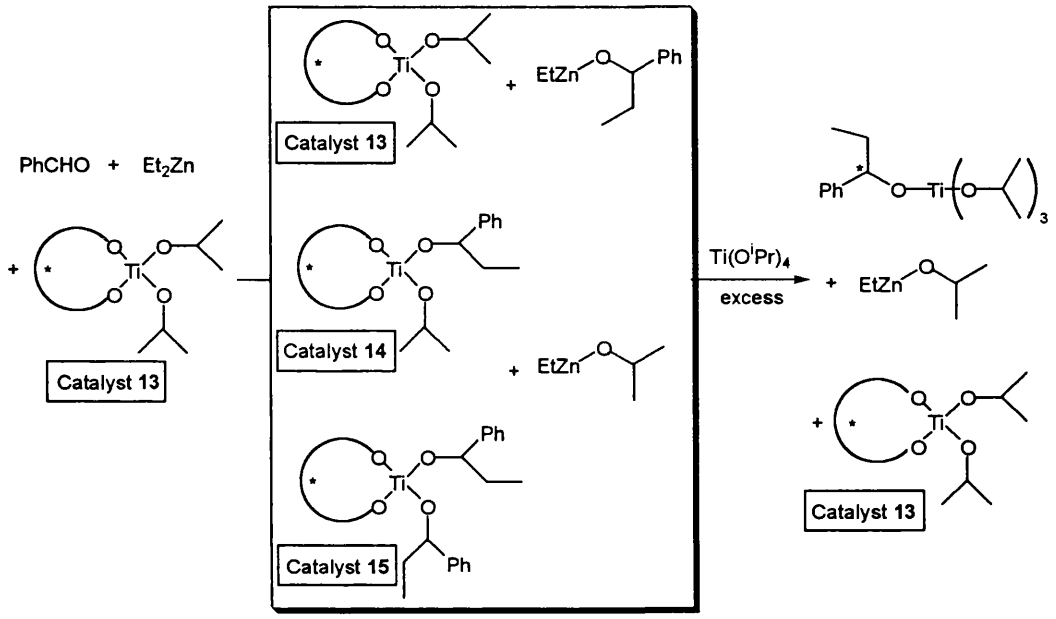
[$(EtO)_4Ti$]$_4$

Scheme 22

The above findings are compatible with the following mechanistic considerations, illustrated for the β-substituted complex (**12**) in **Scheme 22**. Due to steric hindrance to coordination, there exists fast dynamics of ligand exchange at the Ti-site in the bulky TADDOLate complex. The Ti center bearing four ^{i}PrO groups achieves the preferred, stable hexacoordination by aggregation (*cf.* the section of the crystal structure of $(EtO)_4Ti$[56] in **Scheme 22**) or by attachment to some donor atoms, therefore it undergoes ligand exchange more slowly than the TADDOL titanate. Thus, the chiral titanate is catalytically the more active species than Ti(O^iPr)$_4$.

The fact that the combination of chiral titanate and achiral Ti(O^iPr)$_4$ provided a more enantioselective catalyst than using the chiral titanate alone is most intriguing and was explained by the fact that new chiral titanate catalysts are formed as the reaction proceeds (See **Scheme 23**). The original titanate catalyst (**13**) is in equilibrium with titanates containing the product alkoxy ligands catalyst (**14**) and (**15**), and these newly formed titanates give rise to altered selectivities. Catalysts (**14**) and (**15**) are much less

effective at inducing enantioselectivity in the reaction when (*R*)- or (*S*)-1-phenyl propoxy ligands are coordinated to the seven membered Ti-containing ring of the titanate (**12**). Therefore, the addition of excess $Ti(O^iPr)_4$ can be viewed as a pool for the product alkoxides, and as a means to reconstitute the original catalyst; as shown for the catalysts (**14**) and (**15**) which are converted back to catalyst (**13**).

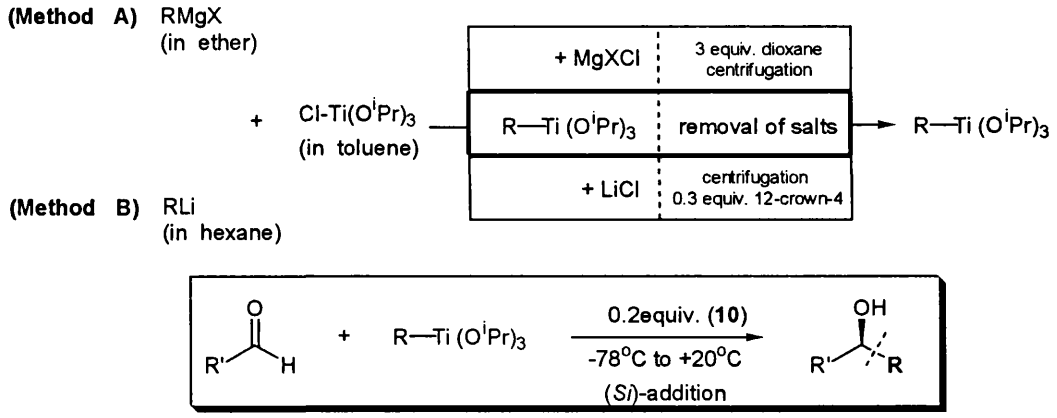


Scheme 23

1.3.2 Enantioselective addition of Alkyl- and Aryl- Titanium derivatives to aldehydes

Although the Ti-(TADDOLate)(O^iPr)$_2$ mediated dialkylzinc addition to aldehydes gives impressive enantioselectivities,[48,54,55,57] there remains an inherent disadvantage: it is chemically uneconomical, only one of the two groups from the dialkylzinc being transferred to the aldehyde. Seebach's group[58] have developed a method to overcome this problem, using R–Ti(O^iPr)$_3$ as the organometallic partner for the addition to aldehydes, and the Ti-(TADDOLate)(O^iPr)$_2$ (**10**) as the catalyst. The zinc-free, monometallic system is also more promising for large-scale applications, and there is also less ambiguity in terms of mechanistic interpretation.

The enantioselective addition to aldehydes is performed with 1.2 equiv. of freshly prepared R–Ti(O^iPr)$_3$, 0.2 equiv. of Ti-(TADDOLate)(O^iPr)$_2$ (**10**), and 1.0 equiv. of an aldehyde in toluene. The reactants are mixed at –78°C and are allowed to warm to room temperature overnight (**Scheme 24**). Both alkyl- and aryl-triisopropoxy-titanium compounds are used which are formed *in situ* from the corresponding alkyl- and aryl-lithium or Grignard compounds and Cl–Ti(O^iPr)$_3$. It is found that the LiCl and MgXCl salts, generated in the transmetallation step, drastically reduce the enantioselectivity. In toluene these salts are insoluble and can therefore be separated by centrifugation. The best results were obtained when 1,4-dioxane was added (**Method A** in **Scheme 24**) to complete the precipitation of magnesium salts, or when the remaining traces of Li-cations were removed by complexation with 12-crown-4 (**Method B** in **Scheme 24**). Both methods **(A)** and **(B)** for the removal of the salts give essentially the same enantioselectivities in the subsequent addition reaction.



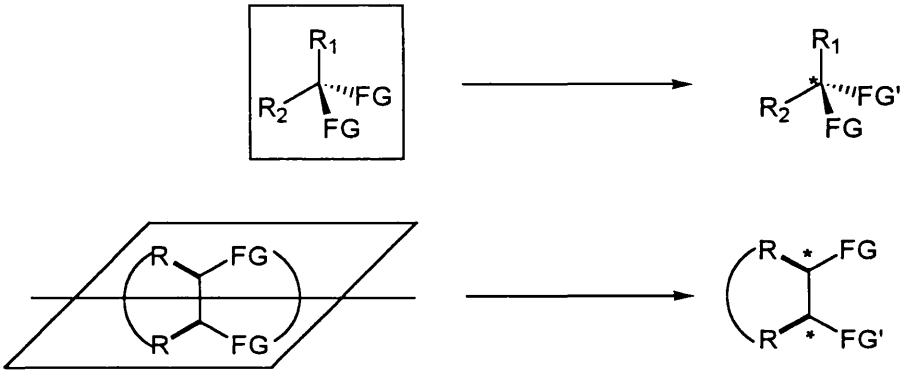
Scheme 24

The reaction of benzaldehyde with simple alkyl–Ti(O^{i}Pr)$_3$ and CH_2=$CHCH_2CH_2$–Ti(O^{i}Pr)$_3$ gives enantioselectivities of ⩾ 99:1. Aliphatic aldehydes give high selectivities, too ⩾ 96:4. Nucleophiles with functionalised alkyl groups can be added with selectivities ⩾ 96:4.

In general, the characteristic features of this reaction are very similar to those of the Ti–(TADDOLate)(O^{i}Pr)$_2$ catalysed dialkylzinc addition to aldehydes.[48,54,59] It is therefore entirely possible that no zinc centre is involved in the rate determining C–C bond-forming step of the previously discussed reaction in the bimetallic mechanism proposed[54] (see **Section 1.3.1 Scheme 23**) both metal centers could be titanium. The preferred addition of the nucleophile is from the *Si*-face of the aldehyde, as in the case of all other reactions carried out with dialkylzinc and Ti-(TADDOLate)(O^{i}Pr)$_2$ (**10**).

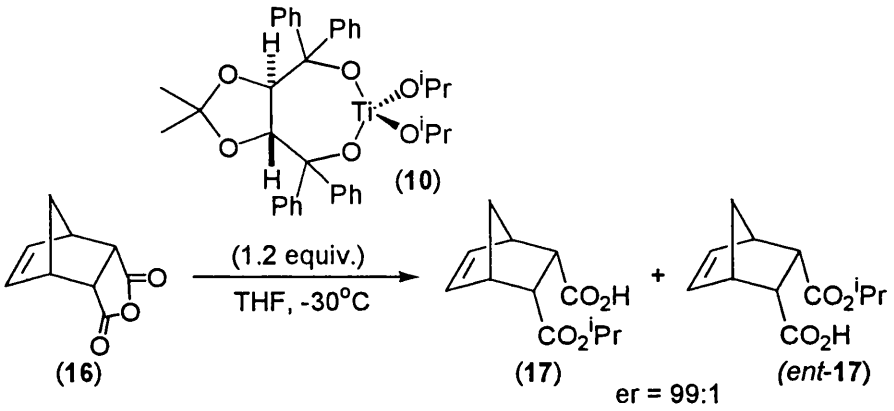
1.3.3 Enantioselective ring opening of *meso*-anhydrides

Enantioselective reactions of C_S-symmetrical molecules containing enantiotopic groups on a so-called prochirality center[60] or in compounds of *meso*-configuration[61] are among the most useful conversions in asymmetric synthesis (**Scheme 25**). The underlying principle has been called 'asymmetric desymmetrisation'.[62] Differentiating between two enantiotopic functional groups in *meso*-compounds leads to the creation of two or more chiral centres. While the ability of enzymes to differentiate between enantiotopic functional groups is well known,[63] the utility of non-enzymatic methods to achieve the same goal has been less well recognised until recently.[64]



Scheme 25

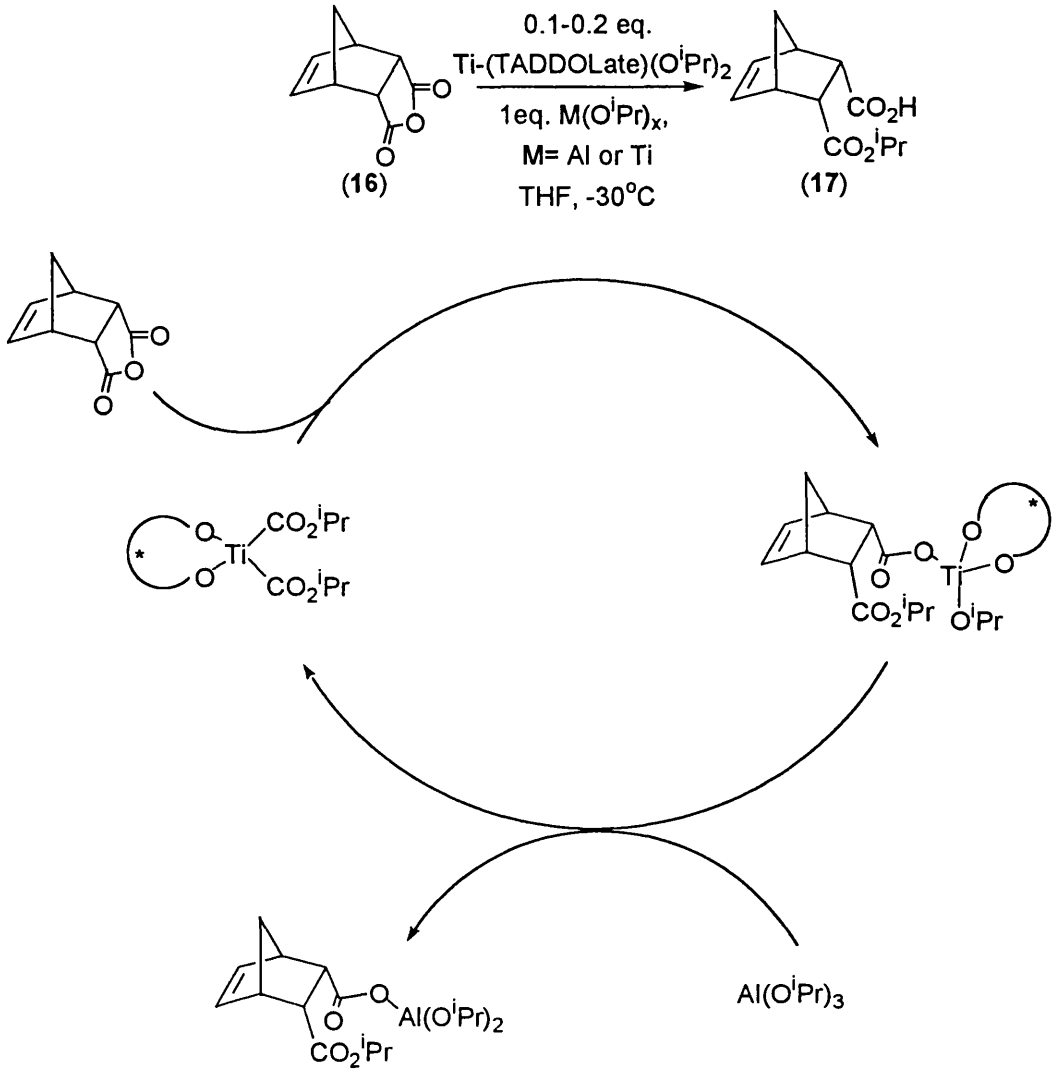
It is already known that $Ti(O^iPr)_4$ catalyses the *trans*-esterification and deacylation processes very cleanly under mild conditions.[44] The group of Seebach[65] have reported that the Lewis acid mediated transfer of an alkoxide ligand, from the chiral ligand sphere of Ti-(TADDOLate)$(O^iPr)_2$, to cyclic *meso* anhydrides afforded the corresponding hemiesters, without any side products.



Scheme 26

Using a stoichiometric amount of Ti-(TADDOLate)(O^{i}Pr)$_2$ (**10**), the commercially available *endo*-Diels–Alder adduct (**16**) of maleic anhydride and cyclopentadiene was opened cleanly to the corresponding isopropyl hemiester (**17**) with an enantiomeric ratio of 99:1. A variety of monocyclic, bicyclic, and tricyclic anhydrides were ring opened by Ti-(TADDOLate)(O^{i}Pr)$_2$ under similar conditions in good yields and with similar enantioselectivities.[65]

The dramatic effect of ligand acceleration[40] (See **Section 1.3.1**) observed in the Ti-(TADDOLate)(O^{i}Pr)$_2$ catalysed addition of a dialkylzinc or an alkyltitanium reagent to an aldehyde,[48,59,66] prompted Seebach to use a sub-stoichiometric amount of Ti-(TADDOLate)(O^{i}Pr)$_2$ in the presence of a stoichiometric amount of Ti(O^{i}Pr)$_4$ in the ring opening reaction of (**16**). As in the foregoing reaction, the addition of Ti(O^{i}Pr)$_4$ would ideally regenenerate the "active" catalyst, but not compete with it in a nonstereoselective ring opening reaction. It was found that the Ti-(TADDOLate)(O^{i}Pr)$_2$ mediated ring opening reaction was 2-3 times faster than the Ti(O^{i}Pr)$_4$ mediated one. Using 15mol% of the Ti-(TADDOLate)(O^{i}Pr)$_2$ (**12**) (β-naphthyl) and 80mol% Ti(O^{i}Pr)$_4$, the hemiester (**17**) was obtained in 80%yield and with 34%ee. Better results were obtained by replacing Ti(O^{i}Pr)$_4$ with Al(O^{i}Pr)$_3$. By using 20mol% of the Ti-(TADDOLate)(O^{i}Pr)$_2$ (**12**) (β-naphthyl) and 80mol% Al(O^{i}Pr)$_3$, the hemiester (**17**) was obtained in 74%yield and with 96%ee. A proposed catalytic cycle is shown in **Scheme 27**.

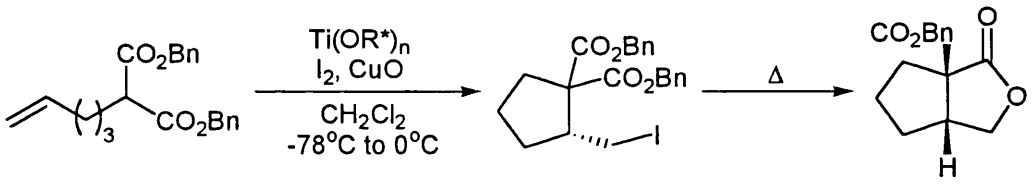

0.1-0.2 eq.
Ti-(TADDOLate)(O^{i}Pr)$_2$
1eq. M(O^{i}Pr)$_x$,
M= Al or Ti
THF, -30°C
(16)
(17)
CO$_2$H
CO$_2$^{i}Pr
Ti
O^{i}Pr
Al(O^{i}Pr)$_2$
Al(O^{i}Pr)$_3$

Scheme 27

1.3.4 Catalytic Asymmetric Iodocarbocyclisation reaction

Since the halocyclisation reaction usually proceeds in the presence of an electrophilic halogenating reagent without the need for any activating catalyst[67], it follows that asymmetric catalysis of these reactions should be difficult be achieve. Nevertheless, Taguchi and coworkers[68] have reported that catalytic asymmetric iodocarbocyclisation can proceed with excellent enantioselectivities (≥95%ee) in the presence of a catalytic amount of Ti(TADDOLate)$_2$.

The iodocarbocyclisation reaction of dibenzyl-4-pentenylmalonate (**18**) was conducted with 1.0 equivalent of a chiral titanium (IV) alkoxide, 1.2 equivalents of I_2, 1.2 equivalents of CuO in CH_2Cl_2 in order to examine the enantioselectivity. Using a 1:1 complex of Ti-(TADDOLate)(O^{i}Pr)$_2$ (**10**) gave a good yield of the cyclised product (**20**) with 32%ee in 86%yield. Furthermore, the use of the 1:2 complex Ti-(TADDOLate)$_2$ (**11**) led to an increase in both enantioselectivity and chemical yield to give the product (**20**) of 85%ee in 96%yield (**Scheme 28**).



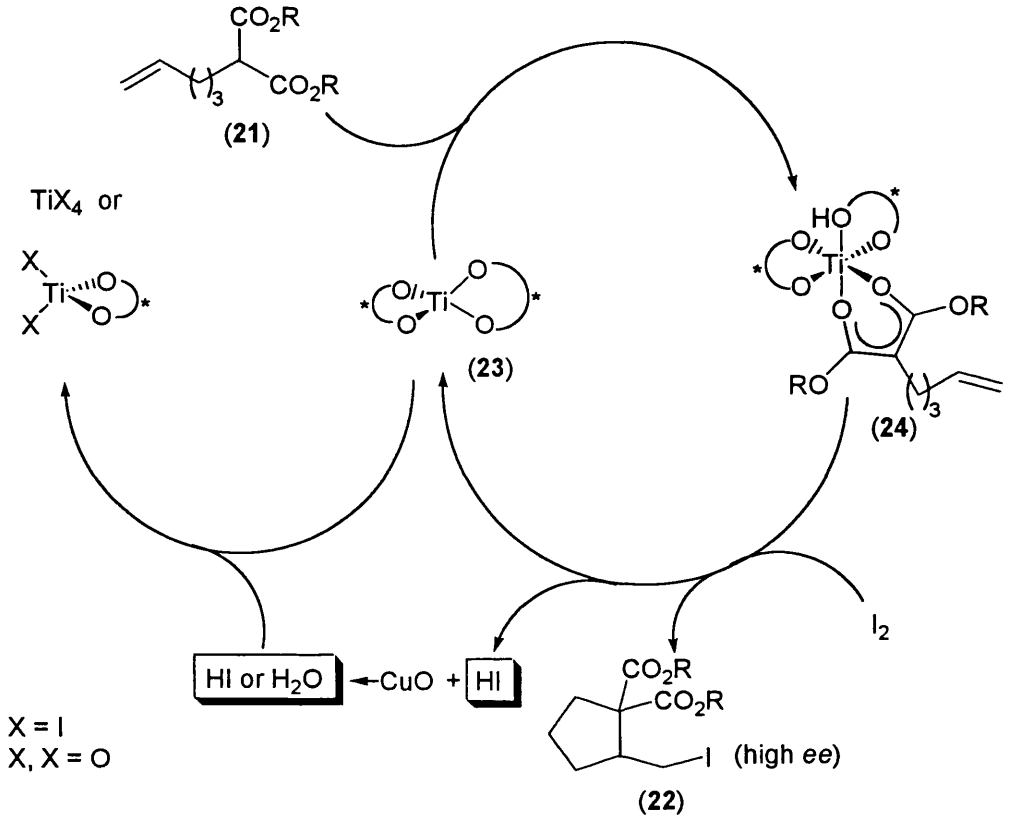
(**18**) (**19**) (**20**)

Ti(OR*)$_n$ (1eq)	Yield (%)	ee(%)
Ti-(TADDOLate)(O^{i}Pr)$_2$ (**10**)	86	32
Ti(TADDOLate)$_2$ (**11**)	96	85

Scheme 28

A mechanism for this reaction has been proposed (**Scheme 29**). Ti(TADDOLate)$_2$ (**23**) promotes the deprotonation of malonate (**21**) to produce the chiral Ti (IV) enolate (**24**). Intramolecular attack of (**24**) on a double bond activated by I_2 may then give the cyclised product (**22**) in a highly enantioselective manner together with the regeneration of the Ti(TADDOLate)$_2$ (**23**) catalyst. In the presence of CuO, however Ti(TADDOLate)$_2$ (**23**) can be converted by HI or H_2O to regenerate other Ti (IV) species such as

(TADDOLate)TiX_2 or TiX_4 (X = I or X_2 = O), which results in the decrease in enantioselectivity and the chemical yield (**Scheme 29**).

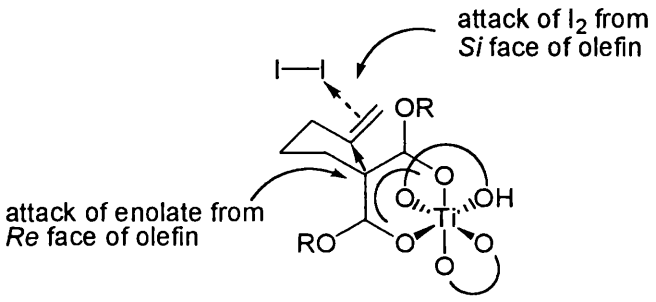


Scheme 29

Thus, the trapping of hydrogen iodide without generation of H_2O would be crucial in order to achieve a catalytic cycle. It was found that when dimethoxy pyridine (DMP) or Et_3N was employed as a hydrogen iodide scavenger, the reaction proceeded smoothly in the presence of 30mol% of Ti(TADDOLate)$_2$ (**11**) to give the cyclised product (**20**) with a higher enantiomeric excess than that obtained in the reaction using a stoichiometric amount of Ti(TADDOLate)$_2$ (**11**) and CuO. The reaction of (**18**) with 30mol% Ti(TADDOLate)$_2$ (**11**), 2 equivalents of DMP and 4 equivalents of I_2 gave the product (**20**) in 97%yield and with 97%ee. Performing the same reaction with Et_3N gave the product (**20**) in 70%yield with 98%ee.

The use of THF as a co-solvent was also found to be beneficial to both the reactivity and enantioselectivity. The reaction with 10mol% Ti(TADDOLate)$_2$ (**11**) in a 4:1 ratio of DCM:THF proceeded in 98%yield even at –78°C to give (**20**) of 98 %ee.

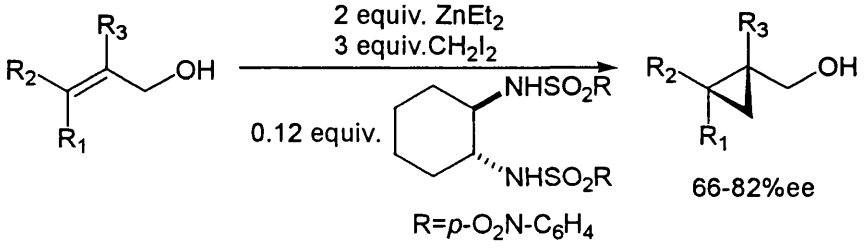
The absolute configurations of the cyclised products (**20**) clearly indicates that the reaction of (**18**) proceeds in the same enantiofacial selective manner; that is, in all cases with Ti(TADDOLate)$_2$ (**23**) prepared from (*R*,*R*)-TADDOL, the enolate and I_2 attack in a *trans*-addition manner from the *Re* and *Si* faces of the olefin, respectively (**Scheme 30**).



Scheme 30

1.3.5 Enantioselective cyclopropanation of allylic alcohols

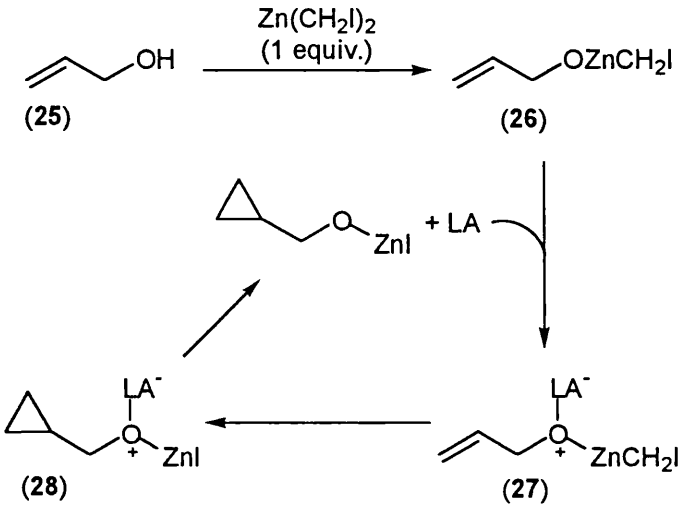
There are very few reported methods for the enantioselective (iodomethyl)zinc mediated cyclopropanation of allylic alcohols compared to most carbon–carbon bond-forming reactions. Good enantioselectivities were reported by the Kobayashi group[69,70] using a catalytic amount of a C_2-symmetric chiral disulfonamide in the (iodomethyl)zinc mediated cyclopropanation of allylic alcohols.



Scheme 31

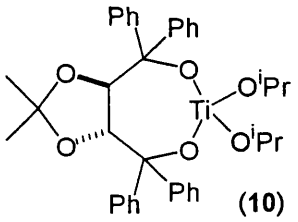
The major drawbacks of this reaction however is that the rate of the uncatalysed reaction is not overwhelmingly different from that of the catalysed process. Kobayashi have reported that a 20%yield of the cyclopropyl derivative was obtained even in the absence of the chiral Lewis acid.

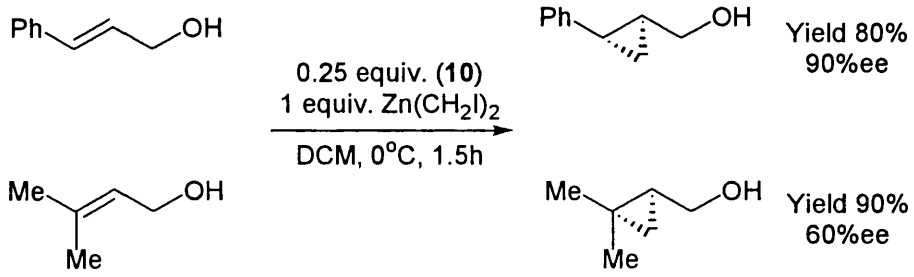
Charette[71] found a new strategy for the Lewis acid catalysed cyclopropanation of allylic alcohols in which the rate of the uncatalysed process is significantly slower than that of the catalysed process. The basis of this new strategy relies on the fact that treatment of an allylic alcohol (**25**) with 1 equivalent of $Zn(CH_2I)_2$ should produce the (iodomethyl)zinc alkoxide (**26**) and CH_3I (**Scheme 32**). These alkoxides do not undergo rapid cyclopropanation at low temperature, based on low temperature NMR experiments.[72] The addition of a Lewis acid to this intermediate however was found to trigger the subsequent cyclopropanation reaction by increasing the electrophilicity of the methylene group upon complexation (**27**). Subsequent formation of the halozinc alkoxide (**28**) and regeneration of the Lewis acid then completed the catalytic cycle.



Scheme 32

Preliminary results using chiral catalysts confirmed that the Lewis acid is involved in the transition state. Enantiomerically enriched cyclopropylmethanol moieties were obtained using 0.25 equivalents of Ti-(TADDOLate)(O^iPr)$_2$ (**10**) in the cyclopropanation reactions **Scheme 33**).

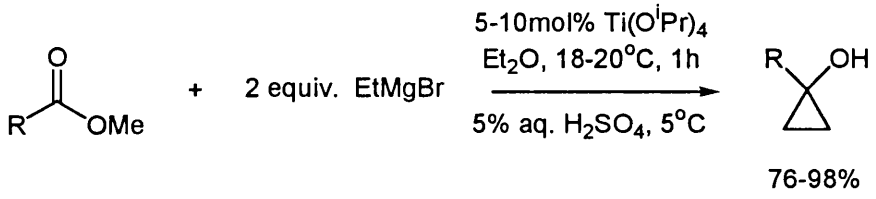




Scheme 33

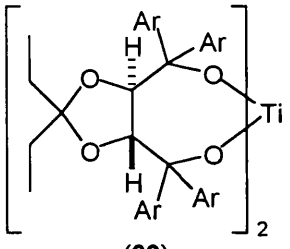
1.3.6 Catalytic enantioselective synthesis of *cis*-1,2-disubstituted cyclopropanols from esters (Kulinkovich reaction)

Kulinkovich have reported the reaction of ethereal ethylmagnesium bromide (3 equiv.) with *n*-alkanoic acid methyl esters in the presence of titanium(IV) isopropoxide (1 equiv.) at –78 to –40°C produces 1-alkylcyclopropanols in good yields.[73] This novel reaction, which in a formal sense involves an ethane dianion ($^{\ominus}CH_2$–$CH_2^{\ominus}$) equivalent, can also be conducted with substoichiometric amounts of $Ti(O^iPr)_4$ (0.05-0.1 equiv.) at 20°C (**Scheme 34**).[74]

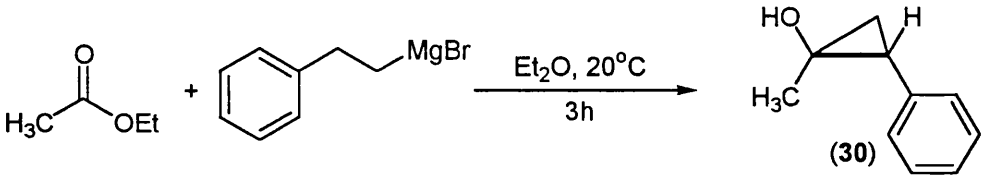


Scheme 34

Subsequently, the Corey group[75] have reported preliminary studies on the development of an enantioselective version of the cyclopropanol synthesis. Especially encouraging was the use of the chiral catalyst (**29**), which afforded chiral cyclopropanol (**30**) as shown in **Scheme 35**. In the case of (**29**), Ar = 3,5-bis(trifluoromethyl)phenyl, 0.3-1equiv, cyclopropanol (**30**) was produced in 65-72% yield and 70-78%ee.



(**29**)

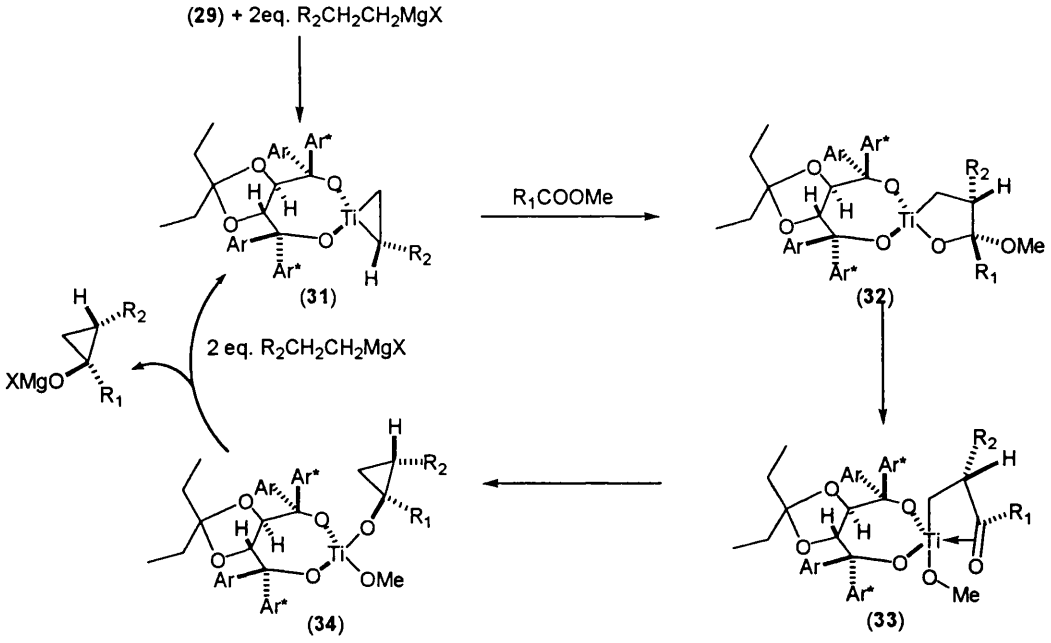


(**30**)

65-72% yield
70-78%ee

Scheme 35

The observed absolute and relative stereochemical preferences for the formation of chiral *cis*-1,2-disubstituted cyclopropanols such as (**30**) are consistent with a titanacyclopropane[74,76] pathway as shown in **Scheme 36**. Thus, reaction of the chiral titanate reagent (**29**) with 2 equiv of Grignard reagent leads stereoselectively to the more stable diastereomeric titanacyclopropane (**31**), in which the substituent R_2 is furthest away from the nearest (axial Ar*) Ar group. The next step, (**31**→**32**) involves position-selective expansion of the titanacyclopropane ring by insertion of the ester carbonyl group between Ti and the more substituted carbon. This bond selective insertion finds precedent in recent work on the zirconium-catalysed carbomagnesiation of olefins[77]. The insertion reaction (**31**→**32**) is also diastereoselective for the geometry in which the two larger groups R_1 and R_2 are *trans* to one another. Oxidative addition of the MeO–C linkage of (**32**) to Ti leads to intermediate (**33**) in which there is a face-specific π-donor coordination of C=O group to Ti(IV). Subsequent reductive elimination affords the *cis*-1,2-disubstituted cyclopropanol complex (**34**), the absolute configuration of which agrees with that experimentally determined for (**30**).

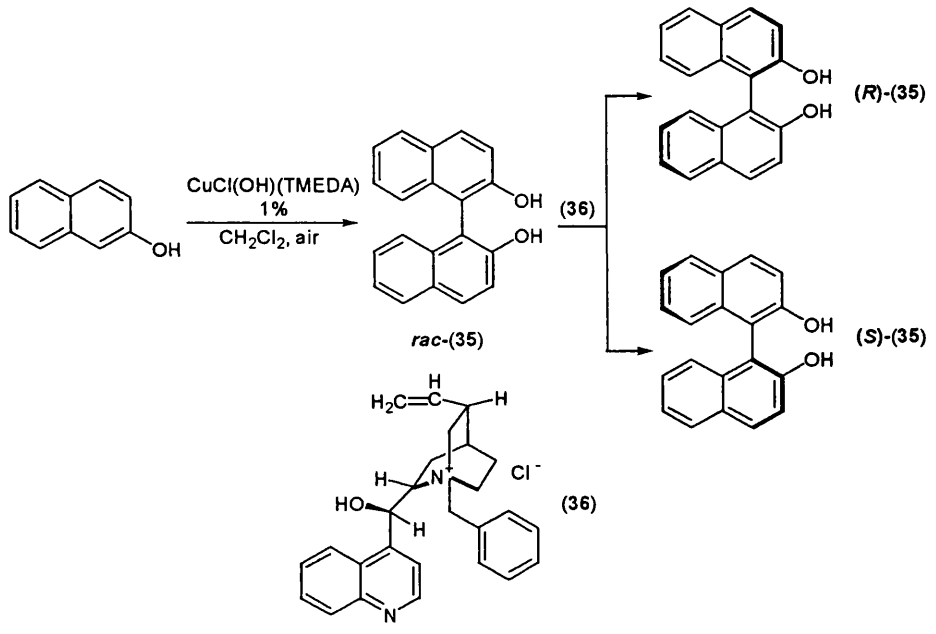


Scheme 36

The third class of ligand which has been extensively investigated in titanium alkoxide chemistry is the so-called BINOL system. Because of their highly stable chiral configuration, 2,2'-substituted 1,1'-binaphthyls have been extensively used to control many asymmetric processes and have demonstrated outstanding chiral discrimination properties.[78,79,80] The rigid structure and the C_2 symmetry play an important role in chiral induction.

1.4 Titanium BINOL complexes

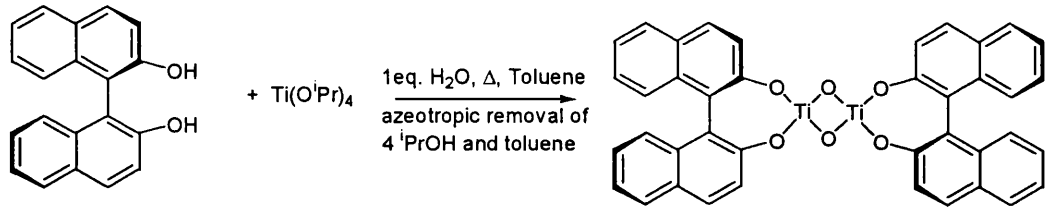
1,1'-Bi-2,2'-naphthol (BINOL), (**35**), often serves as the starting material for obtaining chiral binaphthyl compounds.[78,79,80] The 2,2'-hydroxyls of (**35**) can easily be converted into other functional groups. In addition the 3,3'-, 4,4'-, and 6,6'-positions can be selectively functionalised leading to a variety of binaphthyl derivatives. To resolve racemic (**35**) into its optically pure *R*- and *S*- enantiomers, the use of (8*S*,9*R*)-(-)-*N*-benzyl cinchonidinium chloride (**36**) is considered the simplest and most efficient laboratory procedure (**Scheme 37**).[81,82] Racemic (**35**) is produced on a large scale from the oxidative coupling of 2-naphthol in air in the presence of a copper catalyst (**Scheme 37**).[83,84]



Scheme 37

1.4.1 Enantioselective Ene reaction of glyoxylates

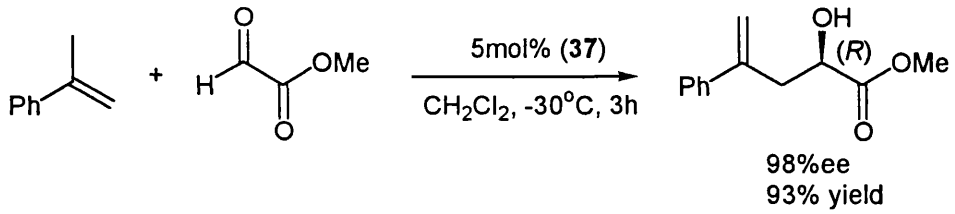
Nakai[85] reported a new type of chiral BINOL derived titanium complex (**37**). This complex is prepared *in situ* by mixing equimolar quantities of $Ti(O^iPr)_4$ and (*R*)-BINOL in toluene containing one equivalent of water under reflux followed by removal of the isopropanol liberated and complete removal of toluene under reduced pressure. The product serves as an efficient and moisture tolerable enantioselective catalyst for the glyoxylate-ene reaction. The ^1H NMR spectrum of the resulting complex (**37**), coupled with molecular weight measurements, led to the proposed μ-oxo dimer structure shown for the new catalyst (**Scheme 38**).



(37)

Scheme 38

Using complex (**37**) as a catalyst, the ene reaction of α-methylstyrene with methyl glyoxylate in dichloromethane provided the ene product in a remarkably high enantiomeric purity (98%ee) and chemical yield (93%) (**Scheme 39**).

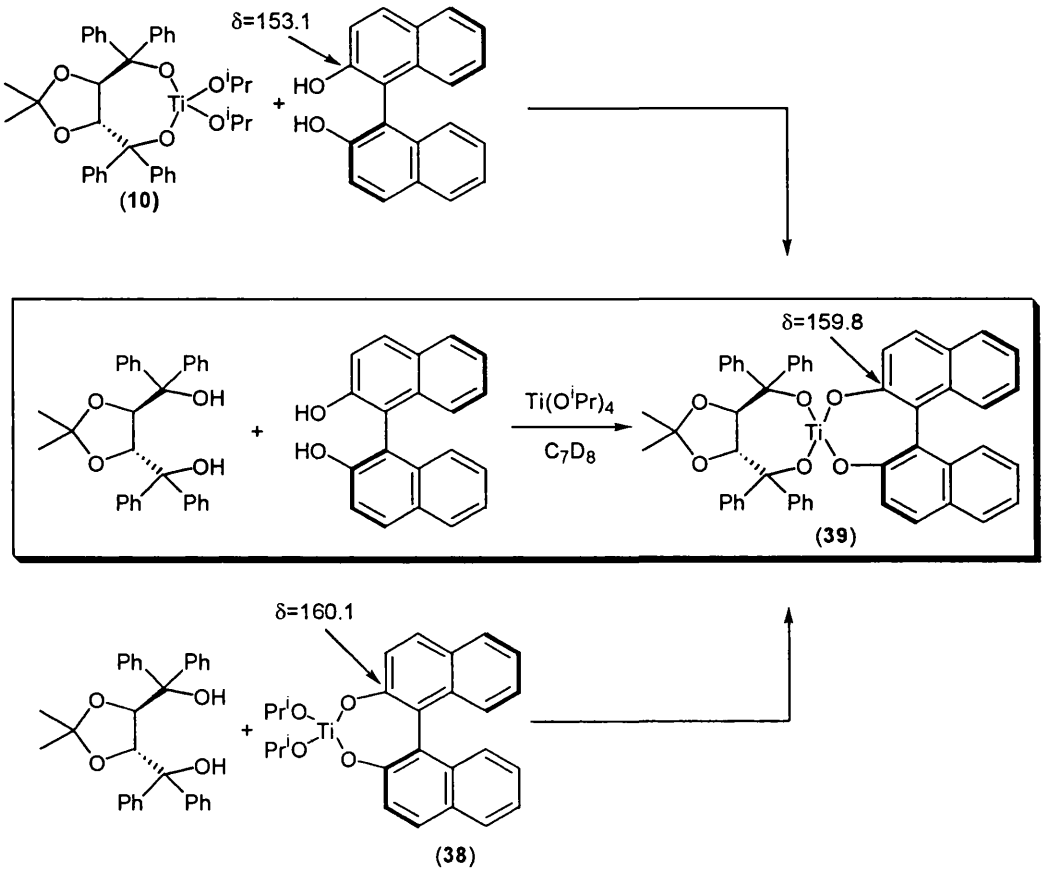


Scheme 39

In a more empirical approach, Mikami[86] have reported the self-assembley of a chiral titanium catalyst from an achiral precursor such as $Ti(O^iPr)_4$ and two different chiral diol components as exemplified for the two catalysts (**Scheme 40 and 41**), each of which can be prepared by three routes.

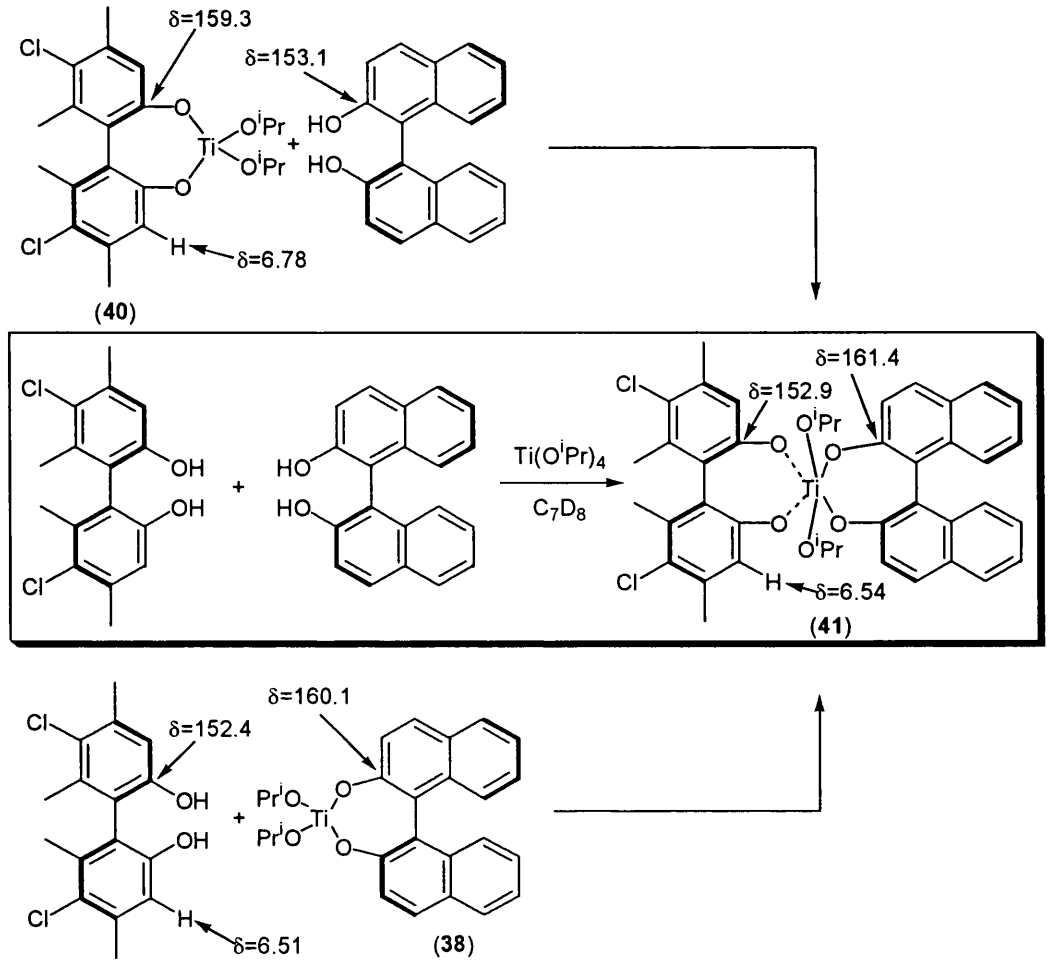
Thus, the combination of (*R*)-BINOL and (*R*)-TADDOL with $Ti(O^iPr)_4$ in a molar ratio of 1:1:1 provided a single chiral titanium complex. The Ti-(BINOLate)(TADDOLate) complex

(**39**) was characterised by ^{13}C and ^{1}H NMR spectroscopy in d_8 toluene. These NMR spectroscopic studies also confirmed the absence of any other complexes, especially the symmetrically substituted Ti-(TADDOLate)$_2$ and Ti-(BINOLate)$_2$. However complex (**39**) can also be obtained from Ti-(TADDOLate)(O^{i}Pr)$_2$ (**10**)[54] by addition of (*R*)-BINOL and from Ti-(BINOLate)(O^{i}Pr)$_2$ (**38**)[87,89,90] by addition of (*R*)-TADDOL (**Scheme 40**).



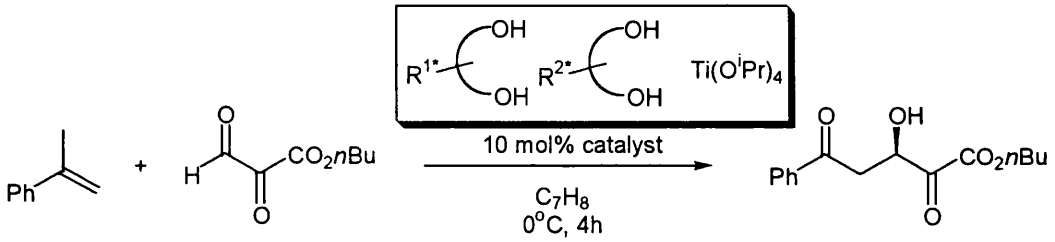
Scheme 40

In similar fashion, Ti-(BINOLate)(5-Cl-BIPOLate)(O^{i}Pr)$_2$ (**41**) (5-Cl-BIPOL = 5,5'-dichloro-4,4',6,6'-tetramethyl-2,2'-biphenol) can be prepared from Ti(O^{i}Pr)$_4$ by treatment with (*R*)-BINOL and a more acidic diol such as (*R*)-5-Cl-BIPOL.[88] Both the addition of (*R*)-5-Cl-BIPOL to Ti-(BINOLate)(O^{i}Pr)$_2$ (**38**) and the addition of (*R*)-BINOL to Ti-(5-Cl-BIPOLate)(O^{i}Pr)$_2$ (**40**)[88] afforded the complex (**41**), whose formation as the sole product of the reaction was again characterised by ^{1}H and ^{13}C NMR spectroscopy (**Scheme 41**).



Scheme 41

The importance of this selective multi-component self-assembly has been demonstrated in the enantioselective catalysis of the carbonyl-ene reaction and the results clearly indicate that a highly enantioselective catalyst is formed. The catalyst was prepared by mixing the components in a molar ratio of 1:1:1 and used *in situ* with 10mol% of catalyst employed with respect to olefin and glyoxylate (**Scheme 42**).



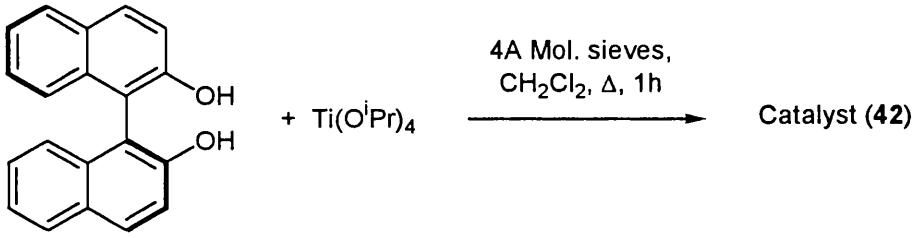
Ti-(BINOLate)(TADDOLate) (**39**) = 91%ee, 50%yield

Ti-(BINOLate)(5-Cl-BIPOLate)(O^iPr)$_2$ (**41**) = 97%ee, 66%yield

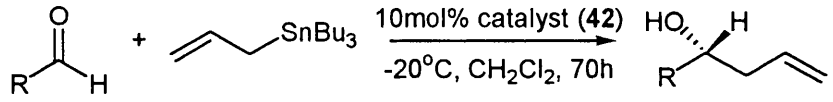
Scheme 42

1.4.2 Catalytic Asymmetric Allylation of Aldehydes (CAA reactions)

The Keck group[89] have reported high levels of enantioselectivity in the catalytic asymmetric allylation of aldehydes. There are two methods to prepare the catalyst. In the first procedure, the catalyst (**42**) was prepared by heating a 1:1 mixture of (*R*)- or (*S*)-BINOL and $Ti(O^iPr)_4$ with powdered 4A molecular sieves at reflux in dichloromethane (**Method A**). A second procedure (**Method B**) is identical, except that a 2:1 BINOL/ titanium stoichiometry was used and a catalytic amount of acid (CF_3SO_3H or CF_3CO_2H) was also required for optimum results. Using 10mol% of catalyst (**42**), the reaction of allyl-tri-*n*-butylstannane with aldehydes provided the corresponding homoallyl alcohols with enantiomeric purities of 77-96% (**Scheme 43**).



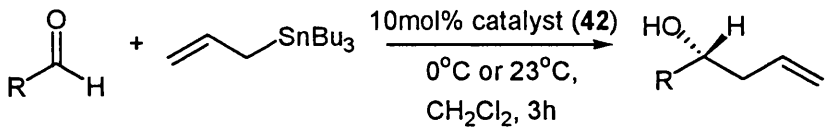
Method A [1:1 ratio BINOL : $Ti(O^iPr)_4$]
Method B [2:1 ratio BINOL : $Ti(O^iPr)_4$], cat. CF_3SO_3H or CF_3CO_2H



Method A: 89-96%ee, 42-93%yield
Method B: 77-96%ee, 78-98%yield

Scheme 43

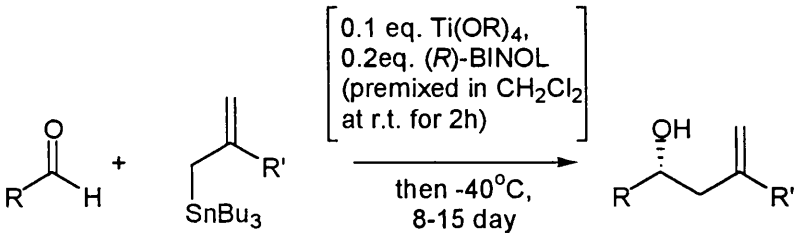
The same group later reported a simplified and highly efficient version for reactions using the 2:1 BINOL/Ti catalytic system[90] in which catalyst (**42**) preparation was accomplished under strictly homogeneous conditions. In addition, the allyl addition reactions could then be conducted at more convenient temperatures. Reactions in the presence of 10mol% catalyst (**42**) at 0°C or 23°C provided homoallyl alcohols in comparable enantiomeric purity with the previous results (see **Scheme 43 and 44**).



0°C : 83-95%ee, 59-94%yield
23°C: 71-96%ee, 58-92%yield

Scheme 44

Using similar procedures to those published by Keck[89,90], Brückner[91] have reported highly enantioselective additions of β-substituted allylstannanes to aldehydes. Functionalised allyl-tri-*n*-butyl stannanes can add their β-substituted allyl groups with or without heteroatoms in the side chain to aldehydes with a high degree of enantiocontrol, when the reaction is catalysed by a species generated *in situ* from 10mol% of $Ti(OEt)_4$ or $Ti(O^iPr)_4$ and 20mol% of enantiopure BINOL. The enantioselectivities of most additions could be further increased by allowing the catalyst components to react for approximately 2h, rather than only 1h, before the reagent and the aldehyde were added (**Scheme 45**).

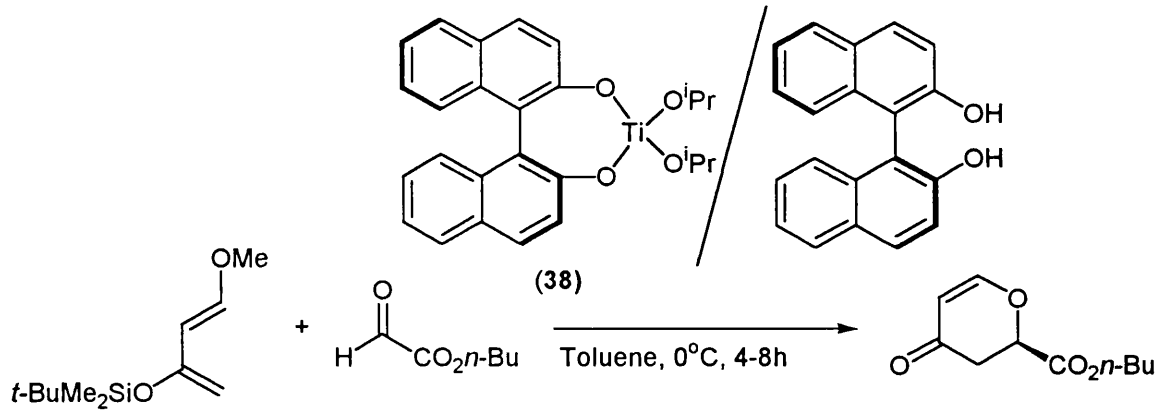


Scheme 45

1.4.3 Asymmetric catalysis of Diels-Alder reactions

The Mikami group[92] have also described how the further addition of a chiral activator can selectively activate one enantiomer of a chiral catalyst, with the new diastereoisomeric complex giving higher enantioselectivity than that achieved by the single enantiomer itself, in addition to a higher level of catalytic efficiency. This was demonstrated in the titanium(IV) catalysed Diels-Alder reaction of a Danishefsky diene with a glyoxylate ester.

The catalyst was prepared by mixing chiral diols such as BINOL or TADDOL and $Ti(O^iPr)_4$ at a ratio of 1:1 in toluene for 20min, then adding one equivalent of chiral activator such as 5-Cl-BIPOL or BINOL. The Diels-Alder reaction was carried out *in situ* through further addition of the Danishefsky diene and glyoxylate at 0°C (**Scheme 46**).



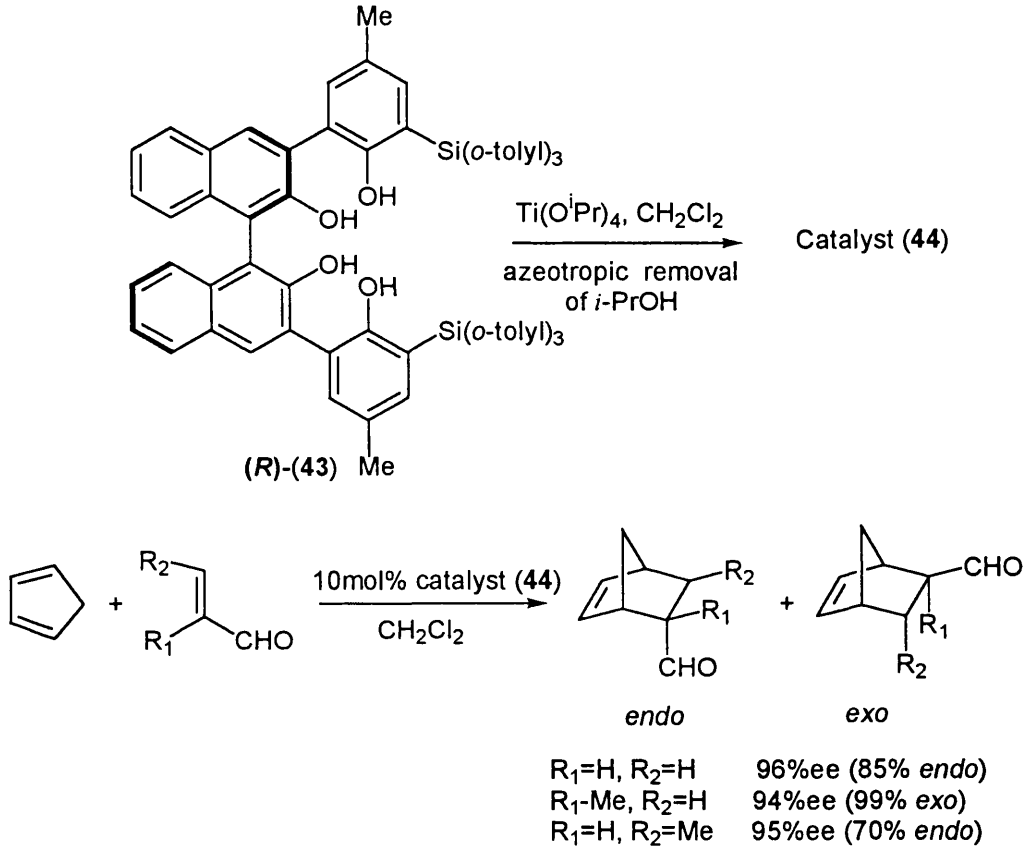
Scheme 46

Significantly high asymmetric induction was observed using Ti-(BINOLate)$(O^iPr)_2$ (**38**) and the (*R*)-BINOL activator especially when compared to the values obtained using the Ti-(BINOLate)$(O^iPr)_2$ (**38**) catalyst without the addition of further chiral diol (40%, 5%ee).

The Yamamoto group[93] have recently reported a new type of chiral helical titanium reagent, prepared from $Ti(O^iPr)_4$ and a chiral ligand derived from optically pure BINOL. These reagent have been successfully utilised as efficient chiral templates for the conformational fixation of α,β-unsaturated aldehydes, thereby allowing efficient

enantioface differentiation of the substrates in asymmetric Diels-Alder reactions with dienes, regardless of reaction temperature.

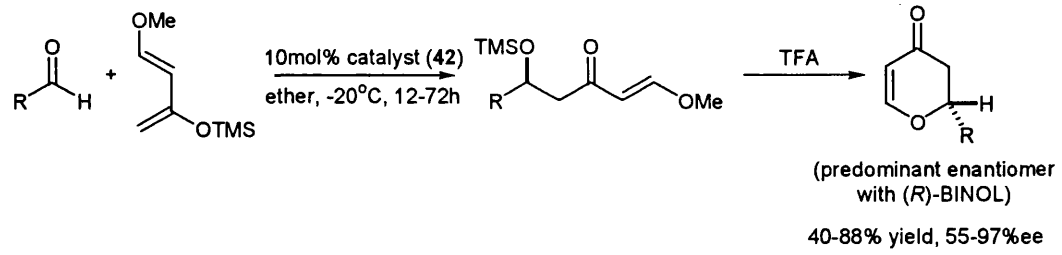
The chiral titanium reagent (**44**) was prepared by treatment of (***R***)-(**43**) with $Ti(O^iPr)_4$ with azeotropic removal of isopropanol. Using α,β-unsaturated aldehydes and dienes in the presence of 10mol% titanium catalyst (**44**), the Diels-Alder adducts were produced with a uniformly high level of enantioselectivity (81-98%ee). These reactions can be conducted at temperatures between −78°C and 0°C, while still maintaining a high level of asymmetric induction (**Scheme 47**).



Scheme 47

Keck *et al.*[94] also reported the use of chiral titanium catalyst (**42**) developed for the CAA reaction in the enantioselective hetero Diels-Alder reaction of Danishefsky's diene with aldehydes (**See section 1.4.2**). The method which produced the best result involves using a 2:1 BINOL/$Ti(O^iPr)_4$ stoichiometry in the presence of 4A MS and 0.003 equiv. CF_3CO_2H in ether. Using 10mol% of catalyst (**42**), the reaction of a variety of aldehydes

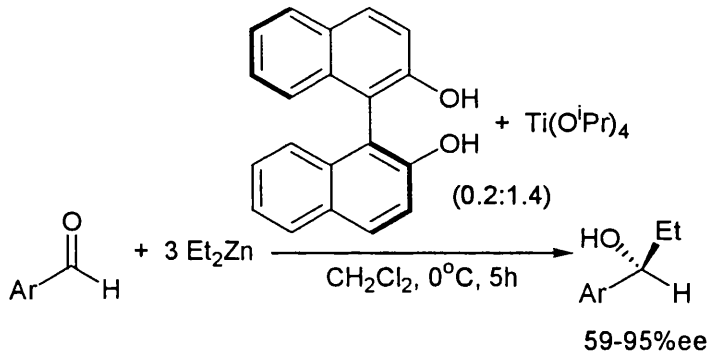
with 1-methoxy-3-[(trimethylsilyl)oxyl]-butadiene afforded the corresponding Mukaiyama aldol products, which were subsequently cyclised by exposure to CF_3CO_2H in CH_2Cl_2 to yield dihydropyrones (50-88%) with good to excellent enantiomeric excess (75-97%) (**Scheme 48**).



Scheme 48

1.4.4 Dialkylzinc addition to aldehydes

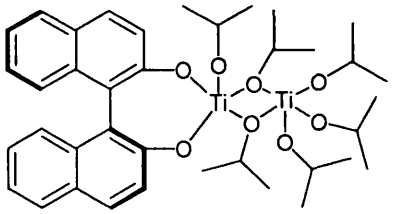
The enantioselective addition of diethylzinc to aldehydes was reported by Chan[95] and conveniently achieved by using a catalyst prepared *in situ* by mixing 1.4 equivalents of $Ti(O^iPr)_4$ with 0.2 equivalents of *S*- or *R*-BINOL. Optical yields as high as 95% were observed (**Scheme 49**).



Scheme 49

Later, in a more detailed publication, Nakai[96] stated that the generation of Ti-(BINOLate)$(O^iPr)_2$ (**38**), from mixing a 1:1 ratio of BINOL with $Ti(O^iPr)_4$, is only acting as a pre-catalyst. By using NMR experiments to identify the actual catalytic species, it was found that complex (**38**) readily reacts with excess $Ti(O^iPr)_4$ to form a new species probably identical with complex (**45**) which might act as the actual asymmetric catalyst. Although the exact structure is not yet known, the reported structures of related

complexes[97] lead to the proposed dimeric structure having one BINOL ligand and six isopropoxy ligands (**Scheme 50**).



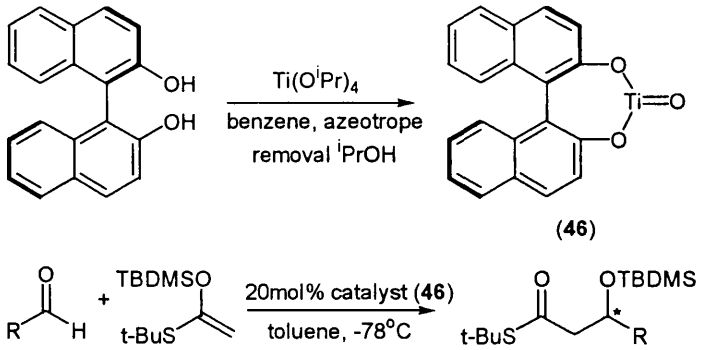
45

Scheme 50

1.4.5 Mukaiyama aldol reaction

The Mukaiyama group[98] have found that the use of [(*R*)-1,1-benzenediolato-(-2-)-O,O']-oxotitanium (**46**) is very effective in the asymmetric aldol reaction of silyl enol ethers with aldehydes.

The catalyst (**46**) was prepared by mixing a stoichiometric amount of (*R*)-BINOL with $(^{i}PrO)_2Ti{=}O$[99] in benzene, followed by azeotropic removal of isopropanol. The reaction of a variety of aldehydes with silyl enol ethers of thioesters, in the presence of 20mol% (**46**), afforded the corresponding aldol adducts in 36-85%ee (**Scheme 51**).



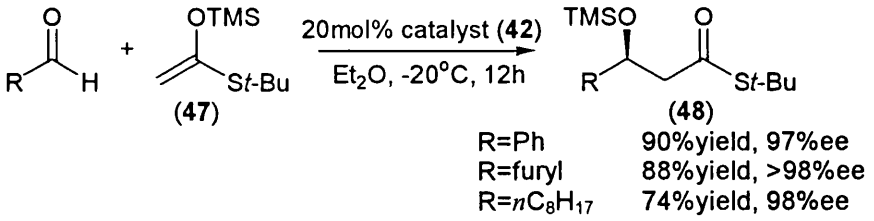
Scheme 51

Keck *et al.*[100] reported the use of their titanium complex (**42**), described earlier in the catalytic asymmetric allylation (CAA) reaction, in the enantioselective Mukaiyama aldol condensation. The titanium complex was prepared by two methods: (**A**) heating (*S*)-BINOL, $Ti(O^{i}Pr)_4$ and 4A MS in refluxing CH_2Cl_2 for 1h, with 1:1 stoichiometry of

BINOL/Ti,[89,101] and (**B**) stirring a solution of (*S*)-BINOL and $Ti(O^iPr)_4$ at 2:1 stoichiometry for 1h, again in CH_2Cl_2.[90,101]

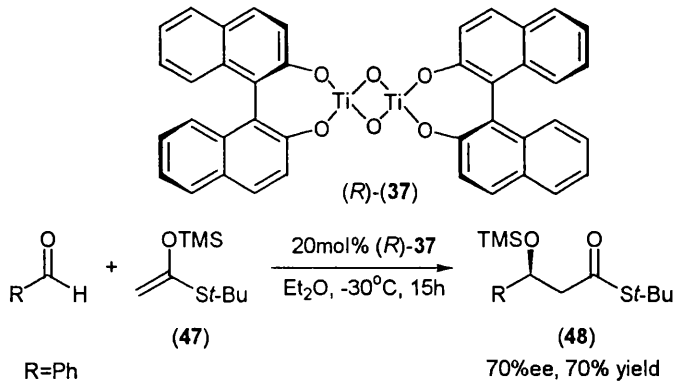
Catalytic enantioselective Mukaiyama aldol condensation of 1-(*tert*-butylthio)-1-((trimethylsilyl)oxy)ethene (**47**) with benzaldehyde using 20mol% of the titanium complex (**42**), prepared by **method B**, led to isolation of the aldol adduct (**48**) in 86% yield with 91%ee. Performing the same reaction using titanium complex, generated by **method A**, resulted in isolation of the aldol adduct in 90% yield with 97%ee.

These conditions were employed with a series of alkyl, aryl, and α,β-unsaturated aldehydes. The results are unifomly excellent in terms of both isolated yield (74-90%) and enantiomeric excess (89->98%) (**Scheme 52**).



Scheme 52

Nakai *et al.*[85] have also reported that the titanium-BINOL μ-oxo dimer (**37**) (see **Section 1.4.1**) serves as an enantioselective catalyst for the aldol reaction of benzaldehyde with the 1-(*tert*-butylthio)-1-((trimethylsilyl)oxy)ethene (**47**) to afford adduct (**48**) with 70%ee in 70%yield (**Scheme 53**).



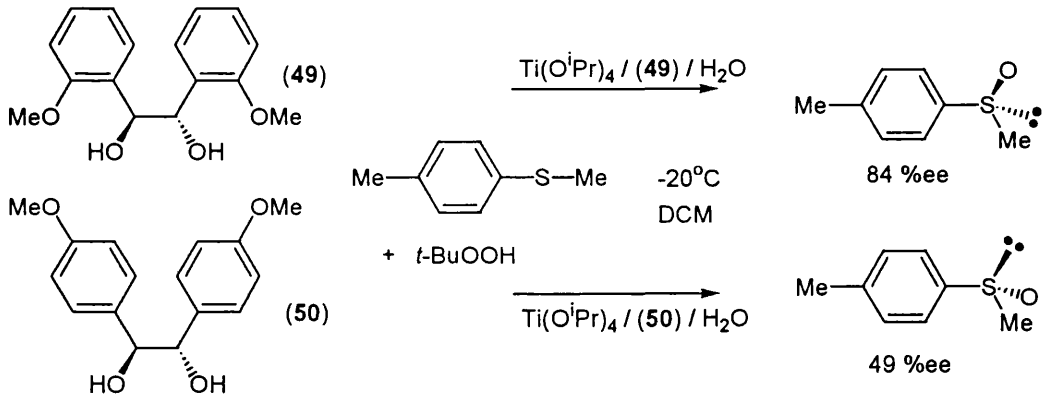
Scheme 53

Finally, for titanium alkoxides a variety of other ligand systems not derived either from tartrate or from BINOL have been explored.

1.5 Other Titanium Catalysts

1.5.1 Oxidation of sulfides to sulfoxides

In a contrasting study by Yamamoto[102], it was found that sulfoxidation of methyl *p*-tolyl sulfide gave the corresponding sulfoxide with 84 %ee using 1,2-bisaryl-1,2-ethanediol as the chiral ligand. Interestingly, there was a reversal of absolute configuration in going from the bis(*o*-anisyl) ligand (**49**) to the bis-(*p*-anisyl) ligand (**50**) of the same absolute configuration (**Scheme 54**).

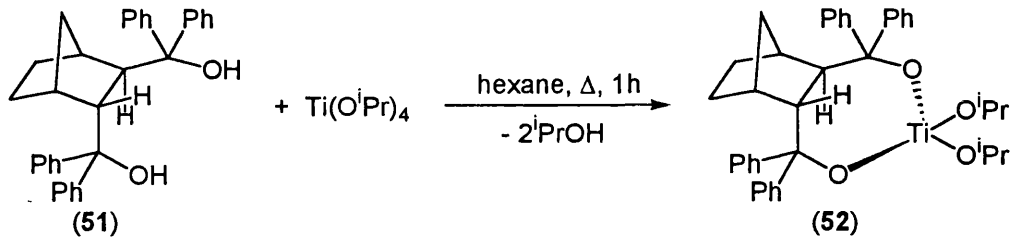


Scheme 54

Catalytic conditions have also been developed, by Rosini and Superchi,[103] using a water-modified titanium complex having a 1,2-diphenylethane-1,2-diol as ligand. The authors found experimental conditions, which avoid both the over-oxidation to sulfones and ligand decomposition. The reaction of aryl methyl sulfides was performed at 0°C with 2 equivalents of TBHP in the presence of 5 mol% of the combination $Ti(O^iPr)_4$/1,2-diphenylethane-1,2-diol/H_2O = 1:2:20. This catalytic method allowed 80%ee to be reached for some sulfoxides.

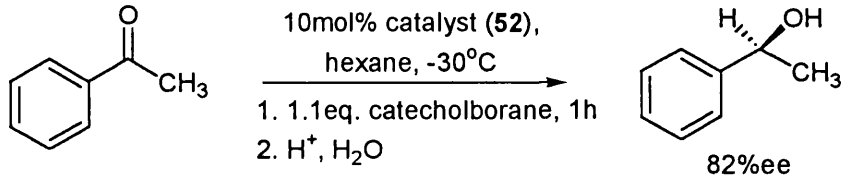
1.5.2 Enantioselective reduction of Ketones with Catecholborane

The use of titanium alkoxides as Lewis acids has also featured in the reduction of the carbonyl group. Wandrey *et al.*[104] reported TADDOL-analogous ligands serves as efficient catalysts in the reduction of prochiral ketones when boranes are used as reducing agents. The corresponding titanium alkoxide (**52**) was prepared *in situ* from 1.15 equivalents of the ligand (**51**) and 1.0 equivalents of titanium(IV) isopropoxide in *n*-hexane by azeotropic removal of isopropanol (**Scheme 55**).



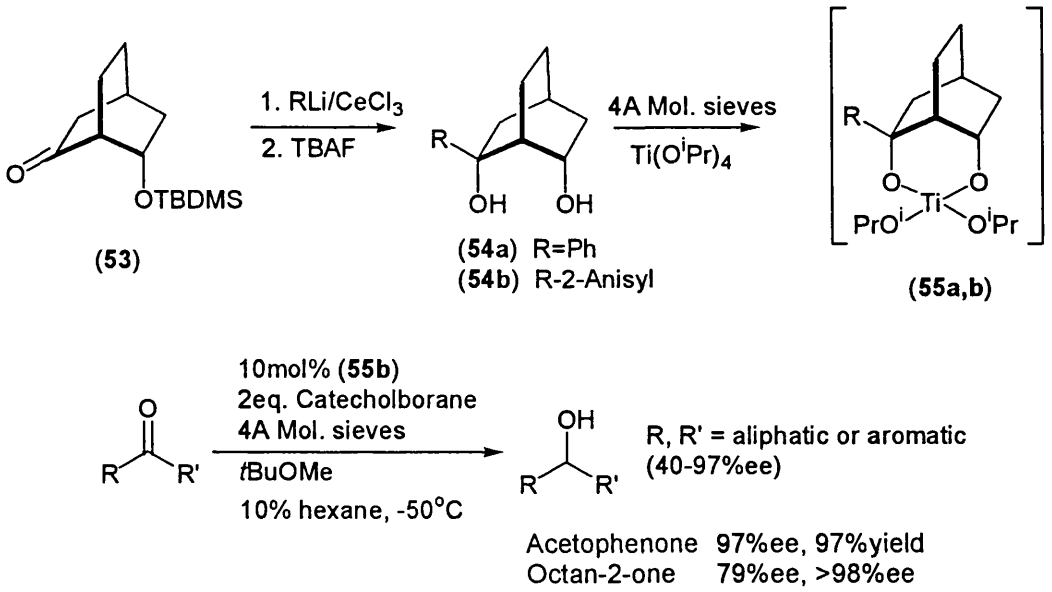
Scheme 55

Using 0.1 equivalents of the catalyst and 1.1 equivalents of catecholborane, a number of aryl ketones can be reduced quantitatively with moderate to good enantioselectivities within 1h (**Scheme 56**).



Scheme 56

The Ti(IV) catalysed reduction of ketones with catecholborane using chiral bidentate diols, (1*R*, 2*R*, 4*S*, 6*S*)-2-phenylbicyclo[2.2.2]octane-2,6-diol (**54a**) and (1*R*, 2*R*, 4*S*, 6*S*)-2-(2-anisyl)bicyclo[2.2.2]octane-2,6-diol (**54b**) has also been described.[105] These were synthesised simply by addition of the corresponding RLi/$CeCl_3$ reagent to the O–TBDMS protected optically active hydroxy ketone **53**, followed by deprotection. The catalysts **55a** and **55b** were then prepared by mixing the diols **54a** and **54b** with Ti(O^{i}Pr)$_4$ in a 1.2:1 ratio in the presence of 4A molecular sieves at 0°C, and then keeping the mixture at room temperature overnight. Powdered molecular sieves need to be activated at 400°C for 5-7h for effective ligand exchange (**Scheme 57**).



(53)

(54a) R=Ph
(54b) R-2-Anisyl

(55a,b)

Scheme 57

Using 10mol% of the catalysts **55a,b**, a series of ketones were reduced to the corresponding alcohols using a stoichiometric amount of catecholborane in 40-97%ee. Fairly high enantiomeric excesses (75-83%) were obtained with linear methyl ketones. These values are among the highest recorded for such substrates.

As we have stated earlier, although titanium alkoxides have featured extensively as Lewis acidic catalysts, the growth of lanthanide alkoxide complexes has grown spectacularly in recent years.

1.6 Lanthanide (III) complexes

Complexes of the lanthanide group consisting of the 15 elements from lanthanum to lutetium in the periodic table, have seen an experimental increase in synthetic use in recent times.[106] The trivalent state is the most common oxidation state for lanthanides. In general, lanthanide (III) complexes, except for the alkoxides, are hard Lewis acids and hence they have a strong affinity towards hard bases such as oxygen donor ligands. This strong oxophilicity is one of the most important characteristics of lanthanide(III) reagents and provides the principal basis for their unique synthetic applications.

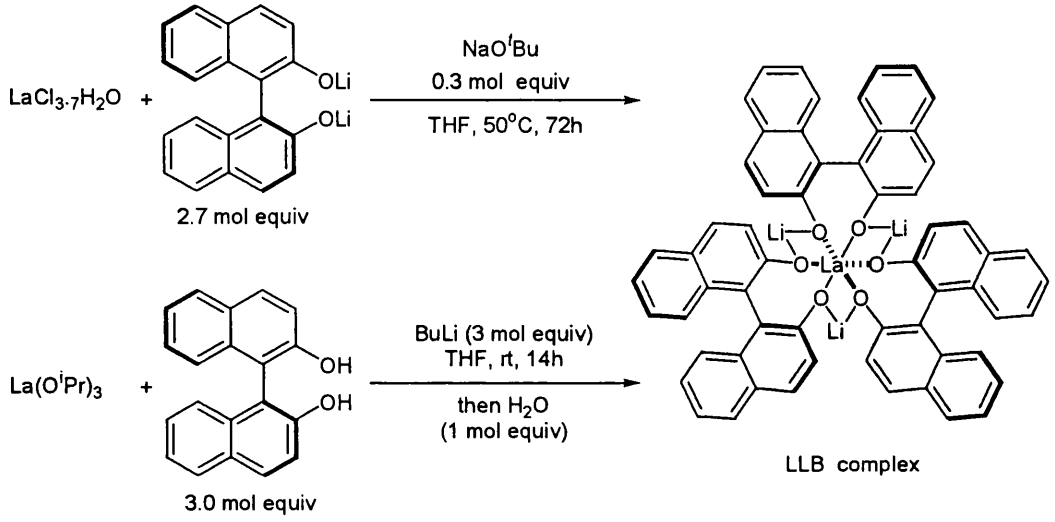
The first class and the most versatile type of lanthanide catalysts are Shibasaki's heterobimetallic complexes, which utilises BINOL as the chiral ligand.

1.6.1 Heterobimetallic Multifunctional Catalysts

The beautiful concept of Shibasaki that heterobimetallic complexes can function as both a Brønsted base and as a Lewis acid, just like an enzyme, has made possible a variety of efficient catalytic asymmetric reactions, and the rare earth-alkali metal complexes such as LnM_3tris(binaphthoxide) complexes (LnMB, Ln=rare earth metal, M=alkali metal) have proven to be especially effective catalysts.

LLB complexes can be synthesised using two procedures. In the first method, treatment of $LaCl_3 \cdot 7H_2O$ with 2.7 molar equivalents of dilithium binaphthoxide and 0.3 molar equivalents of NaO^tBu in THF at 50°C for 50h provided the LLB complex most efficiently.[107] Alternatively LLB can also be prepared from $La(O^iPr)_3$[108] by exposure to 3.0 equivalents of 2,2'-dihydroxy-1,1'-binaphthyl (BINOL) in THF followed by addition of 3.0 equivalents of butyllithium at 0°C (**Scheme 58**). It has been found that the addition of 1.0

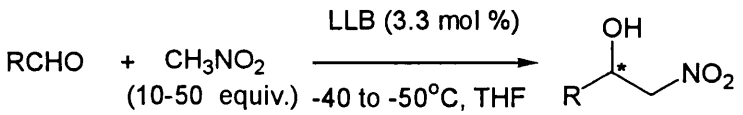
equivalent of water to LLB enhances the activity of the catalyst.[109] A variety of asymmetric heterobimetallic complexes such as PrLB, NdLB, SmLB, EuLB, GdLB, and YbLB can be synthesised from these two experimental methods. These complexes are stable enough to be handled in air and in organic solvents that contain small amounts of water (such as THF, DCM, and toluene).



Scheme 58

1.6.2 LLB in Catalytic Asymmetric Nitroaldol Reactions with Nitromethane

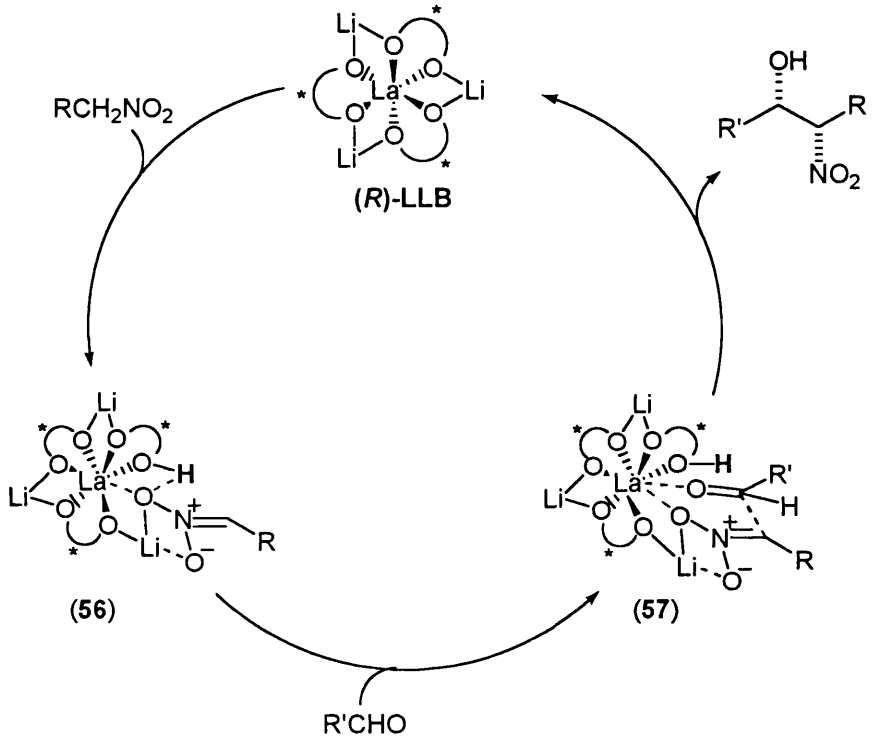
The nitroaldol or Henry reaction is a very powerful synthetic protocol for organic chemists,[110,111] and the work of the Shibasaki group represented the first discovery of a general and effective asymmetric nitroaldol reaction, even including noncatalytic varieties with a stoichiometric amount of an asymmetric base. Thus, treatment of an aldehyde at –40 to –50°C with 10-50 equivalents of nitromethane in the presence of 3.3mol% of an optically pure LLB catalyst typically gives the nitroaldol adduct in over 90%ee (**Scheme 59**).



Scheme 59

Catalytic asymmetric nitroaldol reactions promoted by LLB or its derivatives require at least 3.3mol% of asymmetric catalyst for efficient conversion. Even so, the reaction is

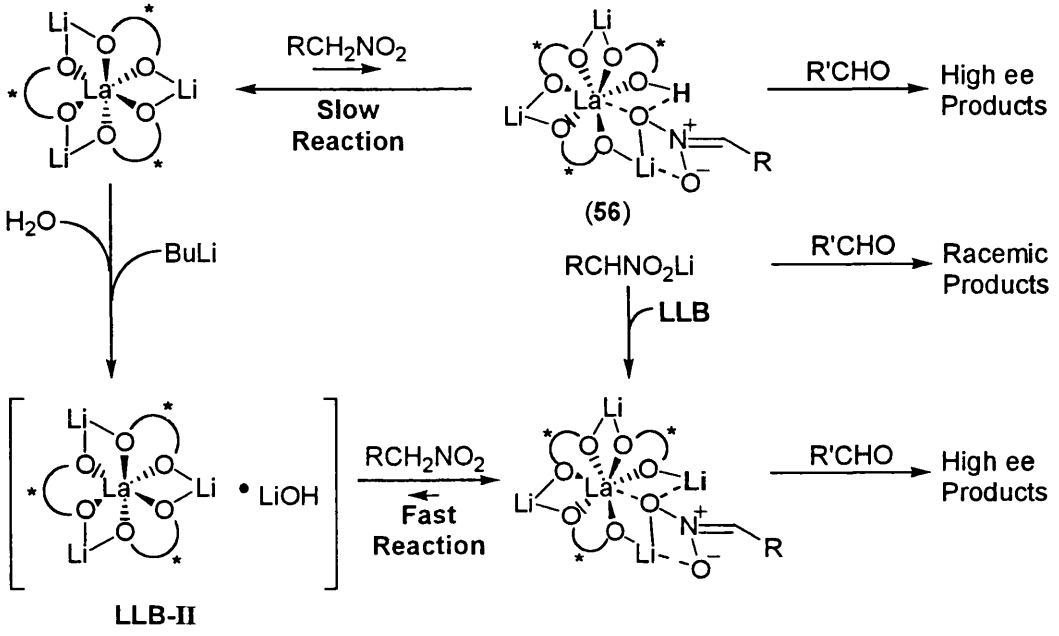
rather slow, requiring 3-6days. A proposed mechanism can explain the slow reaction (**Scheme 60**). The lithium nitronate (**56**) is first generated in a slow reaction. The postulated intermediate (**56**) cannot be detected, probably due to its low concentration. This maybe associated with the generation of an acidic OH group in close proximity. Addition of the aldehyde provides intermediate (**57**). The final reaction regenerates the LLB catalyst and gives the final product.



Scheme 60

The acidic proton can be removed from (**56**) by treatment with 1.0 equivalent of base to the LLB catalyst. The optimised reaction "only" requires 1mol% of a second-generation LLB (LLB-**II**, prepared from LLB), 1.0 equivalent of H_2O, and 0.9 equivalents of butyllithium then promoted efficient catalytic asymmetric nitroaldol reactions. Moreover, the use of LLB-**II** (3.3 mol%) accelerated these reactions. The structure of LLB-**II** has not yet been determined. However, it has been proposed that it is a complex of LLB and LiOH. A proposed reaction course for an improved catalytic asymmetric nitroaldol reaction is shown in **Scheme 61** and involves treatment of lithium nitronate (0.9mol%, generated from the corresponding nitroalkane and butyllithium) with LLB (1mol%). The

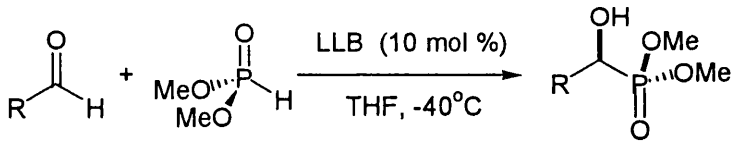
nitroaldol reaction then proceeds to give enantioselectivity comparable with LLB-II catalyst (**Scheme 61**).



Scheme 61

1.6.3 Catalytic Asymmetric Hydrophosphonylations of Aldehydes

In recent years α-hydroxy-phosphonates have attracted much attention due to their wide-ranging biological activity[112] and their usefulness as synthetic intermediates for other biologically important phosphoryl compounds.[113,114]

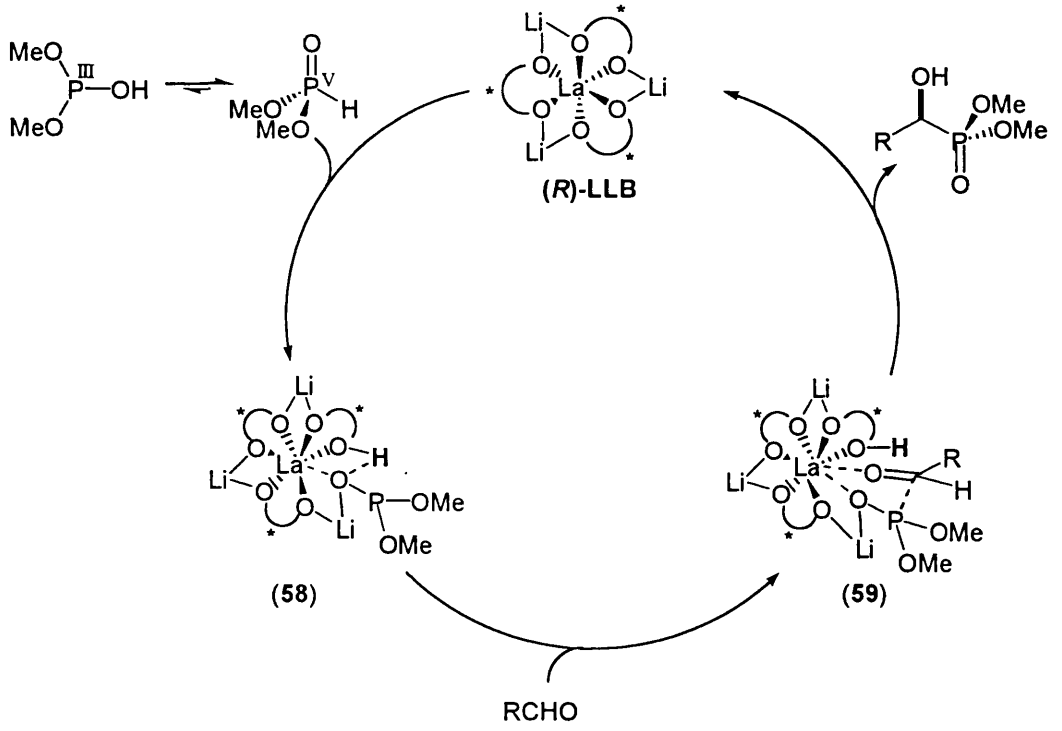


R=Ph, Cinnamyl

Scheme 62

In the presence of 10mol% of LLB complex, hydrophosphonylation of benzaldehyde and cinnamaldehyde with 1.3 equivalents of dimethyl phosphite in THF at –40°C afforded the corresponding α-hydroxy phosphonates in 76% ee (79% yield) and 72%ee (78% yield), respectively (**Scheme 62**). Interestingly, upon slow addition of the aldehydes the enantiomeric excesses of both α-hydroxy phosphonate adducts were increased to 83%ee (73% yield) and 79%ee (88% yield), respectively.

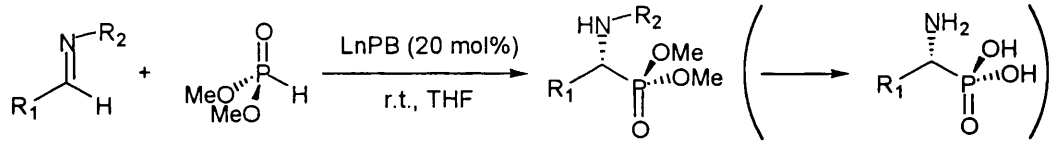
The effect of slow addition of the aldehyde on the enantioselectivity can be reasoned as follows: For the hydrophosphonylation of relatively unreactive aldehydes the activated phosphite (**58**) can only react with aldehydes, which are *pre*-coordinated to the Lanthanum atom (**59**). In the case of reactive aldehydes such as benzaldehyde and cinnamaldehyde, the Li-activated phosphite can undergo a competing reaction with the unactivated aldehyde. Therefore, if such aldehydes are added in one portion, the enantioselectivity of the reaction will be reduced. In contrast, the effect of slow addition of aldehyde minimises the amount of unactivated aldehyde present in solution. This allows the catalytic cycle to complete and regenerate the active catalyst, and the aldehyde activation is facilitated. Reactive aldehydes should, therefore, be added slowly in order to avoid the side reaction that proceeds without activation of the aldehyde by LLB (**Scheme 63**).



Scheme 63

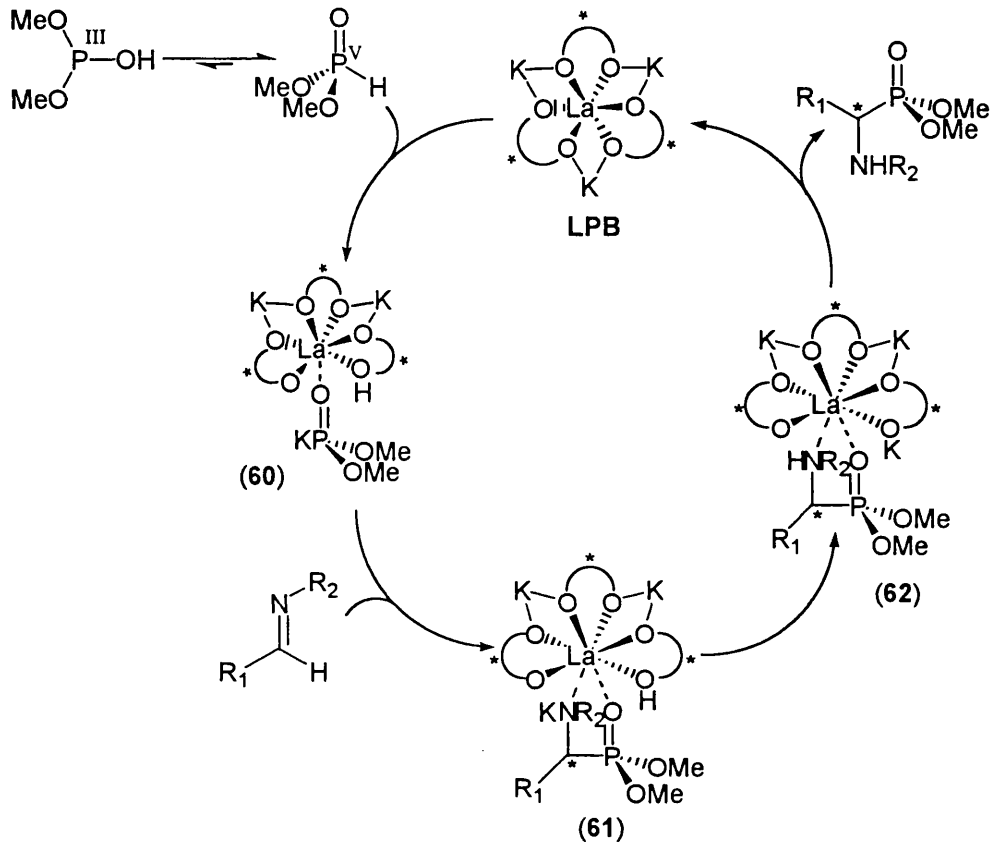
1.6.4 Catalytic Asymmetric Hydrophosphonylation of Imines by Rare Earth / Potassium / BINOL Catalysts (LnPB)

α-Aminophosphonates are also interesting compounds because they are considered to be structural analogues of the corresponding α-amino acids and transition state mimics in peptide hydrolysis. The uses of α-aminophosphonates as peptide mimics,[114] haptens for catalytic antibodies,[115] enzyme inhibitors,[116] antibiotics and pharmacological agents[117] are well-documented. The present methodology provides the first catalytic asymmetric hydrophosphonylation of imines with LnK_3tris(binaphthoxide) complexes (LnPB) to give optically active α-amino phosphonates in modest to high enantiomeric excess.[118]



Scheme 64

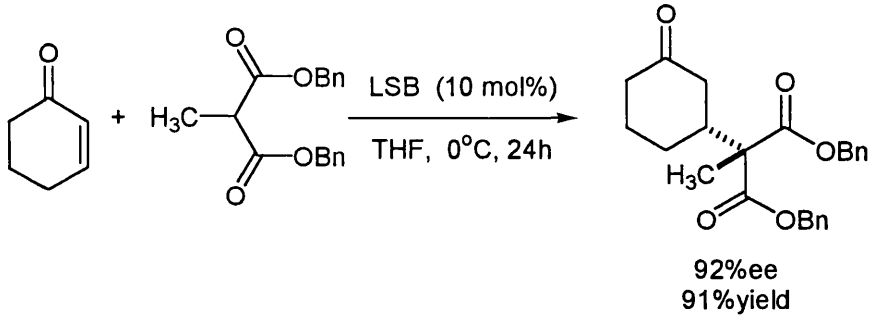
Treatment of substituted imines with 1.5 equivalents of dimethyl phosphite and 20mol% of LPB in THF/toluene (1/7) at room temperature gave the corresponding α-amino phosphonate with 38-96%ee in 38-97% yield (**Scheme 64**). The proposed mechanism of this catalytic asymmetric hydrophosphonylation is shown in **Scheme 65**. Deprotonation of dimethyl phosphite by LPB lead to the generation potassium dimethyl phosphite, which immediately coordinates to the strongly oxophilic Lanthanum atom to form intermediate (**60**).[119] The addition of an imine to intermediate (**60**) gave an optically active potassium salt of the α-aminophosphonate (**61**), which, after an α-aminophosphonate and LPB proton-exchange reaction (**62**), completes the catalytic cycle.



Scheme 65

1.6.5 Catalytic Asymmetric Michael Reactions Promoted by LSB

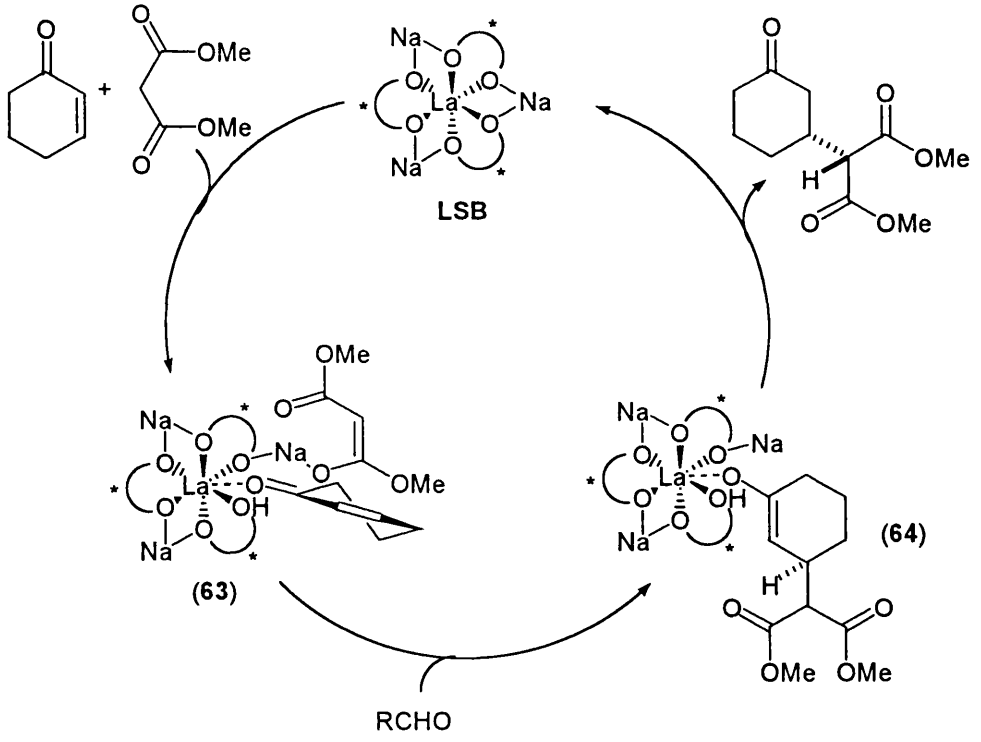
Catalytic asymmetric Michael reactions are one of the most important synthetic methods for obtaining asymmetric centers.[120] Lanthanum/sodium/BINOL complexes (LSB) are effective in the catalytic asymmetric Michael reaction of various enones and malonates to give Michael adducts in up to 92 %ee and almost quantitative yield (**Scheme 66**).[121,122]



Scheme 66

Using both NMR studies and computational simulation,[121,123] a mechanism has been proposed for the catalytic asymmetric Michael reaction catalysed by LSB. With

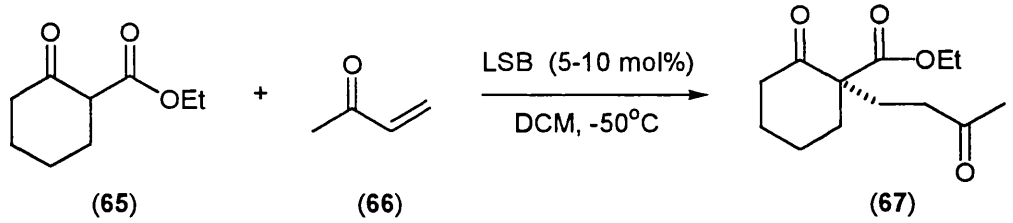
cyclohexenone coordinated to the Lanthanum metal cation, the plane of the ring should be almost parallel to the closest naphthyl ring system. This facilitates attack by the coordinated sodium enolate of dimethyl malonate to give the Michael adduct. The resulting sodium enolate of the optically active Michael adduct can then abstract a proton from the acidic OH group to regenerate the LSB catalyst (**Scheme 67**). Therefore the basic LSB complex also acts as a Lewis acid and controls the orientation of the carbonyl function to activate the enone attack. The multifunctional nature of the LSB catalyst makes possible the formation of Michael adducts with high enantiomeric purity even at room temperature.



Scheme 67

In both catalytic asymmetric Michael reactions and nitroaldol reactions, the enones and aldehydes appear to coordinate to the rare-earth metal. This raises the question as to why LSB is more effective for catalytic asymmetric Michael reactions, while LLB is preferred for catalytic asymmetric nitroaldol reactions. Although it is still unclear, it is assumed that slight differences in bond lengths in chelate structures such as (**63**) and (**64**) as well as in bite angle for the BINOL moiety caused by varying the alkali metal are responsible for this effect.

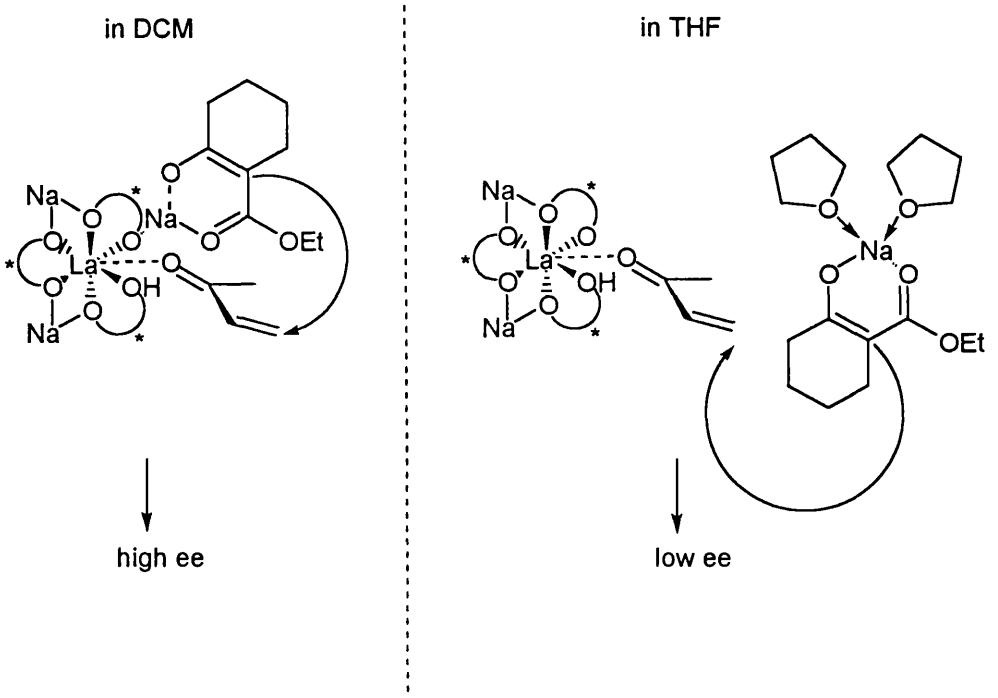
LSB can also be applied to catalytic asymmetric Michael reaction in which the asymmetric centre is induced on the side of the adduct originating from the Michael donor. The reaction of (**65**) with (**66**) in THF and 10 mol% of LSB gave (**67**) with 23 %ee, whereas the reaction in toluene afforded (**67**) with 75 %ee (**Scheme 68**). When LSB was reduced to 5mol% the enantiomeric excess of (**67**) declined to 25 %ee. Slow addition of (**65**) while still maintaining a low level of catalyst gave (**67**) with a high enantiomeric excess (89%). In marked contrast, the asymmetric Michael reaction in toluene catalysed by 5mol% of LSB in DCM gave (**67**) in 89 %yield and 91 %ee without the need for slow addition (**Scheme 68**). Moreover, the reaction is not affected by the choice of rare-earth metal.[124]



(**65**) (**66**) (**67**)

Scheme 68

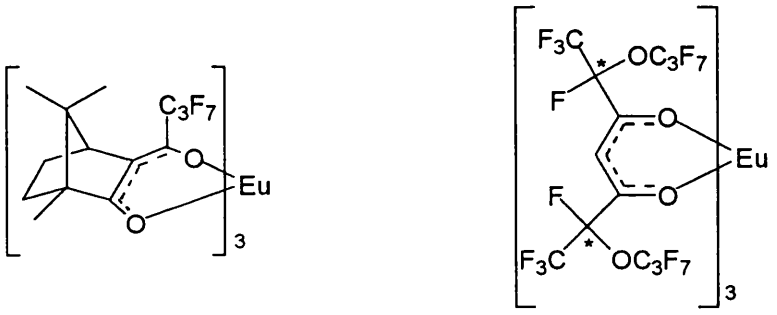
Slow addition of the β-keto ester and use of DCM as solvent are generally quite effective methods for preventing reduction of the enantiomeric excess in various Michael adducts. On the other hand, malonates give adducts with high enantiomeric purity regardless of the solvent used.[121] These results can be rationalised by comparing the p*K*a of a β-keto ester with that of a malonate; the former is significantly more acidic. Therefore, the concentration of the resulting Na-enolate can be expected to be greater in the case of the β-keto ester. Furthermore, this Na-enolate will react with an enone more slowly than the Na-enolate derived from a malonate. The combination of rapid formation and longer lifetime increases the likelihood of dissociation of the Na-enolate from the chelated ensemble to give a product of lower enantiomeric purity. In less polar DCM the Na-enolate would, remain part of the ensemble to afford the product with a high enantiomeric excess (**Scheme 69**). Slow addition of the β-keto ester also acts to limit undesired ligand exchange between BINOL moieties and the Michael donor.



Scheme 69

1.7 Europium reagents

Although Europium(III) complexes such as $Eu(hfc)_3$ and $Eu(dppm)_3$ are very familiar to organic chemists as NMR shift agents, the use of Eu complexes as synthetic reagents is a much more recent event (**Scheme 70**).



$Eu(hfc)_3$ $Eu(dppm)_3$

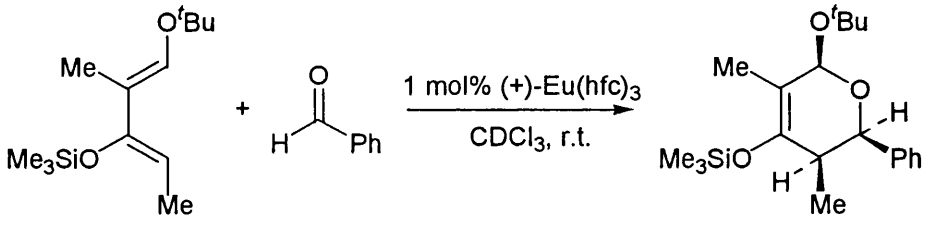
Scheme 70

$Eu(hfc)_3$: tris(3-heptafluorobutyryl-*d*-camphorato)-europium(III)

$Eu(dppm)_3$: tris[di(perfluoro-2-propoxypropionyl)methanato]europium(III)

1.7.1 Hetero Diels-Alder reactions

In 1983 Danishefsky[125] demonstrated the usefulness of (+)-$Eu(hfc)_3$ as an asymmetric catalyst for the hetero Diels-Alder reaction (**Scheme 71**).

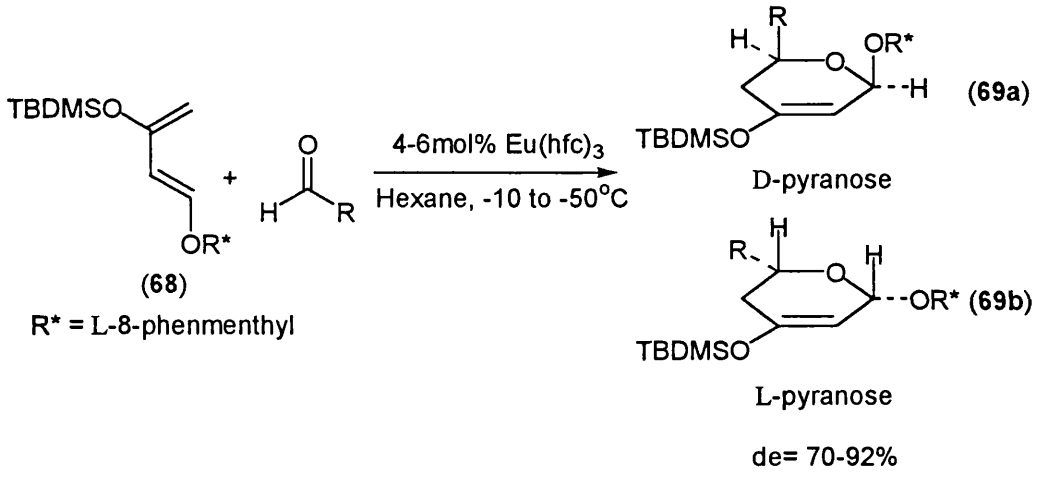


42%ee

Scheme 71

Although modest enantiomeric excesses were obtained, application of this reaction to chiral butadienes with the chiral (+)-$Eu(hfc)_3$ catalyst exhibited striking interactivities, resulting in diastereofacial excesses of up to 95%.[126] Reactions of butadiene (**68**), using L-8-phenmenthyl as the chiral auxiliary, with benzaldehyde in the presence of (+)-$Eu(hfc)_3$ in hexane from -78°C to -20°C, afforded a 96:4 ratio of L-pyranose (**69b**) : D-pyranose (**69a**). Treatment of (**69b**) with TFA in DCM afforded a 75% overall yield of

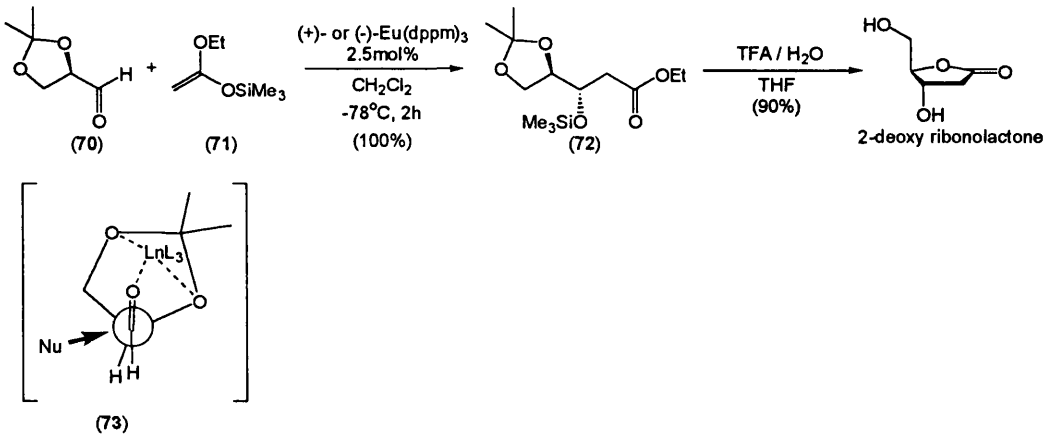
optically pure L-dihydropyranone. Thus, very simple chemistry is now available for obtaining optically pure or highly enriched L-2,3-dihyropyrones, and given the availability of D-8-phenmenthol and the antipodal (–)-Eu(hfc)$_3$, D-pyranones can also be fashioned (**Scheme 72**).



Scheme 72

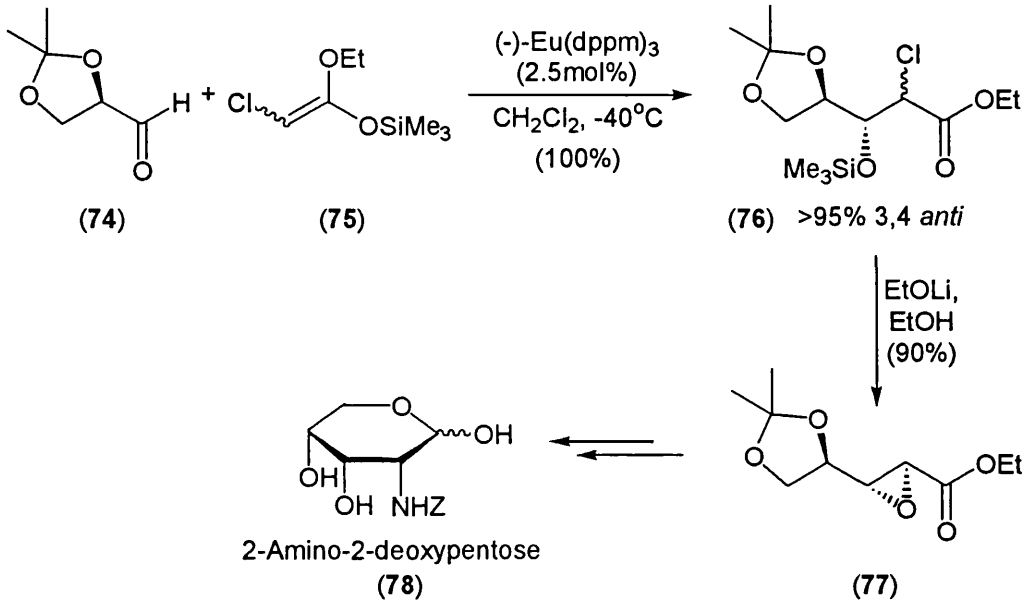
1.7.2 Michael reaction of aldehydes with ketene silyl acetals

Mikami *et al.*[127] reported the asymmetric synthesis of 2-deoxy-D-ribonolactone catalysed by the lanthanide(III) aldol reacton with ketene silyl acetals (KSA) of acetate. Acetate derived KSA (**71**) reacts readily with aldehyde (**70**) even at -78°C within 2h in the presence of a catalytic amount of (+)- or (–)-Eu(dppm)$_3$ (2.5mol%) in dichloromethane to give the corresponding *O*-silylated aldol adducts (**72**) in quantitative yield (**Scheme 73**). The 3,4-*anti* adduct (**72**) was obtained in 95% diastereoselectivity. The observed *anti*-diastereofacial selectivity is reasonably explained by the tridentate chelation (**73**) which exists by virtue of the high coordination numbers found in the lanthanides.



Scheme 73

2-Amino-2-deoxypentose can be synthesised *via* the 2,3-epoxide intermediate (**77**) by using α-chloroacetate-derived KSA (**75**) as the enolate component to define the desired stereochemistry at C-2 after epoxidation of the aldol adduct (**76**) (**Scheme 74**). The aldol reaction of (**74**) and (**75**) occurs using the conditions above to give (**76**) in quantitative yield as an epimeric mixture at C-2. Subsequent treatment of (**76**) with lithium ethoxide (1.1 equiv.) in ethanol at 0°C for 2h to give the 2,3-*trans*-epoxide (**77**) stereoselectively in 90% isolated yield. This compound has previously been converted into 2-amino-2-deoxypentose (**78**) (**Scheme 74**).[128]



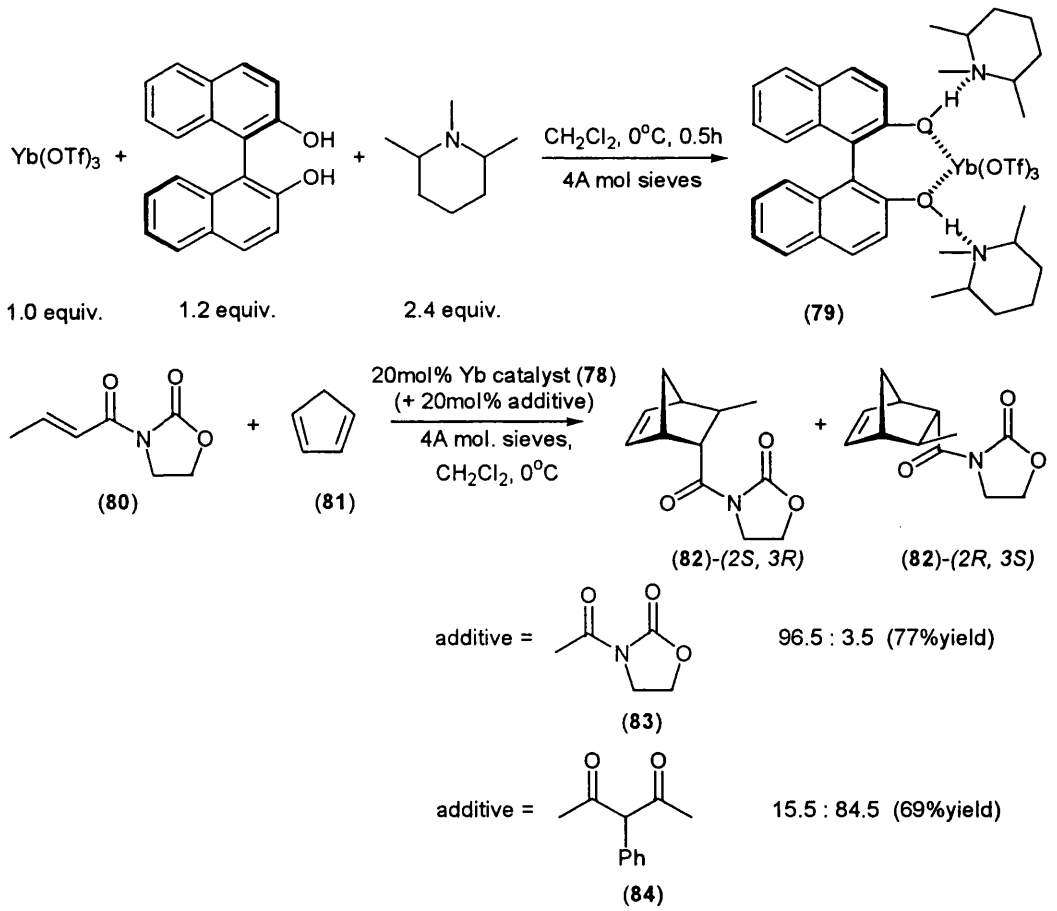
Scheme 74

While Shibasaki has dominated the use of rare-earth metals, other groups have also contributed to the ever-increasing literature of rare-earth metal asymmetric catalysis.

1.8 Other Lanthanide catalysts

1.8.1 Asymmetric Diels-Alder reaction

Kobayashi[129] have reported the asymmetric Diels-Alder reaction using a new chiral catalyst (**79**) prepared from ytterbium trifluoromethanesulfonate, (*R*)-BINOL, and a tertiary amine (**Scheme 75**). In the presence of the catalyst, 3-acyl-1,3-oxazolidin-2-ones (**80**) reacted with cyclopentadiene (**81**) to afford the *endo*-Diels-Alder adducts (**82**) in high yields and with good to excellent enantiomeric excesses.



Scheme 75

The unique structure shown in **Scheme 75** was indicated by ^{13}C NMR and IR. The precise structure and coordination have not yet been revealed. The most characteristic

feature of the catalyst was the existence of hydrogen bonds between the phenolic hydrogens of (*R*)-BINOL and the nitrogen atoms of the tertiary amine groups.

Although this catalyst has a unique structure, ageing was found to take place. It has been reported that additives such as 3-acetyl-1,3-oxazolidin-2-one (**83**) and 3-phenylacetylacetone (PAA) (**84**) were effective not only in stabilising the catalyst, but also in controlling the enantiofacial selectivities in the Diels-Alder reaction.[130] When 3-acetyl-1,3-oxazolidin-2-one (**83**) was combined with the catalyst, the *endo* product (**82**) was obtained in 93%ee and the absolute configuration of the product was 2*S*, 3*R*. On the other hand, when PAA (**84**) was used as an additive, the reverse enantiofacial selectivity was observed, providing the *endo* product (**82**) with the absolute configuration 2*R*,3*S* in 69%ee.

1.9 Conclusions

Many of the reactions in asymmetric catalysis, which we have illustrated in the previous sections fulfil the many of the criteria for an ideal catalyst.[131]

Thus, in the ideal world, a good chiral ligand should fulfil all of the following criteria:

1. It must be coordinated to the metal during the step in which the chiral centre on the substrate is created, and not exert merely a chiral medium effect.
2. The catalytic activity when the chiral ligand is present should be reasonably good relative to that of the achiral catalyst.
3. The structure of the ligand should allow for various chemical modifications to be made in order to permit the synthesis of variants. In this way optimal ligand-substrate matches can be sought.
4. The synthesis of the ligand must be relatively easy. If possible, resolution is to be avoided, the starting material being a cheap one taken from the "chiral pool".
5. It is desirable to be able to get both antipodes of the ligand.

The foregoing introduction has hopefully highlighted that many spectacular advances have been made in enantioselective catalysis in recent years through the selection of a transition metal or rare-earth metal alkoxide as the key molecular partner.

It is also highly significant to note that all of the chiral ligands described are C_2 symmetric, since the presence of a C_2 symmetric axis dramatically reduces the number of possible competing diastereomeric transition states. Nevertheless, such an element often leads to increased hindrance at the active site and hence to slower reactions and this balance should also be borne to mind.

Finally, as careful examination of the successful reactions in the review will reveal, the discovery of a useful catalyst can still border on the "alchemical", in spite of our best efforts to achieve "designer ligands". Thus, the addition of a drop of water, a change in

solvent, or the addition of an extra component can often have a very dramatic effect in raising the observed enantiomeric excesses for a given reaction. Even a *posteriori* rationalisation is often impossible in such cases and enantioselective catalysis can still be said to be a black art demanding dedicated experimentation.

Part 2. Results & Discussion

RESULTS AND DISCUSSION

2.1 Introduction

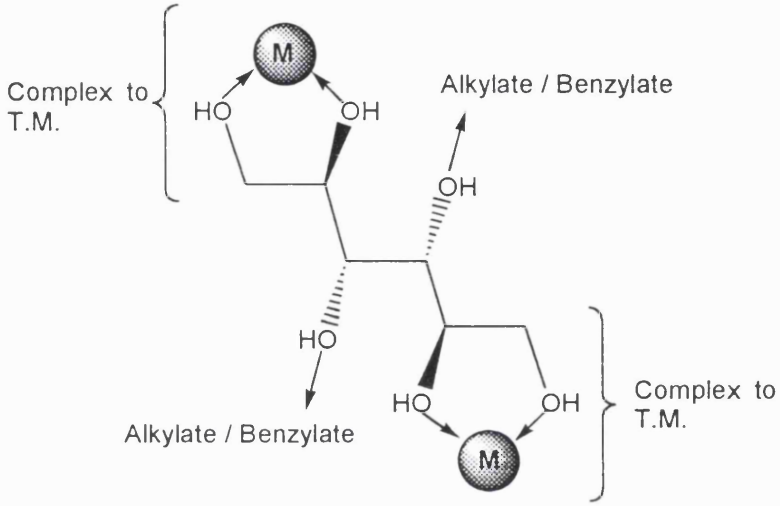
The foregoing introduction has hopefully highlighted that the use of Lewis acidic chiral metal complexes as catalysts has proven to be an extremely important area within enantioselective methodology for organic synthesis. In addition, it is also clear, that in spite of the very impressive array of catalysts which have been prepared, the "success" of any given reaction may well hinge on the subtleties such as the choice of solvent or the presence or absence of additional ligands such as water for which even a *posteriori* rationalisation is difficult. Furthermore, careful examination of these reactions such as the Sharpless epoxidation and TADDOLate chemistry which have proven to be especially useful reveals that while the pervasive element of C_2 symmetry lies at the heart of the original design concept, the detailed structure of the catalytically active species can often be considerably more complex than was originally envisioned.

In essence, it can be stated that new catalytic systems often involve, to a very considerable degree, a voyage of discovery. With these thoughts in mind, we decided to approach the preparation of a new family of Lewis acid catalysts by deliberate incorporation of a design element which would ensure that the exact outcome of the reaction could ***not*** be predicted in advance, but would emerge only as the outcome of careful experimental work.

Whilst the strategy of selecting a pre-meditated experiment of uncertain outcome flies in the face of fashion and accepted wisdom it does require some thought and ensures moreover that novel structure which would rarely, if ever, be conceived in the first instance, can emerge. The *modus operandi* of this philosophy is best illustrated by the concrete example of the case illustrated below.

2.1.1 Our strategy

The cheap and readily available sugar, D-mannitol, was chosen as the precursor for our chiral ligand for three reasons. Firstly, the molecule is C_2 symmetric and the importance of C_2 symmetry in asymmetric catalysis has been discussed earlier (**Section 1.9**). Secondly, it has six readily functionalised hydroxyl groups, and finally, it has four already installed chiral centres.

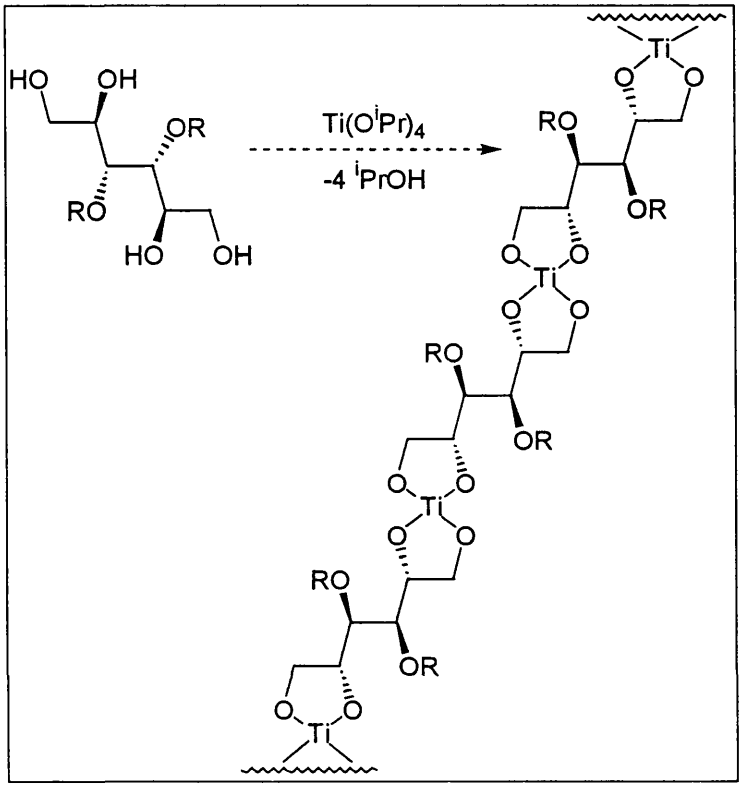


Scheme 76

The basis of our strategy was to alkylate the hydroxyl groups at the 3- and 4- positions, thereby leaving the free tetrol at the 1-,2-,5-,6- positions ready for complexation with a "tetrahedrally coordinated" transition metal (e.g. Ti, Zr, Hf) (**Scheme 76**). Titanium was chosen in the first instance because of the proven utility of chiral titanium alkoxide as effective asymmetric catalysts (**See Chapter 1**).

Complexation of the C_2 symmetric tetrol, instead of the usual C_2 symmetric diol adopted in many systems, with titanium(IV) isopropoxide in a 1:1 ratio can then in principle lead to a number of possible structures. One such possibility is that, a long titanium-D-mannitol polymer/oligomer would be obtained, and because the ligand is C_2 symmetric the chiral environment at each titanium centre would be identical, and this could be a good material for solid phase catalysis (**Scheme 77**). As outlined above however, the structure of the titanium alkoxide cannot be predicted until the chemistry has been carried out and cyclic

dimers, trimers and higher rings could also be imagined as well as linear oligomers with isopropoxy end groups.

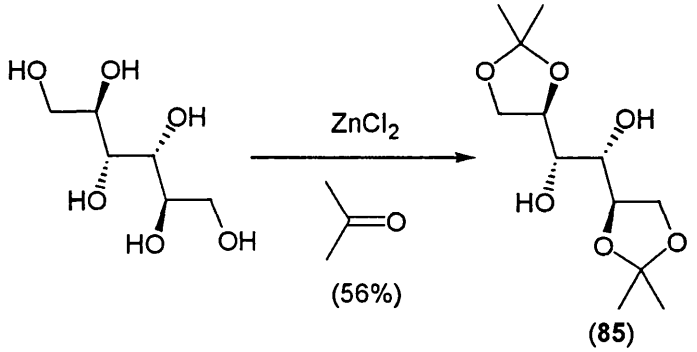


Scheme 77

2.2 Synthesis of the titanium complex

2.2.1 Synthesis of the chiral ligand

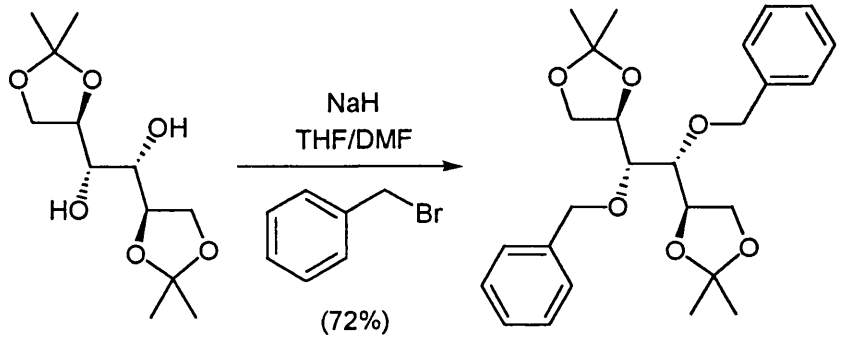
Preparation of the desired ligand, involved initial pairwise acetonide protection of the 1-,2- ,5-,6- hydroxyl groups of D-mannitol, by stirring in acetone with freshly fused zinc(II) chloride (**Scheme 78**).[132]



(85)

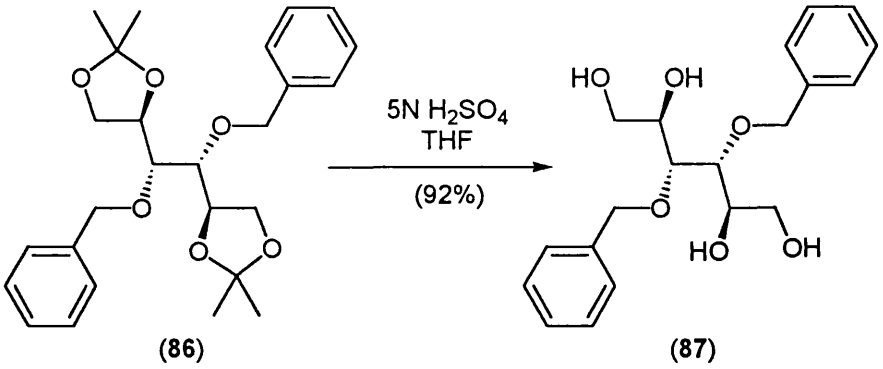
Scheme 78

The subsequent benzylation of *1,2:5,6-di-O-isopropylidene-D-mannitol* (**85**) was then performed using benzyl bromide in the presence of sodium hydride as base in THF/DMF. This is due to the ability of DMF as a dipolar aprotic solvent to solvate cations, thus making the alkoxide a much better nucleophile (**Scheme 79**).



Scheme 79

Acetonide deprotection of *3,4-di-O-benzyl-1,2:5,6-di-O-isopropylidene-D-mannitol* (**86**) was then achieved by stirring with a 5N aqueous sulfuric acid solution in THF to provide the desired chiral ligand (**87**) (**Scheme 80**).

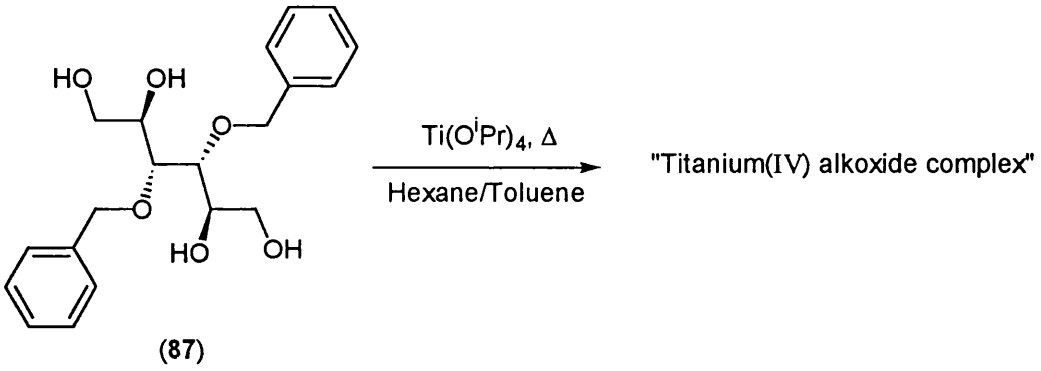


Scheme 80

2.2.2 Formation of the chiral titanium complexes

In an initial preliminary screening study, the complexation of the *3,4-di-O-benzyl-D-mannitol* (**87**) with titanium(IV) isopropoxide was performed in a mixture of toluene and hexane under reflux conditions. This resulted in the generation of a suspension of off-white solid in a yellow solution. The purification procedure required filtration of the yellow

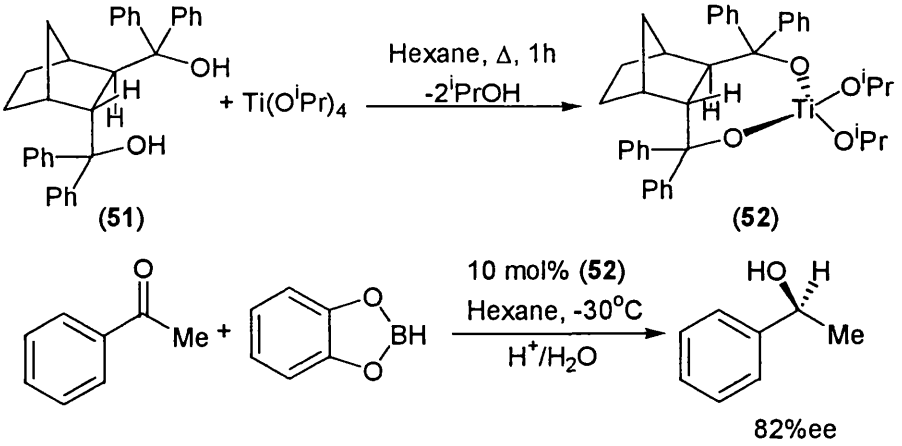
solution from the solid followed by precipitation of the titanium complex with hexane. The precipitate was then washed with more hexane and used directly for a subsequent asymmetric reaction (**Scheme 81**).



(87)

Scheme 81

In order to begin the evaluation of our chiral titanium complex as a potential catalyst for asymmetric synthesis, a recently reported asymmetric reduction of prochiral ketones using a chiral diol complexed to titanium as a catalyst (**52**) and with catecholborane as the stoichiometric reagent was randomly selected as a reference reaction for comparative purposes (**Scheme 82**).[104]



(51) **(52)**

Scheme 82

Acetophenone was chosen as the substrate for our model enantioselective catecholborane reduction using approximately 40mol% (titanium in terms of the ketone) of the synthesised chiral titanium complex, dissolved in toluene and cooled to –15°C. Addition of acetophenone to the complex followed by 1.1 equivalents of catecholborane

produced a colour change from colourless to deep red/brown. After workup, the enantiomeric purity of the product alcohol was determined by chiral gas chromatography and / or polarimetry.

2.2.3 Initial Results

Whilst the initial results, detailed in the experimental section, revealed that the "titanium complex" did indeed lead to chiral induction, the results were frustratingly irreproducible and suggested that other titanium species generated could also be compromising the enantioselectivity (**Table 2**).

With the objective of achieving some degree of consistency, several parameters and methods were carried out to optimise the procedure for the synthesis of the titanium complex as outlined below:

A. A Dean and Stark apparatus was employed to remove any traces of water that might be in the *3,4-di-O-benzyl-D-mannitol* (**87**). It also drives off any free isopropanol liberated in the reaction, ensuring the reaction goes to completion.
B. To ensure that our starting material is completely dry, it was pre-dried in a vacuum oven at 80°C in the presence of phosphorus pentoxide.
C. Freshly distilled solvent was replenished after the removal of isopropanol and any traces of water.
D. Varying the ratio of the hexane:toluene mixture in the synthesis of the titanium complex has an effect on the enantioselectivity. A 2:1 ratio of hexane:toluene mixture was found to provide the best conditions.
E. Using a filter tip cannula in the purification of the titanium complex provided more consistent enantioselectivity.

Results of the reductions

Titanium complex	Substrate	Temp. (°C)	Rxn time (h)	Equiv. Borane	$[\alpha]_D^{23}$	%ee	% Yield
A (88)	Acetophenone	-20	20	1.1	-33	56	37
A (89)	Acetophenone	-10	25	1.1	-31	52	80
A (90)	Acetophenone	0	20	1.1	-7	---	82
B (91)	Acetophenone	-10	19	2x1.1	-18.2	---	81
B (92)	Acetophenone	-10	28	2x1.1	-7.2	---	95
C (93)	Acetophenone	-15	20	1.1	-22.2	43	91
C (94)	Acetophenone	-15	18	1.1	-11.8	26	89
D (95)	Acetophenone	-10	24	1.1	-1.3	---	50
D (96)	Acetophenone	-10	24	2x1.1	-7.5	---	75
E (97)	Acetophenone	-10	24	1.1	-20.7	34	66
E (98)	Acetophenone	-15	19	1.1	-37.6	64	80
E (99)	Acetophenone	-15	16	1.1	---	46	100
E (100)	Acetophenone	-15	13	1.1	---	46	75

Table 2

Although the enantiomeric excesses of the product were initially irreproducible (titanium complex **A**, **B**, **C**, **D**, **Table 2**). The above optimisations did eventually lead to more consistent results (titanium complex **E**, **Table 2**). Some generalisations can be made from these results. The titanium complex favours the generation of the *S*-enantiomer, using acetophenone as the substrate. As expected, lowering the temperature of reduction yielded higher enantiomeric excesses (See **Table 2** entry **88**, **89**, **90**). We reasoned that the main factor responsible for the inconsistency lie in the fact that the exact quantity of the generated "active titanium complex" is not known, since over half of the titanium/mannitol mixture was removed as an insoluble precipitate (based on the weight of recovered insoluble precipitate). In actual fact, approximately 20mol% of an unknown "insoluble titanium complex" were used for the asymmetric reduction. Clearly, our next objective was to resolve this unsatisfactory state of affairs.

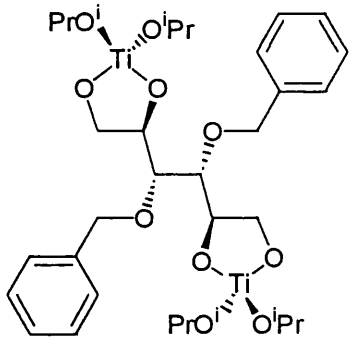
2.3 Isolation of a novel titanium species

At this stage, when more reproducible results had been achieved, it was decided to isolate the titanium species responsible for the observed enantioselective reductions. After careful optimisation of the synthesis of the chiral titanium alkoxide we were able to isolate the major product from the reaction, which was, to our surprise, perfectly stable on the open laboratory bench and did not appear to hydrolyse. The optimised procedure for synthesis of the titanium complex involves refluxing *3,4-di-O-benzyl-D-mannitol* (**87**) with titanium(IV) isopropoxide in a 2:1 mixture of hexane:toluene at 100°C for 4h. Leaving the reaction overnight to slowly cool to room temperature in the oil bath improves the yield. Then the solvent was completely removed from the reaction mixture. The resultant solid was dissolved in DCM, and any insoluble material present at this stage was removed by careful filtration. The DCM solution was then concentrated *in vacuo* and precipitated using diethyl ether to give a white solid. The white solid was filtered and washed with more ether to remove any ether soluble titanium species. Finally, the product was dried under vacuum to give the titanium alkoxide usually in around 40-50% yield, although yields as high as 85% have been achieved.

2.3.1 Characterisation of the titanium complex

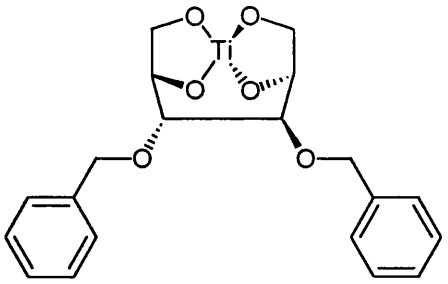
Now that we were able to isolate the major titanium complex we could then set about analysing the structure. The ^{1}H and ^{13}C NMR spectra of this material were surprisingly simple and showed that only a single compound was present (**Appendix A**). The simplicity of the NMR also demonstrated that this material had a high order of symmetry. Four possible types of structure which could give rise to NMR spectra of such simplicity were initially considered:

a)



The bimetallic mannitol monomer was immediately ruled out since there is no isopropyl signals in the NMR.

b)

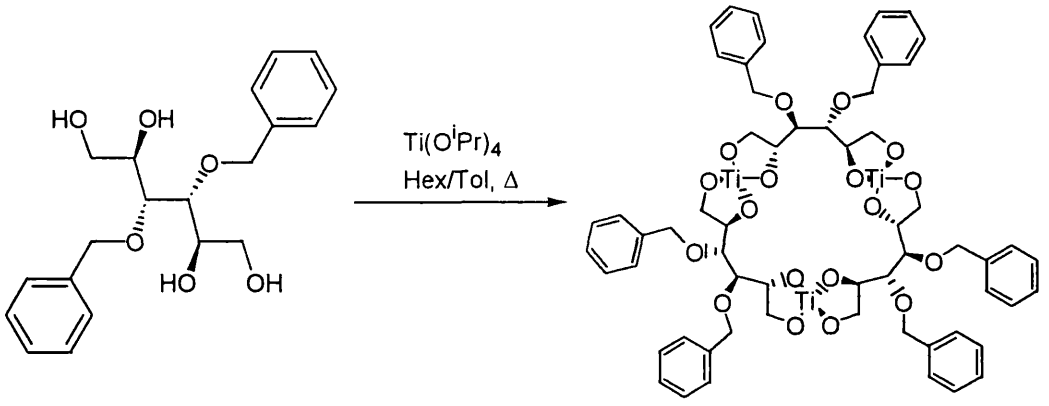


Whilst the monomeric structure with one titanium atom chelating both terminal diols would in theory fit with the NMR, molecular models suggested that it was impossibly strained and hence unlikely to form.

c) A titanium-D-mannitol polymer/oligomer in which the terminal ispopropyl signals are dwarfed by the sheer length of the chain and with a perfect supramolecular structure leading to magnetic equivalence of all atoms was possible (See **Scheme 77**).

d) The most probable postulated structure was a cyclic dimer (C_2 symmetry), or trimer (C_3 symmetry), or tetramer (C_4 symmetry) etc. This was supported by the C/H microanalysis. All of these cyclic structures give an identical C/H ratio and so ideally mass spectral analysis was required to determine the structure.

Although obtaining a successful mass spectrum of the catalyst seemed at first like misguided optimism, it was, to our delight, possible and a strong peak at (MH^+, 1219) consistent with a cyclic trimeric structure was obtained. Even more remarkable was the fact that there was very little further fragmentation, with the molecular ion peak completely dominating the spectrum (**Appendix B**). Expansion of the parent ion shows a cluster of peaks representing the different combinations of isotopes of titanium [^{46}Ti (7.93%), ^{47}Ti (7.78%), ^{48}Ti (73.94%), ^{49}Ti (5.51%), ^{50}Ti (5.34%)]. This isotope distribution pattern acts as a fingerprint because a compound containing one, two or three titanium atoms will have a different isotope distribution pattern. Comparison with a computer generated isotope distribution pattern (**Appendix C**) for the compound $C_{60}H_{67}O_{18}Ti_3$ with the mass spectrum obtained confirmed that both traces are almost identical (See **Appendix D**). We can therefore conclude with certainty on the basis of the NMR, microanalysis and mass spectral studies that the catalyst is a cyclic trimer with C_3 symmetry (**Scheme 83**).



(87) **(101)**

Scheme 83

To confirm the structure of the titanium alkoxide (**101**), we then set about growing crystals of this material in order to obtain an X-ray structure. It should be stated that for almost two years during the cause of this work, efforts were continuously made to grow crystals suitable for X-ray diffraction studies. Good quality crystals were obtained using DCM/ether, toluene/ether and ethyl acetate/ether solvent systems. Unfortunately, we were plagued by effloresence and to our extreme frustration, even when crystals which diffracted well at low temperature were finally obtained, the structure could not be solved because of disordered solvent molecules within the crystal.

A molecular model of the complex was generated with the help of Zeneca Agrochemicals. From these models (**Appendix E**), we can see a C_3 rotational axis in the middle of the ring. There are no $3C_2$ rotational axis perpendicular to the C_3 axis, this is because titanium is tetrahedral. This suggests that the titanium trimer has a C_3 point group.

2.3.2 Optimisations

It was then possible to demonstrate that the soluble *titanium 3,4-di-O-benzyl-D-mannitol trimer* (**101**) was indeed the species responsible for the observed enantiomeric excess in the catecholborane reduction of acetophenone. Thus, reduction of acetophenone with 1.1 equivalents of catecholborane in the presence of 16mol% of the trimer gave 72%ee. The next step is to optimise the conditions for high enantioselectivity.

Better enantioselectivity was observed by replacing toluene with DCM as the solvent. This is probably due to the fact that the *titanium 3,4-di-O-benzyl-D-mannitol trimer* (**101**) is more soluble in DCM, thus making it a better homogenous Lewis acid. It was found that the optimal temperature for conducting such asymmetric reductions was at –20°C and using 16mol% of the *titanium 3,4-di-O-benzyl-D-mannitol trimer* (**101**). This provided the same enantiomeric excess as using 1 equivalent of the titanium alkoxide (**101**). Ideally, higher enantioselectivity could be achieved by slow addition of catecholborane, thus minimising the opportunity of non-enantioselective catecholborane reduction with an

unactivated ketone. However, it was found that slightly lower enantiomeric excess was observed even with a greater amount (40mol%) of *titanium 3,4-di-O-benzyl-D-mannitol trimer* (**101**) (**Table 3**).

Substrate	**Cat. mol%**	**Temp (°C)**	**Rxn time (h)**	**Equiv. borane**	**Solvent**	**%ee (GC)**	**SM:Prod (GC)**
Acetophenone (**102**)	100	–20	4	1.1	Toluene	72	1:3.6
Acetophenone (**103**)	40	–20	19	1.1*	Toluene	62	1:1.1
Acetophenone (**104**)	**16**	**–20**	**3**	**1.1**	**DCM**	**72**	**no SM**
Acetophenone (**105**)	16	–78-r.t.	24	1.1	DCM	36	1:1.7
Acetophenone (**106**)	16	r.t.	16	1.0	DCM	17	1:1.7

**Slow addition of catecholborane in toluene over 6h.*

Table 3

It was also of interest to follow the progress of the reaction by chiral gas chromatography. A reaction using 5mol% of titanium alkoxide (**101**) in the catecholborane reduction of acetophenone at –20°C was accordingly performed. After 1.5h, an aliquot of the reaction was taken for GC analysis every hour. The reaction seemed to have stopped after 1.5h, as the three GC traces of the reaction gave virtually identical results. The reaction was left overnight for complete reduction, but the conversion remained the same. The reduction provided the alcohol in 62%ee (**Table 4**).

Time (h)	**%ee (GC)**	***S*:*R* (GC)**	**SM:Prod (GC)**
1.5	62	81:19	1.0:2.7
2.5	64	86:14	1.0:2.7
4.5	66	83:17	1.0:2.5
21.0	62	81:19	1.0:2.6

Conditions: 5mol% of *titanium trimer* (**101**), toluene, –15°C, (**107**).

Table 4

Since the above result showed that the reaction finished much more quickly than anticipated, the same reaction was then analysed at shorter time intervals and with more titanium alkoxide (**101**), 16mol%. An aliquot of the reaction was analysed every 15min, the results show high enantioselectivity (80%ee) for the first 15min of the reaction. For the first 30min, the rate of reaction increased dramatically, while the enantioselectivity only dropped by about 6%ee. After 30min, further reaction was very slow and the optimum enantiomeric excess of 72% was achieved (**Table 5**).

Time (min)	%ee (GC)	*S*:*R* (GC)	SM:Prod (GC)
15	80	90:10	1.0:0.8
30	74	87:13	1.0:2.1
45	76	88:12	1.0:2.2
60	72	86:14	1.0:2.5

Conditions: 16mol% of *titanium trimer* (**101**), toluene, –20°C, (**108**).

Table 5

We also tried to increase the rate of the reaction by adding 2.2 equivalents of catecholborane. The enantioselectivity was measured at even closer intervals of time. After 5min, the enantioselectivity remained the same 68%ee (*cf.* 72%ee with 1.1eq. catecholborane) and the reaction was completed in just 30min (**Table 6**).

Time (min)	%ee (GC)	*S*:*R* (GC)	SM:Prod (GC)
1	50	75:25	1.0:0.2
5	70	85:15	1.0:0.9
10	68	84:16	1.0:3.8
15	68	84:16	1.0:12.3
30	68	84:16	No S.M
45	68	84:16	No S.M

Conditions: 16mol% of *titanium trimer* (**101**), toluene, –20°C, 2.2 eq. catecholborane, (**109**).

Table 6

In another experiment, a stock solution of catecholborane (0.83M in toluene at –20°C) was prepared and used to reduce 1mmol of acetophenone in the presence of 16mol%

titanium alkoxide (**101**). The enantioselectivity was measured after adding small amounts of catecholborane (0.166mmol) to the reaction at 20min intervals. The catecholborane was pre-cooled and added in small quantities with the idea that this may enhance the enantioselectivity since an excess of borane is minimised. The results however showed no enhancement in the observed enantiomeric excess (70%ee) (**Table 7**).

Time (min)	%ee (GC)	*S*:*R* (GC)	SM:Prod (GC)
200	70	85:15	1.0:4.3
220	70	85:15	1.0:7.1
240	70	85:15	1.0:16.1
260	70	85:15	Traces of SM
280	72	86:14	Traces of SM
300	70	85:15	No SM

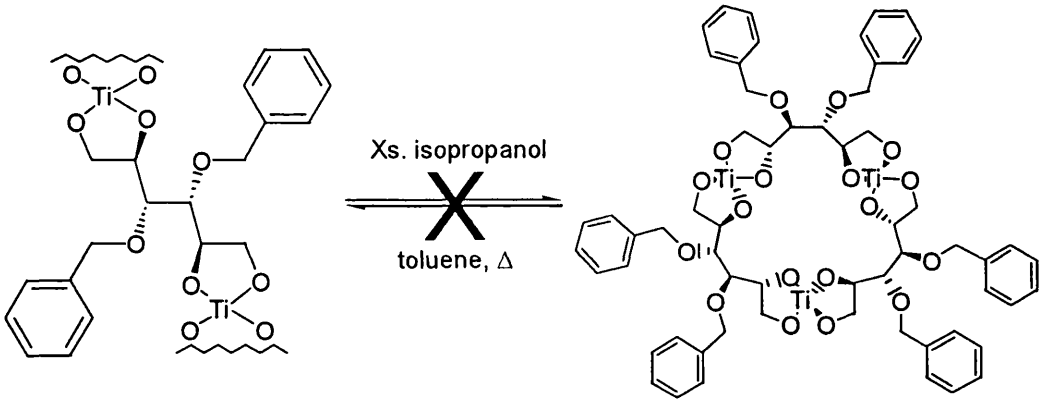
Conditions: 16mol% of *titanium trimer* (**101**), toluene, –20°C, catecholborane [0.83M in toluene (3mL)] at –20°C was added (17mol%) every 20min, (**110**).

Table 7

In conclusion, the results showed that the enantioselectivity of the reaction seems to reach the maximum enantioselectivity (*ca.* 80%ee) very rapidly. After that, the enantioselectivity tails off slowly and remains constant through the remainder of the reaction (*ca.* 72%ee). Using 1.1 equiv. of catecholborane, the rate of reaction in the first 30min is extremely fast and then slows down considerably, whereas the use of 2.2 equiv. of catecholborane gives complete reaction in only 30min.

2.3.3 Attempted regeneration of the insoluble by-products in the synthesis of the titanium trimer (101)

Whilst the C_3 symmetrical titanium trimer (**101**) corresponds, on average, to 40-50% of the crude catalyst mixture the remaining by-product is an orange-yellow amorphous solid. This was analysed using NMR and mass spectrometry and found to be essentially polymeric material. An attempt to regenerate a further quantity of the titanium trimer (**101**) was then carried out by refluxing this by-product in toluene and an excess of isopropanol was added to ensure reversibility (**Scheme 84**). Unfortunately this attempt only recovered a small amount <2-3% of the chiral tetrol and no further *titanium 3,4-di-O-benzyl-D-mannitol trimer* (**101**) was isolated. The intriguing question therefore remains as to whether the trimer, which seems to be indefinitely stable both in the solid state and in solution, is in fact a thermodynamic product of the overall exchange reaction between *3,4-di-O-benzyl D-mannitol* (**87**) and titanium(IV) isopropoxide.



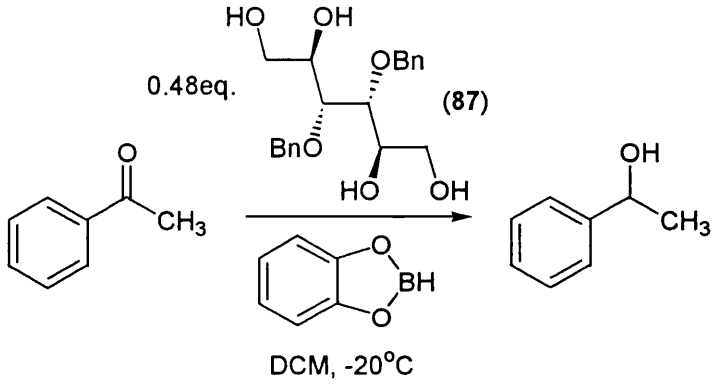
(101)

Scheme 84

2.3.4 Blank experiments

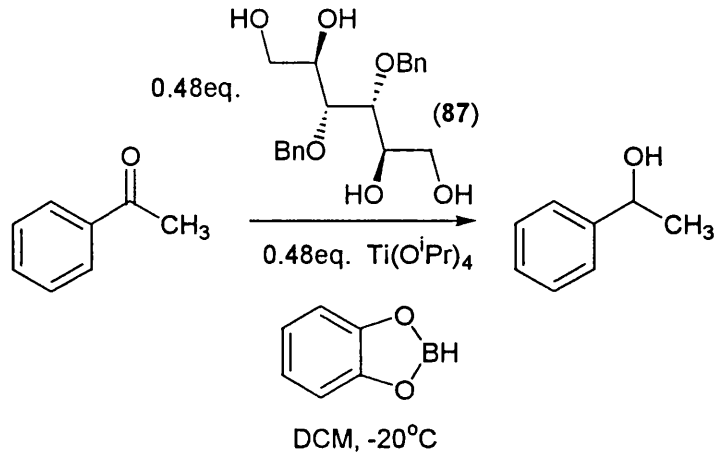
Two blank experiments were performed to confirm that the chiral titanium alkoxide (**101**) is necessary for asymmetric induction:

1. The reduction of acetophenone (**111**) using a stoichiometric amount of catecholborane in the presence of only the chiral ligand (**87**) (0.48equiv. corresponds to 0.16 equiv. titanium alkoxide) afforded traces of the corresponding racemic alcohol detectable by gas chromatography (**Scheme 85**).



Scheme 85

2. In a similar fashion, the reduction of acetophenone (**112**) using a stoichiometric amount of catecholborane in the presence of a 0.48 equivalents of a 1:1 mixture of titanium(IV) isopropoxide and the chiral ligand (**87**) afforded only traces of the corresponding racemic alcohol as detected by GC (**Scheme 86**).

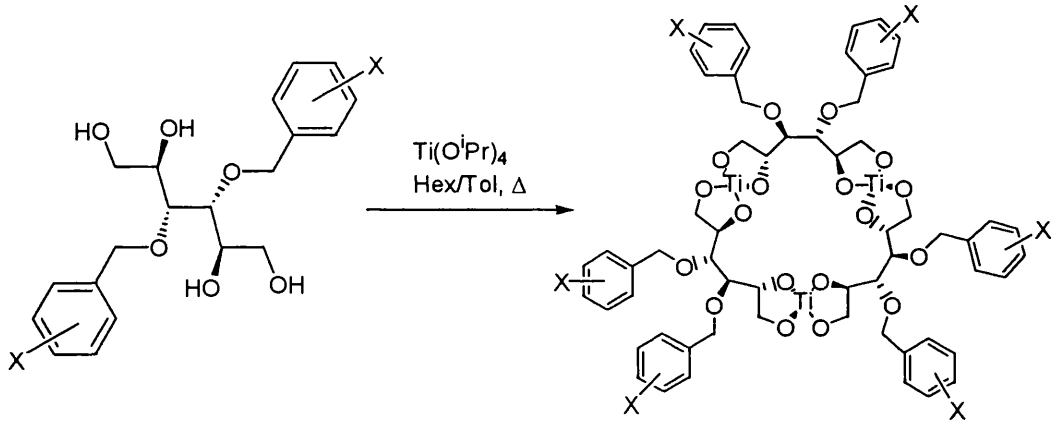


Scheme 86

2.4 Titanium trimer analogues

In the course of our work, opportunity was also taken to prepare a number of different titanium-mannitol trimers based on the use of substituted 3,4-di-*O*-benzyl ethers of D-mannitol (**Scheme 87**). Three reasons prompted this study: *viz*

1. To demonstrate that other titanium-D-mannitol trimers can be formed and that the trimeric structure is the "thermodynamic sink" of the reaction.
2. Using substituted titanium-mannitol trimer analogues may result in more efficient catalysts.
3. Substituted titanium-mannitol trimer analogues could produce crystals of sufficient quality for a successful structure elucidation by X-ray diffraction.



Scheme 87

2.4.1 Robotic synthesis

We were fortunate that Zeneca agrochemical was very interested in this work and has offered some robot time to synthesise a library of 3,4-di-substituted-D-mannitol benzyl ethers. However, our existing method for ligand preparation was not suitable for robotic synthesis as it involved the use of sodium hydride in the "open air" and the evolution of hydrogen would be a fire hazard. A more suitable benzylation method was therefore employed, by treatment of *1,2:5,6-di-O-isopropylidene-D-mannitol* (**86**) with potassium hydroxide in dimethyl sulfoxide followed by the addition of the corresponding substituted benzyl halide.[133] This in fact gave a higher yield than the previous method. A more efficient acetonide deprotection procedure was also employed, by heating the substrate in aqueous acetic acid at 60°C.[134] Complexation of 3,4-di-*O*-ethers of D-mannitol with $Ti(O^iPr)_4$ yielded the corresponding titanium-substituted D-mannitol trimer (**Scheme 87**).

The spectral data (^1H, ^{13}C, LRMS, HRMS, and MA) obtained for these complexes are all indicative of symmetrical trimer formation as observed in the case of the original catalyst. They all show the same high degree of symmetry and they are all white amorphous solids, which are stable on the open bench.

The possibilities for asymmetric induction of these titanium alkoxides was demonstrated once again, by the reduction of acetophenone using catecholborane as the stoichiometric reducing agent. Using 16mol% titanium complex in DCM at –20°C, the enantiomeric excess of 1-phenylethanol was measured (GC) for each of the titanium alkoxide complexes (**Table 8**).

2.4.2 Reduction of acetophenone using titanium 3,4-di-*O*-substituted benzyl-D-mannitol trimer

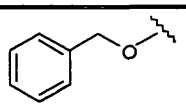
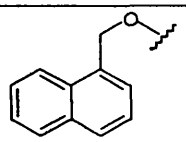
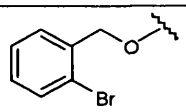
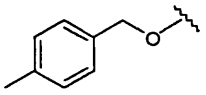
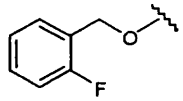
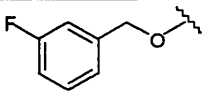
Titanium complex-substituted benzyl ethers	Mass of titanium complex		Enantiomeric purity		Yield	
	mg	mmol	%ee	*R:S*	mg	%
 (101)	98	0.08	72	14:86	58	95
 (113)	122	0.08	48	26:74	38	62
 (114)	135	0.08	58	21:79	43	71
 (115)	104	0.08	54	23:77	50	82
 (116)	106	0.08	62	19:81	41	68
 (117)	106	0.08	66	17:83	40	65

Table 8

All of the titanium alkoxide catalysts shown in **Table 8** were able to reduce acetophenone to the *S*-enriched alcohol. However, even the best of the new catalysts, (*titanium 3,4-di-O-3'-fluorobenzyl-D-mannitol trimer*, **117**) provided the alcohol in 66%ee, was not as good as the original unsubstituted titanium-mannitol trimer (**101**), providing the alcohol in 72%ee.

Attempts were also made to crystallise these substituted titanium-mannitol trimers, but once again, to our dismay, none of the titanium complexes produced crystals good enough for X-ray analyses. Solvents including toluene, benzene, acetonitrile, diethyl ether, dichloromethane, chloroform, ethyl acetate, petroleum ether, hexane, pentane, ethanol, methanol and tetrahydrofuran were used.

2.5 Other boranes for asymmetric reduction of prochiral ketones

Within our programme of attempted optimisation a selection of boranes was also tested for greater enantioselectivity in the asymmetric reduction of prochiral ketones. These included BH_3.THF (1M in THF) (**118**), $BH_3.NMe_3$ (**119**), $BH_3.PPh_3$ (**120**), 9-BBN (0.5M in THF) (**121**), and $BH_3.SMe_2$ (2M in THF) (**122-129**). These boranes were examined in the standard reduction of acetophenone in the presence of *titanium trimer* (**101**).

2.5.1 Asymmetric reduction of acetophenone using $BH_3{\cdot}SMe_2$ complex

To our initial surprise, all the boranes tested, save one, gave only trace amounts of racemic product, as detected by gas chromatography. Using $BH_3.SMe_2$ complex (2M in THF) as the stoichiometric reductant did however provide an enantioselective reaction. The results of the reduction under a variety of conditions are shown in **Table 9**.

Trimer (101) (mol%)	Temp. (°C)	Solvent	Time (h)	%ee (GC)	*R*:*S* (GC)	SM:Prod (GC)
16 (**122**)	-20 for 18h then r.t.	DCM	120	24	62:38	1.0:1.0
16 (**123**)	-20 for 16h then r.t.	THF	96	6	53:47	1.0: 1.8
16 (**124**)	r.t.	DCM	18	12	56:44	1.0: 11.7
16 (**125**)	0 for 6h then r.t.	DCM	18	18	59:41	1.0: 11.2
16 (**126**)	-20 for 18h then r.t	DCM	96	18	59:41	1.0: 0.7
32(**127**)	-20 for 18h then r.t.	DCM	96	22	61:39	1.0: 42.1
32 (**129**)	-78 to r.t. over 16h	DCM	144	24	62:38	1.0: 0.6
100 (**129**)	-50 to r.t. over 18h	DCM	48	28	64:36	1.0: 3.0

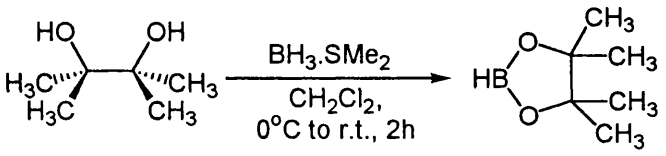
Table 9

The best result obtained was 28%ee, but very interestingly the product formed is now *R*-enriched as compared with the *S*-enriched product obtained using catecholborane. Wandrey[104] has also made the same observation when replacing catecholborane with the $BH_3.SMe_2$ complex in the reduction of acetophenone mediated by his chiral titanium alkoxide (**52**), in which 22%ee was obtained. It is worth noting that in order to obtain significant conversion the reaction has to be warmed to room temperature. Clearly, however, catecholborane still provides the best enantioselectivity.

2.5.2 Hydrobenzoin as a ligand for chiral boranes

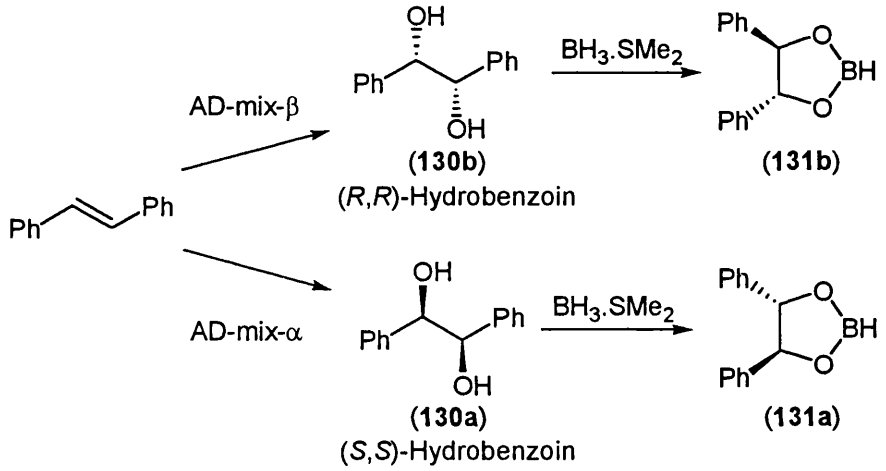
Efforts were also made to use a chiral borane in the hope of providing double asymmetric induction with our chiral titanium alkoxide (**101**). Enantiomerically enriched hydrobenzoin was selected as the chiral ligand for the borane because both enantiomers can be easily prepared by the Sharpless dihydroxylation of *trans*-stilbene.[135]

To prepare the chiral borane, a procedure analogous to that reported by Knochel[136] for the preparation of pinacolborane from pinacol and $BH_3.SMe_2$ complex in CH_2Cl_2 was used (**Scheme 88**).



Scheme 88

Thus, the analogous reaction was performed using (*S*),(*S*)- and (*R*),(*R*)-hydrobenzoin (**130a,b**) synthesised from the reaction reported by Sharpless using AD-mix-α and AD-mix-β respectively (**Scheme 89**).



Scheme 90

The chiral boranes (**131a,b**) prepared from hydrobenzoin (**130a,b**) were then used in the asymmetric reduction of acetophenone. Using the borane derived from (*R*),(*R*)-(+)-hydrobenzoin (**130b**) without any titanium alkoxide catalyst, reaction was slow and the best enantioselectivity recorded from two attempts was 32%ee, favouring the *S*-enantiomer. To our surprise, the borane derived from (*S*),(*S*)-(–)-hydrobenzoin (**130a**) without any titanium alkoxide catalyst gave essentially racemic product (2%ee, favouring the *R*-enantiomer) (**Table 10**). These results suggests that other species maybe generated and therefore effecting the reproducibility of the reagent.

Titanium trimer (101) (mol%)	Hydrobenzoin (130) (*R*),(*R*)- or (*S*),(*S*)-	Temp. (°C)	Solvent	Enantiomeric purity	
				%ee (GC)	*R*:*S*
0 (132)	(*R*),(*R*)-	–20	DCM	32	34:66
16 (133)	(*R*),(*R*)-	–20	DCM	0	50:50
0 (134)	(*S*),(*S*)-	–20	DCM	2	51:49
16 (135)	(*S*),(*S*)-	–20	DCM	6	53:47
0 (136)	(*R*),(*R*)-	–20	DCM	18	41:59
16 (137)	(*R*),(*R*)-	–20	DCM	6	47:53

Table 10

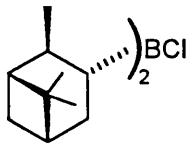
However, these boranes are used with the titanium trimer in the reduction of acetophenone. In the presence of 16mol% titanium-mannitol trimer (**101**) and using borane derived from (*R*),(*R*)-(+)-hydrobenzoin (**130b**), the reduction of acetophenone provided only racemic alcohol and from a second attempt gave 6%ee ,favouring the *S*-enantiomer. The analogous reaction was performed using borane derived from (*S*),(*S*)-(–)-hydrobenzoin (**130a**), similar enantiomeric excess (6%, favouring *R*-enantiomer) was observed (**Table 10**). It is worth noting that these reactions are extremely slow, this maybe due to the use of a sterically hindered borane.

In conclusion, the generation of the chiral borane was not successful, however it does show that the reactivity of the borane is very slow. The addition of the titanium trimer does not seem to enhance the rate or the enantioselectvity of the reaction. Further detailed experimentation is required to synthesise the chiral borane, in order to investigate this problem.

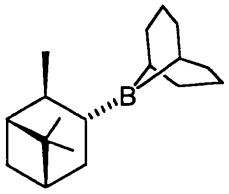
2.6 Other reagents for asymmetric reduction of prochiral ketones

In order to place our own results into context, it is appropriate at this stage to describe some of the established reagents and catalysts for the enantioselective reduction of prochiral ketones. Many approaches have been utilised to obtain optically active alcohols and, at present, there are six reagents and catalysts that are extensively used in asymmetric reduction.[137] These six reagents (**Scheme 90**) are:

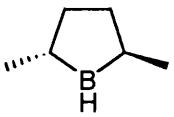
(**138**) diisopinocampheylchloroborane Ipc_2Cl, (DIP-Chloride™); (**139**) *B*-isopinocampheyl-9-borabicyclo[3.3.1]nonane, (Alpine-Borane™); (**140**) 2,5-dimethyl-borolane; (**141**) BINAL-H; (**142**) oxazaborolidines and (**143**) BINAP-Ru complexes.



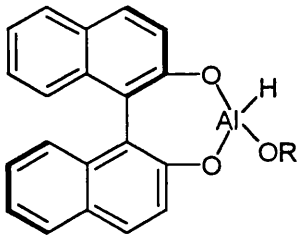
(**138**) DIP-Chloride
(Brown)



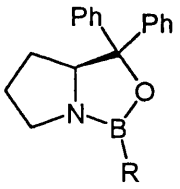
(**139**) Alpine-Borane
(Midland)



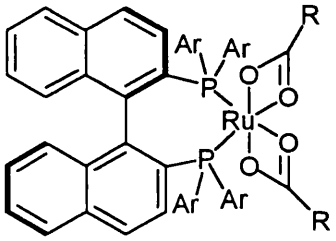
(**140**) 2,5-Dimethylborolane
(Masammune)



(**141**) BINAL-H
(Noyori)



(**142**) Oxazaborolidines
(Corey)



(**143**) BINAP-Ru complexes
(Noyori)

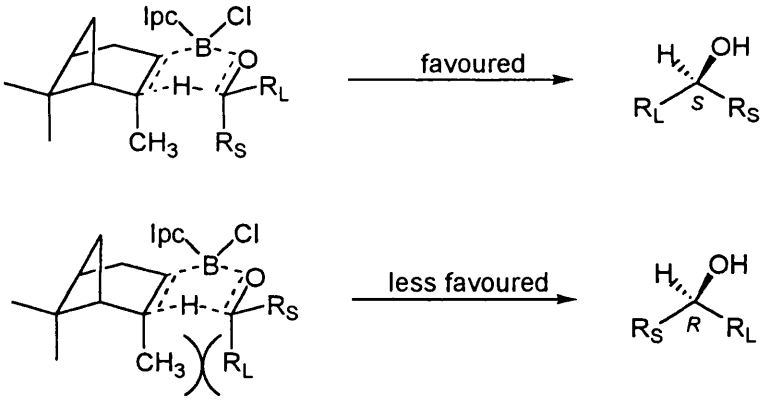
Scheme 90

These of course can be subdivided into stoichiometric reagents and catalysts:

2.6.1 Stoichiometric reagents

1 Chlorodiisopinocampheylborane (138) (DIP-Chloride)[138]

Both of the isomers of this reagent have been synthesised from commercially available (+)- and (–)-α-pinene. It is a very good chiral reducing agent for aromatic alkyl and α-tertiary alkyl ketones. The incorporation of the halogen on the boron makes it a stronger Lewis acid with a resulting increase in its reactivity towards carbonyl compounds. This reagent reduced acetophenone to the corresponding alcohol in 72% yield with 98%ee.[139] It is not a suitable reagent for simple ketones like 2-butanone, 3-methyl-2-butanone and enone types. The mechanism of reduction is similar to that proposed by Midland for Alpine-Borane (See **Scheme 91**); with a six-membered cyclic, "boat-like" transition state in which the larger appendage of the carbonyl group (R_L) lies in the equatorial position.



(–)-Ipc_2BCl

Scheme 91

2 *B*-3Pinanyl-9-borabicyclo[3.3.1]nonane (139) (Alpine-Borane)[140]

This reagent is prepared by hydroboration of α-pinene with 9-borabicyclo[3.3.1]nonane (9-BBN). Alpine-Borane is very effective in transferring the β-hydride to one of the prochiral faces of acetylenic ketones. Unfortunately, it is not possible to reduce simpler aliphatic and aromatic ketones under normal conditions. This is due to a side reaction caused by the reduction of the substrate by 9-BBN which is formed via a slow unimolecular dissociation of Alpine-Borane.[141] Although reaction of less reactive ketones with Alpine-Borane is very slow and enantioselectivity is poor, selectivity could be

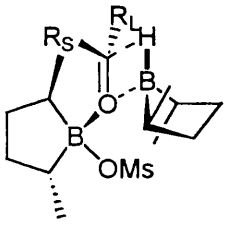
improved by increasing the rate of reaction because the side reaction could be suppressed by taking advantage of high pressure to increase the rate of reduction. At 2000atm, acetophenone is reduced with complete enantioselectivity.[142] A six-membered boat like transition state (**Scheme 92**) has been proposed for the reduction in which the larger appendage of a carbonyl group lies in the equatorial position in order to avoid steric interactions with the methyl group of the reagent.

favoured disfavoured

Scheme 92

3 2,5-Dimethylborolanes (140)[137]

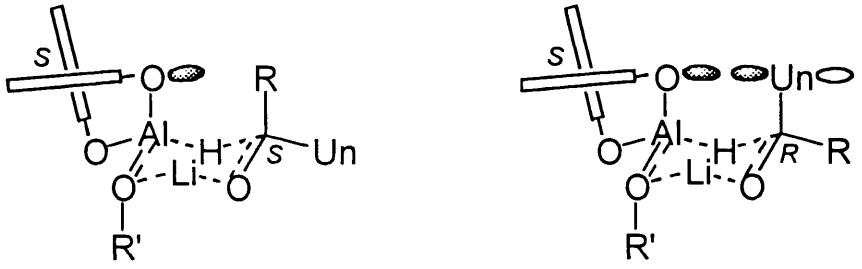
The enantioselective reduction of aliphatic ketones like 2-butanones, 4-methyl-2-pentanone, and others where both appendages of the carbonyl group are sterically similar, is a very challenging problem. Masammune's ligand (*R,R*)- or (*S,S*)-2,5-dimethylborolane has proven to be very efficient in reducing those type of ketones.[143,144] A mixture of chiral 2,5-dimethylborolane (1 equiv.) and 2,5-dimethylborolanyl methanesulfonate (0.2 equiv.), which plays a catalytic role, provides an efficient system for enantioselective reduction.[145] 2,5-Dimethylborolane exists as dimer and is in equilibrium with its monomeric form. The mechanism of the reduction has been studied by Masamune[144] and it is proposed that the boron atom of the mesylate co-ordinates with the carbonyl group *syn* to the smaller appendage, and the 2,5-dimethylborolane approaches the activated ketone in the manner shown in **Scheme 93**.



Scheme 93

4 BINAL-H (141)[137]

Noyori has devised the chiral hydride reagents (*R*)-BINAL-H and its enantiomer (*S*)-BINAL-H by modification of lithium aluminium hydride with equimolar amounts of (*R*)- or (*S*)-[1,1'-binaphthyl]-2,2'-diol and a simple alcohol.[146,147] The reducing agent exhibits exceptionally high enantioface differentiating ability in the reduction of diverse unsaturated carbonyl compounds such as aromatic ketones, alkynylic ketones, olefinic ketones, and aldehydes, etc. The sense and extent of asymmetric induction are highly dependent on the nature of the additional alcohol used. Simple alcohols like methanol and ethanol gave the best results. Reduction of acetophenone with (*R*)-BINAL-H under optimal conditions gave 95%ee. A six-membered transition state model **Scheme 94** has been proposed to account for the observed selectivity in the reduction of ketones. The equatorial unsaturated (Un) group and the axial saturated group (R) attached to the carbonyl function are differentiated by virtue of their electronic nature.



favoured disfavoured

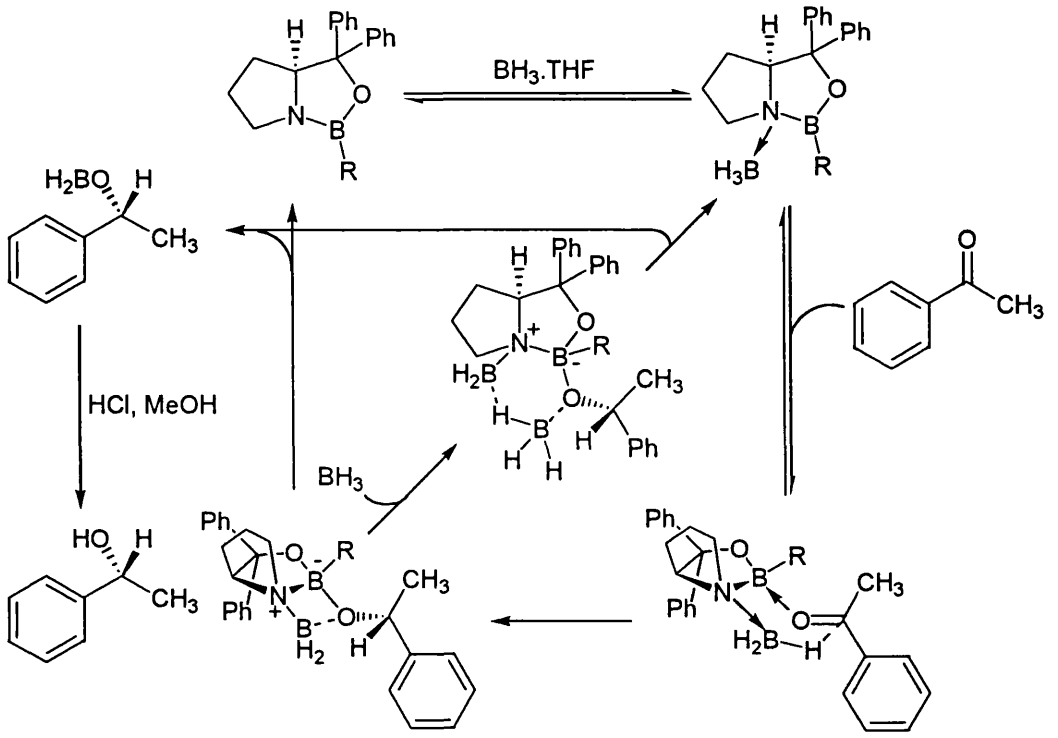
Scheme 94

2.6.2 Catalytic reagents

While stoichiometric reagents have certainly demonstrated their value, the invention of catalytic alternatives is of course especially appealing and in principle more efficient. Within this area, the following reactions have proven to be particularly impressive.

5 3-oxa-1-aza-2-borabicylo[3.(2,3 or 4).0]alkanes (142) (Oxazaborolidines)[148]

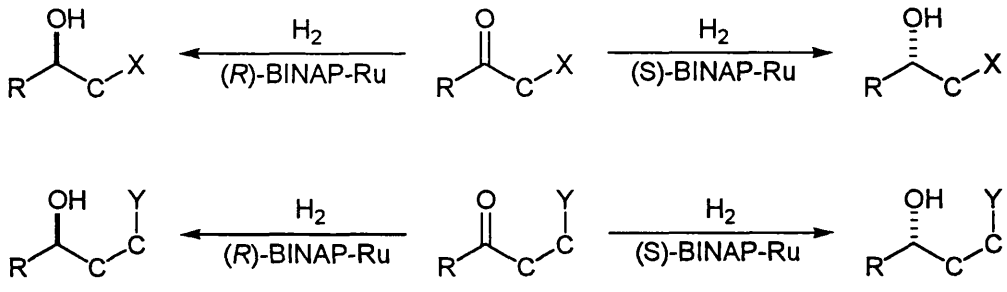
The basic framework has been simply prepared from the corresponding amino alcohols and an alkylboronic acid. The oxazaborolidine catalyst behaves like an enzyme in the sense that it binds with both the substrate ketone and the borane reducing agent bringing them closer and, after the reaction is over, it releases them and itself becomes free. Because of the enzyme-like catalytic activity, it has been named a *chemzyme*.[149,150] The experimental method is very simple, a variety of borane sources like BH_3-THF, BH_3-SMe_2, and catecholborane as reductants in conjunction with 10mol% of the catalysts have been used. The yield of the optically active alcohol product is quantitative in almost every case. The reduction of acetophenone gives the alcohol in 97%ee. Oxazaborolidines are presently the most versatile and recommended catalysts for enantioselective reduction of ketones. The proposed mechanism is shown in **Scheme 95**.



Scheme 95

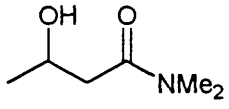
6 BINAP-Ru Complex (143)[151]

The elegant work of Noyori should also be considered in this context. Noyori has demonstrated the application of chiral phosphine complexes of Ru in the enantioselective hydrogenation of carbonyl compounds. A variety of functionalised ketones can be hydrogenated with synthetically useful enantioselectivities and in a predictable manner with the aid of RuX_2(BINAP) [empirical formula; X=Cl, Br, I; prepared by mixing $Ru(OCOCH_3)_2$(binap) and HX in a 1:1 mole ratio] (**Scheme 96**).[152,153] The general sense of the asymmetric induction indicates that the key factor in the enantioface differentiation is the simultaneous coordination of the carbonyl oxygen and heteroatom, X or Y, to the Ru atom forming a five- and six- membered chelate ring, respectively.

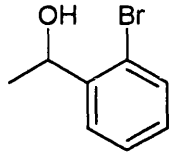


X,Y = heteroatom

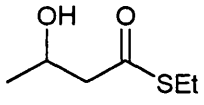
C = sp^2 or nonstereogenic sp^3 carbon



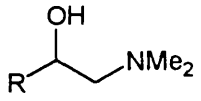
96%ee



92%ee

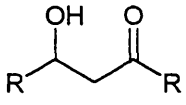


93%ee



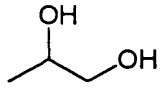
93-96%ee

R = Me, ^{i}Pr, ^{t}Bu, Ph

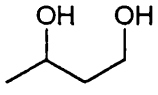


94-100%ee

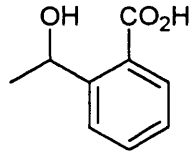
R = Me or Ph



92%ee



98%ee

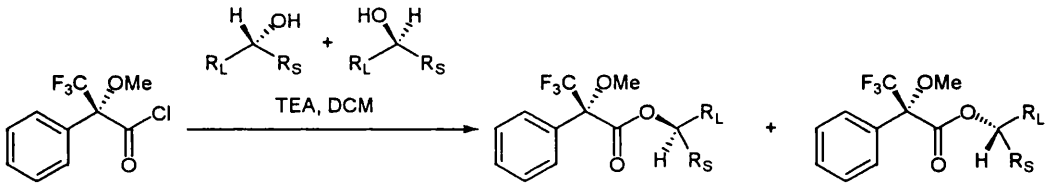


92%ee

Scheme 96

2.7 Catecholborane reduction in the presence of titanium complex (101)

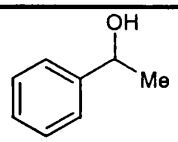
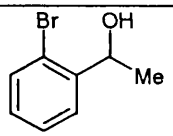
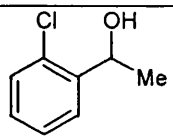
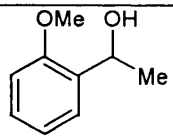
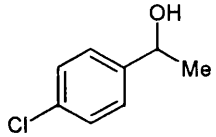
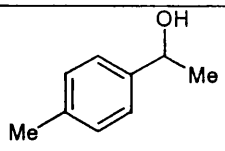
The formidable array of reagents and catalysts described in **Section 2.6**, together with those centred around titanium which have already been described in the introductory chapter, merely serve to illustrate that enormous progress has been made in recent years in enantioselective reduction of the carbonyl group. At this stage it was therefore appropriate to examine a range of carbonyl compounds using our titanium trimer as the Lewis acid in order to probe the spatial features, which could influence enantioselectivities. The *titanium 3,4-di-O-benzyl-D-mannitol trimer* (**101**) was therefore employed to reduce a series of aromatic prochiral ketones under the set of standard conditions, which had been optimised for acetophenone reduction. Using one equivalent of catecholborane and 16mol% of chiral titanium alkoxide (**101**) in DCM at –20°C, the prochiral ketone was accordingly reduced to the corresponding alcohol. The enantiomeric purity of the alcohol was measured from the diastereomeric ratio of the corresponding Mosher's esters using ^{19}F and ^{1}H NMR (**Scheme 97**).[154]



Scheme 97

The use of the α-methoxy-α-trifluoromethylphenylacetyl derivative offers the distinct advantage, over other reagents having only proton resonances, that determinations of enantiomeric composition based upon fluorine resonances are usually more reliable, since the fluorine signals are simple and in an uncongested region.

2.7.1 Reduction of substituted aryl methyl ketone derivatives

Alcohol (Yield)	^{1}H %ee			^{19}F %ee		
	%ee	d.r	(OMe) ppm	%ee	d.r	(CF_3) ppm
 (60%) (**144**)	62	19:81	3.42, 3.48	68	16:84	71.9, 72.1
 (57%) (**145**)	62	19:81	3.45, 3.51	62	19:81	71.9, 72.0
 (47%) (**146**)	66	17:83	3.45, 3.51	66	17:83	71.9, 72.0
 (56%) (**147**)	40	30:70	3.45, 3.50	40	30:70	71.9, 72.1
 (42%) (**148**)	56	22:78	3.39, 3.48	54	23:77	71.9, 72.1
 (68%) (**149**)	52	24:76	3.42, 3.48	58	21:79	72.0, 72.2

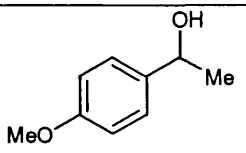
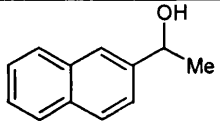
 (31%) (**150**)	0	50:50	3.38, 3.47	0	50:50	72.0, 72.2
 (92%) (**151**)	48	26:74	3.39, 3.51	46	27:73	71.8, 72.1

Table 11

The results for a range of aromatic methyl ketones are shown in **Table 11**. Substitution of a halogen at the *ortho* position of the aromatic ring was found to give slightly lower enantiomeric excesses than with the parent acetophenone. *o*-Chloroacetophenone, however provided better ee's than the *o*-bromoacetophenone, probably due to the relative steric environment around the carbonyl. To our surprise, substitution at the *para* position led to lower ee's and in the case of the methoxy group, no enantiofacial selectivity whatsoever was observed. This may reflect the oxophilicity of a titanium atom complexing to the methoxy group, thus leaving the "free" carbonyl exposed for an uncontrolled reduction. By way of contrast, a methoxy group at the *ortho* position of the aromatic ring gave a moderate 40%ee. While it was hoped that increasing the difference between the size of R_L (aromatic group), from phenyl to 2-naphthyl, and R_S (the methyl group) would yield better enantioselectivity, this was not found to be the case.

2.7.2 Reduction of phenyl alkyl ketones

It was also of interest to probe the nature and size of the alkyl group attached to the ketonic carbonyl since the differing electronic requirements of an aromatic ring and the alkyl group can also be factors which are as important as "size".

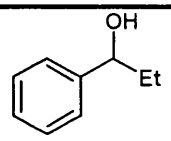
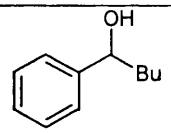
Alcohol (Yield)	^{1}H %ee			^{19}F %ee		
	%ee	d.r	(OMe) ppm	%ee	d.r	(CF_3) ppm
 (17%) (**152**)	66	17:83	3.38, 3.47	66	17: 83	71.8, 72.0
 (51%) (**153**)	78	11:89	3.37, 3.47	72	14:86	71.8, 72.0

Table 12

In the event, a slight improvement in enantioselectivity was observed when the alkyl chain was lengthened (**Table 12**).

2.7.3 Reduction of hetero-aromatic methyl ketones

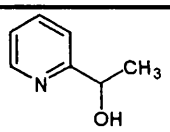
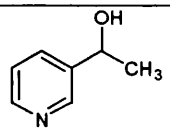
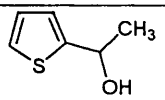
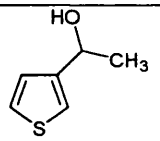
Alcohol (Yield)	^{1}H %ee			^{19}F %ee		
	%ee	d.r	(OMe) ppm	%ee	d.r	(CF_3) ppm
 (57%) (**154**)	0	50:50	3.40, 3.52	no res	no res	no res
 (32%) (**155**)	6	47:53	3.39, 3.49	16	42:58	71.8, 72.0
 (65%) (**156**)	52	24:76	3.40, 3.47	54	23:77	72.0, 72.3
 (42%) (**157**)	28	36:64	3.40, 3.48	28	36:64	71.9, 72.1

Table 13

Heteroaromatic rings such as pyridine and thiophene were also examined. Pyridines turned out to be very poor substrates, whereas thiophenes gave better enantioselectivities, since thereby indicating that the nitrogen lone pair is probably an excellent competitive Lewis base. With the thiophenes, higher enantioselectivities were obtained when the carbonyl group was adjacent to the sulfur atom, titanium may complex to the sulfur atom and hence bring the carbonyl group closer to the catalytic centre for reduction (**Table 13**).

2.7.4 Reduction of other ketones

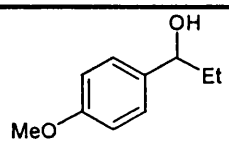
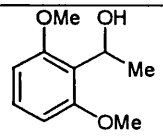
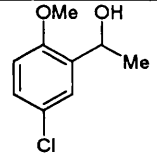
Alcohol (Yield)	^{1}H %ee			^{19}F %ee		
	%ee	d.r	(OMe) ppm	%ee	d.r	(CF_3) ppm
 (36%) (**158**)	0	50:50	3.36, 3.46	0	50:50	71.8, 72.1
 (22%) (**159**)	20	40:60	3.43, 3.50	24	38:62	72.3, 72.6
 (56%) (**160**)	62	19:81	3.44, 3.53	64	18:82	71.7, 72.1

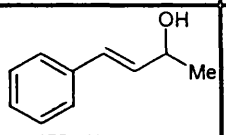
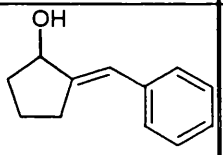
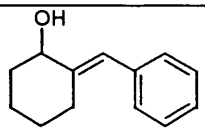
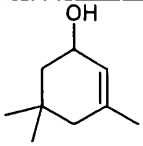
Table 14

It was hoped that placing two methoxy groups in the *ortho*-position of the phenyl ring would provide higher enantioselectivity, since 2-methoxyacetophenone provided 40%ee. Instead, a decrease in enantioselectivty was observed. A surprisingly, good result of 62%ee was observed however with 5-chloro-2-methoxyacetophenone as the substrate (*cf.* 2-methoxyacetophenone 40%ee). The possible complexation of titanium with a methoxy group in the *para*-position was again confirmed by the use of 4-methoxypropiophenone as the substrate, which also gave no enantioselectivity (**Table 14**).

2.7.5 Reduction of enones

The efficient enantioselective reduction of α,β-unsaturated carbonyl compounds has always proven to be a significant challenge. Even in the case of the highly successful oxazaborolidines,[148] which give high enantioselectivities for both exo-[155] and endocyclic enones requires the presence of an alkyl[156,157] or halogen[158] substituent at the α-carbon of the enone unit to achieve steric differentiation of the carbonyl oxygen atom lone pairs.

As shown in **Table 15** however, and perhaps not unexpectedly, the titanium trimer was largely unsuccessful in securing satisfactory enantiomeric excesses for a representative range of acyclic, and exo- and endocyclic enones. Future work on the introduction of substituents at the α-position should also be undertaken in this area.

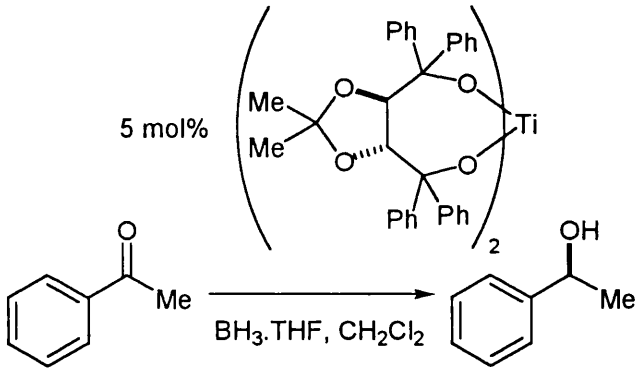
Substrate (Yield)	(101) mol%	Temp. (°C)	Reaction time (h)	Equiv. borane	Solvent	%ee
 (57%) (**169**)	16	−20	15	1.1	DCM	0
 (77%) (**175**)	16	−20	4	1.1	DCM	5.5*
 (72%) (**176**)	16	−20	6	1.1	DCM	25*
 (quant.) (**177**)	16	−20	4	1.1	Toluene	36

*analysed using HPLC with thanks to Professor Tim Gallagher.

Table 15

Although our results cannot stand comparison against the best of the existing methodologies for the asymmetric reduction of prochiral ketones, they are reasonably impressive when compared against other chiral titanium alkoxide catalysts.

Thus, as we have already noted, Wandrey[104] utilised chiral bicyclic diols as ligands in the asymmetric reduction of acetophenone. When complexed to titanium, the corresponding alcohol was obtained in 82%ee (see **Section 1.5.2**). Later, Frejd[105] also reported the use of chiral bicyclic diols (BODOLs) as effective ligands. Acetophenone was successfully reduced using catecholborane in 97%ee (see **Section 1.5.2**). DiMare and Lindsley[159] examined three optically pure titanium alkoxides as prospective catalyst Ti-(TADDOLate)(O^iPr)$_2$, Ti-(TADDOLate)$_2$ and Ti(O-menthyl)$_4$] in the catecholborane and BH_3.THF reductions of acetophenone. All three catalysts gave low enantioselectivities, with the best result of 24%ee observed with 5mol% Ti-(TADDOLate)$_2$ and BH_3.THF in CH_2Cl_2 (**Scheme 98**).



24%ee

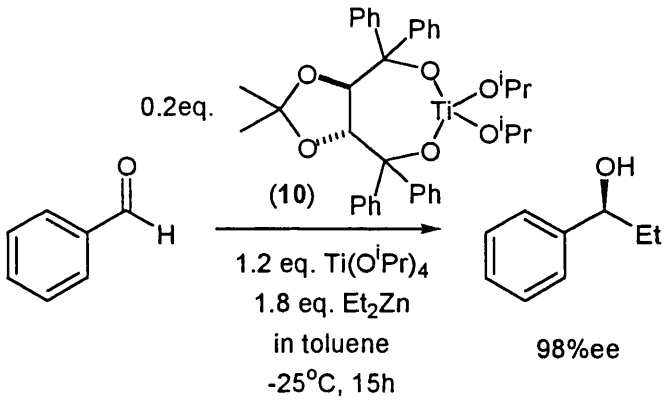
Scheme 98

2.8 Titanium trimer (101) in other asymmetric reactions

Whilst our series of catecholborane reductions using the titanium trimer (**101**) as a Lewis acid were being carried out, we were also, at the same time, screening a wide variety of other asymmetric reactions. The most logical approach to adopt was to begin with existing reactions which are already known to be catalysed by chiral titanium alkoxides. In the event, as the reader will discover, this phase of our studies proved to be a perplexing contrast to our initial success, as cultured overleaf.

2.8.1 Diethylzinc addition to benzaldehydes

The most well known titanium alkoxide catalyst for asymmetric diethyl zinc addition to aldehydes is probably Ti-(TADDOLate)(O^iPr)$_2$ (**10**) devised by Seebach[59] (See **Section 1.3.1**). This reaction was attempted using the *titanium 3,4-di-O-benzyl-D-mannitol trimer* (**101**) instead of Ti-(TADDOLate)(O^iPr)$_2$ (**Scheme 99**).



Scheme 99

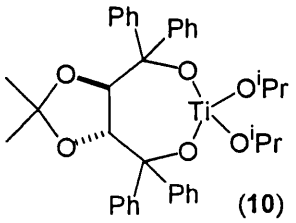
Although, under Seebach's optimised conditions, the additional use of achiral Ti(O^iPr)$_4$ did not compete in the reaction to hinder the enantioselectivity (**See Section 1.3.1**). We decided not to use Ti(O^iPr)$_4$ in the initial studies. The reaction however afforded no product (**165**). The same reaction was then performed in the presence of 1.2 equivalents of Ti(O^iPr)$_4$, resulted only in formation of trace amounts of racemic product as judged by GC (**166**). Raising the temperature up to 0°C did not speed up the reaction noticeably (**167**). This study is summarised in **Table 16**.

(101) mol%	Solvent	Temp. (°C)	Et_2Zn (equiv.)	Ti(O^iPr)$_4$ (equiv.)	Time (h)	%ee	% Yield
20 (**165**)	Toluene	–25	1.2	0	96	---	S.M.
20 (**166**)	Toluene	–15	1.2	1.2	48	0	22
20 (**167**)	Toluene	0	1.1	1.2	20	0	---

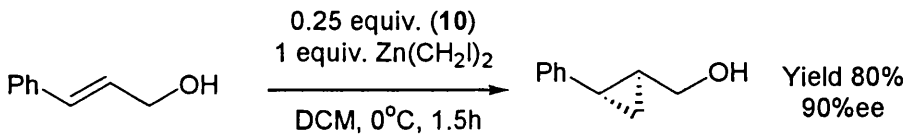
Table 16

2.8.2 The enantioselective (iodomethyl)zinc mediated cyclopropanation of allylic alcohols

Charette[71] found that the cyclopropanation of cinnamyl alcohol in the presence of Ti-(TADDOLate)(O^iPr)$_2$ (**10**) afforded the corresponding cyclopropane in 90%ee (**Scheme 100**).



(**10**)



Scheme 100

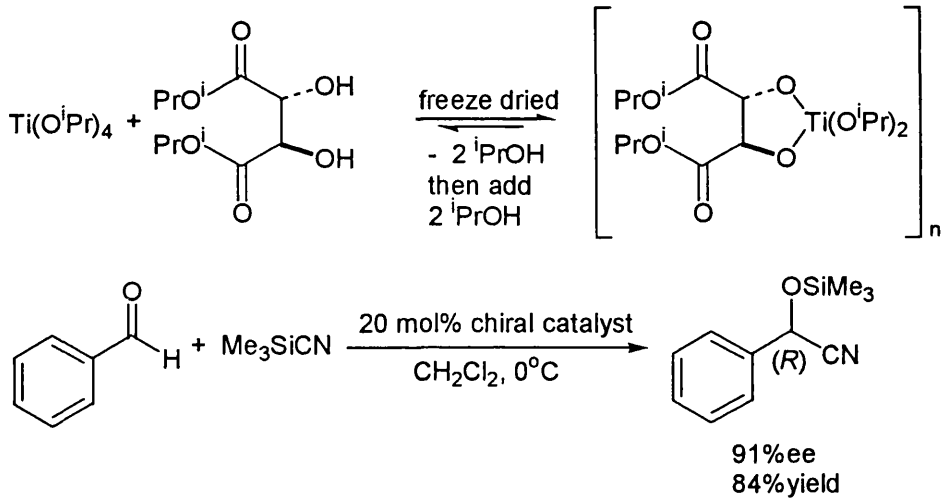
We therefore attempted the cyclopropanation of cinnamyl alcohol using Charette's methodology in which the substrate is firstly reacted with bis(iodomethyl)zinc followed by addition of Lewis acid. However when this reaction was performed in the presence of 15mol% of the titanium trimer, only racemic cyclopropanated product was formed. Using the reverse addition method (*viz.*, premixing the bis(iodomethyl)zinc with the Lewis acid and then adding the substrate) did not result in any increase either in enantioselectivity or yield. Finally, a cyclopropanation was performed in the absence of any titanium Lewis acid, this afforded the cyclopropanated product in similar yields. It was therefore concluded that the use of *titanium 3,4-di-O-benzyl-D-mannitol trimer* (**101**) did not provide any significant effect either as a Lewis acid or in terms of enantioselectivity. These observations are collected in **Table 17**.

(101) mol%	Solvent	Temp. (°C)	$Zn(CH_2I)_2$ (equiv.)	$Ti(O^iPr)_4$ (equiv.)	Time (h)	%ee	%Yield
0 (**168**)	DCM	–20	1.0	0.15	18	0	35
15 (**169**)	DCM	–20	1.0	0	17	0	29
(Reverse addition) 15 (**170**)	DCM	–20	1.0	0	15	0	22
0 (**171**)	DCM	–20	1.0	0	16	0	21

Table 17

2.8.3 Trimethylsilyl cyanide addition to aldehydes

Oguni[42] demonstrated the use of a modified Sharpless catalyst in the enantioselective addition of trimethylsilyl cyanide to aldehydes to afford optically active silylated cyanohydrins with an enantiomeric excess of 91% (**Scheme 101**).



Scheme 101

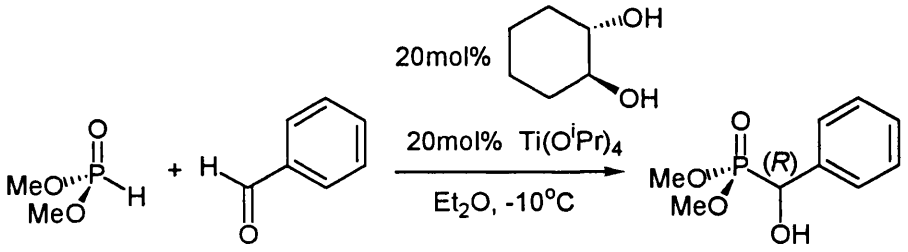
The cyanosilylation of benzaldehyde using 20mol% $Ti(O^iPr)_4$ provided the corresponding cyanohydrin in 82% yield after hydrolysis (**172**). The use of 20mol% of *titanium 3,4-di-O-benzyl-D-mannitol trimer* (**101**) in the cyanosilyation of benzaldehyde resulted in formation of racemic cyanohydrin (**173**). Neither temperature variation nor the amount of TMSCN added influenced the enantioselectivity (**174**, **175**) (**Table 18**).

Trimer (101) mol%	Solvent	Temp. (°C)	TMSCN (equiv.)	$Ti(O^iPr)_4$ (equiv.)	Time (h)	%ee	Yield
0 (172)	DCM	r.t.	2.28	0.2	1	0	82
20 (173)	DCM	r.t.	1.2	0	72	0	22
20 (174)	DCM	0	2.28	0	1	0	15
20 (175)	DCM	–78	1.5	0	24	0	15

Table 18

2.8.4 Phosphite addition to aldehydes (Pudovik reaction)

The groups of Spilling[160] and Shibuya[161] have reported the use of chiral titanium alkoxide catalysts in the hydrophosphonylaton of aldehydes to afford the corresponding α-hydroxy-phosphonate in good to moderate enantiomeric excesses (**Scheme 102**).



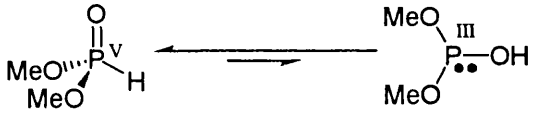
Scheme 102

For our own studies, cinnamaldehyde was initially used as the substrate because it gave the best enantioselectivity in the publication reported by Spilling.[160] The addition of dimethyl phosphite to cinnamaldehyde was tested using 20mol% titanium-mannitol trimer (**101**) under the experimental conditions developed by Spilling. The reaction produced the corresponding racemic α-hydroxyphosphonate (**177**), in comparable yield to a reaction catalysed by $Ti(O^iPr)_4$ (**176**). When benzaldehyde was used as the substrate, no product was isolated at –20°C (**179**). The reaction temperature was warmed to 0°C and the solvent was changed to toluene. When these conditions were employed a small amount of product was isolated (3-6%) (**181**, **182**). The addition of dimethyl phosphite to *N*-(4-chloro benzylidene) benzylamine was also attempted (**183**, **184**), all the starting material has been consumed to give the same two unknown compounds for both reactions (**Table 19**).

Substrate	$Ti(O^iPr)_4$ (mol%)	Trimer (101) (mol%)	Solvent	Temp. (°C)	Time (h)	$[\alpha]_D^{23}$	Yield
Cinnamaldehyde **(176)**	20	0	DCM	–10	18	---	33
Cinnamaldehyde **(177)**	0	20	DCM	–10	18	-1.7	27
Benzaldehyde **(178)**	20	0	DCM	–20	18	---	22
Benzaldehyde **(179)**	0	20	DCM	–20	18	---	SM recov.
Benzaldehyde **(180)**	20	0	toluene	0	15	---	48
Benzaldehyde **(181)**	0	20	toluene	0	15	-0.2	3
Benzaldehyde **(182)**	0	20	toluene	0	15	-2.6	6
N-(4-chloro benzylidene) benzylamine **(183)**	20	0	DCM	–10	18	---	no SM, 2 by-prod
N-(4-chloro benzylidene) benzylamine **(184)**	0	20	DCM	–10	18	---	no SM, 2 by-prod

Table 19

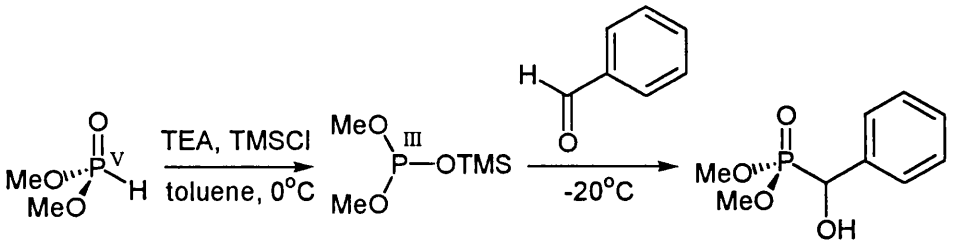
In the Pudovik reaction, the dimethyl phosphite exists in tautomeric equilibrium between phosphorus(V) and the more nucleophilic phosphorus(III) species. This equilibrium favours the more stable phosphorus(V) and hence without activation of the phosphite, the reaction would be very slow (**Scheme 103**).



Scheme 103

We were aware however that Rees and Afarinkia[162] had reported that the addition of trimethylsilyloxy phosphorus(III) derivatives, generated *in situ*, to imines provides a mild, selective and high yielding route to α-aminoalkylphosphonate esters. The reagent was generated from the phosphite *in situ* with chlorotrimethylsilane and triethylamine in dichloromethane at 0°C. The reported chlorotrimethylsilane mediated reactions all worked well under mild conditions (0°C to room temperature in dichloromethane, with aqueous workup), to give better yields and cleaner reactions than the neat uncatalysed, thermal reactions.

This methodology was therefore employed with the addition of the chiral titanium alkoxide complex (**101**). Using benzaldehyde as the substrate and toluene as the solvent, at –20°C, the reaction proceeded to give racemic product in only 5% yield (**185**) (**Scheme 104**). Changing the solvent to THF resulted in better yield (20%)(**186**), but warming the temperature to 0°C did not improve the yield (**187**). Both reactions gave very low enantioselectivities. Using the imine, *N*-(4-chloro benzylidene) benzylamine, the reaction proceeded, in the absence of any chiral catalyst, to afford the product in a moderate yield (48%) (188). By the addition of 20mol% titanium-mannitol trimer (**101**) and performing the same reaction using the same imine at a lower temperature provided the product in a higher yield. Unfortunately however the enantioselectivity was minimal as revealed in (**189**) **Table 20**.



Scheme 104

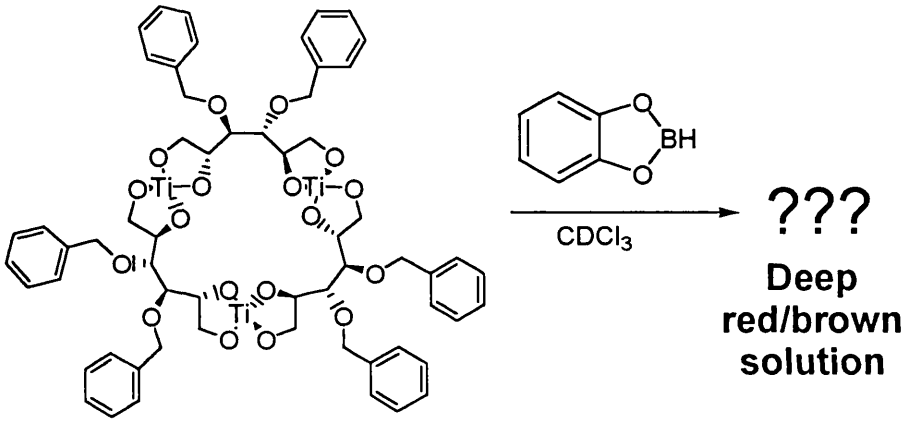
Substrate	Trimer (87) (mol%)	Solvent	Temp. (°C)	Time (h)	$[\alpha]_D^{23}$	Yield
Benzaldehyde **(185)**	20	Toluene	–20	15	-2	5
Benzaldehyde **(186)**	20	THF	–20	15	-2.7	20
Benzaldehyde **(187)**	20	THF	0	19	-3.4	22
N-(4-chloro benzylidene) benzylamine **(188)**	0	DCM	0 to r.t.	20	---	48
N-(4-chloro benzylidene) benzylamine **(189)**	7	DCM	–20	19	-1.2	56

Table 20

Clearly the stark contrast between the borane reductions and the uniformly unsuccessful attempts to achieve enantioselectivity in cyclopropanation reactions or addition to nucleophiles other than hydride was of immediate interest, and therefore deserving of study in its own right.

2.9 Mechanistic investigation of titanium trimer (101) with catecholborane

The testing of other asymmetric reactions, using the titanium trimer (**101**) as the catalyst, have so far proved unsuccessful. Therefore, we turned our interest back to the catecholborane reduction of prochiral ketones, in the hope of understanding the mechanism and thus finding the key for other asymmetric reactions. The fundamental difference between the catecholborane reduction and the other asymmetric reactions tested is, upon addition of catecholborane to the titanium trimer (**101**), a deep red/brown solution was generated (**Scheme 105**).



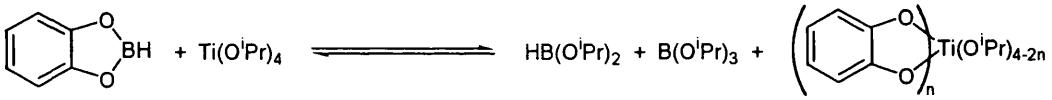
Scheme 105

Careful re-examination of the communication by Wandrey,[104] published in 1995, and which had indeed inspired us to select the catecholborane reduction, revealed that no mention was made of any colour change taking place with their catalyst system. In 1997, a similar publication was reported by Frejd,[105] using optically active BODOLs (**54a,b**) in the Ti(IV)-catalysed reduction of ketones with catecholborane. Yet again, these authors mentioned only that the exact nature of the active catalyst is difficult to assess with certainty and that other similar systems experienced the same problem.[17,53f,54]

Further searching of the literature then revealed two papers, one by DiMare and Lindsley.[159] and the other by Burgess[163] which were published in 1994. DiMare and Lindsley reported that the combination of $Ti(O^iPr)_4$ and catecholborane 1:10 in the presence or absence of a carbonyl substrate immediately gives dark red solutions when dilute, or red-black precipitates when concentrated, this being exactly the same

observation as in our catalytic system. Examination of the supernatant liquid by ^{13}C NMR from a concentrated sample prepared from a 1:1 mixture of $Ti(O^iPr)_4$/catecholborane in $CDCl_3$ showed no signals associated with catechol. The UV-Vis spectra of dilute 1:1 $Ti(O^iPr)_4$/catecholborane in CH_2Cl_2 solution displayed absorptions at 242nm (ε 7,500) and 380nm (broad; ε 3,400). ^{11}B NMR spectroscopy of the CH_2Cl_2 solutions from a 1:5 mixture of $Ti(O^iPr)_4$ and catecholborane showed unreacted catecholborane, $HB(O^iPr)_2$, and small amounts of a product consistent with the formula $(C_6H_4O_2)B(O^iPr)$. A 1:1 ratio gives predominantly $B(O^iPr)_3$ and small amounts of $HB(O^iPr)_2$.

The conclusion was reached that rapid metathesis takes place when $Ti(O^iPr)_4$ and catecholborane are combined, leading to titanium catecholate complexes, known to be deeply coloured (red-brown-black) solids with similar UV-VIS spectra,[164] and several boron containing species depending upon the stoichiometry (**Scheme 106**).



n=1,2

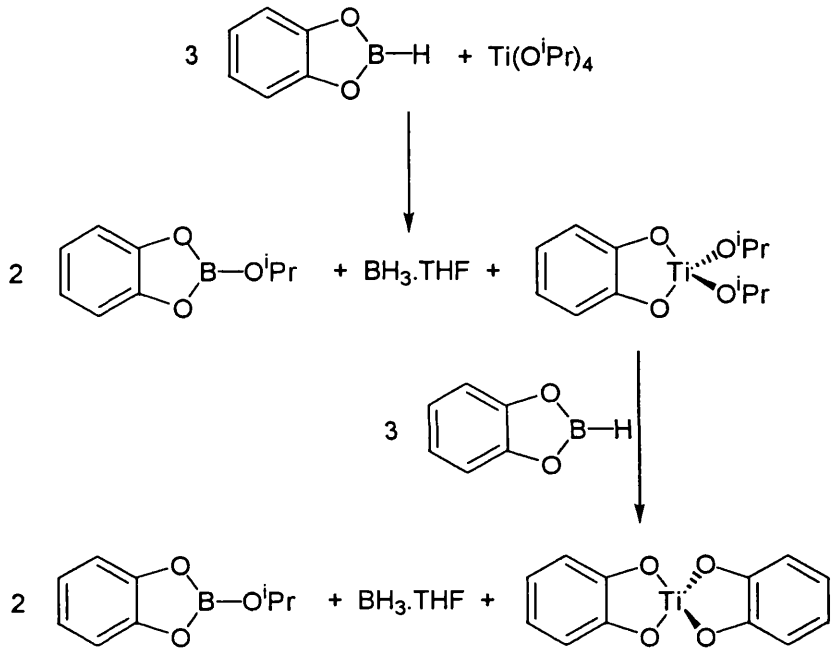
Scheme 106

DiMare concluded his report by stating that the acceleration of catecholborane and BH_3.THF reductions of ketones by titanium alkoxides are due to reactions involving transmetallation to produce a complex series of alkoxyborohydride species and borohydride itself.

In the same year Burgess[163] investigated the origin of the titanium(IV) isopropoxide promoted hydroboration of alkenes using catecholborane, and also recorded that the combination of $Ti(O^iPr)_4$ with catecholborane in THF gives a deep red solution. A red solid could be isolated after removal of solvent and excess catecholborane under reduced pressure. The ^{13}C NMR spectrum of this material corresponded to that published previously for $Ti(O_2C_6H_4)_2$,[165] although these spectra were poor due to

paramagnetism caused by electron transfer from the aromatic catechol moieties to the metal centre.

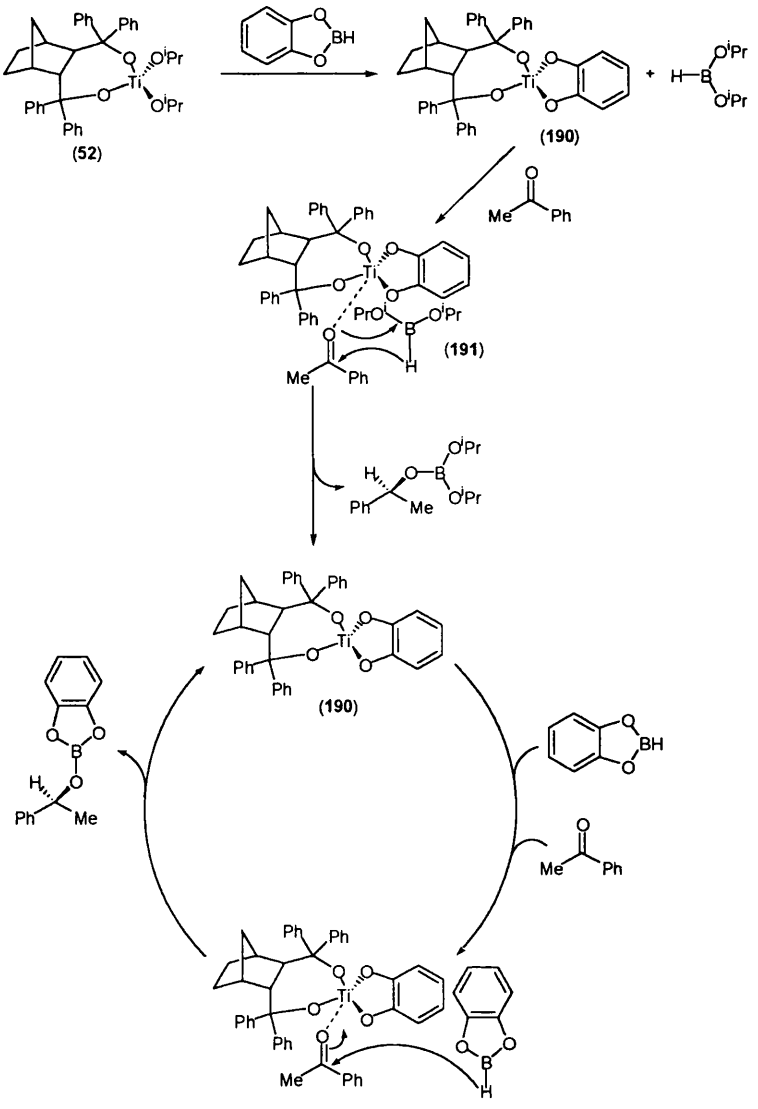
These authors also recorded the ^{11}B NMR spectrum of the reaction mixture from $Ti(O^iPr)_4$ and catecholborane and showed that, in addition to $Ti(O_2C_6H_4)_2$, $BH_3.THF$ and $^iPrOBO_2C_6H_4$ were also formed. A possible rationale for these results lies once again in the disproportionation reaction shown in **Scheme 107**.



Scheme 107

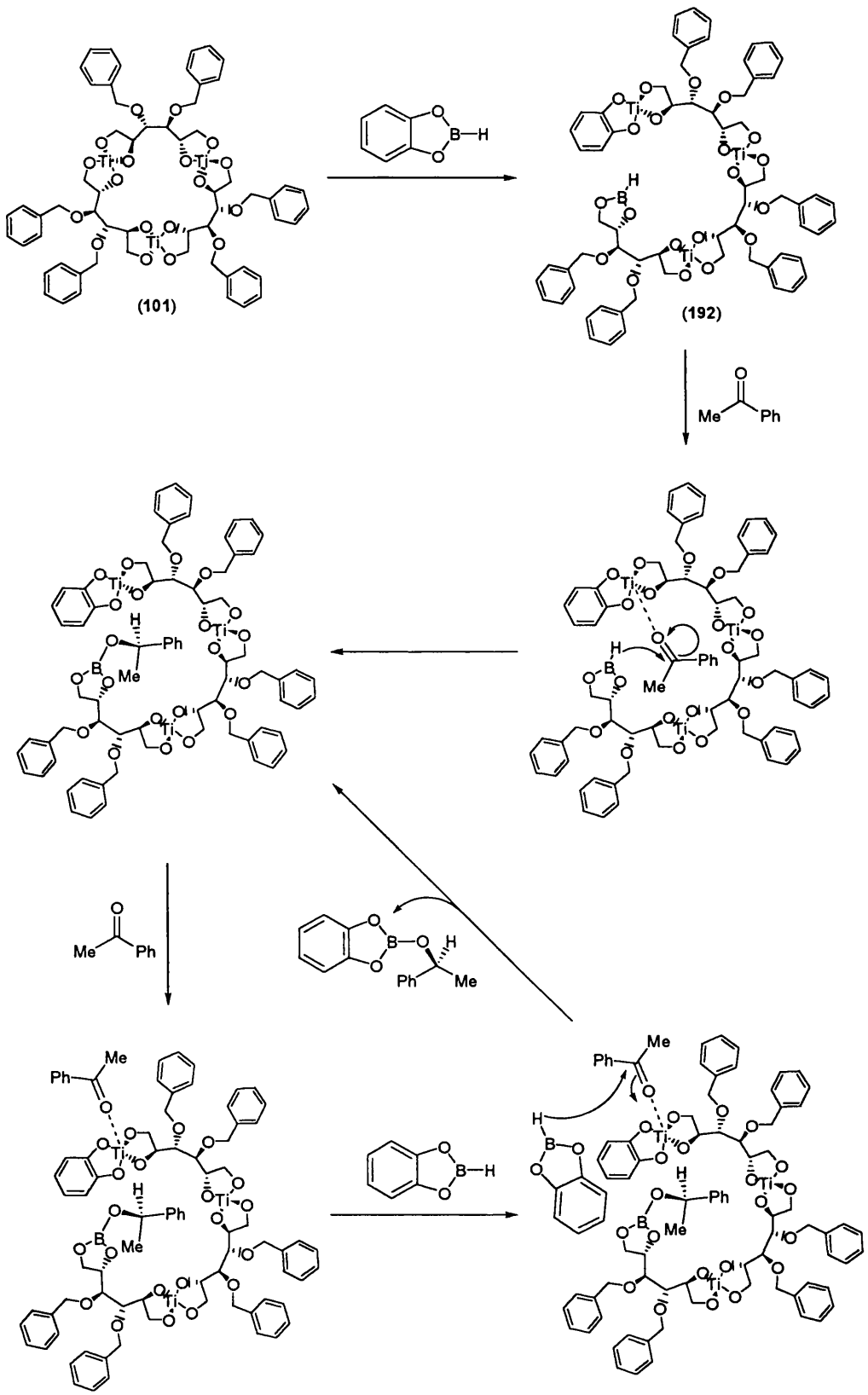
Further evidence for the postulate shown in **Scheme 107** was obtained by monitoring the progress of the reaction by multinuclear NMR. The ^{13}C NMR spectrum revealed immediate consumption of $Ti(O^iPr)_4$ and initial formation of $^iPrOBO_2C_6H_4$ and an unknown species. It could be $(^iPrO)_2Ti(O_2C_6H_4)$, the initial product from redistribution of the ligands on boron and titanium; however this is not easily checked as mixtures of $Ti(O^iPr)_4$ and catechol did not provide a convenient route to an authentic sample of this complex. During the same time period, the ^{11}B NMR of this reaction in THF showed signals for $^iPrOBO_2C_6H_4$, catecholborane and $BH_3.THF$. The intensity of the resonance corresponding to $BH_3.THF$ slowly increased and an additional signal with a relatively low intensity corresponding to $B_2(O_2C_6H_4)_3$ was also observed.

Bearing these publications in mind, a mechanism can be proposed for the asymmetric reduction reported by Wandrey.[104] Initial titanium-boron exhange will provide one equivalent of complex (**190**) and one equivalent of $(^{i}PrO)_2BH$. Complexation of acetophenone to the Lewis acidic titanium centre (**191**) then activates the carbonyl for enantioselective hydride delivery from either $(^{i}PrO)_2BH$ or catecholborane. $(^{i}PrO)_2BH$ is probably the more reactive of the two and hence likely to be less enantioselective. This affords the boronate ester of 1-phenylethanol with regeneration of a putative catalytic species (**190**). It is possible that the $(^{i}PrO)_2BH$ is only generated once and thereafter the reduction of the carbonyl can occur using only catecholborane (**Scheme 108**). Therefore the synthesised titanium complex (**52**) is a catalyst precursor.



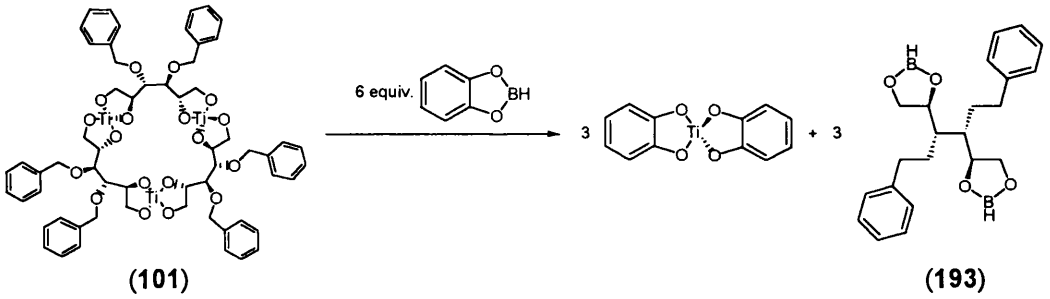
Scheme 108

An analogous mechanism can be proposed for the reaction of the titanium trimer (**101**) **Scheme 109**. In the first instance, the boron-titanium exchange must cause the titanium complex to break up to form a titanium catecholate at one end and a dialkoxy borane at the other terminus (**192**). The next steps in the reaction are less clear, inasmuch as hydride can be delivered either in intramolecular fashion from the opened trimer or by catecholborane itself in solution. If we follow the previous mechanism, then an intramolecular dialkoxyborane hydride delivery will take place providing the boronate ester within the structure of the catalyst until reaction is quenched. The rest of the acetophenone may then be complexed to the titanium catecholate and reduced with catecholborane to form a chiral boronate ester, thus regenerating a possible opened catalyst. A wide variety of variants on this theme are still however possible depending on the overall number of transmetallation sequences which occur.



Scheme 109

Additional complexity arises however since our titanium complex contains three titanium atoms as opposed to the single titanium atom in Wandrey's complex. This means that a maximum of six transmetallations can take place per molecule of titanium complex (**101**). We believe that the boron-titanium transmetallation is a fast process in our reaction because of the immediate generation of a deep red colour, but we do not know to what extent that these exchanges continue. In the reaction 16mol% of the titanium complex (**101**) was employed, this equates to 48 mol% of titanium atom. If, at the extreme limit, six transmetallations do take place then 48mol% of titanium dicatecholate and 48mol% of the chiral bis-borane (**193**) would be generated, (**Scheme 110**) thus consuming all of the catecholborane. In this instance the reduction of acetophenone would not involve catecholborane at all.



(101) **(193)**

Scheme 110

2.9.1 NMR experiments

With these thoughts in mind, we then decided to carry out some NMR experiments in an effort to discover the true catalytic species in the asymmetric reduction. Initial NMR studies on the addition of catecholborane to a solution of the titanium complex (**101**) in $CDCl_3$ were carried out at room temperature (**Scheme 105**). These experiments involved the addition of one, two and then an excess number of equivalents of catecholborane (per titanium atom) to the titanium complex (**101**). On addition of the first equivalent of catecholborane, the spectrum remained much the same. When the second equivalent of catecholborane was added, the spectrum started to change, suggesting that the trimer was beginning to lose its symmetry. Excess catecholborane gave a very complex spectrum, which was difficult to interpret, and only indicative of the fact that the initial trimer had lost its symmetry (see **Appendix F**).

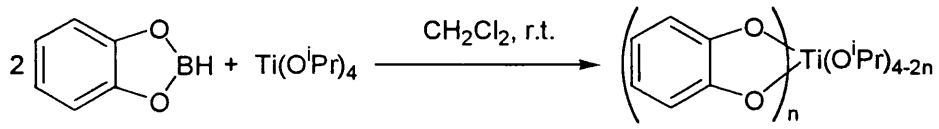
All of the NMR analyses described, above and below, were initially performed using $CDCl_3$ as the deuterated solvent. However, since the titanium catecholate species is paramagnetic and gives a very broad NMR signals, analysis proved very difficult. However, we noted that d^6-DMSO was a very good solvent for NMR analyses as sharp signals were observed. Before any NMR analyses were carried out, it was of course necessary to record the NMR spectra of the *titanium 3,4-di-O-benzyl-D-mannitol trimer* (**101**) in d^6-DMSO. A different NMR spectrum would mean that DMSO is complexed to the titanium alkoxide. Comparison of both NMR spectra showed that all of the signals are almost the same (**Table 21**).

Assignments	^{1}H NMR in $CDCl_3$ (ppm)	^{1}H NMR in d^6-DMSO (ppm)
6H, 3x3-H and 3x4-H	3.73-3.75	3.78-3.80
6H, 3x1-$H_{(trans)}$ and 3x6-$H_{(trans)}$	4.42-4.45	4.22-4.24
6H, 3xCH_2	4.57-4.59	4.59-4.62
6H, 3xCH_2	4.81-4.84	4.70-4.74
6H, 3x1-$H_{(cis)}$ and 3x6-$H_{(cis)}$	4.88-4.94	4.80-4.87
6H, 3x2-H and 3x5-H	5.03-5.09	5.05-5.17

Table 21

Before carrying out any experiments, it was necessary to prepare the species that might be generated in the reaction between titanium trimer (**101**) and catecholborane so they can be compared. The preparation of titanium catecholate species was attempted and a simulation of the number of transmetallation that takes place between the titanium trimer (**101**) and catecholborane would also be helpful. The following experiments were therefore carried out:

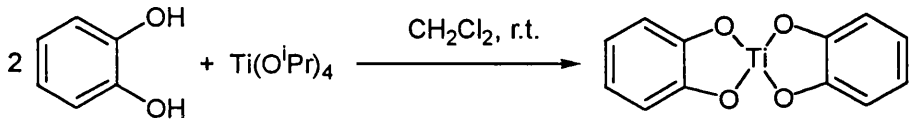
1. Efforts were made to synthesise the titanium dicatecholate (**194**) using two equivalents of catecholborane with one equivalent of titanium(IV) isopropoxide in dichloromethane at room temperature. Removal of the solvent and analysis by NMR however showed only isopropanol and the starting material, titanium(IV) isopropoxide. A new set of signals (6.10-6.15 and 6.41-6.45ppm) was thought to be a titanium catecholate (**Scheme 111**).



(194)

Scheme 111

2. Reactions to generate the titanium dicatecholate (**195**) using two equivalents of catechol with one equivalent of titanium(IV) isopropoxide in dichloromethane at room temperature were also performed. Removal of the solvent and analysis by NMR showed isopropanol and small amounts of the starting material catechol (6.57-6.60 and 6.70-6.73ppm), with the major product being what we believe to be the titanium dicatecholate (AA'BB' signals at 6.09-6.15 and 6.40-6.46ppm). This set of signals is closely related to those in the previous experiment above (**Scheme 112**).



(195)

Scheme 112

Mass spectrometry, was also used to deduce a possible structure. Fast atom bombardment (FAB) mass spectrometry proved to be of little use because the whole molecule seemed to disintegrate. Chemical ionisation (CI) mass spectrometry, a milder method, did not provide evidence for the desired titanium mono- or dicatecholate complex. Interestingly, there were peaks showing compounds that consists of more than one titanium atom (easily seen due to its distinctive isotope distribution pattern), such as 469.2, 842.2, and 873.1. The peak at 469.2 is consistent with the formula $(C_6H_4O_2)_3Ti_3$ indicative of bridged species being present.

3. Reactions of the *titanium 3,4-di-O-benzyl-D-mannitol trimer* (**101**) with one, two and three equivalents of catecholborane were conducted (**196**). After twenty minutes the reaction was quenched with the corresponding amount of 3,5-dinitrobenzoic acid. The solvent was removed and the residue was analysed using NMR (**Table 22**). The idea of using 3,5-dinitrobenzoic acid to quench the reaction was that the borane in the transmetallated trimer would be quenched to give a product containing 3,5-dinitrobenzoate groups attached to the boron atoms. It was intended that the signals of this product would be shifted downfield (8-9ppm) on the NMR, due to the electron-withdrawing effect of the nitro groups, and therefore not obstructing the rest of the NMR region for analysis.

Catecholborane (1M DCM)		**Titanium 3,4-di-*O*-benzyl-D-mannitol trimer (101)**		**3,5-dinitrobenzoic acid**	
mmol	**mL**	**mmol**	**mg**	**mmol**	**mg**
0.2	0.2	0.2	224	0.2	43
0.4	0.4	0.2	224	0.4	86
0.6	0.6	0.2	224	0.6	129

Table 22

1:1, 2:1, and 3:1 ratio of catecholborane and titanium alkoxide (**101**) all gave the same NMR spectra. The titanium catecholate species (6.11-6.14 and 6.42-6.46ppm) are easily identified. The nitro-aromatic signals (8.91 and 9.01) were observed but the accompanying catechol signals are absent. All the protons associated with the titanium (**101**) alkoxide are absent. Two sets of new signals are obtained but could not be interpreted (3.35-4.09 and 4.51-4.76ppm).

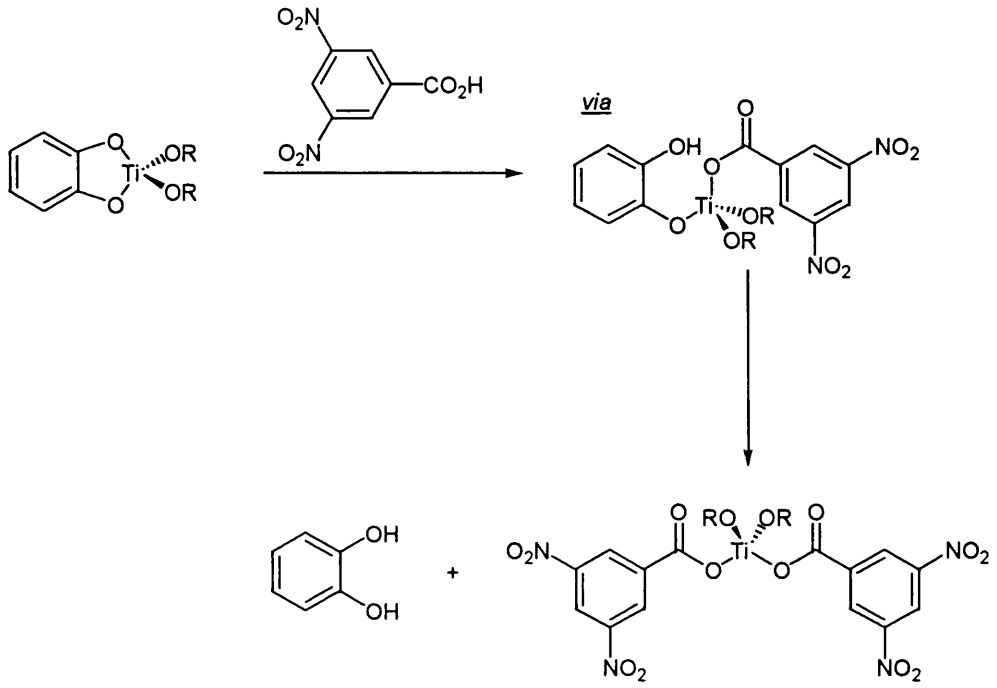
The NMR experiment was performed virtually under the same normal reaction conditions, except that the titanium trimer (**101**) was premixed with one, two and three equivalents of catecholborane for 20min. This was done to check whether the number of initial transmetallations has any effect in enantiomeric excess of the final product. The enantioselective reduction of acetophenone was performed (**197**) at –20°C using 20mol% titanium alkoxide (**101**) (premixed with catecholborane). Acetophenone was added followed by the remaining catecholborane, making it up to one equivalent. The reaction was stirred overnight and quenched with 3,5-dinitrobenzoic acid. The enantiomeric purity of the alcohol was analysed using chiral GC and the residue was analysed by NMR. It is interesting that all three experimental procedures afforded the alcohol with the same enantioselectivity (**Table 23**).

Titanium trimer (101)		**Catechol-borane (1M DCM)**		**Aceto-phenone**		**Catechol-borane (1M DCM)**		**3,5-dinitro-benzoic acid**		**Enan-tiomeric purity**
mmol	mg	mmol	mL	mmol	mL	mmol	mL	mmol	mg	%ee
0.2	244	0.2	0.2	1	0.12	0.8	0.8	1	212	56
0.2	244	0.4	0.4	1	0.12	0.6	0.6	1	212	56
0.2	244	0.6	0.6	1	0.12	0.4	0.4	1	212	54

Table 23

1:1, 2:1, and 3:1 ratio of catecholborane and titanium alkoxide (**101**) all provided the same NMR spectra. The titanium catecholate species (6.11-6.14 and 6.42-6.46ppm) are observed. The starting material acetophenone and the product 1-phenylethanol were also observed. 3,5-Dintrobenzoic acid (8.90 and 9.01ppm) and catechol (6.57-6.60 and 6.69-6.72ppm) are observed. The two new sets of signals recorded in the previous experiment are absent. Mass spectrometry was also used to analyse the residues (CI) only revealed fragments of *3,4-di-O-benzyl-D-mannitol* (**87**).

In retrospect, this approach is probably flawed since 3,5-dinitro benzoic acid can also protonate the catecholate and hence create a very good leaving group (**Scheme 113**).



Scheme 113

Thus, the addition of catecholborane to *titanium 3,4-di-O-benzyl-D-mannitol trimer* (**101**) in a 1:1, 2:1, or 3:1 stoichiometry suggests that the perfect symmetry of the titanium alkoxide complex is lost. They all provided the same NMR suggesting that only a single species is responsible for observed enantioselectivity. This material has not yet been isolated and cannot be characterised with the data obtained. The identifiable new products generated from the reduction of acetophenone are catechol, 1-phenylethanol and a titanium catecholate type species.

2.9.2 UV-Vis Experiments

With NMR experiments proving unsuccessful in terms of understanding the mechanism in the titanium trimer mediated catecholborane reduction, it was hoped that UV-Vis experiments would provide us with greater insight into this reaction. Lindsley and DiMare[169] had already reported the molar absorption coefficient of a dilute 1:1 $Ti(O^iPr)_4$/catecholborane in CH_2Cl_2 solution (at 242nm, ε7500; at 380nm, ε3800). From the Beer-Lambert Law the stoichiometry of titanium catecholate species, generated in the reaction of titanium trimer with catecholborane, can be predicted from the magnitude of the absorbance (**Equation 1**).

$$A = \log\frac{I_o}{I} = \varepsilon c l$$

A=absorbance
ε=molar absorption coefficient
c=concentration
l=pathlength

Equation 1

In order to measure the UV-Vis spectra two factors have to be noted:

1. The UV-Vis spectra of a 1:1 and a 2:1 ratio of catechol with $Ti(O^iPr)_4$ and catecholborane with $Ti(O^iPr)_4$ (blank reactions) have to be measured for comparison.
2. As the titanium trimer (**101**) has three titanium atoms the blank reactions have to be carried out at the correct concentration to emulate the generation of one, two, and three equivalents of both the generation of titanium mono- and di-catecholate.

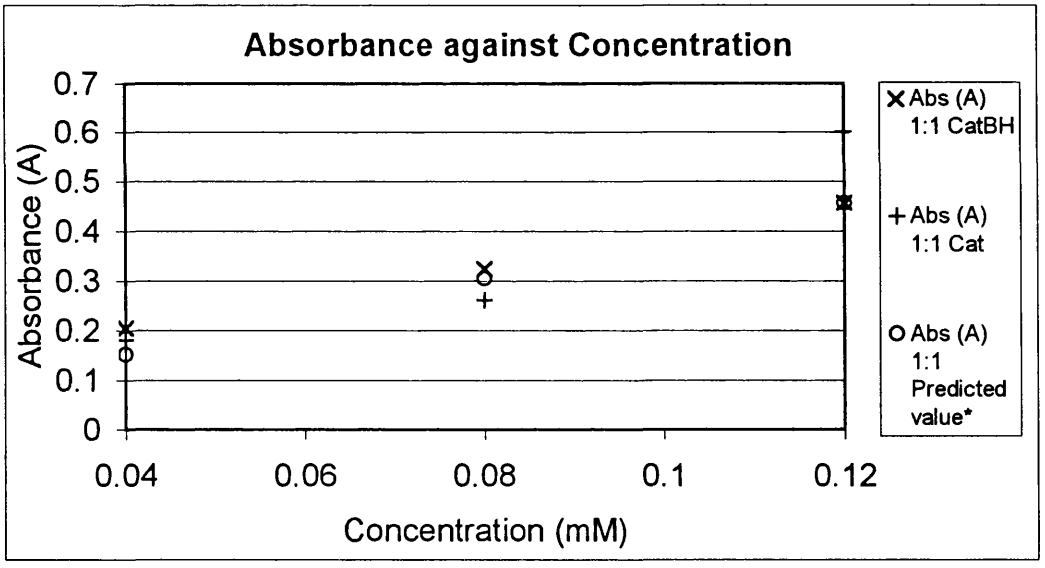
1 1:1 ratio of the catechol moiety and $Ti(^{i}OPr)_4$

Catecholborane (26μL, 0.24mmol) and catechol (26mg, 0.24mmol) were mixed separately with $Ti(O^{i}Pr)_4$ (73μL, 0.24mmol) in dichloromethane (10mL [0.024M], 15mL [0.016M] and 30mL [0.008M]). The mixture was stirred for 20 minutes and 50μL of the mixture was diluted to 10mL using dichloromethane, this solution was used to measure the UV-Vis spectra. The values obtained from mixing catechol and catecholborane with $Ti(O^{i}Pr)_4$ in dichloromethane correlated well with the predicted values (**Table 24**, **Chart 1**).

Conc (mM) of Ti	Abs (A) 1:1 CatBH	Abs (A) 1:1 Cat	Abs (A) 1:1 Predicted value*
0.12	0.456	0.600	0.456
0.08	0.324	0.260	0.304
0.04	0.204	0.180	0.152

* Predicted values based on ε=3800 at 380nm.

Table 24



CatBH=catecholborane
Cat=catechol

Chart 1

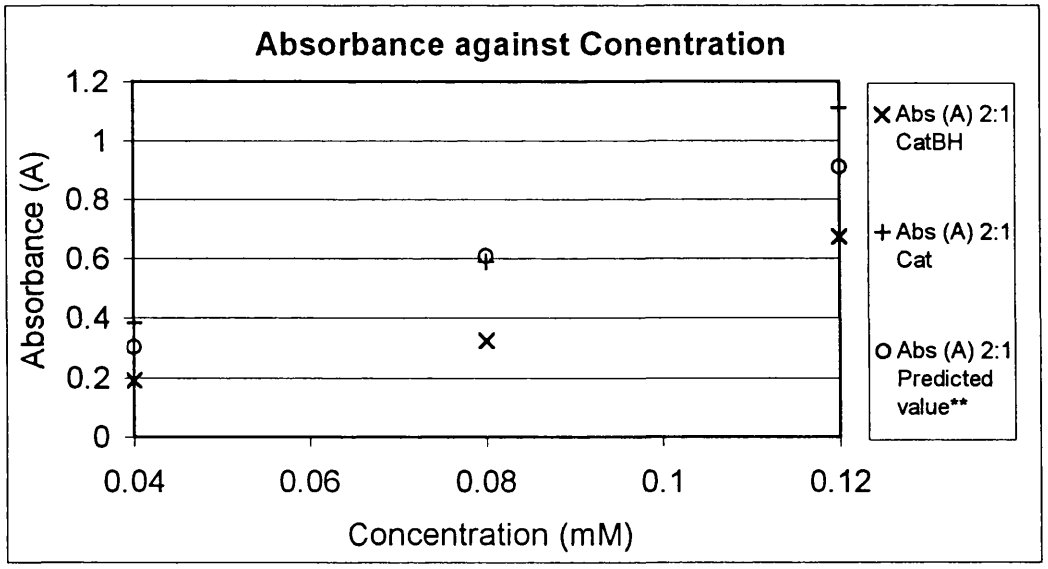
2 2:1 ratio of the catechol moiety $Ti(O^iPr)_4$

The same procedure was used to make up the solutions for UV-Vis measurements but 0.48mmol of catechol and catecholborane were employed. The catecholborane seemed to be reacting slower with $Ti(O^iPr)_4$ than catechol, as the results from the catechol mixture correlate well with the predicted values whereas the results from the catecholborane mixture gave roughly the same values as the 1:1 mixture (**Table 25**, **Chart 2**).

Conc (mM) of Ti	Abs (A) 2:1 CatBH	Abs (A) 2:1 Cat	Abs (A) 2:1 Predicted value**
0.12	0.672	1.110	0.912
0.08	0.324	0.590	0.608
0.04	0.192	0.384	0.304

** Predicted values based on ε=3800 at 380nm and double the concentration.

Table 25



CatBH=catecholborane
Cat=catechol

Chart 2

3 UV-Vis of Titanium trimer with $Ti(O^iPr)_4$

The conditions used were identical to the experimental conditions for ketone reduction. Therefore, titanium trimer (**101**) (98mg, 0.08mmol) and catecholborane (0.11mL, 1mmol) in dichloromethane (10mL) was used (8mM) and the mixture was cooled to –20°C. After each time interval, 50μL of the mixture was diluted to 10mL using dichloromethane to make a 0.04mM solution for UV analysis. By running this UV experiment at the same concentration as the blank experiments, we hoped to compare the absorbances and therefore deduce how quickly and to what extent the titanium trimer (**101**) breaks down.

From the data shown below, during the first five minutes the absorbances are in the region of 0.3. We can therefore speculate that two equivalents of titanium mono-catecholate or one equivalent of titanium di-catecholate has been generated, suggesting one breakage of the titanium metallo-cycle. For the next hour, the absorbance stayed at 0.5-0.6 region, which correlated to the generation of two equivalents of titanium di-catecholate and the loss of two titaniums in the titanium trimer. After 1.5h, the data showed that the molecule has almost completely broken up (**Table 26**, **Chart 3**).

Time (min)	1	5	15	30	45	60	90	105
Absorbance (A)	0.29	0.36	0.47	0.53	0.6	0.59	0.8	0.76

Table 26

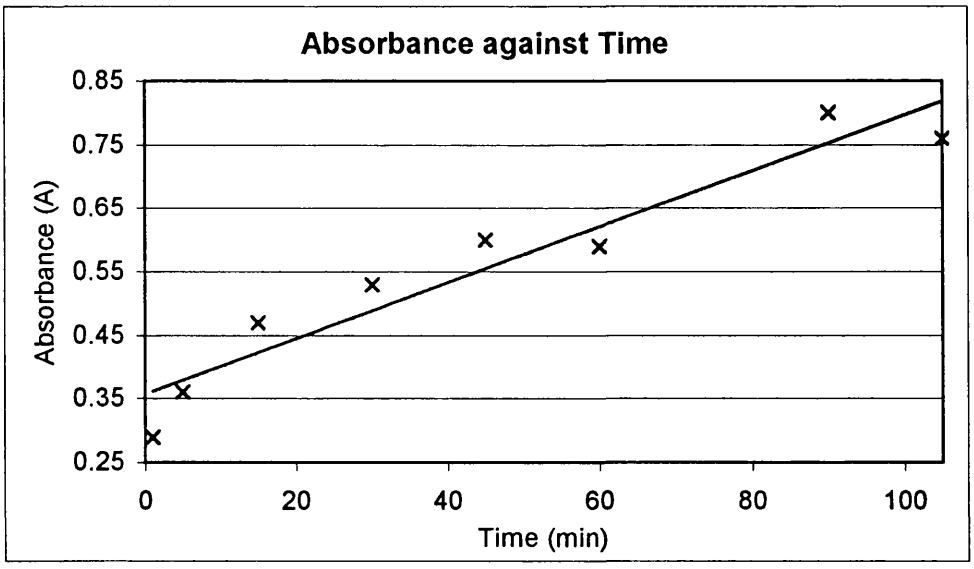


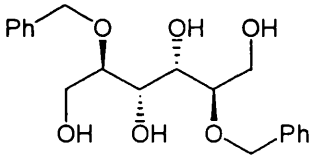
Chart 3

In essence, these UV-Vis experiments have shown that the titanium trimer (**101**) breaks up very rapidly on addition of catecholborane and complete destruction to give three equivalents of titanium di-catecholate occurs within 2 hours.

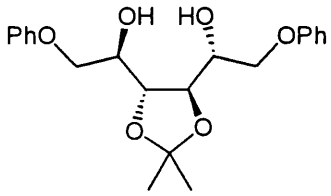
Therefore from both the NMR and UV studies we can only conclude that *titanium 3,4-di-O-benzyl-D-mannitol trimer* (**101**) acts as a precursor in the enantioselective reduction of prochiral ketones using catecholborane as the stoichiometric reducing agent. The mechanism for this reaction is certainly not a straightforward chiral Lewis acid interaction with the substrate thus inducing chirality to the molecule and more detailed experiments must be carried out in order understand the mechanism. Thus far, we only know that boron-titanium exchange does occur to provide titanium catecholate species, which have an intense red colour.

2.10 The Selection and Synthesis of other chiral ligands

Throughout the course of this work, efforts were also ongoing to develop other potential chiral ligands using the discovery philosophy and D-mannitol as the starting material. Accordingly, it was decided to examine the 1,3-diol relationship present in *2,5-di-O-benzyl-D-mannitol* (**198**) when complexed to titanium. We also wished to prepare additional C_2 symmetric diols of D-mannitol. Since the TADDOLs are a very versatile and effective family of catalysts for a number of asymmetric reactions (see **Section 1.3**), we decided to synthesise a similar ligand using D-mannitol as the starting material. *1,6-Di-O-phenyl-3,4-isopropylidene-D-mannitol* (**199**) has a similar structure to the TADDOLs, but also has the advantage of having two chiral centres closer to the titanium (**Scheme 114**).



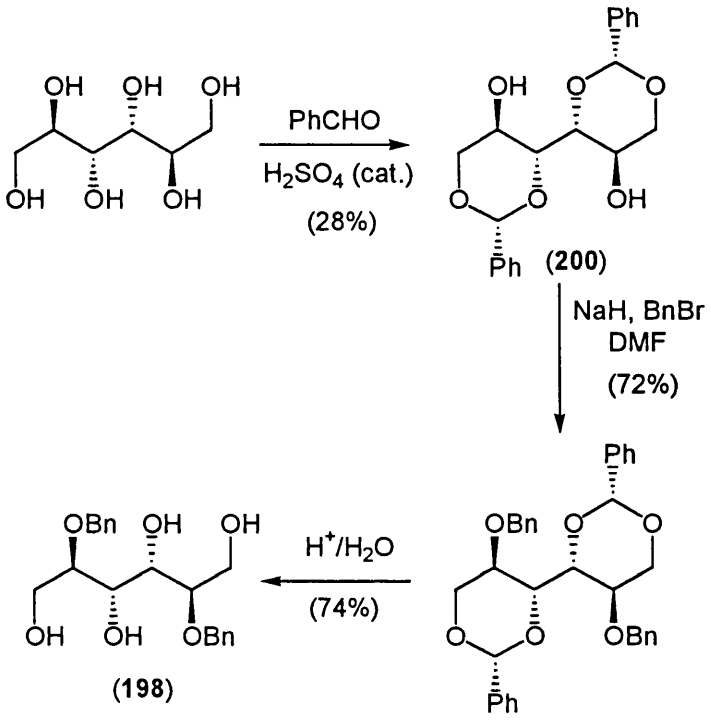
(198)



(199)

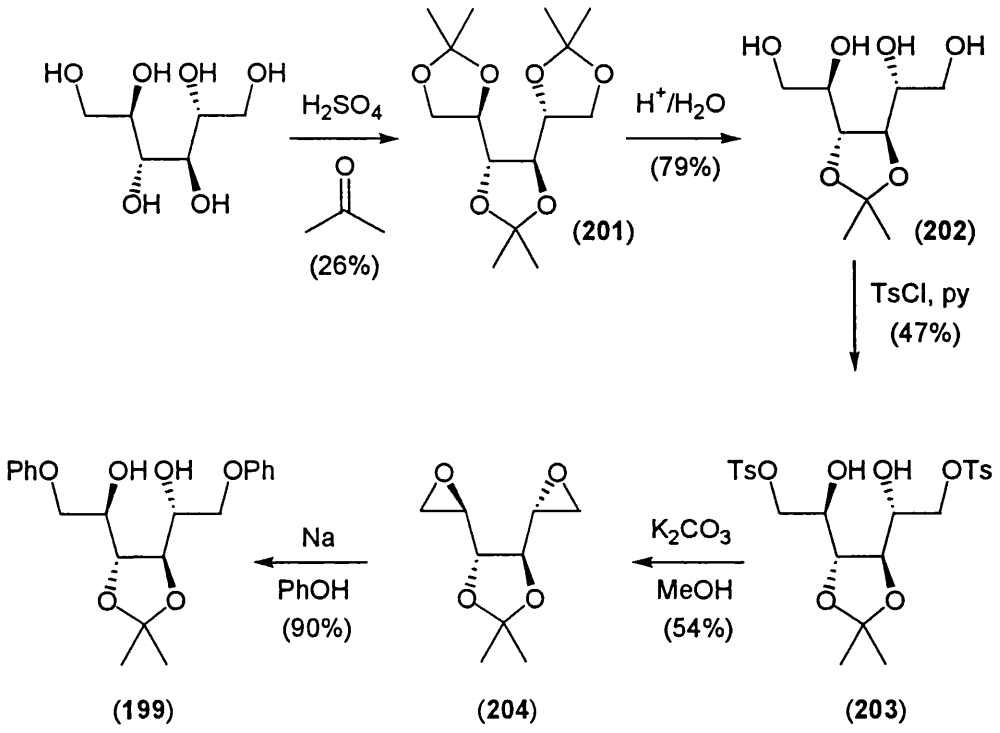
Scheme 114

The preparation of the chiral ligand *1,3:4,6-di-O-benzylidene-D-mannitol* (**200**) involves benzylide protection of the 1,3 and 4,6 diol units by stirring with benzaldehyde and a catalytic amount of H_2SO_4 in DMF for 4 days (**Scheme 115**).[166] The subsequent benzylation of *1,3:4,6-di-O-benzylidene-D-mannitol* (**199**) was then performed by treatment of the tetrol with sodium hydride and benzyl bromide in DMF.[167] Deprotection of the two benzylidene groups, by heating in aqueous acid then provided *2,5-di-O-benzyl-D-mannitol* (**198**) (**Scheme 115**). [167]



Scheme 115

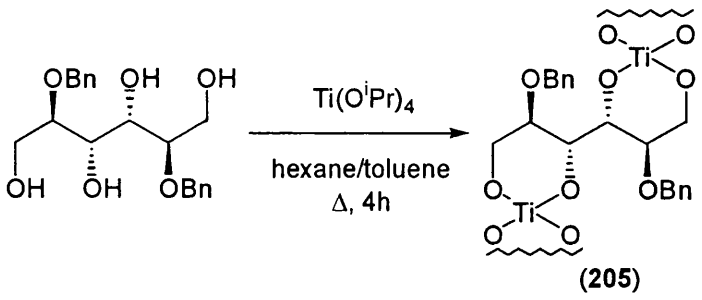
The synthesis of *1,6-di-O-phenyl-3,4-isopropylidene-D-mannitol* (**199**) initial protection of all the hydroxyl groups of D-mannitol, using acetone and H_2SO_4, to afford *1,2,3:4,5,6-tri-O-isopropylidene-D-mannitol* (**201**).[168] Deprotection of the two terminal acetonides with aqueous acid provided *3,4-O-isopropylidene-D-mannitol* (**202**).[169] Tosylation of the two primary hydroxyl groups, using tosyl chloride in pyridine then gave *1,6-di-O-tosyl-3,4-O-isopropylidene-D-mannitol* (**203**),[168] which on intramolecular displacement of the tosylate using potassium carbonate in methanol afforded *1,2:5,6-di-O-anhydro-3,4-O-isopropylidene-D-mannitol* (**204**).[168] Finally, treatment of *1,2:5,6-di-O-anhydro-3,4-O-isopropylidene-D-mannitol* (**204**) with sodium phenoxide in benzene provided the desired ligand (**199**) (**Scheme 116**).[170]



Scheme 116

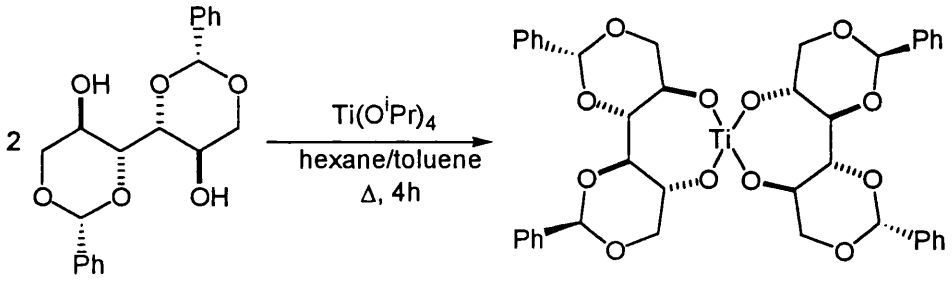
2.10 Complexation of chiral ligands to transition metals

Considerable efforts were made to complex these three chiral ligands to the transition metals, titanium, and/or lanthanum. The 1:1 complexation of the *2,5-di-O-benzyl-D-mannitol* (**198**) with titanium(IV) isopropoxide was attempted using identical conditions to those developed for the synthesis of *titanium 3,4-di-O-benzyl-D-mannitol trimer* (**101**) (**Scheme 117**). The structure of this material (**205**) could not however be characterised by NMR, MS. We tested this unknown complex in the enantioselective reduction of acetophenone. Furthermore, using the optimised conditions, the reduction of acetophenone (**206**) using catecholborane did not afford any alcohol (after 18h).



Scheme 117

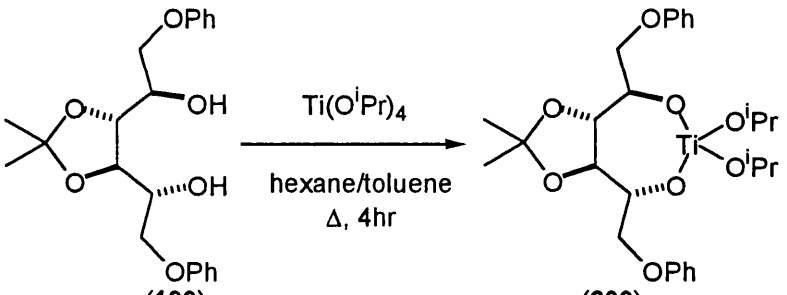
We also tried to use the C_2 symmetric diol *1,3:4,6-di-O-benzylidene-D-mannitol* (**200**) as a ligand for complexation to titanium (**Scheme 118**). Using two equivalents of the chiral ligand with one equivalent of $Ti(O^iPr)_4$ under the same conditions for the preparation of the titanium trimer (**101**), might be expected to synthesise the chiral titanium alkoxide (**207**). Once again however the structure of this material could not be characterised by NMR and MS. Complex (**207**) was used to test the enantioselective reduction of acetophenone (**208**) using the optimised conditions but did not catalyse the reaction and only afforded the corresponding racemic alcohol in trace amounts.



(207)

Scheme 118

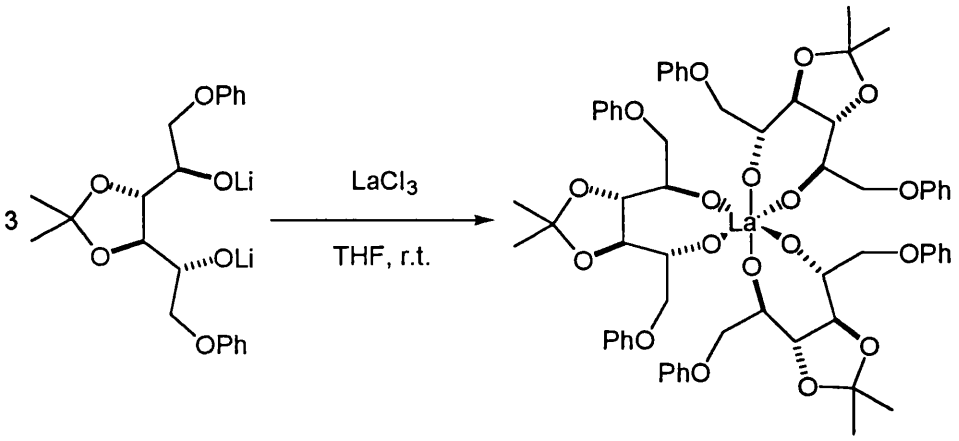
Initial screening experiments were also performed using *1,6-di-O-phenyl-3,4-isopropylidene-D-mannitol* (**199**) which has a similar structure to the TADDOLs (*cf.* **Scheme 18**) (**Scheme 119**). We wished to generate the more reactive titanium alkoxide (**209**) with two labile isoproxy ligands around the titanium, equimolar quantities of diol and $Ti(O^iPr)_4$ were used, the structure however is unknown. When this "titanium alkoxide" (**209**) was tested for the asymmetric induction in the diethylzinc addition to benzaldehyde (**210**), using the same conditions as Seebach,[60] the corresponding alcohol was however produced as a racemic mixture in 59% yield. Complex (**209**) was also used to test the enantioselective reduction of acetophenone (**211**) using the optimised conditions affording the corresponding racemic alcohol in trace amounts.



(199) **(209)**

Scheme 119

This C_2 symmetric chiral ligand (**199**) was also used for complexation to lanthanum(III) in an attempt to generate structures similar to Shibasaki's LLB heterobimetallic complexes (**212**) (See **Section 1.6.1**). The reaction was performed using three equivalents of the lithium alkoxide of the chiral diol (**199**), generated using *n*-butyllithium, and lanthanum(III) chloride.[171] Although the resultant solid was analysed using NMR and MS, the exact structure cannot be characterised. This is due to poor integration and broad signals recorded using the NMR. (**Scheme 120**).



(212)

Scheme 120

Using 125mg (5mol% according to the structure proposed above) of the lanthanum alkoxide complex, both the dimethyl phosphite and the trimethyl silyl ester of dimethyl phosphite addition to benzaldehyde were attempted. Both reactions provided the desired product in 56% (**213**) and 18% (**214**) yields respectively. Unfortunately however, racemic product was observed by derivatisation to the corresponding Mosher's esters and analysis using GC.

Unfortunately, because of time constraints, and also because of ongoing work with the titanium trimer, further work on these potentially interesting ligands could not be pursued. Clearly however, both in terms of selecting the metal, tuning its Lewis acidity, and also incorporating additional control elements on, for example, the aromatic rings, a wealth of reactions have yet to be carried out.

2.11 Conclusions and Perspectives

The primary objective of the present thesis was to demonstrate that, by careful pre-selection of a polydentate carbohydrate ligand, its subsequent reaction with a metal alkoxide could be guaranteed to produce a new complex whose structure could not be predicted in advance. In this respect, the isolation of a series of novel C_3 symmetrical chiral trinuclear cyclic titanium alkoxide complexes from the exchange reactions of a range of substituted 3,4-di-*O*-benzyl-D-mannitol derivatives with titanium(IV) isopropoxide has certainly succeeded, if not perhaps at a supramolecular level. As always, chemistry knows best.

In terms of their use as chiral catalysts, our work, despite investigating a range of asymmetric reactions, has been less successful, with the stoichiometric catecholborane reduction of prochiral ketones mediated by the titanium trimer proving to be the reaction of greatest practical value. A range of prochiral ketones was reduced to the corresponding alcohols with the reduction of acetophenone providing the S-enriched enantiomer in 62%ee. Whilst the results showed that the titanium trimer works well with aromatic ketones, cyclic enones such as isophorone proved less successful.

Interestingly, the use of a range of boranes in the asymmetric reduction led to the discovery that $BH_3.SMe_2$ gave the opposite *R*-enriched enantiomer, 28%ee, to catecholborane for the reduction of acetophenone.

The mechanism of the catecholborane reduction was studied using NMR and UV-Vis experiments. Although, no definitive intermediates could be characterised, the mechanism was shown to be very complex and certainly involves the rapid transmetallation between catecholborane and the titanium trimer. More detailed experiments are required for the investigation of this mechanism.

Three other ligands, 1,3:4,6-di-*O*-benzylidene-D-mannitol, 2,5-di-*O*-benzyl-D-mannitol and 1,6-di-*O*-benzyl-3,4-isopropylidene-D-mannitol, were also synthesised and used for complexation with transition metals such as titanium and lanthanum. Although the structures of these complexes have not yet been characterised, they have been tested for asymmetric induction in some carbonyl addition reactions. Initial results however were considerably less successful than in the case of the titanium trimer.

Nevertheless, the present thesis has shown that the discovery approach, although experimentally time consuming can be rewarding. The preparation and reactivity of the titanium trimer embodied in this thesis has confirmed the viability of the method. Moreover, the pre-selection of inexpensive but multidentate carbohydrate ligands, when combined with the wide range of co-ordinating geometry for transition metals, indicates that many more complexes remain to be explored using such philosophy.

Part 3. Experimental

3.1 General Experimental Procedures

Melting points were determined using Reichert hot stage and are uncorrected. Optical rotation were determined using a 'POLAAR 2000' instrument from Optical activity Ltd.

Infrared spectra were recorded as thin films on KBr plates or as KBr discs on a Perkin-Elmer FT-IR 1605 instrument.

^{1}H NMR Spectra were recorded at 400MHz on a Varian-400 or a Bruker AMX-400 and at 300MHz on a Bruker AMX-300 spectrometer. ^{13}C Spectra were recorded at 100Mhz or 75MHz on the instruments above. Chemical shifts (δ) are quoted in parts per million (ppm) and are referenced to the residual solvent peak. ^{19}F Spectra were recorded at 282MHz on the instrument above. Chemical shifts (δ) are quoted in parts per million (ppm) and are referenced to $CFCl_3$. Coupling constants are quoted to the nearest Hertz for all spectra. The abbreviations used to indicate multiplicity are s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet doublet; m, multiplet; br, broad.

Low resolution mass spectra were recorded under either electron impact, atmospheric pressure chemical ionisation, or fast atom bombardment conditions on a VG 305 or a VG ZAB SE mass spectrometer at the School of Pharmacy, University of London. Only molecular ions, fragments from the molecular ions and other major peaks are reported.

High resolution mass spectra were recorded using a VG 7070b mass spectrometer by the School of Pharmacy Mass Spectrometry Service.

Microanalyses were performed by Mr. Alan Stone and Mrs. Jill Maxwell, Christopher Ingold Laboratories, University College London.

X-ray crystallography were attempted by Dr. J. Steed at King's College London and Dr A. Slawin at Loughborough University.

Analytical thin layer chromatography was performed on pre-coated glass backed plates (Merck Keisegel $_{F254}$). Components were visualised with ultraviolet light (254nm), and by staining with iodine, basic potassium permanganate, acidic ammonium molybdate (IV), or acidic anisaldehyde; all followed by heat.

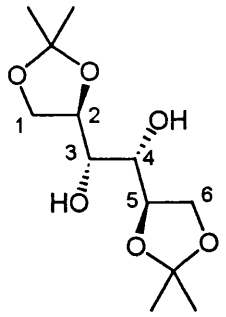
Flash chromatography was carried out using BDH silica 40-673μm. Gas chromatography was performed on a Hewlett Packard 5890A machine (flame ionisation detector) with a Supelco Beta Dex 30m x 0.25mm chiral column using helium as the carrier gas and a SGE BPX5 25m x 0.50mm column using hydrogen as the carrier gas. Analytical high pressure liquid chromatography was performed on a Shimadzu HPLC apparatus with an OJ Daicel cellulose chiral column (250mm x 4.6mm). UV-Vis spectroscopy was performed on a Beckman DU®70 spectrophotometer.

PE refers to petroleum ether. Dimethyl formamide was dried with anhydrous $MgSO_4$ and distilled over Linde type 4A molecular sieves under reduced pressure. Diethyl ether was distilled from sodium-benzophenone ketyl, as was tetrahydrofuran. Dichloromethane was distilled from calcium hydride. Toluene and benzene were distilled from sodium. Methanol was distilled from magnesium turnings. Triethylamine and pyridine were distilled over calcium hydride.

All reactions were performed using oven-dried glassware.

3.2 Synthesis of precursors for titanium trimer (101) and its derivatives

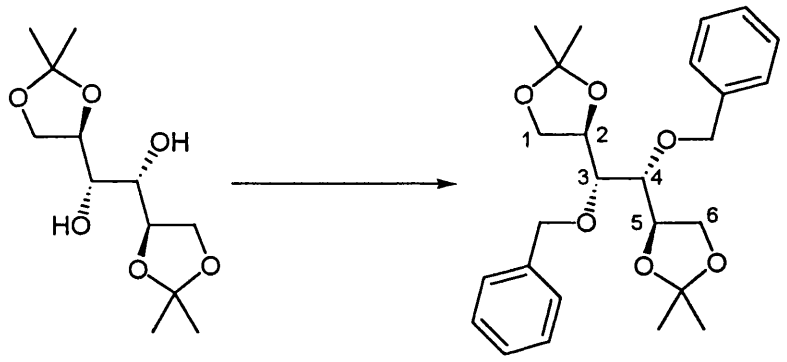
Preparation of 1,2:5,6-di-O-isopropylidene-D-mannitol (85)[132]



(85)

D-Mannitol (10g, 55mmol) and freshly fused anhydrous zinc(II) chloride (60g, 440mmol) in acetone (300mL) was stirred at room temperature for 19h. The reaction was poured into a mixture of K_2CO_3 (70g) in water (70mL) and ether (300mL). A white precipitate formed, the solution was filtered off and a further addition of 1:1 ether:acetone was used to extract the precipitate. Concentration *in vacuo* gave an off-white solid. The solid was taken up portionwise with hexane under reflux for 20min and was filtered while hot. Concentration *in vacuo* afforded *1,2:5,6-di-O-isopropylidene-D-mannitol* (**85**) (8.12g, 56%) as white crystalline needles; **m.p.** 119-122°C, lit.,[172] 121.8-123.4°C; $[\alpha]_D^{23}$ =+1.7° (c=2, CH_3OH), lit.,[172] +1.9° (c=2, CH_3OH); **^{1}H NMR** (400MHz, $CDCl_3$): δ 1.36 (6H, s, 2xCH_3), 1.42 (6H, s, 2xCH_3), 2.55-2.57 (2H, d, *J* 7Hz, 2xOH), 3.73-3.77(2H, dd, *J* 2, 6Hz, 3-H and 4-H), 3.95-3.99 (2H, dd, *J* 6, 9Hz, 1-$H_{(cis)}$ and 6-$H_{(cis)}$), 4.10-4.14 (2H, dd, *J* 6, 9Hz, 1-$H_{(trans)}$ and 6-$H_{(trans)}$), 4.17-4.21 (2H, ddd, *J* 6, 12Hz, 2-H and 5-H); **^{13}C NMR** (100MHz, $CDCl_3$): δ 25.2 (CH_3), 26.7 (CH_3), 66.7, 71.2, 76.3, 109.4 (CMe_2).

General procedure for benzylation of 1,2:5,6 di-O-isopropylidene-D-mannitol (85)



(85) **(86)**

To a stirred solution of sodium hydride (60% dispersion on mineral oil; 11.5g, 286mmol) in 2:1 THF:DMF (250mL) was added *1,2:5,6-di-O-isopropylidene-D-mannitol* (**85**) (25g, 95mmol) dissolved in 2:1 THF:DMF (250mL). After hydrogen evolution had ceased, benzyl chloride (24.2mL, 210mmol) in 2:1 THF:DMF (50mL) was slowly added and the reaction was stirred for of 17h. The reaction was quenched with water (200mL) and the aqueous phase extracted with ether (2x500mL) and washed with brine (200mL). Drying ($MgSO_4$) and concentration *in vacuo* gave a yellow oil. Flash chromatography (SiO_2, 30% ether in PE 30-40) afforded *3,4,-di-O-benzyl-1,2:5,6 di-O-isopropylidene-D-mannitol* (**86**) (30.08g, 72%) as a white solid whose data are tabulated below.

Improved general procedure for the benzylation of 1,2:5,6 di-O-isopropylidene-D-mannitol (86)[133]

1,2:5,6-di-O-isopropylidene-D-mannitol (**85**) (1g, 3.81mmol) in DMSO (76mL) was added finely powdered potassium hydroxide (2.57g, 45.91mmol) and stirred for 15min. Benzyl bromide (1.62mL, 13.6mmol) was slowly added and the reaction. After 2.5h, the reaction was quenched MeOH at 0°C. The mixture was partitioned with DCM (95mL) and washed with water (3x95mL). Drying ($MgSO_4$) and concentration *in vacuo* gave a yellow oil. Flash chromatography (SiO_2, 30% ether in PE 30-40) afforded *3,4,-di-O-benzyl-1,2:5,6 di-O-isopropylidene-D-mannitol* (**86**) (1.52g, 94%) as a white solid whose data are tabulated below.

3,4-Di-O-benzyl-1,2:5,6-di-O-isopropylidene-D-mannitol **(85)** (1.52g, 94%) as a white solid; **m.p.** 36-39°C; $[\alpha]_D^{23}$ =+39.5° (c=1, $CHCl_3$), lit.,[173] +37.2° (c=1, $CHCl_3$); **IR** (KBr disc/cm^{-1}): $\tilde{\nu}_{max}$ 3448.2, 2991.7, 2903.6, 1498.1, 1454.2, 1373.5, 1268.5, 1204.8, 1166.0, 1118.8, 1047.8, 980.9, 854.8, 737.8, 695.6; **^{1}H NMR** (400MHz, $CDCl_3$): δ 1.31 (6H, s, 2xCH_3), 1.40 (6H, s, 2xCH_3), 3.76-3.78 (2H, dd, *J* 6Hz, 3-H and 4-H), 3.81-3.85(2H, dd, *J* 6, 8Hz, 1-$H_{(trans)}$ and 6-$H_{(trans)}$), 3.96-4.00 (2H, dd, *J* 6Hz, 8Hz, 1-$H_{(cis)}$ and 6-$H_{(cis)}$), 4.21-4.23 (2H, dd, *J* 6Hz, 2-H and 5-H), 4.68 (4H, s, 2xCH_2), 7.24-7.31 (10H, m, 2xPh); **^{13}C NMR** (100MHz, $CDCl_3$): δ 25.9 (CH_3), 30.4 (CH_3), 34.5, 39.8, 45.8, 120.9, 121.5 (CMe_2), 127.7(Ph), 128.0 (Ph), 128.3 (Ph), 138.2 (Ph); ***m/z*** (FAB): 441 ($[M-H]^+$, 53%), 427 ($[M-CH_3]^+$, 44%); **Anal.** Calcd. for $C_{26}H_{34}O_6$: C, 70.56; H, 7.81%, Found: C, 70.69; H, 7.81%.

3,4-Di-O-1'methylnaphthalene-1,2:5,6-di-O-isopropylidene-D-mannitol **(215)** (1.50g, 72%) as a white solid; **m.p.** 64°C; $[\alpha]_D^{23}$ =+25.2° (c=1, $CHCl_3$); **IR** (KBr disc/cm^{-1}): $\tilde{\nu}_{max}$ 3854.3, 3448.5, 2985.8, 1370.1; **^{1}H NMR** (400MHz, $CDCl_3$): δ 1.27 (6H, s, 2xCH_3), 1.38 (6H, s, 2xCH_3), 3.54-3.58 (2H, dd, *J* 7, 8Hz, 1-$H_{(trans)}$, 6-$H_{(trans)}$), 3.71-3.75(2H, dd, *J* 6, 8Hz, 1-$H_{(cis)}$ and 6-$H_{(cis)}$), 3.89-3.91 (2H, d, *J* 6Hz, 3-H and 4-H), 4.20-4.23 (2H, ddd, *J* 6Hz, 2-H and 5-H), 4.09-5.19 (4H, AB dd, J_{AB} 12Hz, 2xCH_2), 7.38-7.48 (8H, m, Ar), 7.78-7.84 (4H, m, Ar), 8.05-8.08 (2H, m, Ar); **^{13}C NMR** (100MHz, $CDCl_3$): δ 25.0 (CH_3), 26.5 (CH_3), 66.8, 72.0, 75.5, 79.6, 108.4 (CMe_2), 123.9(Ar), 125.1 (Ar), 125.6 (Ar), 126.0 (Ar), 126.6 (Ar), 128.4 (Ar), 128.5 (Ar), 131.5 (Ar), 133.6 (Ar), 133.8 (Ar); ***m/z*** (FAB): 565 (MNa^+, 52%).

3,4-Di-O-2'-bromobenzyl-1,2:5,6-di-O-isopropylidene-D-mannitol **(216)** (1.81g, 79%) as a white solid; **m.p.** 63-64°C; $[\alpha]_D^{23}$ =+31.0°, c=1, $CHCl_3$); **IR** (KBr disc/cm^{-1}): $\tilde{\nu}_{max}$ 2988.4, 2926.9, 2865.7, 1474.3, 1377.8, 1339.6, 1216.7, 1214.0, 1156.4, 1068.0, 941.9, 846.1, 751.6, 664.9, 517.0; **^{1}H NMR** (400MHz, $CDCl_3$): δ 1.33 (6H, s, 2xCH_3), 1.41 (6H, s, 2xCH_3), 3.90-3.92 (2H, d, *J* 6Hz, 3-H and 4-H), 3.39-3.97 (2H, dd, *J* 7, 8Hz, 1-$H_{(trans)}$ and 6-$H_{(trans)}$), 4.02-4.07 (2H, dd, *J* 6, 8Hz, 1-$H_{(cis)}$ and 6-$H_{(cis)}$), 4.31-4.36 (2H, dd, *J* 6Hz, 2-H and 5-H), 4.75-4.85 (4H, AB dd, J_{AB} 13Hz, 2xCH_2), 7.12-7.16 (2H, m, Ar), 7.29-7.33 (2H, m, Ar), 7.51-7.53 (4H, m, Ar); **^{13}C NMR** (100MHz, $CDCl_3$): δ 25.2 (CH_3), 26.6 (CH_3), 66.8. 73.6, 75.7, 80.5, 108.6 (CMe_2), 122.3 (Ar), 127.4 (Ar), 128.9 (Ar), 129.2 (Ar), 132.3 (Ar), 137.7 (Ar); ***m/z*** (FAB): 601 (M^+, 11%), 585 ($[M-CH_3]^+$, 67%); **HRMS** (FAB) for $C_{26}H_{33}O_6Br_2$: Requires 599.0644, Found 599.0675; **Anal.** Calcd. for $C_{26}H_{32}O_6$: C, 52.02; H, 5.37; Br, 26.62%, Found: C, 51.99; H, 5.38; Br 26.24%.

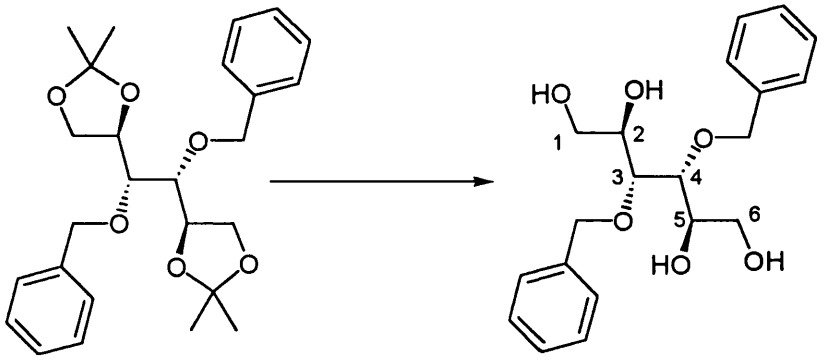
3,4-Di-O-4'-methylbenzyl-1,2:5,6-di-O-isopropylidene-D-mannitol **(217)** (1.61g, 90%) as a white solid; **m.p.** 50-52°C; $[\alpha]_D^{23}$ =+45.5°, (c=1, $CHCl_3$); **IR** (KBr disc/cm^{-1}): $\tilde{\nu}_{max}$ 2988.8, 2902.6, 1518.2, 1458.1, 1375.3, 1263.1, 1211.0, 1167.6, 1108.1, 1056.7, 977.5, 864.8, 804.4, 485.1; **^{1}H NMR** (400MHz, $CDCl_3$): δ 1.34(6H, s, 2xCH_3), 1.42(6H, s, 2xCH_3), 2.34(6H, s, 2x*p*-CH_3), 3.76-3.78(2H, d, *J* 6Hz, 3-H and 4-H), 3.82-3.86(2H, dd, *J* 7, 8Hz, 1-$H_{(trans)}$ and 6-$H_{(trans)}$), 3.98-4.02(2H, dd, *J* 6, 8Hz, 1-$H_{(cis)}$ and 6-$H_{(cis)}$), 4.02-4.25(2H, m, 2-H and 5-H), 4.66(4H, s, 2xCH_2), 7.13-7.15(4H, AB d, J_{AB} 8Hz, Ar), 7.21-7.23(4H, AB d, J_{AB} 8Hz, Ar); **^{13}C NMR** (100MHz, $CDCl_3$): δ 21.1 (CH_3), 25.2 (CH_3), 26.7 (CH_3), 66.8, 74.4, 75.9, 79.7, 108.4 (CMe_2), 128.1 (Ar), 129.0 (Ar), 135.2 (Ar), 137.4 (Ar); ***m/z*** (FAB): 493 (MNa^+, 64%), 469 (MH^+, 52%); **HRMS** (FAB) for $C_{28}H_{38}O_6Na$ (MNa^+): Requires 493.2566, Found 493.2583; **Anal.** Calcd. for $C_{28}H_{38}O_6$: C, 71.46; H, 8.14%, Found: C, 71.39; H, 8.29%.

3,4-Di-O-2'-fluorobenzyl-1,2:5,6-di-O-isopropylidene-D-mannitol **(218)** crude NMR of the product was clean, so no purification was needed for the deprotection step; $[\alpha]_D^{23}$ =+38.8°, (c=1, $CHCl_3$); **IR** (KBr disc/cm^{-1}): $\tilde{\nu}_{max}$ 2986.3, 2934.9, 2886.3, 1619.6, 1588.2, 1492.2, 1457.4, 1376.5, 1346.1, 1231.8, 1161.7, 1110.9, 1072.3, 940.1, 852.2, 758.8; **^{1}H NMR** (400MHz, $CDCl_3$): δ 1.32(6H, s, 2xCH_3), 1.40(6H, s, 2xCH_3), 3.80-3.81(2H, d, *J* 6Hz, 3-H and 4-H), 3.86-3.90(2H, dd, *J* 7, 8Hz, 1-$H_{(trans)}$ and 6-$H_{(trans)}$), 3.98-4.02(2H, dd, *J* 6, 8Hz, 1-$H_{(cis)}$ and 6-$H_{(cis)}$), 4.22-4.25(2H, dd, *J* 6Hz, 2-H and 5-H), 4.74(4H, s, 2xCH_2), 6.98-7.03(2H, m, Ar), 7.06-7.10(2H, m, Ar), 7.24-7.26(2H, m, Ar), 7.35-7.40(2H, m, Ar); **^{13}C NMR** (100MHz, $CDCl_3$): δ 25.1 (CH_3), 26.6 (CH_3), 66.6, 68.1, 75.7, 80.2, 108.6, 115.1-115.3 (Ar), 124.0 (Ar), 125.2-125.3 (Ar), 129.6 (Ar), 130.6 (Ar), 159.5-161.9 (Ar); ***m/z*** (FAB): 501 (MNa^+, 13%), 479 (M^+, 13%); **Anal.** Calcd. for $C_{26}H_{32}O_6F_2$: C, 65.26; H, 6.74%, Found: C, 65.05; H, 6.68%.

3,4-Di-O-3'-fluorobenzyl-1,2:5,6-di-O-isopropylidene-D-mannitol **(219)** crude NMR of the product was clean, so no purification was needed for the deprotection step; $[\alpha]_D^{23}$ =+37.0°, (c=1, $CHCl_3$); **IR** (KBr disc/cm^{-1}): $\tilde{\nu}_{max}$ 2986.5, 2935.4, 2889.1, 1618.2, 1590.9, 1488.5, 1452.4, 1376.6, 1344.5, 1256.4, 1215.5, 1141.5, 1070.0, 930.9, 858.0, 784.7, 749.4, 685.7; **^{1}H NMR** (400MHz, $CDCl_3$): δ 1.32(6H, s, 2xCH_3), 1.39(6H, s, 2xCH_3), 3.74-3.76(2H, dd, *J* 6Hz, 3-H and 4-H), 3.83-3.89(2H, dd, *J* 6, 8Hz, 1-H and 6-H), 3.99-4.03(2H, dd, *J* 6, 8Hz, 1-H and 6-H), 4.20-4.23(2H, dd, *J* 6Hz, 2-H and 5-H), 4.68(4H, s, 2xCH_2), 6.94-6.97(2H, m, Ar), 7.01-7.07(4H, m, Ar), 7.25-7.28(2H, m, Ar); **^{13}C NMR** (100MHz, $CDCl_3$): δ 25.2 (CH_3), 26.7 (CH_3), 66.8, 73.8, 75.6, 80.2, 108.7(CMe_2), 114.5-114.7(Ar), 123.1 (Ar), 129.8 (Ar), 140.7 (Ar), 161.6-164.0 (Ar); ***m/z*** (FAB): 479 (M^+, 19%); **Anal.** Calcd. for $C_{26}H_{32}O_6F_2$: C, 65.26; H, 6.74, Found: C, 65.17; H, 6.69%.

General deprotection procedure for

substituted 3,4-di-O-benzyl-1,2:5,6-di-O-isopropylidene-D-mannitol derivatives



(86) (87)

3,4,-Di-O-benzyl-1,2:5,6-di-O-isopropylidene-D-mannitol (**86**) (30g, 68mmol) in THF (300mL) and 5N H_2SO_4 (300mL) was stirred for 2.5h. The reaction was quenched with $NaHCO_{3(sat.)}$ until no effervescence and extracted with ether (2x600mL). The combined organic phase was washed with brine (300mL) and dried ($MgSO_4$). Concentration *in vacuo* gave a yellow oil which was chromatographed (SiO_2, 10% MeOH in ether) to afford *3,4-di-O-benzyl-D-mannitol* (**87**) (16.95g, 69%) as a white solid whose data was tabulated below.

Improved general deprotection procedure for

substituted 3,4-di-O-benzyl-1,2:5,6-di-O-isopropylidene-D-mannitol derivatives[134]

3,4,-Di-O-benzyl-1,2:5,6-di-O-isopropylidene-D-mannitol (**86**) (2.54g, 5.74mmol) in 50% aqueous acetic acid (12.5mL) was stirred for 4h at 60°C. The reaction was quenched with $NaHCO_{3(sat.)}$ until no effervescence and extracted with ether (2x100mL). The combined organic phase was washed with brine (100mL) and dried ($MgSO_4$). Concentration *in vacuo* gave a yellow oil which was chromatographed (SiO_2, 10% MeOH in ether) to afford *3,4-di-O-benzyl-D-mannitol* (**87**) (1.92g, 92%) as a white solid whose data was tabulated below.

3,4-Di-O-benzyl-D-mannitol **(87)** (1.92g, 92%) as a white solid; **m.p.** 75-76°C, lit.,[174] 76-78°C; $[\alpha]_D^{23}$ =+11.1° (c=1, $CHCl_3$), lit.,[174] $[\alpha]_D^{23}$ =+10.3° (c=1, $CHCl_3$); **IR** (KBr disc/cm^{-1}): $\tilde{\nu}_{max}$ 3394.9, 2900.0, 2364.5, 1654.3, 1458.0, 1059.9, 697.6; **^{1}H NMR** (400MHz, $CDCl_3$): δ 2.27-2.30 (2H, br.t, *J* 6Hz, OH), 3.52-3.53 (2H, d, *J* 4Hz, OH), 3.67-3.95 (8H, m, 2x1-H and 2-H and 3-H and 4-H and 5-H and 2x6-H), 4.96 (4H, s, 2xCH_2), 7.24-7.53 (10H, m, 2xPh); **^{13}C NMR** (100MHz, $CDCl_3$): δ 63.2, 71.4, 73.8, 76.7, 128.3 (Ph), 128.4 (Ph), 128.6 (Ph), 136.9 (Ph); ***m/z*** (FAB): 385 (MNa^+, 58%), 363 (MH^+, 23%); **Anal.** Calcd. for $C_{20}H_{26}O_6$: C, 66.28; H, 7.23%, Found: C, 66.20; H, 7.10%.

D-Mannitol-3,4-di-(1'-methylnaphthyl)-ether **(220)** as a white solid; **m.p.** 104-107°C; $[\alpha]_D^{23}$ =+12.5° (c=1, $CHCl_3$); **IR** (KBr disc/cm^{-1}): $\tilde{\nu}_{max}$ 3484.0, 2929.0, 1083.3, 1046.2, 774.0; **^{1}H NMR** (400MHz, CD_3OD): δ 3.57-3.62 (2H, dd, *J* 6, 11Hz, 1-$H_{(trans)}$ and 6-$H_{(trans)}$), 3.73-3.77 (2H, dd, *J* 3, 11Hz, 1-$H_{(cis)}$ and 6-$H_{(cis)}$), 3.93-3.97 (2H, m, 2-H and 5-H), 4.05-4.05 (2H, d, *J* 8Hz, 3-H and 4-H), 5.09-5.25 (4H, AB dd, J_{AB} 12Hz, 2xCH_2), 7.35-7.39 (6H, m, Ar), 7.43-7.45 (2H, d, *J* 3Hz, Ar), 7.52-7.84 (4H, m, Ar), 8.07-8.10 (2H, m, Ar); **^{13}C NMR** (100MHz, CD_3OD): δ 62.8, 70.9, 71.9, 78.4, 123.0 (Ar), 124.3 (Ar), 124.7 (Ar), 125.1 (Ar), 125.3 (Ar), 127.4 (Ar), 127.5 (Ar), 130.9 (Ar), 133.1 (Ar), 133.7 (Ar); ***m/z*** (FAB): 485 (MNa^+, 54%).

D-Mannitol-3,4-di-(o-bromobenzyl)-ether **(221)** (0.94g, 83%) as a white solid; **m.p.** 113-116°C; $[\alpha]_D^{23}$ =+47.6°, c=1, acetone); **IR** (KBr disc/cm^{-1}): $\tilde{\nu}_{max}$ 3599.3, 3428.3, 2924.3, 1459.1, 1084.2, 1026.8, 748.0, 561.8; **^{1}H NMR** (400MHz, $CDCl_3$): δ 2.58 (2H, br.s, 2xOH), 3.68-4.01 (10H, m 2x1-H and 2-H and 3-H and 4-H and 5-H and 2x6-H and 2xOH), 4.66-4.75 (4H, AB dd, J_{AB} 12Hz, 2xCH_2), 7.12-7.17 (2H, dd, *J* 8Hz, Ar), 7.25-7.27 (2H, dd, *J* 7Hz, Ar), 7.39-7.41 (2H, d, *J* 8Hz, Ar), 7.51-7.53 (2H, d, *J* 8Hz, Ar); **^{13}C NMR** (100MHz, $CDCl_3$): δ 63.3, 71.5, 73.1, 77.7, 123.3 (Ph), 127.6 (Ph), 129.6 (Ph), 130.0 (Ph), 132.8 (Ph), 136.5 (Ph); ***m/z*** (FAB): 543 (MNa^+, 9%); **HRMS** (FAB) for $C_{20}H_{24}O_6Br_2Na$: Requires 540.9837, Found 540.9850; **Anal.** Calcd. for $C_{20}H_{24}O_6Br_2$: C, 46.18; H, 4.65; Br, 30.72%, Found: C, 46.49; H, 4.57; Br 30.98%.

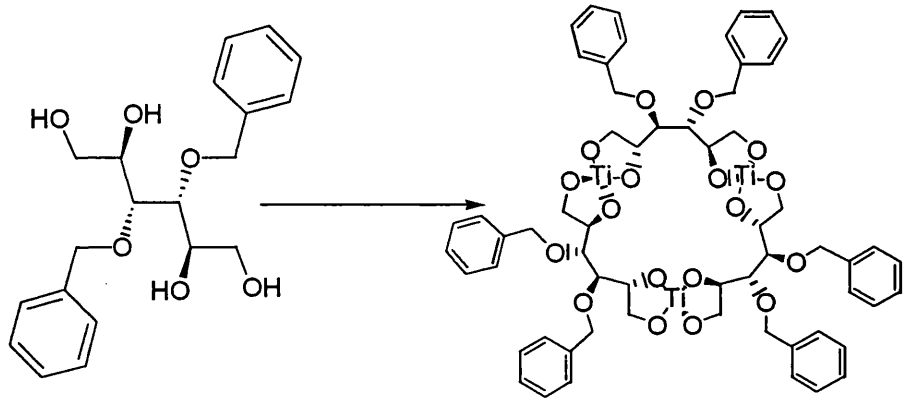
D-Mannitol-3,4-di-(p-methylbenzyl)-ether **(222)** (0.77g, 77%) as a white solid; **m.p.** 83-85°C; $[\alpha]_D^{23}$ =+18.2°, (c=1, $CHCl_3$); **IR** (KBr disc/cm^{-1}): $\tilde{\nu}_{max}$ 3328.5, 2921.5, 1517.9, 1411.9, 1321.8, 1218.3, 1088.2, 1034.3, 1039.0, 984.0, 880.6, 799.7, 551.4; **^{1}H NMR** (400MHz, $CDCl_3$): δ 2.32(6H, s, 2x*p*-CH_3), 3.06(2H, br.s, 2xOH), 3.65-4.02(10H, m, 2x1-H and 2-H and 3-H and 4-H and 5-H and 2x6-H and 2xOH), 4.51-4.60(4H, AB dd, J_{AB} 11Hz, 2xCH_2), 7.11-7.13(4H, AB d, J_{AB} 8Hz, Ar), 7.16-7.19(4H, AB d, J_{AB} 8Hz, Ar); **^{13}C NMR** (100MHz, $CDCl_3$): δ 21.2 (CH_3), 63.4, 71.5, 73.6, 77.3, 128.4 (Ar), 129.2 (Ar), 134.3 (Ar), 137.9 (Ar); ***m/z*** (FAB): 413 (MNa^+, 100%), 391 (MH^+, 7%); **HRMS** (FAB) for $C_{22}H_{30}O_6Na$: Requires 413.1940 Found 413.1915; **Anal.** Calcd. for $C_{22}H_{30}O_6$: C, 67.67; H, 7.74%, Found: C, 67.51; H, 7.73%.

D-Mannitol-3,4-di-(o-fluorobenzyl)-ether **(223)** (1.054g, 69% over 2 steps) as a white solid; **m.p.** 54-57°C; $[\alpha]_D^{23}$ =+41.6°, (c=1, acetone); **IR** (KBr disc/cm^{-1}): $\tilde{\nu}_{max}$ 3362.5, 2933.0, 2364.7, 1620.5, 1589.3, 1495.9, 1458.2, 1403.9, 1235.6, 1074.5, 934.5, 878.9, 759.9; **^{1}H NMR** (400MHz, $CDCl_3$): δ 2.54-2.56(2H, br.s, 2xOH), 3.63-3.95(10H, m, 2x1-H and 2-H and 3-H and 4-H and 5-H and 2x6-H and 2xOH), 4.64-4.73(4H, AB dd, J_{AB} 11Hz, 2xCH_2), 7.00-7.11(4H, m, Ar), 7.23-7.34(4H, m, Ar); **^{13}C NMR** (100MHz, $CDCl_3$): δ 63.3, 67.7, 71.4, 77.8, 115.3-115.6 (Ar), 124.3 (Ar), 130.2 (Ar), 130.8 (Ar), 159.7 (Ar), 162.2 (Ar); ***m/z*** (FAB): 421 (MNa^+, 100%); **Anal.** Calcd. for $C_{20}H_{24}O_6F_2 \cdot H_2O$: C, 57.69; H, 6.29%. Found: C, 58.79; H, 6.41%.

D-Mannitol-3,4-di-O-(m-fluorobenzyl)-ether **(224)** (1.048g, 69% over 2 steps) as a white solid; **m.p.** 60-62°C; $[\alpha]_D^{23}$ =+48.6°, (c=1, acetone); **IR** (KBr disc/cm^{-1}): $\tilde{\nu}_{max}$ 3322.6, 2916.7, 1592.1, 1453.9, 1257.9, 1034.6, 878.7, 779.5, 681.5, 557.4; **^{1}H NMR** (400MHz, $CDCl_3$): δ 2.91-2.92(2H, br.s, 2xOH), 3.67-3.93(10H, m, 2x1-H and 2-H and 3-H and 4-H and 5-H and 2x6-H and 2xOH), 4.56-4.64(4H, AB dd, J_{AB} 12Hz, 2xCH_2), 6.92-7.02(6H, m, Ar), 7.22-7.27(2H, m, Ar); **^{13}C NMR** (100MHz, $CDCl_3$): δ 63.3, 71.5, 73.2, 78.0, 114.6-115.0, 123.3 (Ar), 130.1 (Ar), 140.0 (Ar), 161.6 (Ar), 164.0 (Ar); ***m/z*** (FAB): 421 (MNa^+, 100%), 399 (MH^+, 48%); **Anal.** Calcd. for $C_{20}H_{24}O_6F_2$: C, 60.29; H, 6.07%. Found: C, 60.19; H, 6.02%.

3.3 Synthesis of titanium trimer (101) and its derivatives

General procedure for the preparation of titanium 3,4-di-O-benzyl-D-mannitol trimer (101)



(87) **(101)**

3,4-di-O-benzyl-D-mannitol (**87**) (1g, 2.8mmol) in hexane (100mL) and toluene (50mL) was heated to reflux. Titanium(IV) isopropoxide (0.8mL, 2.4mmol) was added to the reaction, a white precipitate formed on addition, and refluxed for 4h. The reaction was cooled to room temperature overnight and concentrated *in vacuo*. The residue was taken up in DCM and any insoluble materials were filtered off. The resultant solution was concentrated *in vacuo*. A white solid was precipitated out using ether. Filtration followed by washing with ether several times to remove any soluble titanium species afforded *titanium 3,4-di-O-benzyl-D-mannitol trimer* (**101**) (0.39g, 40%) as a white solid whose data are tabulated below.

Titanium 3,4-di-O-benzyl-D-mannitol trimer (**101**) (0.39g, 40-85%) as a white solid; **m.p.** 203-209°C (dec.); $[\alpha]_D^{23}$ =+51.5° (c=1, $CHCl_3$); **IR** (KBr disc/cm^{-1}): $\tilde{\nu}_{max}$ 3450.6, 2863.2, 1497.9, 1452.3, 1353.3, 1306.4, 1220.8, 1139.2, 1061.5, 995.7, 903.0, 735.4, 700.0, 649.9; **^{1}H NMR** (400MHz, $CDCl_3$): δ 3.73-3.75 (6H, dd, *J* 2, 7Hz, 3x3-H and 3x4-H), 4.42-4.45 (6H, dd, *J* 4, 10Hz, 3x1-$H_{(trans)}$, 3x6-$H_{(trans)}$), 4.57-4.59 (6H, AB d, J_{AB} 11Hz, 3xCH_2), 4.81-4.84 (6H, AB d, J_{AB} 11Hz, 3xCH_2), 4.88-4.94 (6H, dd, *J* 10Hz, 3x1-$H_{(cis)}$ and 3x6-$H_{(cis)}$), 5.03-5.09 (6H, m, 3x2-H and 3x5-H), 7.14-7.32 (30H, m, 6xPh); **^{13}C NMR** (100MHz, $CDCl_3$): δ 76.5, 79.3, 85.4. 88.6, 127.6(Ph), 128.0 (Ph), 128.5 (Ph), 137.4 (Ph); ***m/z*** (FAB): 1219 (MH^+, 100%); **HRMS** (FAB) for $C_{60}H_{67}O_{18}Ti_3$: Requires 1219.2766, Found 1219.2740; **Anal.** Calcd. for $C_{60}H_{66}O_{18}Ti_3$: C, 59.13; H, 5.46%, Found: C, 58.93; H, 5.29%.

Titanium 3,4-di-O-1-(methyl)naphthyl-D-mannitol trimer (**113**) (0.20g, 34%) as a white solid; **m.p.** 183-186°C(dec.); $[\alpha]_D^{23}$ =+178.5 (c=0.2°, $CHCl_3$); **IR** (KBr disc/cm^{-1}): $\tilde{\nu}_{max}$ 3449.1, 2924.2, 2856.3, 1063.9, 993.3; **^{1}H NMR** (400MHz, $CDCl_3$): δ 3.90-3.93 (6H, dd, *J* 2, 7Hz, 3x3-H and 3x4-H), 4.28-4.32 (6H, dd, *J* 4, 11Hz, 3x1-$H_{(trans)}$, 3x6-$H_{(trans)}$), 4.70-4.76 (6H, dd, *J* 11Hz, 3x1-$H_{(cis)}$ and 3x6-$H_{(cis)}$), 5.03-5.06 (6H, AB d, J_{AB} 12Hz, 3xCH_2), 5.06-5.17 (6H, m, 3x2-H and 3x5-H), 5.32-5.36 (6H, AB d, J_{AB} 12Hz, 3xCH_2), 7.21-7.25 (6H, m, Nap), 7.29-7.33 (12H, m, Nap), 7.39-7.43 (6H, m, Nap) 7.68-7.80 (18H, m, Nap); **^{13}C NMR** (100MHz, $CDCl_3$): δ 74.2, 79.3, 85.5. 88.6, 123.1 (Nap), 125.2 (Nap), 125.6 (Nap), 125.7 (Nap), 126.2 (Nap), 128.6 (Nap), 130.8 (Nap), 133.1 (Nap), 133.5(Nap); ***m/z*** (FAB): 1519 (M^+, 71%); **HRMS** (FAB) for $C_{84}H_{79}O_{18}Ti_3$: Requires 1519.3705, Found 1519.3750.

Titanium 3,4-di-O-2'-bromobenzyl-D-mannitol trimer **(114)** (0.44g, 44%) as a white solid; **m.p.** 220°C (dec.); $[\alpha]_D^{23}$ =+56.4°, (c=1, $CHCl_3$); **IR** (KBr disc/cm^{-1}): $\tilde{\nu}_{max}$ 3448.2, 2856.5, 1442.2, 1063.6, 995.3, 905.5, 750.3, 649.4; **^{1}H NMR** (400MHz, $CDCl_3$): δ 3.84-3.87 (6H, dd, *J* 2, 7Hz, 3x3-H and 3x4-H), 4.41-4.45 (6H, dd, *J* 4, 11Hz, 3x1-$H_{(trans)}$ and 3x6-$H_{(trans)}$), 4.63-4.66 (6H, AB d, J_{AB} 12Hz, 3xCH_2), 4.82-4.85 (6H, AB d, J_{AB} 12Hz, 3xCH_2), 4.88-4.94 (6H, dd, *J* 11Hz, 3x1-$H_{(cis)}$ and 3x6-$H_{(cis)}$), 5.10-5.13 (6H, m, 3x2-H and 3x5-H), 7.06-7.10 (6H, m, Ar), 7.19-7.27 (12H, m, Ar), 7.43-7.45 (6H, d, *J* 8Hz, Ar); **^{13}C NMR** (100MHz, $CDCl_3$): δ 75.5, 79.3, 85.5, 88.4, 122.1 (Ar), 127.5 (Ar), 128.6 (Ar), 129.1 (Ar), 132.5 (Ar), 136.8 (Ar); ***m/z*** (FAB): 1693 (MH^+, 100%); **Anal.** Calcd. for $C_{60}H_{60}O_{18}Br_6Ti_3$: C, 42.20; H, 3.58; Br, 28.33%. Found: C, 42.59; H, 3.57; Br 31.54%.

Titanium 3,4-di-O-4'-methylbenzyl-D-mannitol trimer **(115)** (0.49g, 80%) as a white solid; **m.p.** 164-167°C(dec.); $[\alpha]_D^{23}$ =+52.4°, (c=1, $CHCl_3$); **IR** (KBr disc/ cm^{-1}): $\tilde{\nu}_{max}$ 3447.8, 2862.7, 1515.3, 1307.7, 1063.0, 944.0, 903.4, 804.8, 649.0, 480.4; **^{1}H NMR** (400MHz, $CDCl_3$): δ 2.32 (18H, s, *p*-CH_3), 3.69-3.71 (6H, dd, *J* 2, 6Hz, 3x3-H and 3x4-H), 4.40-4.44(6H, dd, *J* 4, 10Hz, 3x1-$H_{(trans)}$ and 3x6-$H_{(trans)}$), 4.52-4.54 (6H, AB d, J_{AB} 10Hz, 3xCH_2), 4.79-4.82 (6H, AB d, J_{AB} 10Hz, 3xCH_2), 4.86-4.92 (6H, dd, *J* 10Hz, 3x1-$H_{(cis)}$ and 3x6-$H_{(cis)}$), 5.02-5.04 (6H, m, 3x2-H and 3x5-H), 7.06-7.12 (24H, AB dd, J_{AB} 8Hz, Ar); **^{13}C NMR** (100MHz, $CDCl_3$): δ 21.2 (CH_3), 76.4, 79.3, 85.3, 88.6, 127.8 (Ar), 129.2 (Ar), 134.4 (Ar), 137.8 (Ar); ***m/z*** (FAB):no peaks found; **Anal.** Calcd. for $C_{66}H_{78}O_{18}Ti_3$: C, 60.66; H, 6.09%. Found: C, 60.83; H, 6.03%.

Titanium 3,4-di-O-2'-fluorobenzyl-D-mannitol trimer (**116**) (0.42g, 47%) as a white solid; **m.p.** 186-189°C(dec.); $[\alpha]_D^{23}$ =+43.0°, (c=1, $CHCl_3$); **IR** (KBr): $\tilde{\nu}_{max}$ 3448.7, 2863.0, 2365.6, 1591.0, 1489.4, 1453.0, 1351.4, 1257.7, 1141.6, 1063.6, 992.2, 903.0, 784.9, 689.7, 652.2, 490.4; **^{1}H NMR** (400MHz, $CDCl_3$): δ 3.73-3.75 (6H, dd, *J* 2, 6Hz, 3x3-H and 3x4-H), 4.40-4.44 (6H, dd, *J* 4, 10Hz, 3x1-$H_{(trans)}$ and 3x6-$H_{(trans)}$), 4.56-4.58 (6H, AB d, J_{AB} 11Hz, 3xCH_2), 4.73-4.76 (6H, AB d, J_{AB} 11Hz, 3xCH_2), 4.89-4.94 (6H, dd, *J* 10Hz, 3x1-$H_{(cis)}$ and 3x6-$H_{(cis)}$), 5.05-5.11 (6H, m, 3x2-H and 3x5-H), 6.82-6.84 (6H, m, Ar), 6.86-6.88 (6H, m, Ar), 6.93-6.97 (6H, m, Ar), 7.21-7.27 (6H, m, Ar); **^{13}C NMR** (100MHz, $CDCl_3$): δ 75.5, 79.1, 85.5, 88.4, 114.0-115.0 (Ar), 122.6 (Ar), 130.0-130.1 (Ar), 139.7 (Ar), 161.6 (Ar), 164.0 (Ar); **m/z**(FAB): 1327 (M+H, 100%); **HRMS** (FAB) for $C_{60}H_{61}O_{18}F_6Ti_3$: Requires 1327.2201, Found 1327.2316; **Anal.** Calcd. for $C_{60}H_{60}O_{18}F_6Ti_3$: C, 54.32; H, 4.56%, Found: C, 53.64; H, 4.37%.

Titanium 3,4-di-O-3'-fluorobenzyl-D-mannitol trimer (**117**) (0.44g, 49%) as a white solid; **m.p.** 167-170°C(dec.); $[\alpha]_D^{23}$ =+45.8°, (c=1, $CHCl_3$); **IR** (KBr disc/cm^{-1}): $\tilde{\nu}_{max}$ 3425.2, 2867.8, 1620.0, 1587.9, 1492.6, 1457.8, 1399.3, 1354.5, 1310.9, 1233.5, 1188.1, 1062.7, 955.7, 904.1, 842.3, 758.2, 649.6, 476.9; **^{1}H NMR** (400MHz, $CDCl_3$): δ 3.71-3.74 (6H, dd, *J* 2, 6Hz, 3x3-H and 3x4-H), 4.35-4.39 (6H, dd, *J* 4, 11Hz, 3x1-$H_{(trans)}$ and 3x6-$H_{(trans)}$), 4.60-4.63 (6H, AB d, J_{AB} 11Hz, 3xCH_2), 4.82-4.88 (6H, dd, *J* 11Hz, 3x1-$H_{(cis)}$ and 3x6-$H_{(cis)}$), 4.90-4.93 (6H, AB d, J_{AB} 11Hz, 3xCH_2), 4.99-5.05 (6H, m, 3x2-H and 3x5-H), 6.98-7.03 (6H, m, Ar), 7.04-7.09 (6H, m, Ar), 7.20-7.27 (12H, m, Ar); **^{13}C NMR** (100MHz, $CDCl_3$): δ 70.0, 79.1, 85.6, 88.4, 115.3-115.5 (Ar), 124.1 (Ar), 124.5 (Ar), 130.0 (Ar), 159.3 (Ar), 161.8 (Ar); ***m/z*** (FAB): 1327 (MH^+, 100%); **HRMS** (FAB) for $C_{60}H_{61}O_{18}F_6Ti_3$: Requires 1327.2201, Found 1327.2316; **Anal.** Calcd. for $C_{60}H_{60}O_{18}F_6Ti_3$: C, 54.32; H, 4.56%, Found: C, 53.33; H, 4.50%.

3.4 Initial results of asymmetric reduction of acetophenone

Preparation of the titanium complex (88)

To a two neck 100mL round bottom flask equipped with a Dean-Stark apparatus was added *3,4-di-O-benzyl-D-mannitol* (**87**) (1g, 2.8mmol), hexane (100mL) and toluene (50mL). The mixture was heated to reflux and 10mL of solvent was collected. Titanium(IV) isopropoxide (0.8mL, 2.6mmol) was added to the mixture, a white precipitate formed. The reaction was refluxed for a total of 72h. A suspension of white precipitate in a clear yellow solution was obtained. The yellow solution was transferred to a 250mL round bottom flask, *via* a syringe, leaving the white precipitate. Hexane (100mL) was added to the yellow solution, a white solid formed. The supernatant liquid was removed from the flask and the white solid was washed with more hexane (3x60mL). The resultant white solid was used without analysis or further purification.

Preparation of the titanium complex (89)

To a two neck 100mL round bottom flask equipped with a Dean-Stark apparatus was added *3,4-di-O-benzyl-D-mannitol* (**87**) (1g, 2.8mmol), hexane (100mL) and toluene (30mL). The mixture was heated to reflux and 10mL of solvent was collected. Titanium(IV) isopropoxide (0.8mL, 2.6mmol) was added to the mixture, a white precipitate formed. The reaction was refluxed for a total of 72h. A suspension of white precipitate in a clear yellow solution was obtained. The yellow solution was transferred to a 250mL round bottom flask, *via* a syringe, leaving the white precipitate. Hexane (100mL) was added to the yellow solution, a white precipitate formed. The supernatant liquid was removed from the flask and the white solid was washed with more hexane (3x60mL). The resultant white solid was used without analysis or further purification.

Preparation of the titanium complex (90)

To a two neck 100mL round bottom flask equipped with a Dean-Stark apparatus was added *3,4-di-O-benzyl-D-mannitol* (**87**) (1g, 2.8mmol), hexane (100mL) and toluene (50mL). The mixture was heated to reflux, 10mL of solvent was collected. Titanium(IV) isopropoxide (0.8mL, 2.6mmol) was added to the mixture, a white precipitate formed. The reaction was refluxed for a total of 20h. A suspension of white precipitate in a clear yellow solution was formed. The yellow solution was transferred to a 250mL round bottom flask, *via* a syringe, leaving the white precipitate. Hexane (100mL) was added to the yellow solution, a white precipitate formed. The supernatant liquid was removed from the flask and the white solid was washed with more hexane (2x40mL). The resultant white solid was used without analysis or further purification.

Preparation of the titanium complex (91)

In a two-neck 250ml round bottom flask, *3,4-di-O-benzyl-D-mannitol* (**87**) (0.58g, 1.6mmol) was dissolved in a minimum amount of chloroform. The chloroform was removed under high vacuum. A Dean-Stark apparatus was attached and toluene (25mL) and hexane (50mL) was added. The mixture was heated to reflux until all the solids have dissolved and 10mL of solvent was collected. Titanium(IV) isopropoxide (0.4mL, 1.3mmol) was added to the mixture, a white precipitate formed. The reaction was refluxed for a total of 24h. A suspension of white precipitate in a clear yellow solution was formed. The yellow solution was transferred to another 250mL round bottom flask using a cannula leaving the white precipitate. Hexane (25mL) was added to the yellow solution, a white precipitate formed. The supernatant liquid was removed from the flask and the white solid was washed with more hexane (2x25mL). The resultant white solid was dissolved in toluene (50mL) and used without analysis or further purification.

Preparation of the titanium complex (92)

In a two-neck 250ml round bottom flask, *3,4-di-O-benzyl-D-mannitol* (**87**) (0.53g, 1.46mmol) was dissolved in a minimum amount of chloroform. The chloroform was removed under high vacuum. A Dean-Stark apparatus was attached and toluene (25mL) and hexane (50mL) was added. The mixture was heated to reflux until all the solids have dissolved and 10mL of solvent was collected. Titanium(IV) isopropoxide (0.8mL, 1.3mmol) was added to the mixture, a white precipitate formed. The reaction was refluxed for a total of 24h. A suspension of white precipitate in a clear yellow solution was formed. The yellow solution was transferred to another 250mL round bottom flask using a cannula leaving the white precipitate. Hexane (25mL) was added to the yellow solution, a white solid formed. The supernatant liquid was removed from the flask and the white solid was washed with more hexane (2x25mL). The resultant white solid was dissolved in toluene (50mL) and used without analysis or further purification.

Preparation of the titanium complex (93)

In a two-neck 250ml round bottom flask equipped with a Dean-Stark apparatus was added *3,4-di-O-benzyl-D-mannitol* (**87**) (0.5g, 1.4mmol), toluene (25mL) and, hexane (50mL). The mixture was heated to reflux until all the solids have dissolved and 25mL of solvent was collected. Toluene (25mL) was added followed by titanium(IV) isopropoxide (0.4mL, 1.3mmol), a white precipitate formed. Another 10mL of solvent was collected and was replenished with toluene (10mL). The reaction was refluxed for a total of 18h. A suspension of white precipitate in a clear yellow solution was formed. The yellow solution was transferred to another 250mL round bottom flask using a cannula leaving the white precipitate. Hexane (25mL) was added to the yellow solution, a white solid formed. The supernatant liquid was removed from the flask and the white solid was washed with more hexane (3x5mL). The resultant white solid was dissolved in toluene (50mL) and used without analysis or further purification.

Preparation of the titanium complex (94)

In a two-neck 250ml round bottom flask equipped with a Dean-Stark apparatus, *3,4-di-O-benzyl-D-mannitol* (**87**) (0.5g, 1.4mmol) and toluene (50mL) was added. The mixture was heated to reflux until all the solids have dissolved and 25mL of solvent was collected. Toluene (25mL) was added followed by hexane (25mL). Titanium(IV) isopropoxide (0.4mL, 1.3mmol) was added, a white precipitate formed. The reaction was refluxed for a total of 18h. A suspension of white precipitate in a clear yellow solution was formed. The yellow solution was transferred to another 250mL round bottom flask using a cannula leaving the white precipitate. Hexane (25mL) was added to the yellow solution, a white solid formed. The supernatant liquid was removed from the flask and the white solid was washed with more hexane (3x5mL). The resultant white solid was dissolved in toluene (50mL) and used without analysis or further purification.

Preparation of the titanium complex (95)

In a two-neck 250ml round bottom flask equipped with a Dean-Stark apparatus, *3,4-di-O-benzyl-D-mannitol* (**87**) (0.53g, 1.46mmol), toluene (25mL) and hexane (50mL) was added. The mixture was heated to reflux until all the solids have dissolved and 10mL of solvent was collected. Titanium(IV) isopropoxide (0.8mL, 1.3mmol) was added to the mixture, a white precipitate formed. The reaction was refluxed for a total of 70h. A suspension of white precipitate in a clear yellow solution was formed. The yellow solution was transferred to another 250mL round bottom flask using a cannula leaving the white precipitate. Hexane (25mL) was added to the yellow solution, a white solid formed. The supernatant liquid was removed from the flask and the white solid was washed with more hexane (2x25mL). The resultant white solid was dissolved in toluene (50mL) and used without analysis or further purification.

Preparation of the titanium complex (96)

In a two-neck 250ml round bottom flask equipped with a Dean-Stark apparatus, *3,4-di-O-benzyl-D-mannitol* (**87**) (0.5g, 1.4mmol), toluene (25mL) and hexane (50mL) was added. The mixture was heated to reflux until all the solids have dissolved and 10mL of solvent was collected. Titanium(IV) isopropoxide (0.4mL, 1.3mmol) was added to the mixture, a white precipitate formed. The reaction was refluxed for a total of 72h. A suspension of white precipitate in a clear yellow solution was formed. The yellow solution was transferred to another 250mL round bottom flask using a cannula leaving the white precipitate. Hexane (25mL) was added to the yellow solution, a white solid formed. The supernatant liquid was removed from the flask and the white solid was further washed with hexane (3x5mL). The resultant white solid was dissolved in toluene (50mL) and used without analysis or further purification.

Preparation of the titanium complex (97)

In a two-neck 250ml round bottom flask equipped with a Dean-Stark apparatus, *3,4-di-O-benzyl-D-mannitol* (**87**) (0.5g, 1.4mmol), toluene (50mL) and hexane (25mL) was added. The mixture was heated to reflux until all the solids have dissolved and 10mL of solvent was collected. Titanium(IV) isopropoxide (0.52mL, 1.75mmol) was added, a white precipitate formed. The reaction was refluxed for a total of 22h. A suspension of white precipitate in a clear yellow solution was formed. The yellow solution was transferred to another 250mL round bottom flask using a fliter tip cannula leaving the white precipitate. Hexane (50mL) was added to the yellow solution, a white solid formed. The supernatant liquid was removed from the flask and the white solid was washed with more hexane (3x30mL). The resultant white solid was dissolved in toluene (50mL) and used without analysis or further purification.

Preparation of the titanium complex (98)

In a two-neck 250ml round bottom flask equipped with a Dean-Stark apparatus, *3,4-di-O-benzyl-D-mannitol* (**87**) (0.5g, 1.4mmol), toluene (25mL) and hexane (50mL) was added. The mixture was heated to reflux until all the solids have dissolved and 10mL of solvent was collected. Titanium(IV) isopropoxide (0.4mL, 1.3mmol) was added, a white precipitate formed. 25mL of solvent was removed from the reaction and a 2:1 mixture of hexane/toluene (25mL) was replenished. The reaction was refluxed for a total of 20h. A suspension of white precipitate in a clear yellow solution was formed. The yellow solution was transferred to another 250mL round bottom flask using a filter tip cannula leaving the white precipitate. Hexane (50mL) was added to the yellow solution, a white solid formed. The supernatant liquid was removed from the flask and the white solid was further washed with hexane (3x10mL). The resultant white solid was dissolved in toluene (50mL) and used without analysis or further purification.

Preparation of the titanium complex (99)

In a two-neck 250ml round bottom flask equipped with a Dean-Stark apparatus, *3,4-di-O-benzyl-D-mannitol* (**87**) (0.5g, 1.4mmol), toluene (25mL) and hexane (50mL) was added. The mixture was heated to reflux until all the solids have dissolved and 10mL of solvent was collected. Titanium(IV) isopropoxide (0.4mL, 1.3mmol) was added, a white precipitate formed. 25mL of solvent was removed from the reaction and a 2:1 mixture of hexane/toluene (25mL) was replenished. The reaction was refluxed for a total of 20h. A suspension of white precipitate in a clear yellow solution was formed. The yellow solution was transferred to another 250mL round bottom flask using a filter tip cannula leaving the white precipitate. Hexane (50mL) was added to the yellow solution, a white solid formed. The supernatant liquid was removed from the flask and the white solid was washed with more hexane (3x10mL). The resultant white solid was dissolved in toluene (50mL) and used without analysis or further purification.

Preparation of the titanium complex (100)

In a two-neck 250ml round bottom flask equipped with a Dean-Stark apparatus, *3,4-di-O-benzyl-D-mannitol* (**80**) (0.5g, 1.4mmol) was added toluene (25mL) and hexane (50mL). The mixture was heated to reflux until all the solids have dissolved and 10mL of solvent was collected. Titanium(IV) isopropoxide (0.4mL, 1.3mmol) was added, a white precipitate formed. 25mL of solvent was removed from the reaction and a 2:1 mixture of hexane/toluene (25mL) was replenished. The reaction was refluxed for a total of 8h. A suspension of white precipitate in a clear yellow solution was formed. The yellow solution was transferred to another 250mL round bottom flask using a filter tip cannula leaving the white precipitate. Hexane (50mL) was added to the yellow solution, a white solid formed. The supernatant liquid was removed from the flask and the white solid was washed with more hexane (3x10mL). The resultant white solid was dissolved in toluene (50mL) and used without analysis or further purification.

General procedure for the attempted reduction of acetophenone

(144)

Titanium complex (**88**) in toluene (100mL) was cooled to -20°C. Acetophenone (0.7mL, 6mmol) was added followed by catecholborane (0.8mL, 7.7mmol). The reaction was monitored using TLC. The reaction was quenched using 1N HCl (50ml). The mixture was extracted with ethyl acetate (3x50ml) and washed 1N NaOH (3x50ml). The organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed (SiO_2, 40% ether in PE 30-40) to afford *1-phenylethanol* (**144**) (0.27g, 37%) as a colourless oil.

Results for the attempted reduction of acetophenone

in the presence of the synthesised titanium complex

Titanium complex	Temp (°C)	Equiv. of borane	Time (h)	% Yield	Enantioselectivity	
					$[\alpha]_D^{23}$	chiral GC
(88)	–20	1.1	72	37	–33	56
(89)	–10	1.1	25	80	–31	52
(90)	0	2.2	20	82	–7	---
(91)	–10	1.1	14	81	–18.2	---
(92)	–10	1.1 (4h) 1.1*	28	95	–7.2	---
(93)	–15	1.1 (20h) 1.1*	28	91	–22.2	43
(94)	–15	1.1	18	89	–11.8	26
(95)	–10	1.1	20	50	–1.3	---
(96)	–10	1.1 (2h) 1.1*	24	75	–7.5	---
(97)	–10	1.1	24	66	–20.7	34
(98)	–15	1.1	19	80	–37.6	64
(99)	–15	1.1	16	---	---	46
(100)	–15	1.1	13	---	---	46

*After X hours another 1.1eq. catecholborane was added.

3.5 Isolation of titanium trimer (101) and Optimisations

Preparation of the titanium complex (101)

In a two-neck 250ml round bottom flask equipped with a Dean-Stark apparatus, *3,4-di-O-benzyl-D-mannitol* (**87**) (1g, 2.8mmol) was added toluene (50mL) and hexane (100mL). The mixture was heated to reflux until all the solids have dissolved and 10mL of solvent was collected. Titanium(IV) isopropoxide (0.8mL, 2.6mmol) was added, a white precipitate formed. 50mL of solvent was removed from the reaction and a 2:1 mixture of hexane/toluene (50mL) was replenished. After 2h another 15mL of solvent was removed from the reaction. The reaction was refluxed for a total of 20h. A white precipitate in a clear yellow solution was formed. The yellow solution was transferred to another 250mL round bottom flask using a filter cannula. Hexane (100mL) was added to the yellow solution, an off-white precipitate formed. The mixture was concentrated *in vacuo*. The residue was dissolved in toluene (100mL) and any insoluble solid was filtered off. More hexane was added to the toluene solution, a white precipitate formed. This was filtered and the white solid was washed with more hexane (3x20mL). NMR of this material showed only one product (See **Appendix A and B**).

Reduction of Acetophenone (107)

Titanium 3,4-di-O-benzyl-D-mannitol trimer (**101**) (210mg, 0.17mmol) in toluene (50mL) was cooled to −15°C. Acetophenone (0.35mL, 3mmol) was added followed by catecholborane (0.4mL, 3.3mmol). The reaction was monitored using **Chiral GC**, by taking aliquots from the reaction.

Time (h)	%ee	*S*:*R*	Starting material:product
1.5	62	81:19	1.00:2.65
2.5	64	86:14	1.00:2.67
4.5	66	83:17	1.00:2.53
21.0	62	81:19	1.00:2.58

Reduction of Acetophenone (108)

Titanium 3,4-di-O-benzyl-D-mannitol trimer (**101**) (200mg, 0.16mmol) in toluene (15mL) was cooled to –20°C. Acetophenone (0.12mL, 1mmol) was added followed by catecholborane (0.12mL, 1.1mmol). The reaction was monitored using **Chiral GC**, by taking aliquots from the reaction.

Time (min)	%ee	*S:R*	Starting material:product
15	80	90:10	1.00:0.80
30	74	87:13	1.00:2.05
45	76	88:12	1.00:2.20
60	72	86:14	1.00:2.47

Reduction of Acetophenone (109)

Titanium 3,4-di-O-benzyl-D-mannitol trimer (**101**) (200mg, 0.16mmol) in toluene (15mL) was cooled to –20°C. Acetophenone (0.12mL, 1mmol) was added followed by catecholborane (0.24mL, 2.2mmol). The reaction was monitored using **Chiral GC**, by taking aliquots from the reaction.

Time (min)	%ee	*S:R*	Starting material:product
1	50	75:25	1.00:0.19
5	70	85:15	1.00:0.91
10	68	84:16	1.00:3.83
15	68	84:16	1.00:12.29
30	68	84:16	No S.M
45	68	84:16	No S.M

Reduction of Acetophenone (110)

A stock solution was prepared using catecholborane (0.27mL, 2.48mmol) dissolved in toluene (3mL) and cooled to –20°C. *Titanium 3,4-di-O-benzyl-D-mannitol trimer* (**101**) (200mg, 0.16mmol) in toluene (15mL) was cooled to –20°C. Acetophenone (0.12mL, 1mmol) was added. The stock solution of catecholborane (0.2mL, 0.17mmol) was added in 20min periods. The reaction was monitored using **Chiral GC**, by taking aliquots from the reaction.

Time (min)	%ee	*S*:*R*	Starting material:product
200	70	85:15	1.00:4.25
220	70	85:15	1.00:7.13
240	70	85:15	1.00:16.06
260	70	85:15	Traces of starting material
280	72	86:14	Traces of starting material
300	70	85:15	No starting material

Reduction of Acetophenone (102)

Titanium 3,4-di-O-benzyl-D-mannitol trimer (**101**) (507mg, 0.416mmol) in toluene (10mL) was cooled to –20°C. Acetophenone (48μL, 0.416mmol) was added followed by catecholborane (57μL, 0.524mmol). The reaction was monitored using TLC. The reaction was stopped after 2h and quenched with 1N HCl (5mL). The mixture was extracted with ethyl acetate (3x10mL) and washed 1N NaOH (3x10mL). The organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was filtered through a pad of silica using ether and analysed; **Chiral GC**: 72%ee, starting material:product 1.00:3.61.

Reduction of Acetophenone (103)

A stock solution was prepared using catecholborane (57μL, 0.524mmol) dissolved in toluene (3mL). *Titanium 3,4-di-O-benzyl-D-mannitol trimer* (**101**) (200mg, 0.164mmol) in toluene (10mL) was cooled to –20°C and added acetophenone (48μL, 0.416mmol). The

stock solution of catecholborane was added to the reaction over 6 hours and stirred for a total of 19h. The reaction was quenched with 1N HCl (5mL). The mixture was extracted with ethyl acetate (3x10mL) and washed 1N NaOH (3x10mL). The organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was filtered through a pad of silica with ether and analysed; **Chiral GC**: 66%ee, starting material:product 1.00:1.10

Reduction of Acetophenone (104)

Titanium 3,4-di-O-benzyl-D-mannitol trimer (**101**) (98mg, 0.08mmol) in DCM (15mL) was cooled to –20°C. Acetophenone (59μL, 0.5mmol) was added followed by catecholborane (70μL, 0.55mmol). The reaction was stopped after 3h and quenched with 1N HCl (5mL). The mixture was extracted with ethyl acetate (3x10mL) and washed 1N NaOH (3x10mL). The organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was filtered through a pad of silica with ether and analysed; **Chiral GC**: 72%ee, no starting material detected.

Reduction of Acetophenone (105)

Titanium 3,4-di-O-benzyl-D-mannitol trimer (**101**) (98mg, 0.08mmol) in DCM (15mL) was cooled to –78°C. Acetophenone (59μL, 0.5mmol) was added followed by catecholborane (70μL, 0.55mmol). The reaction was stirred at –78°C for 1day and the reaction was warmed to –50°C for 5h and to room temperature overnight. At each stage an aliquot was removed from the reaction and analysed using **Chiral GC**.

Temperature (°C)	%ee	*R*:*S*	Starting material:product
–78	---	---	Trace amount of product
–50	34	33:67	1.00:0.63
20	36	32:68	1.00:1.69

Reduction of Acetophenone (106)

Titanium 3,4-di-O-benzyl-D-mannitol trimer (**101**) (98mg, 0.08mmol) in DCM (10mL) was added acetophenone (59μL, 0.5mmol) followed by catecholborane (70μL, 0.5mmol) and stirred for 16h. An aliquot was taken from the reaction for GC analysis. The reaction was stirred for a total of 32h and quenched with 1N HCl (5mL). The mixture was extracted with ethyl acetate (3x10mL) and washed 1N NaOH (3x10mL). The organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was filtered through a pad of silica with ether and analysed; **Chiral GC**: **After 16hr**: 17%ee, *R*:*S* 41.5:58.5, starting material:product 1.00:1.72; **After 32hr**: 17%ee, *R*:*S* 41.5:58.5, starting material:product 1.00:1.72.

3.6 Reduction of a range of prochiral ketones

General procedure for sodium borohydride reduction of prochiral ketones

Acetophenone (0.12mL, 1mmol) in MeOH (5mL) was added sodium borohydride (76mg, 2mmol) portionwise. The reaction was stirred for 1h and was quenched with water. The mixture was extracted with DCM (3x10mL) and dried over $MgSO_4$ and concentrated *in vacuo* and the residue was filtered through a pad of silica with ether. The solvent was evaporated to afford *1-phenyl-1-ethanol* (**144**) as a colourless oil.

General procedure for catecholborane reduction of prochiral ketone in the presence of titanium 3,4-di-O-benzyl-D-mannitol trimer

Acetophenone (59μL, 0.5mmol) and *titanium 3,4-di-O-benzyl-D-mannitol trimer* (**101**) (100mg, 0.082mmol) in DCM (10mL) was cooled to −20°C. Catecholborane (70μL, 0.55mmol) was added and the reaction was stirred overnight. The reaction was quenched with 1N HCl (10mL) and the mixture was extracted with ether (3x10mL). The organic phase was washed with 1N NaOH (3x10mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed (SiO_2, 40% ether in PE 30-40) to afford *1-phenyl-1-ethanol* (**144**) (37mg, 60%) as a colourless oil.

1-Phenylethanol[175] (**144**) (37mg, 60%); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 3354.7, 2973.6, 2360.5, 1492.8, 1450.5, 1368.7, 1294.6, 1203.3, 1076.2, 1010.0, 899.9, 759.9, 698.3, 605.3, 538.2; **^{1}H NMR** (400MHz, $CDCl_3$): δ 1.47-1.49 (3H, d, *J* 6Hz, CH_3), 4.85-4.89 (1H, m, CH), 7.24-7.38 (5H, m, Ph); **^{13}C NMR** (100MHz, $CDCl_3$): δ 25.1 (CH_3), 70.4 (CH), 125.3 (Ph), 127.4 (Ph), 128.5 (Ph), 145.8 (Ph); ***m/z*** (FAB): 107 ($[M-CH_3]^+$, 100%), 105 ($[M-OH]^+$, 66%).

1-(2'-Bromophenyl)ethanol[176] (**145**) (57mg, 57%); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 3346.9, 2974.3, 2361.6, 1591.0, 1568.1, 1468.8, 1440.2, 1368.3, 1262.7, 1200.1, 1091.5, 1024.4, 753.5, 668.0; **^{1}H NMR** (400MHz, $CDCl_3$): δ 1.45-1.47 (3H, d, *J* 6Hz, CH_3), 5.20-5.23 (1H, q, *J* 6Hz, CH), 7.08-7.12 (1H, ddd, *J* 2, 8Hz, Ph), 7.30-7.34 (1H, ddd, *J* 1, 8Hz, Ph), 7.47-7.50 (1H, dd, *J* 1, 8Hz, Ph), 7.55-7.58 (1H, dd, *J* 2, 8Hz, Ph); **^{13}C NMR** (100MHz, $CDCl_3$): δ 23.6 (CH_3), 69.2 (CH), 121.7 (Ar), 126.6 (Ar), 127.8 (Ar), 128.8 (Ar), 132.6 (Ar), 144.6 (Ar) ; ***m/z*** (FAB): 185 ($[M-OH]^+$, 37%), 183 ($[M-OH]^+$, 37%); **HRMS** (FAB) for C_8H_8Br: Calcd. 182.9809, Found 182.9800.

1-(2'-Chlorophenyl)ethanol[176] (**146**) (37mg, 47%); **^{1}H NMR** (300MHz, $CDCl_3$): δ 1.46-1.49 (3H, d, *J* 6Hz, CH_3), 5.24-5.31 (1H, br.q, *J* 6Hz, CH), 7.17-7.32 (3H, m, Ar), 7.56-7.59 (1H, m, Ph).

1-(2'-Methoxyphenyl)ethanol[176] (**147**) (42mg, 56%); **^{1}H NMR** (300MHz, $CDCl_3$): δ 1.48-1.50 (3H, d, *J* 7Hz, CH_3), 3.85 (3H, s, OCH_3), 5.04-5.11 (1H, q, *J* 7Hz, CH), 6.85-6.88 (1H, dd, *J* 1, 8Hz, Ar), 6.92-6.97 (1H, ddd, *J* 1, 7Hz, Ar), 7.20-7.24 (1H, ddd, *J* 2, 8Hz, Ar), 7.30-7.34 (1H, dd, *J* 2, 8Hz, Ar).

1-(4'-Chlorophenyl)ethanol[176] (**148**) (37mg, 47%); **^{1}H NMR** (300MHz, $CDCl_3$): δ 1.44-1.47 (3H, d, *J* 6Hz, CH_3), 4.83-4.90 (1H, q, *J* 6Hz, CH), 7.27-7.32 (4H, m, Ar); **^{13}C NMR** (100MHz, $CDCl_3$): δ 25.3 (CH_3), 69.7 (CH), 126.8 (Ar), 128.6 (Ar), 133.1 (Ar), 144.2 (Ar).

1-(4'-Methylphenyl)ethanol[176] (**149**) (46mg, 68%); **^{1}H NMR** (400MHz, $CDCl_3$): δ 1.46-1.48 (3H, d, *J* 6Hz, CH_3), 2.32 (3H, s, CH_3), 4.83-4.88 (1H, q, *J* 6Hz, CH), 7.13-7.15 (2H, AB d, J_{AB} 8Hz, Ar), 7.24-7.26 (2H, AB d, J_{AB} 9Hz, Ar).

1-(4'-Methoxy)phenylethanol[176] (**150**) (23mg, 31%) ; **^{1}H NMR** (400MHz, $CDCl_3$): δ 1.45-1.47 (3H, d, *J* 6Hz, CH_3), 3.78 (3H, s, OCH_3), 4.82-4.84 (1H, q, *J* 6Hz, CH), 6.85-6.87 (2H, AB d, J_{AB} 9Hz, Ar), 7.27-7.29 (2H, AB d, J_{AB} 8Hz, Ar); **^{13}C NMR** (100MHz, $CDCl_3$): δ 25.0 (CH3), 55.3 (OCH3), 70.0 (CH), 113.8 (Ar), 126.6 (Ar), 137.9 (Ar), 158.9 (Ar).

1-(2-Naphthyl)ethanol[176] (**151**) (79mg, 92%); **^{1}H NMR** (400MHz, $CDCl_3$): δ 1.55-1.57 (3H, d, *J* 6Hz, CH_3), 1.95 (1H, br.s, OH), 5.02-5.07 (1H, q, *J* 6Hz, CH), 7.43-7.50 (3H, m, Ar), 7.78-7.83 (4H, m, Ar); **^{13}C NMR** (100MHz, $CDCl_3$): δ 25.0 (CH_3), 70.4 (CH), 123.7 (Ar), 125.7 (Ar), 126.0 (Ar), 127.6 (Ar), 127.8 (Ar), 128.2 (Ar), 132.8 (Ar), 133.2 (Ar), 143.0 (Ar).

1-Phenyl-1-propanol[175] (**152**) (11.5mg, 17%); **^{1}H NMR** (300MHz, $CDCl_3$): δ 0.89-0.94 (3H, t, *J* 7Hz, CH_3), 1.70-1.85 (3H, m, CH_2, OH), 4.57-4.62 (1H, m, CH), 7.23-7.38 (5H, m, Ph); **^{13}C NMR** (100MHz, $CDCl_3$): δ 10.1 (CH_3), 31.9 (CH_2), 76.0 (CH), 125.9 (Ph), 127.0 (Ph), 127.5 (Ph), 128.4 (Ph), 128.5 (Ph), 144.5 (Ph).

1-Phenyl-1-pentanol[175] (**153**) (42mg, 51%); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 3357.8, 3062.8, 3028.8, 2956.3, 2931.6, 2859.7, 1493.5, 1453.9, 1378.3, 1200.5, 1107.8, 1039.9, 1011.4, 910.9, 755.7, 699.5; **^{1}H NMR** (400MHz, $CDCl_3$): δ 0.87-0.90 (3H, t, *J* 7Hz, CH_3), 1.23-1.44 (4H, m, 2xCH_2), 1.66-1.86 (3H, m, CH_2, OH), 4.65-4.68 (1H, br.t, *J* 7Hz, CH), 7.25-7.30 (1H, m, Ph), 7.32-7.35 (4H, m, Ph); **^{13}C NMR** (100MHz, $CDCl_3$): δ 14.0 (CH_3), 22.6 (CH_2), 28.0 (CH_2), 38.8 (CH_2), 74.7 (CH), 125.9 (Ph), 127.5 (Ph), 128.4 (Ph), 144.9 (Ph); ***m/z*** (FAB): 164 (M^+, 24%), 147 ($[M-OH]^+$, 57%).

1-(2'-Pyridyl)-1-ethanol[177] (**154**) (35mg, 57%); **^{1}H NMR** (400MHz, $CDCl_3$): δ 1.49-1.51 (3H, d, *J* 6.55Hz, CH_3), 4.36-4.38 (1H, br,m, OH), 4.86-4.91 (1H, q, *J* 7Hz, CH), 7.17-7.21 (1H, m, Ar), 7.26-7.29 (1H, m, Ar), 7.66-7.70 (1H, m, Ar), 8.51-8.35 (1H, m, Ar); **^{13}C NMR** (100MHz, $CDCl_3$): δ 24.2 (CH_3), 68.8 (CH), 119.7 (Ar), 122.2 (Ar), 136.7 (Ar), 148.1 (Ar), 163.0 (Ar).

1-(3'-Pyridyl)-1-ethanol[178] (**155**) (20mg, 32%); **^{1}H NMR** (300MHz, $CDCl_3$): δ 1.49-1.52 (3H, d, *J* 6Hz, CH_3), 4.89-4.96 (1H, q, *J* 6Hz, CH), 7.24-7.44 (1H, m, Ar), 7.70-7.73 (1H, m, Ar), 8.45-8.58 (2H, m, Ar).

1-(2'Thienyl)-1ethanol[178] (**156**) (42mg, 65%); **^{1}H NMR** (300MHz, $CDCl_3$): δ 1.58-1.60 (3H, d, *J* 6Hz, CH_3), 5.08-5.15 (1H, q, *J* 6Hz, CH), 6.93-6.96 (2H, m, Ar), 7.18-7.24 (1H, m, Ar).

1-(3'Thienyl)-1ethanol[179] (**157**) (27mg, 42%); **^{1}H NMR** (400MHz, $CDCl_3$): δ 1.51-1.52 (3H, d, *J* 6Hz, CH_3), 1.94-1.95 (1H, br.m, OH), 4.94-4.99 (1H, q, *J* 6Hz, CH), 7.09-7.11 (1H, m, Ar), 7.18-7.19 (1H, m, Ar), 7.29-7.31 (1H, m, Ar); **^{13}C NMR** (100MHz, $CDCl_3$): δ 24.4 (CH_3),66.5 (CH), 120.1 (Ar), 125.6 (Ar), 126.1 (Ar), 147.3 (Ar).

1-(4'-Methoxyphenyl)-propan-1-ol[180] (**158**) (30mg, 36%); **^{1}H NMR** (400MHz, $CDCl_3$): δ 0.86-0.90 (3H, t, *J* 7Hz, CH_3), 1.65-1.86 (3H, m, CH_2 and OH), 3.79 (3H, s, OCH_3), 4.51-4.55 (1H, q, *J* 7Hz, CH), 6.85-6.88 (2H, AB d, J_{AB} 10Hz, Ar), 7.23-7.27 (2H, AB d, J_{AB} 10Hz, Ar).

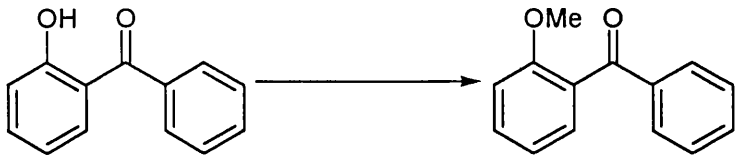
1-(2',6'-Dimethox-phenyl)ethanol (**159**) (20mg, 22%); **^{1}H NMR** (300MHz, $CDCl_3$): δ 1.42-1.45 (3H, d, *J* 7Hz, CH_3), 3.78 (6H, s, 2xOCH_3), 5.18-5.31 (1H, br.m, CH), 6.49-6.52 (2H, d, *J* 8Hz, Ar), 7.08-7.20 (1H, m, Ar).

5'-Chloro-2'-methoxy-1-phenylethanol (**160**) (52mg, 56%); **^{1}H NMR** (300MHz, $CDCl_3$): δ 1.44-1.47 (3H, d, *J* 6Hz, CH_3), 3.82 (3H, s, OCH_3), 5.01-5.08 (1H, q, *J* 6Hz, CH), 6.75-6.79 (1H, d, *J* 9Hz, Ar), 7.15-7.19 (1H, dd, *J* 3, 9Hz, Ar), 7.28-7.29 (1H, d, *J* 5Hz, Ar).

α-Phenyl-2-methoxybenzyl alcohol[181] (**225**) (51mg, 47%); **^{1}H NMR** (400MHz, $CDCl_3$): δ 3.00-3.01 (1H, br.d, *J* 4Hz, OH), 3.80 (3H, s, OCH_3), 6.04-6.06 (1H, br.d, *J* 3Hz, CH), 6.87-6.90 (1H, d, *J* 8Hz, Ar), 6.91-6.96 (1H, dd, *J* 7Hz, Ar), 7.21-7.25 (3H, m, Ar), 7.29-7.33 (2H, m, Ar), 7.37-7.39 (2H, m, Ar).

(E)-4-phenylbut-3-en-2-ol[182] (**161**) (42.2mg, 57%); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 3354.0, 3059.3, 3025.9, 2972.0, 2925.8, 2871.3, 1597.8, 1493.4, 1448.5, 1368.3, 1297.8, 1141.3, 1058.9, 966.6, 942.1, 875.9, 824.6, 748.0, 692.7; **^{1}H NMR** (400MHz, $CDCl_3$): δ 1.37-1.39 (3H, d, *J* 6Hz, CH_3), 4.48-4.52 (1H, m, CH), 6.24-6.30 (1H, dd, *J* 6, 16Hz, HC=), 6.55-6.59 (1H, d, *J* 16Hz, PhHC=), 7.22-7.26 (1H, m, Ph), 7.30-7.34 (2H, m, Ph), 7.37-7.40 (2H, m, Ph); **^{13}C NMR** (100MHz, $CDCl_3$): δ 23.4 (CH_3), 68.9 (CH), 126.4 (Ar), 127.6 (Ar), 128.5 (Ar), 129.4 (Ar), 133.5 (Ar), 136.6 (Ar); ***m/z*** (FAB): 148 (M^+, 78%), 133 ($[M-CH_3]^+$, 36%).

General procedure for methylation of substituted phenols



(226)

2'-Hydroxy benzophenone (1g, 5mmol) in THF (10mL) was added dropwise to a solution of sodium hydride (60% dispersion in mineral oil, 0.4g, 10mmol) in THF (10mL), over 20min. Iodomethane (2.5mmol, 8mmol) in THF (7.5mL) was added slowly to the reaction mixture. The reaction was stirred for 1h at room temperature and then refluxed for 3h. The reaction turned from clear yellow to colourless with a white precipitate (NaI). The reaction was quenched with water (50mL). The mixture was extracted with ether (3x50mL) and washed with brine (50mL). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed (SiO_2, 20% ether in PE 30-40) to afford *2'-methoxy benzophenone* (**226**)[181] (0.89g, 84%) as a colourless oil; **m.p.** 32-34°C, lit.,[183] 36-37°C; **^{1}H NMR** (300MHz, $CDCl_3$): δ 3.70 (3H, s, OCH_3), 6.88-7.02 (2H, m, Ar), 7.32-7.53 (5H, m, Ar), 7.77-7.81 (2H, m, Ar).

1-(2,6-Dimethoxyphenyl)-ethanone[184] (**227**) as a white solid (2 products) isolated yield (0.22g, 24%) mixed spots (0.34g) NMR yield (62%) chromatographed (SiO_2, 20% ether in petrol 30-40, R_f=0.1) S.M all consumed; **m.p.** 71-72°C, lit.,[184] 73°C; **^{1}H NMR** (300MHz, $CDCl_3$): δ 2.47 (3H, s, CH_3), 3.78 (6H, s, 2xOCH_3), 6.52-6.55 (2H, d, *J* 8Hz, Ar), 7.21-7.27 (1H, dd, *J* 8Hz, Ar).

1-(5-Chloro-2-methoxyphenyl)ethanone (**228**) as a yellow solid (2 products) isolated yield (161mg, 17%) mixed spots (533mg) by-product (299mg) chromatographed (SiO_2, 20% Et_2O in petrol 30-40, R_f=0.1) S.M all consumed; **^{1}H NMR** (300MHz, $CDCl_3$): δ 2.58 (3H, s, CH_3), 3.88 (3H, s, OCH_3), 6.87-6.90 (1H, d, *J* 9Hz, Ar), 7.36-7.40 (1H, dd, *J* 3, 9Hz, Ar), 7.67-7.68 (1H, d, *J* 3Hz, Ar).

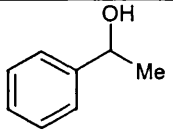
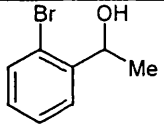
Preparation of (R)-(+)-α-methoxy-α-(trifluoromethyl) phenyl acetic acid chloride (229)[154]

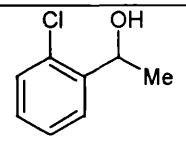
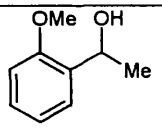
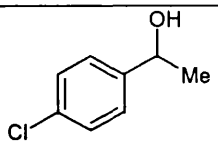
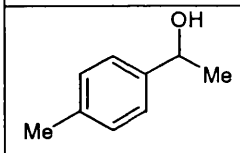
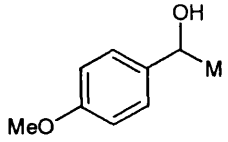
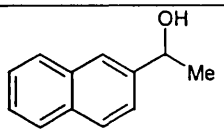
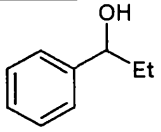
(*R*)-(+)-α-Methoxy-α-(trifluoromethyl)phenyl acetic acid (280mg, 1.2mmol) in oxalyl chloride (0.62mL, 3.36mmol) was refluxed for 1h at 67°C. The excess oxalyl chloride was removed by high vacuum. Benzene (3x5mL) was added to the crude mixture and removed under high vacuum while stirring. The crude (*R*)-(+)-MTPA-Cl (**229**) in DCM (4mL) was used as a 0.3M stock solution; **^{1}H NMR** (300MHz, $CDCl_3$): δ3.40(3H, s, OMe), 7.31-7.40(5H, m, Ph); **^{19}F NMR** (282MHz, $CDCl_3$): δ–71.9(CF_3).

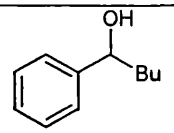
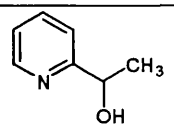
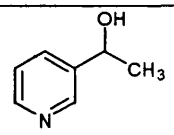
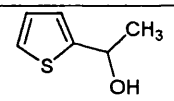
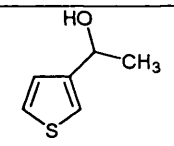
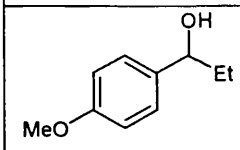
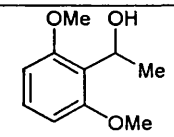
General procedure for preparation of Mosher's ester

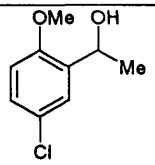
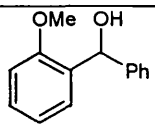
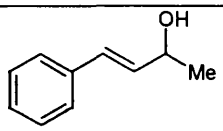
1-Phenylethanol (**144**) (3.7mg, 0.03mmol), triethylamine (8.4μL, 0.06mmol) and a few crystals of dimethylaminopyridine in DCM (0.5mL) was added crude (*R*)-(+)-MTPA-Cl (**229**) (0.3M in DCM) (0.2mL, 0.06mmol) and stirred overnight. The reaction was quenched with water (2mL), extraction with EtOAc (3x2mL) and dried over $MgSO_4$. The resultant solution was filtered through a pad of silica and analysed using ^{1}H and ^{19}F NMR spectroscopy.

Mosher's ester of corresponding alcohol

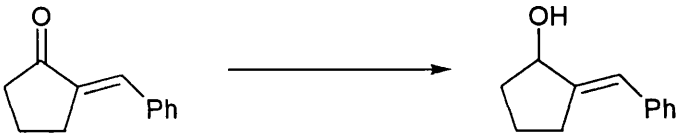
Alcohol	^{1}H %ee			^{19}F %ee		
	%ee	d.r	ppm	%ee	d.r	ppm
 (**144**)	62	19:81	3.42 and 3.48	67	16.5:83.5	71.9 and 72.1
 (**145**)	61	19.4:80.6	3.45 and 3.51	61	19.4:81.6	71.9 and 72.0

 **(146)**	65	17.4:82.6	3.45 and 3.51	65	17.5:82.5	71.9 and 72.0
 **(147)**	41	29.4:70.6	3.45 and 3.50	40	29.7:29.7	71.9 and 72.1
 **(148)**	56	22:78	3.39 and 3.48	54	23:77	71.9 and 72.1
 **(149)**	51	24.5:75.5	3.42 and 3.48	57	21.3:78.7	72.0 and 72.2
 **(150)**	0	50:50	3.38 and 3.47	0	50:50	72.0 and 72.2
 **(151)**	47	26.5:73.5	3.39 and 3.51	45	27.5:72.5	71.8 and 72.1
 **(152)**	66	17:83	3.38 and 3.47	66	17: 83	71.8 and 72.0

 **(153)**	77	11.5:88.5	3.37 and 3.47	72	14:86	71.8 and 72.0
 **(154)**	0	50:50	3.40 and 3.52	n/a	n/a	n/a
 **(155)**	5.5	47.3:53.7	3.39 and 3.49	15	42.4:57.6	71.8 and 72.0
 **(156)**	52	24:76	3.40 and 3.47	54	23:77	72.0 and 72.3
 **(157)**	28	36:64	3.40 and 3.48	28	36:64	71.9 and 72.1
 **(158)**	0	50:50	3.36 and 3.46	0	50:50	71.8 and 72.1
 **(159)**	20	40:60	3.43 and 3.50	23	38.4:61.6	72.3 and 72.6

 **(160)**	62	19:81	3.44 and 3.53	64	18:82	71.7 and 72.1
 **(225)**	Derivatisation into the corresponding Mosher's ester gave an unknown product.					
 **(161)**	0	50:50	3.48 and 3.52	0	50:50	71.9 and 72.0

Reduction of 2-Benzylidene cyclopentanone (162)



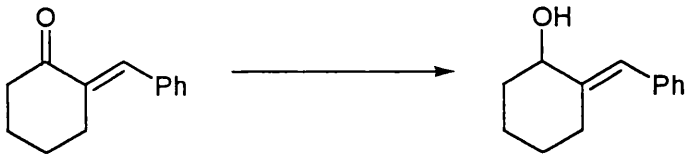
(162)

2-Benzylidene cyclopentanone (34mg, 0.2mmol) and $CeCl_3 \cdot 7H_2O$ (74mg, 0.2mmol) was dissolved in MeOH (4mL). Sodium borohydride (8mg, 0.21mmol) and stirred for 30min. The reaction was quenched with water (3mL) and the mixture was extracted with DCM (3x10mL). The organic extracts were dried over $MgSO_4$ and concentrated *in vacuo.* The residue was chromatographed (SiO_2, 40% ether in PE 30-40) to afford *2-benzylidene cyclopentanol* (**162**) (31mg, 89%); **IR** (KBr disc/cm^{-1}): $\tilde{\nu}_{max}$ 3281.6, 2964.3, 2873.2, 2364.7, 1490.3, 1446.6, 1425.8, 1290.0, 1277.2, 1099.4, 1032.1, 910.4, 873.1, 751.0, 684.8; **^{1}H NMR** (400MHz, $CDCl_3$): δ 1.61-1.79 (3H, m, CH_3), 1.91-2.01 (2H, m, CH_2), 2.54-2.62 (1H, m, CH_2), 2.70-2.78 (1H, m, CH_2), 4.58-4.61 (1H, m, CH), 6.57-6.59 (1H, m, CH), 7.20-7.26 (1H, m, Ph), 7.32-7.38 (4H, m, Ph); **^{13}C NMR** (100MHz, $CDCl_3$): δ 22.5 (CH_2), 29.3 (CH_2), 34.8 (CH_2), 77.3 (CHOH), 123.6 (CH=), 126.5 (C=), 128.3 (Ph), 128.4 (Ph), 137.7 (Ph), 147.7 (Ph); ***m/z*** (FAB): 175 (MH^+, 49%), 157 ($[M\text{-}OH]^+$, 100%).

Reduction of 2-Benzylidene cyclopentanone (162)

Titanium 3,4-di-O-benzyl-D-mannitol trimer (**101**) (98mg, 0.08mmol) in DCM (10mL) was cooled to –20°C. 2-Benzylidene cyclopentanone (86mg, 0.5mmol) was added followed by catecholborane (0.07mL, 0.55mmol). The reaction was monitored using TLC. The reaction was stopped after 4h and quenched with 1N HCl (10mL). The mixture was extracted with ethyl acetate (3x20mL) and washed 1N NaOH (3x10mL). The organic extracts were dried over $MgSO_4$ and concentrated *in vacuo.* The residue was chromatographed (SiO_2, 40% ether in PE 30-40) to afford *2-benzylidene cyclopentanol* (**162**) (67mg, 77%); **Chiral HPLC**: 5.5%ee.

Reduction of 2-Benzylidene cyclohexanone (163)



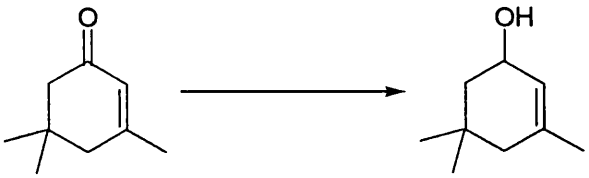
(163)

2-Benzylidene cyclohexanone (37mg, 0.2mmol) and $CeCl_3 \cdot 7H_2O$ (74mg, 0.2mmol) was dissolved in MeOH (4mL). Sodium borohydride (8mg, 0.21mmol) was added and stirred for 30min. The reaction was quenched with water (3mL) and extracted with DCM (3x10mL). The organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed (SiO_2, 40% ether in PE 30-40) to afford *2-benzylidene cyclohexananol* (**163**) (35mg, 93%); **^{1}H NMR** (400MHz, $CDCl_3$): δ 1.43-1.67 (5H, m, 2XCH_2, OH), 1.83-1.90 (1H, m, CH_2), 1.90-2.04 (1H, m, CH_2), 2.09-2.16 (1H, m, CH_2), 2.69-2.75 (1H, m, CH_2), 4.23-4.26 (1H, m, CH), 6.51-6.53 (1H, m, =CH), 7.19-7.34 (5H, m, Ph); **^{13}C NMR** (100MHz, $CDCl_3$): δ 23.2 (CH_2), 26.9 (CH_2), 27.3 (CH_2), 36.5 (CH_2), 73.7 (CHOH), 120.7 (CH=), 126.2 (C=), 128.0 (Ph), 128.9 (Ph), 137.6 (Ph), 144.3 (Ph).

Reduction of 2-Benzylidene cyclohexanone (163)

Titanium 3,4-di-O-benzyl-D-mannitol trimer (**101**) (98mg, 0.08mmol) in DCM (10mL) was cooled to –20°C. 2-Benzylidene cyclohexanone (93mg, 0.5mmol) was added followed by catecholborane (0.07mL, 0.55mmol). The reaction was monitored using TLC. The reaction was stopped after 6h and quenched with 1N HCl (10mL). The mixture was extracted with ethyl acetate (3x20mL) and washed 1N NaOH (3x10mL). The organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed (SiO_2, 40% ether in PE 30-40) to afford *2-benzylidene cyclohexanol* (**163**) (68mg, 72%); **Chiral HPLC**: 25%ee.

Reduction of Isophorone (164)



(164)

Titanium 3,4-di-O-benzyl-D-mannitol trimer (**101**) (98mg, 0.08mmol) in toluene (15mL) was cooled to –20°C. Isophorone (75μL, 0.5mmol) was added followed by catecholborane (70μL, 0.55mmol). The reaction was stirred for 4h and quenched with 1N HCl (5mL). The mixture was extracted with ethyl acetate (3x10mL) and washed 1N NaOH (3x10mL). The organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was filtered through a pad of silica using ether to afford *isophorol* (**164**)[185]; **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 3328.0, 2951.6, 2924.8, 2866.9, 1673.4, 1455.6, 1437.8, 1376.1, 1364.1, 1284.0, 1129.4, 1100.0, 1043.4, 1019.5, 994.1, 949.2, 923.6, 821.5; **^{1}H NMR** (400MHz, $CDCl_3$): δ 0.88 (3H, s, CH_3), 0.99 (3H, s, CH_3), 1.19-1.25 (1H, dd, *J* 9, 12Hz, CH_2), 1.35 (1H, br.m, CH_2), 1.67 (3H, s, CH_3), 1.58-1.86 (2H, m, CH_2), 4.21-4.23 (1H, br.m. CHOH), 5.41-5.42 (1H, m, =CH); **^{13}C NMR** (100MHz, $CDCl_3$): δ 23.5 (CH_3), 26.2, (CH_3), 31.2 (CH_3), 44.1 (CH_2), 45.2 (CH_2), 66.9 (CH), 123.6 $(CMe)_2$, 136.1 (CH=), 153.9 (MeC=)Me; ***m/z***(EI) 140 (M^+, 15%), 125 ($[M–OH]^+$, 100%). **Chiral GC**: 36%ee with no S.M.

3.7 Blank reactions

Reduction of Acetophenone (111)

3,4-Di-O-benzyl-D-mannitol (**87**) (87mg, 0.24mmol) in DCM (10mL) was cooled to –20°C. Acetophenone (59μL, 0.5mmol) was added followed by catecholborane (70μL, 0.55mmol). The reaction was monitored using TLC. The reaction was stopped after **4h** and quenched with 1N HCl (5mL). The mixture was extracted with ethyl acetate (3x10mL) and washed 1N NaOH (3x10mL). The organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was filtered through a pad of silica with ether and analysed; GC: 0%ee; acetophenone:1-phenylethanol 1.00:0.08.

Reduction of Acetophenone (112)

3,4-Di-O-benzyl-D-mannitol (**87**) (87mg, 0.24mmol) and titanium(IV) isopropoxide (70μL, 0.24mmol) in DCM (10mL) was cooled to –20°C. Acetophenone (59μL, 0.5mmol) was added followed by catecholborane (70μL, 0.55mmol). The reaction was monitored using TLC. The reaction was stopped after 4h and quenched with 1N HCl (5mL). The mixture was extracted with ethyl acetate (3x10mL) and washed 1N NaOH (3x10mL). The organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was filtered through a pad of silica with ether and analysed; **Chiral GC**: 0%ee; acetophenone:1-phenylethanol 1.00:0.02.

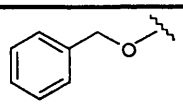
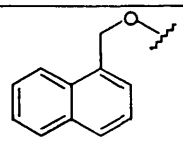
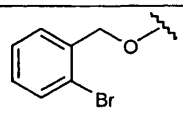
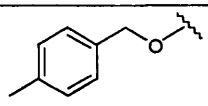
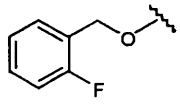
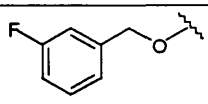
Attempted regeneration of the residue from the synthesis of titanium trimer (101)

Titanium residue (1g) and isopropanol (1mL) in toluene (25mL) was heated to reflux for 15h. The reaction was cooled, the resultant orange solution was concentrated in vacuo. The residue was dissolved in DCM (50mL), any insoluble material was filtered off. The filtrate was concentrated *in vacuo* to afford *3,4-Di-O-benzyl-D-mannitol* (**87**) (23mg).

3.8 Reduction of acetophenone using titanium trimer derivatives

General procedure for catecholborane reduction of acetophenone in the presence of titanium 3,4-di-O-substituted-D-mannitol trimer

Acetophenone (59μL, 0.5mmol) and *titanium 3,4-di-O-benzyl-D-mannitol trimer* (**101**) (98mg, 0.08mmol) in DCM (10mL) was cooled to –20°C. Catecholborane (70μL, 0.55mmol) was added and the reaction was stirred overnight. The reaction was quenched with 1N HCl (10mL) and the mixture was extracted with ether (3x10mL). The organic phase was washed with 1N NaOH (3x10mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed (SiO_2, 40% ether in PE 30-40) to afford *1-phenylethanol* (**144**) as a colourless oil; the product was analysed using **Chiral GC**.

Titanium complex-substituted benzyl ethers	Mass		Enantiomeric purity		Yield	
	mg	mmol	%ee	*R:S*	mg	%
 (**101**)	98	0.08	72	14:86	58	95
 (**113**)	122	0.08	48	26:74	38	62
 (**114**)	135	0.08	58%	21:79	43	71
 (**115**)	104	0.08	54%	23:77	50	82
 (**116**)	106	0.08	62	19:81	41	68
 (**117**)	106	0.08	66	17:83	40	65

3.9 Asymmetric reduction using other boranes

Reduction of Acetophenone (122)

Titanium 3,4-di-O-benzyl-D-mannitol trimer (**101**) (98mg, 0.08mmol) in DCM (10mL) was cooled to –20°C. Acetophenone (59μL, 0.5mmol) was added followed by $BH_3{\cdot}SMe_2$ complex (2M in THF, 0.25mL, 0.5mmol) and the reaction was stirred overnight. The reaction showed no product on TLC. The reaction was warmed to room temperature and the reaction was stirred for another 18h. The reaction still showed no product on TLC. The reaction was stirred for a total of 5day. Formation of some product was shown on TLC. The reaction was quenched with 1N HCl (5mL). The mixture was extracted with ethyl acetate (3x10mL) and washed with 1N NaOH (3x10mL). Drying over $MgSO_4$ and concentration *in vacuo* afforded a yellow oil. The residue was filtered through a pad of silica with ether and analysed; **Chiral GC**: 24%ee *R*:*S* 62:38, starting material:product 1.00:0.95.

Reduction of Acetophenone (123)

Titanium 3,4-di-O-benzyl-D-mannitol trimer (**101**) (98mg, 0.08mmol) in THF (10mL) was cooled to –20°C. Acetophenone (59μL, 0.5mmol) was added followed by $BH_3{\cdot}SMe_2$ complex (2M in THF, 0.25mL, 0.5mmol) and the reaction was stirred for 16h. An aliquot was taken from the reaction for GC analysis. The reaction was warmed to room temperature and stirred for another 16h. Another aliquot was taken from the reaction for GC analysis. Stirring for a total of 4day and the reaction was quenched with 1N HCl (5mL). The mixture was extracted with ethyl acetate (3x10mL) and washed with 1N NaOH (3x10mL). The organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was filtered through a pad of silica using ether and analysed; **Chiral GC**: **After 16h**: 3.4%ee, *R*:*S* 51.7:48.3, starting material:product 1.00:0.33; **After 32h**: 6%ee *R*:*S* 53:47, starting material:product 1.00:1.89; **After 4day**: 6%ee *R*:*S* 53:47; starting material:product 1:1.81.

Reduction of Acetophenone (124)

Titanium 3,4-di-O-benzyl-D-mannitol trimer (**101**) (98mg, 0.08mmol) in DCM (10mL) was added acetophenone (59μL, 0.5mmol) followed by BH_3·SMe_2 complex (2M in THF, 0.25mL, 0.5mmol) and the reaction was stirred for 18h. The reaction was quenched with 1N HCl (5mL). The mixuture was extracted with ethyl acetate (3x10mL) and washed with 1N NaOH (3x10mL). The organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was filtered through a pad of silica using ether and analysed; **Chiral GC**: 12%ee, *R*:*S* 56:44, starting material:product 1.00:11.68.

Reduction of Acetophenone (125)

Titanium 3,4-di-O-benzyl-D-mannitol trimer (**101**) (98mg, 0.08mmol) in DCM (10mL) was cooled to 0°C. Acetophenone (59μL, 0.5mmol) was added followed by BH_3·SMe_2 complex (2M in THF, 0.25mL, 0.5mmol) and the reaction was stirred for 4h. An aliquot was taken from the reaction for GC analysis. The reaction was warmed to room temperature after stirring for 6hr. After 18h, another aliquot was taken for GC analysis. The reaction was stirred for a total of 2day and was quenched with 1N HCl (5mL). The mixture was extracted into the organic phase using ethyl acetate (3x10mL) and washed 1N NaOH (3x10mL). The organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was filtered through a pad of silica using ether and analysed; **Chiral GC**: **After 4h**: 14%ee, *R*:*S* 57:43, starting material:product 1.00:0.13; **After 18h**: 20%ee, *R*:*S* 60:40, starting material:product 1.00:2.01; **After 2day**: 18%ee, *R*:*S* 59:41, starting material:product 1.00:11.23.

Reduction of Acetophenone (126)

Titanium 3,4-di-O-benzyl-D-mannitol trimer (**101**) (98mg, 0.08mmol) in DCM (10mL) was cooled to –20°C. Acetophenone (59μL, 0.5mmol) was added followed by BH_3·SMe_2 complex (2M in THF, 0.25mL, 0.5mmol) and the reaction was stirred for 18h. An aliquot was taken from the reaction for GC analysis. The reaction was warmed to room temperature and stirred for a total of 4day. The reaction was quenched with 1N HCl (5mL) and extracted with ethyl acetate (3x10mL) and washed 1N NaOH (3x10mL). The organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was filtered through a pad of silica using ether and analysed; **Chiral GC**: **After 18h**: 14%ee *R*:*S* 57:43; starting material:product 1.00:0.08; **After 4day**: 18%ee *R*:*S* 59:41, starting material:product 1.00:0.68.

Reduction of Acetophenone (127)

Titanium 3,4-di-O-benzyl-D-mannitol trimer (**101**) (196mg, 0.16mmol) in DCM (10mL) was cooled to –20°C. Acetophenone (59μL, 0.5mmol) was added followed by BH_3·SMe_2 complex (2M in THF, 0.25mL, 0.5mmol) and the reaction was stirred for 18h. An aliquot was taken from the reaction for GC analysis. The reaction was warmed to room temperature and the reaction was stirred for a total of 4day. The reaction was quenched with 1N HCl (5mL). The mixture was extracted into the organic phase using ethyl acetate (3x10mL) and washed 1N NaOH (3x10mL). Drying over $MgSO_4$ and concentration *in vacuo* gave a yellow oil. The residue was filtered through a pad of silica using ether and analysed; **Chiral GC**: **After 18h**: 14%ee, *R*:*S* 57:43, starting material:product 1.00:0.24; **After 4day**: 22%ee, *R*:*S* 61:39, starting material:product 1.00:42.10.

Reduction of Acetophenone (128)

Titanium 3,4-di-O-benzyl-D-mannitol trimer (**101**) (196mg, 0.16mmol) in DCM (10mL) was cooled to –78°C. Acetophenone (59μL, 0.5mmol) was added followed by BH_3·SMe_2 complex (2M in THF, 0.25mL, 0.5mmol) and the reaction was stirred for 8h. An aliquot was taken from the reaction for GC analysis. The reaction was gradually warmed to room temperature over 16h. The reaction was quenched with 1N HCl (5mL). The mixture was extracted into the organic phase using ethyl acetate (3x10mL) and washed 1N NaOH (3x10mL). Drying over $MgSO_4$ and concentration *in vacuo* gave a yellow oil. The residue was filtered through a pad of silica using ether and analysed; **Chiral GC**: **After 8h**: No product detected; **After 22h**: 24%ee, *R*:*S* 62:38, starting material:product 1.00:0.33; **After 2day**: 24%ee, *R*:*S* 62:38, starting material:product 1.00:0.55; **After 6day**: 24%ee, *R*:*S* 62:38, starting material:product 1.00:0.59.

Reduction of Acetophenone (129)

Titanium 3,4-di-O-benzyl-D-mannitol trimer (**101**) (609mg, 0.5mmol) in DCM (10mL) was cooled to –50°C. Acetophenone (59μL, 0.5mmol) was added followed by BH_3·SMe_2 complex (2M in THF, 0.25mL, 0.5mmol) and the reaction was stirred for 5h. An aliquot was taken from the reaction for GC analysis. The reaction was gradually warmed to room temperature over 18h. The reaction was quenched with 1N HCl (5mL) and extracted with ethyl acetate (3x10mL) and washed 1N NaOH (3x10mL). Drying over $MgSO_4$ and concentration *in vacuo* gave a yellow oil. The residue was filtered through a pad of silica using ether and analysed; GC: **After 5h**: no product detected; **After 22h**: 30%ee *R*:*S* 65:35, starting material:product 1.00:1.25; **After 2day**: 28%ee, *R*:*S* 64:36, starting material:product 1.00:2.43; **After 6day**: 28%ee, *R*:*S* 64:36, starting material:product 1.00:3.03.

Attemped reduction of Acetophenone (118)

Titanium 3,4-di-O-benzyl-D-mannitol trimer (**101**) (98mg, 0.08mmol) in DCM (10mL) was cooled to 0°C. Acetophenone (59μL, 0.5mmol) was added followed by BH_3.THF complex (1M in THF, 0.5mL, 0.5mmol) and the reaction was warmed to room temperature after 2h. The reaction was followed by TLC for 2 day, but no product was detected. GC of the reaction showed only a trace amount of racemic alcohol formed.

Attempted reduction of Acetophenone (119)

Titanium 3,4-di-O-benzyl-D-mannitol trimer (**101**) (98mg, 0.08mmol) in DCM (10mL) was cooled to –20°C. Acetophenone (59μL, 0.5mmol) was added followed by BH_3·NMe_3 complex (38mg, 0.5mmol) and the reaction was stirred overnight. The reaction showed no product on TLC. The reaction was warmed to room temperature and the reaction was stirred for another 18h. The reaction still showed no product. The reaction was stirred for a total of 5day, Formation of a small amount product was shown on TLC. The reaction was quenched with 1N HCl (5mL). The mixture was extracted with ethyl acetate (3x10mL) and washed with 1N NaOH (3x10mL). Drying over $MgSO_4$ and concentration *in vacuo* gave a yellow oil. The residue was filtered through a pad of silica using ether and analysed; **Chiral GC**: 0%ee; starting material:product 1.00:0.08.

Attemped reduction of Acetophenone (120)

Titanium 3,4-di-O-benzyl-D-mannitol trimer (**101**) (98mg, 0.08mmol) in DCM (10mL) was added acetophenone (59μL, 0.5mmol) followed by 9-BBN (0.5M in THF, 1mL, 0.5mmol). The reaction was monitored by TLC for 4 day, but no product was detected.

Attemped reduction of Acetophenone (121)

Titanium 3,4-di-O-benzyl-D-mannitol trimer (**101**) (98mg, 0.08mmol) in DCM (10mL) was cooled to 0°C. Acetophenone (59μL, 0.5mmol) was added followed by BH_3.PPh_3 complex (142mg, 0.5mmol). The reaction was warmed to room temperature after 2h. The reaction was monitored by TLC for 2 day, but no product was detected; **Chiral GC**: only trace amount of racemic product was detected.

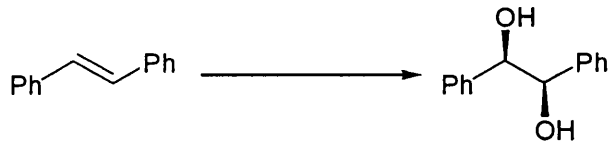
3.10 Chiral hydrobenzoin borane for asymmetric reduction

Asymmetric dihydroxylation of trans-stilbene (130a)[135]

(130a)

t-Butanol (28mL) and distilled water (28mL) was added methane sulfonamide (0.53g, 5.46mmol) followed by AD-mix-α (7.77g). The mixture was cooled to 0°C for 5min. *trans*-Stilbene (1g, 5.33mmol) was added in one portion, the reaction was stirred vigorously for 3h and stored in the refrigerator overnight. The reaction was quenched with sodium sulfite at 0°C and stirred at room temperature for 1h. The mixture was extracted with ethyl acetate (2x80mL) and dried over $MgSO_4$. Recrystallisation with ethyl acetate/PE 30-40 gave a *(S,S)-(–)-hydrobenzoin* (**130a**) (0.78g, 66%) as a white crystalline solid; **m.p.** 146-148°C, lit.,[186] 147-148.5°C; $[\alpha]_D^{23}$ =+76.4° (c=2.5, EtOH) lit.,[186] $[\alpha]_D^{23}$ =+90.1° (c=1, EtOH); **^{1}H NMR** (400MHz, $CDCl_3$): δ 2.82-2.83 (2H, d, *J* 1Hz, 2xCH), 7.10-7.14 (4H, m, 2xPh), 7.20-7.24 (6H, m, 2xPh); **^{13}C NMR** (100MHz, $CDCl_3$): δ 79.4, 127.2 (Ph), 128.2 (Ph), 128.4 (Ph), 140.1 (Ph).

Asymmetric dihydroxylation of trans-stilbene (130b)[135]



(130b)

t-Butanol (28mL) and distilled water (28mL) was added methane sulfonamide (0.53g, 5.46mmol) followed by AD-mix-β (7.77g). The mixture was cooled to 0°C for 5min. *trans*-Stilbene (1g, 5.33mmol) was added in one portion, the reaction was stirred vigorously for 3h and stored in the refrigerator overnight. The reaction was quenched with sodium sulfite at 0°C and stirred at room temperature for 1h. The mixture was extracted with ethyl acetate (2x80mL) and dried over $MgSO_4$. Recrystallisation with ethyl acetate/PE 30-40 gave a *(R,R)-(+)-hydrobenzoin* (**130b**) (0.97g, 82%) as a white crystalline solid; **m.p.** 146-148°C, lit.,[187] 147-148°C; $[\alpha]_D^{23}$ =–78.0° (c=2.5, EtOH), lit.,[187] $[\alpha]_D^{23}$ –90.5° (c=1, EtOH).

General attempted preparation of hydrobenzoin borane (94)[136]

(130a) **(130a)**

In a schlenk tube, *(S,S)-(-)-hydrobenzoin* (**130a**) (1g, 4.67mmol) in DCM (2mL) was cooled to 0°C. A solution of $BH_3{\cdot}SMe_2$ complex (2M in THF, 2.33mL, 4.67mmol) was added dropwise to the reaction and stirred for 1h before warming to room temperature. The reaction was stirred until no evolution of hydrogen was observed. The borane (1.08M) was used without any purification or analysis.

Reduction of acetophenone (132)

Acetophenone (59μL, 0.5mmol) in DCM (2mL) was cooled to –20°C. *(R,R)-(+)-Hydrobenzoin borane* (**131b**) (1.08M in DCM, 0.46mL, 0.5mmol) was added and the reaction was stirred overnight. The reaction was quenched with 1N HCl (5mL). The mixture was extracted with ethyl acetate (3x10mL) and washed 1N NaOH (3x10mL). The organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was filtered through a pad of silica using ether and analysed; **Chiral GC**: 32%ee, *R*:*S* 34:66; starting material:product 1.00:0.18.

Reduction of acetophenone (133)

Titanium 3,4-di-O-benzyl-D-mannitol trimer (**101**) (98mg, 0.08mmol) in DCM (2mL) was cooled to –20°C. Acetophenone (59μL, 0.5mmol) was added and stirred for 10min followed by *(R,R)-(+)-Hydrobenzoin borane* (**131b**) (1.08M in DCM, 0.46mL, 0.5mmol) and stirred overnight. The reaction was quenched with 1N HCl (5mL) and extracted with ethyl acetate (3x10mL) and washed 1N NaOH (3x10mL). The organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was filtered through a pad of silica with ether and analysed; **Chiral GC**: 1%ee, *R*:*S* 51.5:49.5, starting material:product 1.00:0.39.

Reduction of acetophenone (134)

Acetophenone (59μL, 0.5mmol) in DCM (2mL) was cooled to –20°C. *(S,S)-(–)-Hydrobenzoin borane* (**131a**) (1.08M in DCM, 0.46mL, 0.5mmol) was added and the reaction was stirred overnight. The reaction was quenched with 1N HCl (5mL). The mixture was extracted with ethyl acetate (3x10mL) and washed 1N NaOH (3x10mL). The organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was filtered through a pad of silica using ether and analysed; **Chiral GC**: 2%ee, *R*:*S* 51:49; starting material:product 1.00:0.43

Reduction of acetophenone (197)

Titanium 3,4-di-O-benzyl-D-mannitol trimer (**101**) (98mg, 0.08mmol) in DCM (2mL) was cooled to –20°C. Acetophenone (59μL, 0.5mmol) was added and stirred for 10min followed by *(S,S)-(–)-Hydrobenzoin borane* (**131a**) (1.08M in DCM, 0.46mL, 0.5mmol) and stirred overnight. The reaction was quenched with 1N HCl (5mL) and the mixture was extracted with ethyl acetate (3x10mL) and washed 1N NaOH (3x10mL). The organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was filtered through a pad of silica with ether and analysed; **Chiral GC**: 6%ee, *R*:*S* 53:47, starting material:product 1.00:0.26.

Reduction of acetophenone (198)

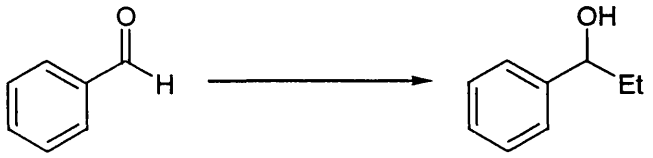
Acetophenone (59μL, 0.5mmol) in DCM (2mL) was cooled to –20°C. *(R,R)-(+)-Hydrobenzoin borane* (**131b**) (1.08M in DCM, 0.46mL, 0.5mmol) was added and the reaction was stirred overnight. The reaction was quenched with 1N HCl (5mL). The mixture was extracted with ethyl acetate (3x10mL) and washed 1N NaOH (3x10mL). The organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was filtered through a pad of silica with ether and analysed; **Chiral GC**: 18%ee *R*:*S* 41:59, starting material:product 1.00:0.59.

Reduction of acetophenone (199)

Titanium 3,4-di-O-benzyl-D-mannitol trimer (**101**) (98mg, 0.08mmol) in DCM (2mL) was cooled to -20°C. Acetophenone (59μL, 0.5mmol) was added and stirred for 10min followed by *(R,R)-(+)-Hydrobenzoin borane* (**131b**) (1.08M in DCM, 0.46mL, 0.5mmol) and stirred overnight. The reaction was quenched with 1N HCl (5mL) and the mixture was extracted with ethyl acetate (3x10mL) and washed 1N NaOH (3x10mL). The organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was filtered through a pad of silica using ether and analysed; **Chiral GC**: 6%ee, *R*:*S* 47:53, starting material:product 1.00:0.91.

3.11 Diethylzinc addition to benzaldehyde

Attempted Diethylzinc addition to benzaldehyde (165)[59]



(165)

Titanium 3,4-di-O-benzyl-D-mannitol trimer (**101**) (0.61g, 0.5mmol) in toluene (20mL) was cooled to –25°C. Benzaldehyde (0.255mL, 2.5mmol) was added followed by dropwise addition of diethylzinc (1M in hexanes, 3mL, 3mmol) over 30min. The reaction was monitored using TLC, no new product was detected after 96h. The reaction was quenched with $NH_4Cl_{(sat.)}$ (8mL) and the mixture was extracted with ether (2x10mL). The combined organic extracts was washed with brine (8mL), dried over $MgSO_4$ and concentrated *in vacuo*; **Chiral GC**: only starting material detected.

Attempted Diethylzinc addition to benzaldehyde (166)[59]

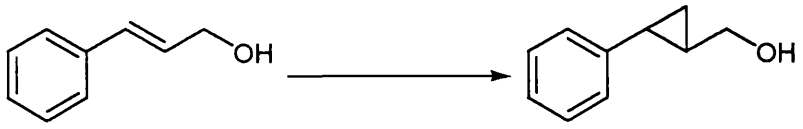
Titanium 3,4-di-O-benzyl-D-mannitol trimer (**101**) (0.61g, 0.5mmol) in toluene (20mL) was cooled to –15°C. Titanium(IV) isopropoxide (0.92mL, 3mmol) was added followed by benzaldehyde (0.255mL, 2.5mmol). Diethylzinc (1M in hexanes, 3mL, 3mmol) was added slowly to the reaction. The reaction was monitored using TLC and quenched after 48h with $NH_4Cl_{(sat.)}$ (8mL). The mixture was extracted with ether (2x10mL) and washed with brine (8mL), dried over $MgSO_4$ and concentrated *in vacuo*. Flash chromatography (SiO_2, 40% ether in PE 30-40) afforded *1-phenyl-1-propanol* (**165**) (7.5mg, 22%); See (**152**) for NMR data; **Chiral GC**: racemic product detected.

Attempted Diethylzinc addition to benzaldehyde (167)[59]

Titanium 3,4-di-O-benzyl-D-mannitol trimer (**101**) (0.244g, 0.2mmol) in toluene (10mL) was cooled to 0°C. Titanium(IV) isopropoxide (0.37mL, 1.2mmol) was added followed by benzaldehyde (0.1mL, 1mmol). Diethylzinc (1M in hexanes, 1.2mL, 1.2mmol) was added slowly to the reaction over 1h. The reaction was stirred for 20h and analysed; **Chiral GC**: racmic product detected.

3.12 Cyclopropanation of cinnamyl alcohol

Cyclopropanation of cinnamyl alcohol (168)[71]



(168)

Methylene diiodide (0.16mL, 2mmol) in DCM (8mL) was cooled to –78°C. Diethylzinc (1M in hexanes, 1mL, 1mmol) was added slowly to the reaction. After 10min, cinnamyl alcohol (137mg, 1mmol) dissolved in DCM (5mL) was added slowly to the reaction over 15min. The reaction was warmed to –20°C and titanium(IV) isopropoxide (45μL, 0.15mmol) was added to the reaction. The reaction turned yellow and back to colourless again. The reaction was stirred for 18h and quenched with water (10mL). Extraction with DCM (2x25mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed (SiO_2, 40% ether in PE 30-40) to afford *3-Phenyl-2,3-methano-1-propanol* (**168**)[188] (53mg, 35%) as a colourless oil; **IR** (KBr disc/cm^{-1}): $\tilde{\nu}_{max}$ 3340.8, 3063.7, 3028.1, 2871.6, 2364.4, 1604.2, 1497.3, 1460.8, 1413.6, 1243.3, 1182.9, 1090.0, 1022.3, 925.9, 875.0, 746.5, 696.7; **^{1}H NMR** (400MHz, $CDCl_3$): δ 0.91-1.00 (2H, m, CH_2), 1.42-1.50 (1H, m, CH), 1.65 (1H, br.s, OH), 1.80-1.86 (1H, m, CH), 3.58-3.67 (2H, m, CH_2), 7.06-7.09 (2H, m, Ph), 7.14-7.18 (1H, m, Ph), 7.24-7.29 (2H, m, Ph); **^{13}C NMR** (100MHz, $CDCl_3$): δ 13.8, 21.2, 25.3, 66.5, 125.6 (Ph), 125.7 (Ph), 128.3 (Ph), 142.4 (Ph); ***m/z*** (FAB): 148 (M^+, 19%), 131 ($[M-OH]^+$, 100%); **Chiral HPLC**: 0%ee (3%^{i}PrOH in hexane 1mL/min).

Attempted enantioselective cyclopropanation of cinnamyl alcohol (169)[71]

Methylene diiodide (0.16mL, 2mmol) in DCM (8mL) was cooled to –78°C. Diethylzinc (1M in hexanes, 1mL, 1mmol) was added slowly to the reaction. After 10min, cinnamyl alcohol (137mg, 1mmol) dissolved in DCM (5mL) was added slowly to the reaction over 15min. The reaction was warmed to –20°C and *titanium 3,4-di-O-benzyl-D-mannitol trimer* (**101**) (183mg, 0.15mmol) was added to the reaction. The reaction was stirred for

17h and quenched with water (10mL). Extraction with DCM (2x25mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed (SiO_2, 40% ether in PE 30-40) to afford *3-Phenyl-2,3-methano-1-propanol* (**168**) (44mg, 29%); **Chiral HPLC**: 0%ee (3%^{i}PrOH in hexane 1mL/min).

Attempted enantioselective cyclopropanation of cinnamyl alcohol (170)[71]

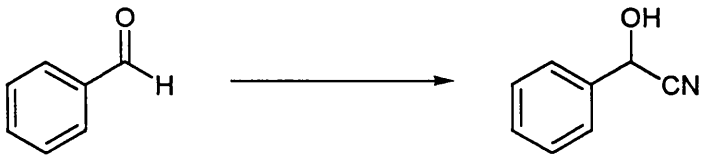
Methylene diiodide (0.16mL, 2mmol) in DCM (8mL) was cooled to –78°C. Diethylzinc (1M in hexanes, 1mL, 1mmol) was added slowly to the reaction. After 10min, *titanium 3,4-di-O-benzyl-D-mannitol trimer* (**101**) (183mg, 0.15mmol) in DCM (5mL) was added slowly, the reaction turned yellow. Cinnamyl alcohol (137mg, 1mmol) dissolved in DCM (5mL) was added slowly to the reaction over 15min. The reaction was warmed to –20°C. The reaction turn back to colorless after 10 min. The reaction was stirred for 15h and quenched with water (10mL). Extraction with DCM (2x25mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed (SiO_2, 40% ether in PE 30-40) to afford *3-Phenyl-2,3-methano-1-propanol* (**168**) (33mg, 22%); **Chiral HPLC**: 0%ee (3%^{i}PrOH in hexane 1mL/min).

Cyclopropanation of cinnamyl alcohol (171)[71]

Methylene diiodide (0.16mL, 2mmol) in DCM (8mL) was cooled to –78°C. Diethylzinc (1M in hexanes, 1mL, 1mmol) was added slowly to the reaction. After 10min, cinnamyl alcohol (137mg, 1mmol) dissolved in DCM (5mL) was added slowly to the reaction over 15min. The reaction was warmed to –20°C. The reaction was stirred for 16h and quenched with water (10mL). Extraction with DCM (2x25mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed (SiO_2, 40% ether in PE 30-40) to afford *3-Phenyl-2,3-methano-1-propanol* (**168**) (31mg, 21%).

3.13 Cyanosilylation of benzaldehyde

Attempted Catalytic Cyanosilylation of benzaldehyde (172)[42b]



(172)

Titanium(IV) isopropoxide (60μL, 0.2mmol) in DCM (10mL) was added trimethylsilylcyanide (0.30mL, 2.28mmol) followed by benzaldehyde (0.10mL, 1mmol) and stirred for 20h. TLC showed no starting material and formation of one product. Stirring in rapidly 1N HCl (10mL) for 1h quenched the reaction. The mixture was extracted with ether (3x10mL), washed with brine (25mL) and dried over $MgSO_4$. The organic extracts was concentrated *in vacuo* and chromatographed (SiO_2, 40% ether in PE 30-40) to afford *mandelonitrile* (**172**)[189] (109mg, 82%) as a colourless oil; **^{1}H NMR** (400MHz, $CDCl_3$): δ 3.35-3.37 (1H, d, *J* 7Hz, OH), 5.48-5.50 (1H, d, *J* 6Hz, CH), 7.41-7.44 (3H, m, Ph), 7.47-7.51 (2H, m, Ph); **^{13}C NMR** (100MHz, $CDCl_3$): δ 63.5 (CH), 118.8 (CN), 126.6 (Ph), 129.2 (Ph), 129.8 (Ph), 135.1 (Ph).

Attempted Catalytic Cyanosilylation of benzaldehyde (173)[42b]

Titanium 3,4-di-O-benzyl-D-mannitol trimer (**101**) (244mg, 0.2mmol) in DCM (10mL) was added trimethylsilylcyanide (0.16mL, 1.2mmol) followed by benzaldehyde (0.10mL, 1mmol) and stirred for 72h. Stirring in rapidly 1N HCl (10mL) for 1h quenched the reaction. The mixture was extracted with ether (3x20mL), washed with brine (25mL) and dried over $MgSO_4$. The organic extracts was concentrated *in vacuo* and chromatographed (SiO_2, 40% ether in PE 30-40) *afforded mandelonitrile* (**172**) (29mg, 22%); $[\alpha]_D^{23}$ =+3° (c=0.2, $CHCl_3$), lit.,[189] (*R*)-(+)- mandelonitrile $[\alpha]_D^{23}$ =+45° (c=1, $CHCl_3$); **Chiral GC**: racemic product was detected.

Attempted Catalytic Cyanosilylation of benzaldehyde (174)[42b]

Titanium 3,4-di-O-benzyl-D-mannitol trimer (**101**) (244mg, 0.2mmol) in DCM (10mL) was cooled to 0°C. Trimethylsilylcyanide (0.16mL, 1.2mmol) was added followed by benzaldehyde (0.10mL, 1mmol) and stirred for 50h. Stirring in rapidly 1N HCl (10mL) for 1h quenched the reaction. The mixture was extracted with ether (3x20mL), washed with brine (25mL) and dried over $MgSO_4$. The organic layer was concentrated *in vacuo* and chromatographed (SiO_2, 40% ether in PE 30-40) afforded *mandelonitrile* (**172**) (20mg, 15%); $[\alpha]_D^{23}$ =+3° (c=0.2, $CHCl_3$); **Chiral GC**: racemic product was detected.

Attempted Catalytic Cyanosilylation of benzaldehyde (175)[42b]

Titanium 3,4-di-O-benzyl-D-mannitol trimer (**101**) (244mg, 0.2mmol) in DCM (5mL) was cooled to –78°C. Benzaldehyde (0.10mL, 1mmol) was added followed by trimethylsilylcyanide (0.20mL, 1.5mmol) and the reaction was stirred for 24h. Stirring in rapidly 1N HCl (10mL) for 1h quenched the reaction. The mixture was extracted with ether (3x20mL), washed with brine (25mL) and dried over $MgSO_4$. The organic layer was concentrated *in vacuo* and chromatographed (SiO_2, 40% ether in PE 30-40) afforded *mandelonitrile* (**172**) (20mg, 15%); **Chiral GC**: racemic product was detected.

3.14 Addition of dimethyl phosphite to aldehydes and imines

Reaction of dimethyl phosphite and cinnamaldehyde (176)[160]

(176)

Titanium(IV) isopropoxide (60μL, 0.2mmol) in DCM (1.75mL) was added freshly distilled cinnamaldehyde (0.13mL, 1mmol) followed by dimethyl phosphite (0.11mL, 1.2mmol). The reaction was placed into the freezer (–10°C approx.) for 18h. The reaction was quenched with distilled water (10mL) and the mixture was extracted with DCM (3x10mL). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed (SiO_2, ethyl acetate) to afford *(1-hydroxy-3-phenyl-2(E)-propenyl) phosphonic acid dimethyl ester* (**176**) (80mg, 33%) as a white solid; **m.p.** 96-98°C, lit.,[190] 98.9-99.6°C; **IR** (KBr disc/cm^{-1}): $\tilde{\nu}_{max}$ 3289.3, 2952.4, 2850.1, 2368.0, 1449.6, 1244.9, 1206.7, 1112.8, 1048.8, 1028.7, 983.9, 840.1, 790.5, 760.4, 701.6, 564.4, 527.5, 503.6; **^{1}H NMR** (400MHz, $CDCl_3$): δ 3.82-3.84 (6H, d, $^3J_{PH}$ 10Hz, 2xOCH_3), 4.59-4.62 (1H, dd, *J* 6Hz, OH), 4.71-4.75 (1H, ddd, *J* 6, $^2J_{PH}$ 19Hz, CH), 6.30-6.37 (1H, ddd, $^3J_{PH}$ 6, J_{trans} 16Hz, HC=), 6.77-6.83 (1H, ddd, $^4J_{PH}$ 5Hz, J_{trans} 16Hz, PhHC=), 7.23-7.41 (5H, m, Ph); **^{13}C NMR** (100MHz, $CDCl_3$): δ 53.6 (d, $^2J_{PC}$ 6Hz, CH_3), 53.8-53.9 (d, $^2J_{PC}$ 8Hz, CH_3), 68.4-70.0 (d, $^1J_{PC}$ 161Hz, CH), 123.5, 126.6, 127.9, 128.5, 132.4-132.6 (d, J_{PC} 13Hz), 136.1; ***m/z*** (FAB): 265 (MNa^+, 19%), 243 (MH^+, 13%), 225 ($[M\text{-}OH]^+$, 100%); **HRMS** (FAB) for $C_{11}H_{15}O_4PNa$: Requires 265.0606, Found 265.0594.

Reaction of dimethyl phosphite and cinnamaldehyde (177)[160]

Titanium 3,4-di-O-benzyl-D-mannitol trimer (**101**) (244mg, 0.2mmol) in DCM (1.75mL) was added freshly distilled cinnamaldehyde (0.13mL, 1mmol) followed by dimethyl phosphite (0.11mL, 1.2mmol). The reaction was placed into the freezer (–10°C approx.) for 18h. The reaction was quenched with distilled water (10mL) and the mixture was extracted with DCM (3x10mL). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed (SiO_2, ethyl acetate) to afford *(1-hydroxy-3-phenyl-2(E)-propenyl) phosphonic acid dimethyl ester* (**176**) (65mg, 27%) as a white solid; $[\alpha]_D^{23}$ =–1.7° (c=1, $CHCl_3$), lit.,[190] $[\alpha]_D^{23}$ =–46° (c=1, $CHCl_3$).

Reaction of dimethyl phosphite and benzaldehyde (178)[160]

(**178**)

Titanium(IV) isopropoxide (0.23mL, 0.78mmol) in DCM (7mL) was added freshly distilled benzaldehyde (0.4mL, 4mmol). The reaction was cooled to –20°C then dimethyl phosphite (0.43mL, 4.8mmol) was added. The reaction was stirred for 18h. The reaction was quenched with distilled water (20mL) and the mixture was extracted with DCM (3x40mL). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed (SiO_2, ethyl acetate) to afford *dimethyl hydroxy (phenyl) methyl phosphonate* (**178**) (190mg, 22%) as a white solid; **m.p.** 91-93°C, lit., [191] 100-101°C; **IR** (KBr disc/cm^{-1}): $\tilde{\nu}_{max}$ 3265.1, 2957.2, 2362.9, 1492.1, 1458.3, 1207.2, 1053.7, 1028.1, 861.7, 834.0, 790.5, 777.5, 700.3, 653.9, 553.1; **^{1}H NMR** (400MHz, $CDCl_3$): δ 3.64-3.66 (3H, d, $^3J_{PH}$ 10Hz, OCH_3), 3.68-3.71 (3H, d, $^3J_{PH}$ 10Hz, OCH_3), 5.02-5.05 (1H, d, $^2J_{PH}$ 11Hz, CH), 7.29-7.38 (3H, m, Ph), 7.45-7.49 (2H, m, Ph); **^{13}C NMR** (100MHz, $CDCl_3$): δ 53.7-53.9 (dd, 2xCH_3), 69.8-71.4 (d, $^1J_{PC}$ CH), 126.9 (Ph), 128.3

(Ph), 128.4 (Ph), 136.0 (Ph); ***m/z*** (FAB): 239 (MNa^+, 52%), 217 (MH^+, 66%), 199 ([M-OH]$^+$, 53%); **HRMS** (FAB) for $C_9H_{14}O_4P$: Requires 217.0630, Found 217.0622.

Reaction of dimethyl phosphite and benzaldehyde (179)[160]

Titanium 3,4-di-O-benzyl-D-mannitol trimer (**101**) (239mg, 0.2mmol) in DCM (1.75mL) was added freshly distilled benzaldehyde (0.1mL, 1mmol). The reaction was cooled to –20°C then dimethyl phosphite (0.11mL, 1.2mmol) was added. The reaction was stirred for 18h. The reaction was quenched with distilled water (10mL) and the mixture was extracted with DCM (3x10mL). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed (SiO_2, ethyl acetate) to afford benzaldehyde and an unknown compound.

Reaction of dimethyl phosphite and benzaldehyde (180)[161a]

Titanium(IV) isopropoxide (0.2mL, 0.65mmol) in toluene (3.3mL) was cooled to 0°C. Dimethyl phosphite (0.45mL, 3.9mmol) in toluene (4mL) was added. The reaction was stirred for 30min, then freshly distilled benzaldehyde (0.33mL, 3.3mmol) was added. The reaction was stirred for 15h and quenched with $NaHCO_{3(sat)}$ (20mL) and the mixture was extracted with DCM (3x40mL). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed (SiO_2, ethyl acetate) to afford *dimethyl hydroxy (phenyl) methyl phosphonate* (**178**) (342mg, 48%) as a white solid.

Reaction of dimethyl phosphite and benzaldehyde (181)[161a]

Titanium 3,4-di-O-benzyl-D-mannitol trimer (**101**) (264mg, 0.65mmol) in toluene (3.3mL) was cooled to 0°C. Dimethyl phosphite (0.45mL, 3.9mmol) in toluene (4mL) was added. The reaction was stirred for 30min, then freshly distilled benzaldehyde (0.33mL, 3.3mmol) was added. The reaction was stirred for 15h and quenched with $NaHCO_{3(sat)}$ (20mL) and the mixture was extracted with DCM (3x40mL). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed (SiO_2, ethyl acetate) to afford *dimethyl hydroxy (phenyl) methyl phosphonate* (**178**) (22mg, 3%) as a

white solid; $[\alpha]_D^{23}$ =–0.2° (c=1, $CHCl_3$), lit.,[191] for dimethyl-(*S*)-hydroxy(phenyl)methyl phosphonate $[\alpha]_D^{23}$ =–46° (c=1, $CHCl_3$).

Reaction of dimethyl phosphite and benzaldehyde (182)[161a]

Titanium 3,4-di-O-benzyl-D-mannitol trimer (**101**) (264mg, 0.65mmol) in toluene (3.3mL) was cooled to 0°C. Dimethyl phosphite (0.45mL, 3.9mmol) in toluene (4mL) was added. The reaction was stirred for 30min, then freshly distilled benzaldehyde (0.33mL, 3.3mmol) was added. The reaction was stirred for 15h and quenched with $NaHCO_{3(sat)}$ (20mL) and the mixture was extracted with DCM (3x40mL). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed (SiO_2, ethyl acetate) to afford *dimethyl hydroxy (phenyl) methyl phosphonate* (**178**) (45mg, 6%) as a white solid; $[\alpha]_D^{23}$ =–2.6° (c=1, $CHCl_3$).

Reaction of dimethyl phosphite and benzaldehyde (185)[162]

Trimethyl silyl chloride (0.5mL, 3.9mmol) was added to a stirred solution of dimethyl phosphite (0.45mL, 3.9mmol) and triethylamine (0.54mL, 3.9mmol) in toluene (10mL) maintained at 0°C. After 10min, *titanium 3,4-di-O-benzyl-D-mannitol trimer* (**101**) (264mg, 0.65mmol) in toluene (10mL) was added to the dimethyl phosphite mixture. The reaction was stirred for 30min and the solution was cooled to –20°C. Benzaldehyde (0.33mL, 3.3mmol) was added. The reaction was stirred for 15h and quenched water (30mL) and the mixture was extracted with DCM (3x60mL). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed (SiO_2, ethyl acetate) to afford *dimethyl hydroxy (phenyl) methyl phosphonate* (**178**) (37mg, 5%) as a white solid; $[\alpha]_D^{23}$ =–2° (c=1, $CHCl_3$).

Reaction of dimethyl phosphite and benzaldehyde (186)[162]

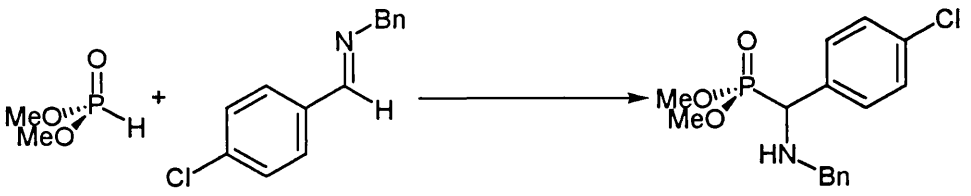
Trimethyl silylchloride (0.5mL, 3.9mmol) was added to a stirred solution of dimethyl phosphite (0.45mL, 3.9mmol) and triethylamine (0.54mL, 3.9mmol) in THF (5mL) maintained at 0°C. After 10min, *titanium 3,4-di-O-benzyl-D-mannitol trimer* (**101**) (264mg, 0.65mmol) in THF (5mL) was added to the dimethyl phosphite mixture. The reaction was stirred for 30min and the solution was cooled to -20°C. Benzaldehyde (0.33mL, 3.3mmol) was added. The reaction was stirred for 15h and quenched distilled water (30mL) and the mixture was extracted with DCM (3x60mL). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed (SiO_2, ethyl acetate) to afford *dimethyl hydroxy (phenyl) methyl phosphonate* (**178**) (144mg, 20%) as a white solid. $[\alpha]_D^{23}$ =–2.7° (c=1, $CHCl_3$)

Reaction of dimethyl phosphite and benzaldehyde (187)[162]

Trimethyl silylchloride (0.5mL, 3.9mmol) was added to a stirred solution of dimethyl phosphite (0.45mL, 3.9mmol) and triethylamine (0.54mL, 3.9mmol) in THF (5mL) maintained at 0°C. After 10min, *titanium 3,4-di-O-benzyl-D-mannitol trimer* (**101**) (264mg, 0.65mmol) in THF (5mL) was added to the dimethyl phosphite mixture. The reaction was stirred for 30min at 0°C. Benzaldehyde (0.33mL, 3.3mmol) was added. The reaction was stirred for 19h and quenched water (30mL) and the mixture was extracted with DCM (3x60mL). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed (SiO_2, ethyl acetate) to afford *dimethyl hydroxy (phenyl) methyl phosphonate* (**178**) (155mg, 22%) as a white solid. $[\alpha]_D^{23}$ =–3.4° (c=1, $CHCl_3$)

Attempted reaction of dimethyl phosphite and

***N*-(4-chlorobenzylidene) benzylamine (183)**[160]



(183)

N-(4-chlorobenzylidene) benzylamine (209mg, 0.9mmol) in DCM (1.75mL) was added titanium(IV) isopropoxide (60μL, 0.2mmol) followed by dimethyl phosphite (0.11mL,1.2mmol). The reaction was placed into the freezer (–10°C) for 18h. The reaction was quenched with water (10mL) and the mixture was extracted with DCM (3x10mL). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed (SiO_2, ethyl acetate) to afford 2 UNKNOWN compounds with no methyl phosphite signals (NMR).

Attempted reaction of dimethyl phosphite and

***N*-(4-chlorobenzylidene) benzylamine (184)**[160]

N-(4-chlorobenzylidene) benzylamine (209mg, 0.9mmol) in DCM (1.75mL) was added *titanium 3,4-di-O-benzyl-D-mannitol trimer* (**101**) (244mg, 0.2mmol) followed by dimethyl phosphite (0.11mL,1.2mmol). The reaction was placed into the freezer (–10°C) for 18h. The reaction was quenched with distilled water (10mL) and the mixture was extracted with DCM (3x10mL). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed (SiO_2, ethyl acetate) to afford 2 UNKNOWN compounds with no methyl phosphite signals (NMR).

Reaction of dimethyl phosphite and *N*-(4-chlorobenzylidene) benzylamine (188)[162]

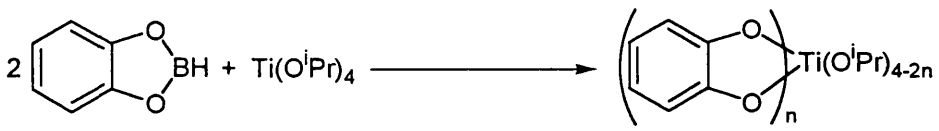
Trimethyl silylchloride (0.35mL, 2.78mmol) was added to a stirred solution of dimethyl phosphite (0.23mL, 2.53mmol) and triethylamine (0.39mL, 2.78mmol) in DCM (40mL) maintained at 0°C. *N*-(4-chlorobenzylidene) benzylamine (546mg, 2.38mmol) was added after 15min and the solution was warmed to room temperature and stirred for 22h. The reaction was poured into distilled water (50mL). The mixture was extracted with DCM (3x75mL), dried over Na_2SO_4 and concentrated *in vacuo*. Chromatography (SiO_2, EtOAc) afforded *dimethyl[α-(benzylamino)-p-chlorobenzyl]phosphonate* (**183**) (395mg, 48%) as an off-white solid; **m.p.** 87-89°C; **IR** (KBr disc/cm^{-1}): $\tilde{\nu}_{max}$ 3291.1, 3026.2, 2954.5, 2857.4, 2345.8, 1492.1, 1241.3, 1188.0, 1125.6, 1092.5, 1062.1, 1029.2, 834.8, 781.7, 758.6, 744.0, 698.0, 568.5; **^{1}H NMR** (400MHz, $CDCl_3$): δ 3.50-3.54 (1H, AB d, J_{AB} 13Hz, CH_2Ph), 3.57-3.58 (3H, dd *J* 2Hz, $^3J_{PH}$ 11Hz, OCH_3), 3.60-3.61 (3H, dd *J* 2Hz, $^3J_{PH}$ 11Hz, OCH_3), 3.77-3.81 (1H, AB d, J_{AB} 13Hz, CH_2Ph), 4.00-4.06 (1H, dd, *J* 1, $^2J_{PH}$ 20Hz, CH), 7.23-7.37 (9H, m, Ph and *p*-Cl phenyl) ; **^{13}C NMR** (100MHz, $CDCl_3$): δ 51.0-51.1 (d, J_{PC} 30Hz), 53.4-53.5 (d, J_{PC} 17Hz), 57.7-59.3 (d, $^1J_{PC}$ 154Hz, CH), 127.2, 128.2, 128.4, 128.5, 128.8, 129.8, 133.8-134.0 (d, J_{PC} 20Hz), 138.8.

Reaction of dimethyl phosphite and *N*-(4-chlorobenzylidene) benzylamine (189)[162]

Trimethyl silylchloride (0.12mL, 1.1mmol) was added to a stirred solution of dimethyl phosphite (90μL, 1mmol) and triethylamine (0.14mL, 1.1mmol) in DCM (20mL) maintained at 0°C. After 20min, the mixture was transferred to a solution containing *N*-(4-chlorobenzylidene) benzylamine (216mg, 1mmol) and *titanium 3,4-di-O-benzyl-D-mannitol* (**101**) (81mg, 0.07mmol), cooled to -20°C. The reaction was stirred for 19h and quenched with water (50mL). The mixture was extracted with DCM (3x75mL), dried over Na_2SO_4 and concentrated *in vacuo*. Chromatography (SiO_2, ethyl acetate) afforded *dimethyl[α-(benzylamino)-p-chlorobenzyl]phosphonate* (**183**) (179mg, 56%) as an off-white solid. $[\alpha]_D^{23}$ =–1.2° (c=1, $CHCl_3$)

3.15 NMR Experiments

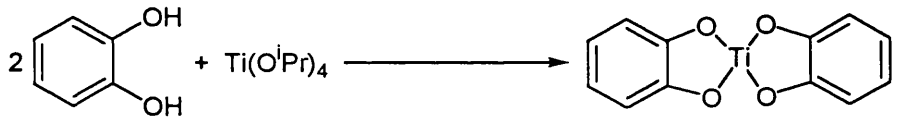
Attempted preparation of titanium catecholates (194)



(194)

Catecholborane (0.2mL, 2mmol) in DCM (2mL) was added titanium(IV) isopropoxide (0.3mL, 1mmol) and stirred for 30min. The reaction was concentrated *in vacuo* and the residue was analysed using NMR spectroscopy. **^{1}H NMR** (300MHz, d^6-DMSO): δ 1.02-1.10 (2xCH_3, ^{i}Pr), 3.72-3.81 (CH, ^{i}Pr), 4.23-4.35 (m), 6.10-6.6.15 (m, Catechol-Ti), 6.31-6.47 (m, Catechol-Ti).

Attempted preparation of titanium dicatecholate (195)



(195)

Catechol (220mg, 2mmol) in DCM (2mL) was added titanium(IV) isopropoxide (0.3mL, 1mmol) and stirred for 30min. The reaction was concentrated *in vacuo* and the residue was analysed using NMR spectroscopy and mass spectroscopy. **^{1}H NMR** (300MHz, d^6-DMSO): δ 1.02-1.04 (2xCH_3, ^{i}Pr), 3.72-3.81 (CH, ^{i}Pr), 6.09-6.15 (m, Ar of catechol-Ti), 6.40-6.6.46 (m, Ar of catechol-Ti), 6.57-6.59 (m, Catechol), 6.69-6.73 (m, Catechol); ***m/z*** (FAB): 307 ($[(C_6H_4O_2)_2Ti+Na+2H+H_2O]^+$, 22%), 289 ($[(C_6H_4O_2)_2Ti+Na+2H]^+$, 10%), 154 ($C_6H_4O_2Na_2^+$, 100%); ***m/z*** (CI): 214 (16%), 182 (21%), 173 (45%), 139 (100%), 109 ($C_6H_4O_2H^+$, 65%).

Attempted NMR experiment (196)

Catecholborane (1M in DCM)		**Titanium 3,4-di-*O*-benzyl-*D*-mannitol trimer (101)**		**3,5-dinitrobenzoic acid**	
mmol	mL	mmol	mg	mmol	mg
0.2	0.2	0.2	224	0.2	43
0.4	0.4	0.2	224	0.4	86
0.6	0.6	0.2	224	0.6	129

Titanium 3,4-di-O-benzyl-D-mannitol trimer (**101**) (244mg, 0.2mmol) in DCM (5mL) in three flasks was added the corresponding amount of catecholborane (1M DCM) as shown on table. The reaction was stirred at room temperature for 20 min. The corresponding amount of 3,5-dinitrobenzoic acid was added to quench the reaction as shown on table. The reaction was concentrated for crude NMR analysis.

1 equivalent of catecholborane to titanium:

^{1}H NMR (300MHz, d^6-DMSO): δ 3.35-4.09 (m, maybe mannitol protons), 4.51-4.88 (m. maybe mannitol protons), 6.11-6.14 (m, Catechol-Ti), 6.42-6.47 (m, Catechol-Ti), 7.22-7.31 (m, Ar), 8.90 (s, Ar of NO_2), 9.01 (s, Ar of NO_2); ***m/z*** (FAB): No peaks detected; ***m/z*** (CI): 375 (9%), 363 ($C_{20}H_{27}O_6^+$, 31%), 285 (27%), 213 (42%), 199 (51%), 181 ($C_{10}H_{13}O_3^+$, 100%).

2 equivalents of catecholborane to titanium:

^{1}H NMR (300MHz, d^6-DMSO): δ 3.39-4.09 (m, maybe mannitol protons), 4.51-4.76 (m, maybe mannitol protons), 6.11-6.14 (m, Catechol-Ti), 6.42-6.45 (m Catechol-Ti), 7.12-7.33 (m, Ar), 8.90 (s, Ar of NO_2), 9.01 (s, Ar of NO_2); ***m/z*** (FAB): No peaks detected; ***m/z*** (CI): 519 (6%), 363 ($C_{20}H_{27}O_6^+$, 33%), 237 (18%), 181 ($C_{10}H_{13}O_3^+$, 100%).

3 equivalents of catecholborane to titanium:

^{1}H NMR (300MHz, d^6-DMSO): δ 3.35-4.09 (m, maybe mannitol protons), 4.51-4.76 (m, maybe mannitol protons), 6.11-6.14 (m, Catechol-Ti), 6.42-6.45 (m, Catechol-Ti), 7.22-7.30 (m, Ar), 8.90 (s, Ar of NO_2), 9.01 (s, Ar of NO_2); ***m/z*** (FAB): No peaks detected; ***m/z*** (CI): 385 (20%), 363 ($C_{20}H_{27}O_6^+$, 71%), 285 (31%), 213 (47%), 181 ($C_{10}H_{13}O_3^+$, 100%), 173 (79%), 136 (57%).

All three NMR spectra are almost identical.

Attempted NMR experiment (197)[368]

Titanium trimer (101)		**Catechol-borane (1M in DCM)**		**Acetophenone**		**Catechol-borane (1M in DCM)**		**3,5-dinitrobenzoic acid**	
mmol	mg	mmol	mL	mmol	mL	mmol	mL	mmol	mg
0.2	244	0.2	0.2	1	0.12	0.8	0.8	1	212
0.2	244	0.4	0.4	1	0.12	0.6	0.6	1	212
0.2	244	0.6	0.6	1	0.12	0.4	0.4	1	212

Titanium 3,4-di-O-benzyl-D-mannitol trimer (**101**) (244mg, 0.2mmol) in DCM (5mL) in three flasks was cooled to –20°C. Catecholborane (1M DCM) was added to each flask, as shown on the second column of the table, and stirred for 20 min. Acetophenone (0.12mL, 1mmol) was added followed by the remaining amount of catecholborane (1M in DCM), as shown on the fourth column of the table. The reaction was stirred overnight and quenched with 3,5-dinitrobenzoic acid (212mg, 1mmol). The reaction was concentrated for crude NMR analysis; **Chiral GC**: 1:1 trimer:CatBH 56%ee. SM:prod 1.0:2.7; 1:2 trimer:CatBH 56%ee, SM:prod 1.0:2.8; 1:3 trimer:CatBH 54%ee, SM:prod 1.0-2.7.

1 equivalent of catecholborane to titanium:

^{1}H NMR (300MHz, d^6-DMSO): δ 1.29-1.31 (d, Me of 1-phenylethanol), 2.57 (s, Me of acetophenone), 3.82-3.84 (d), 4.04-4.07 (d), 4.51-4.61 (m), 4.66-4.73 (q, CH of 1-phenylethanol), 6.11-6.14 (m, Catechol-Ti), 6.42-6.46 (m, Catechol-Ti), 6.57-6.60 (m, Catechol), 6.69-6.73 (m, Catechol), 7.17-7.36 (m, Ar), 7.48-7.54 (m), 7.60-7.65 (m), 7.93-7.96 (m), 8.27 (br.s), 8.89-8.90 (s, Ar of NO_2), 9.00-9.01 (s, Ar of NO_2).

2 equivalents of catecholborane to titanium:

^{1}H NMR (300MHz, d^6-DMSO): See above

3 equivalents of catecholborane to titanium:

^{1}H NMR (300MHz, d^6-DMSO): See above

All three NMR spectra are almost identical.

Titanium 3,4-di-O-benzyl-D-mannitol trimer (**101**): **^{1}H NMR** (300MHz, d^6-DMSO): δ 3.78-3.80 (6H, d, *J* 6Hz, 3x3-H and 3x4-H), 4.22-4.24 (6H, d, *J* 6Hz, 3x1-H, 3x6-H), 4.59-4.62 (6H, AB d, J_{AB} 11Hz, 3xCH_2), 4.70-4.44 (6H, AB d, J_{AB} 11Hz, 3xCH_2), 4.88-4.94 (6H, dd, *J* 10Hz, 3x1-H and 3x6-H), 5.10-5.12 (6H, m, 3x2-H and 3x5-H), 7.14-7.32 (30H, m, 6xPh).

Low temperature ^1H NMR of titanium 3,4-di-O-benzyl-D-mannitol trimer (101)

At ambient temperature: ^1H NMR (400MHz, $CDCl_3$): δ 3.73-3.75 (6H, dd, *J* 2, 7Hz, 3x3-H and 3x4-H), 4.42-4.45 (6H, dd, *J* 4, 10Hz, 3x1-$H_{(trans)}$, 3x6-$H_{(trans)}$), 4.57-4.59 (6H, AB d, J_{AB} 11Hz, 3xCH_2), 4.81-4.84 (6H, AB d, J_{AB} 11Hz, 3xCH_2), 4.88-4.94 (6H, dd, *J* 10Hz, 3x1-$H_{(cis)}$ and 3x6-$H_{(cis)}$), 5.03-5.09 (6H, m, 3x2-H and 3x5-H), 7.14-7.32 (30H, m, 6xPh)

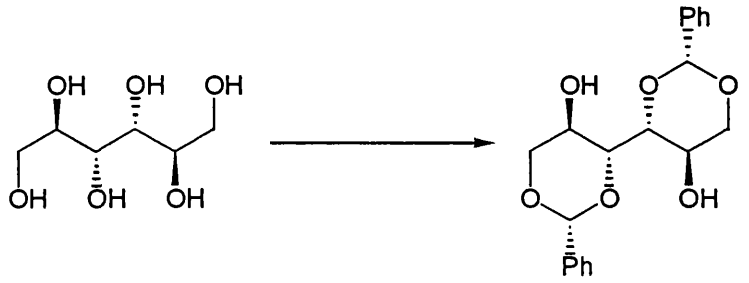
At −20°C: ^1H NMR (400MHz, $CDCl_3$): δ 3.74-3.77 (6H, dd, 3x3-H and 3x4-H), 4.42-4.47 (6H, dd, 3x1-$H_{(trans)}$, 3x6-$H_{(trans)}$), 4.57-4.61 (6H, AB d, 3xCH_2), 4.81-4.83 (6H, AB d, 3xCH_2), 7.14-7.32 (30H, m, 6xPh), 4.91-4.97 (6H, dd, 3x1-$H_{(cis)}$ and 3x6-$H_{(cis)}$), 5.03-5.10 (6H, m, 3x2-H and 3x5-H), 7.15-7.32 (30H, m, 6xPh)

At −40°C: ^1H NMR (400MHz, $CDCl_3$): δ 3.75-3.78 (6H, dd, 3x3-H and 3x4-H), 4.42-4.48 (6H, dd, 3x1-$H_{(trans)}$, 3x6-$H_{(trans)}$), 4.58-4.61 (6H, AB d, 3xCH_2), 4.82-4.85 (6H, AB d, 3xCH_2), 4.93-4.99 (6H, dd, 3x1-$H_{(cis)}$ and 3x6-$H_{(cis)}$), 5.03-5.10 (6H, m, 3x2-H and 3x5-H), 7.15-7.33 (30H, m, 6xPh)

At −60°C: ^1H NMR (400MHz, $CDCl_3$): δ 3.77-3.79 (6H, dd, 3x3-H and 3x4-H), 4.44-4.48 (6H, dd, 3x1-$H_{(trans)}$, 3x6-$H_{(trans)}$), 4.59-4.61 (6H, AB d, 3xCH_2), 4.81-4.85 (6H, AB d, 3xCH_2), 4.95-5.01 (12H, m, 3x1-$H_{(cis)}$ and 3x6-$H_{(cis)}$, 3x2-H and 3x5-H), 7.14-7.32 (30H, m, 6xPh).

3.16 Synthesis of other Ligands and Metal Complexes

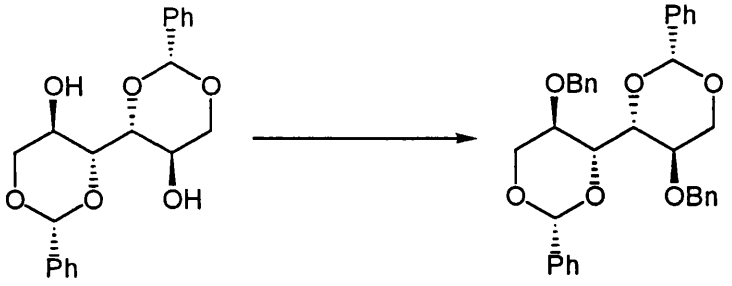
Preparation of 1,3:4,6-di-O-benzylidene-D-mannitol (200)[166]



(200)

To a stirred solution of D-mannitol (25g, 137mmol) in DMF (75mL) was added benzaldehyde (30mL, 295mmol) and H_2SO_4 (5mL, 150mmol). The reaction was stirred for 4day at room temperature and poured into a mixture of ice:water:hexane (150g:50mL:125mL) containing K_2CO_3 (7.5g, 54mmol). The mixture was stirred for 4h and the solids were filtered and washed with PE 30-40 then dissolved in EtOAc. The organic phase was washed with water (3x250mL), dried over $MgSO_4$ and concentrated *in vacuo* to give a white solid. The crude product was recrystallised from MeOH to afford *1,3:4,6-di-O-benzylidene-D-mannitol* (**200**) (13.84g, 28%) as a white solid; **m.p.** 142-151°C, lit.,[166] 192-199°C; $[\alpha]_D^{23}$ =–9.1°, (c=1, acetone), lit.,[166] $[\alpha]_D^{23}$ =–9.1° (c=1, acetone); **IR** (KBr disc/cm^{-1}): $\tilde{\nu}_{max}$ 3482.6, 2979.9, 2957.3, 2858.7, 1496.0, 1449.8, 1364.8, 1311.8, 1225.4, 1162.1, 1050.0, 971.8, 927.4, 779.5, 748.0, 699.7, 651.4, 631.8; **^{1}H NMR** (400MHz, $CDCl_3$): δ 2.96 (2H, br.s, 2xOH), 3.61-3.66 (2H, dd, *J* 11 Hz, 1-$H_{(cis)}$ and 6-$H_{(cis)}$), 4.13-4.24 (4H, m, 2-H 3-H 4-H 5-H), 4.35-4.39 (2H, dd, *J* 5, 11Hz, 1-$H_{(trans)}$ and 6-$H_{(trans)}$), 5.49 (2H, s, 2xCHPh), 7.35-7.38 (6H, m, Ph), 7.43-7.46 (4H, m, Ph); **^{13}C NMR** (100MHz, $CDCl_3$): δ 61.5, 70.5, 80.4, 101.5, 125.9 (Ph), 128.4 (Ph), 129.3 (Ph), 136.9 (Ph); ***m/z*** (FAB): 381 (MNa^+, 32%), 359 (MH^+, 100%); **HRMS** (FAB) for $C_{20}H_{23}O_6$: Requires 359.1495, Found 359.1488.

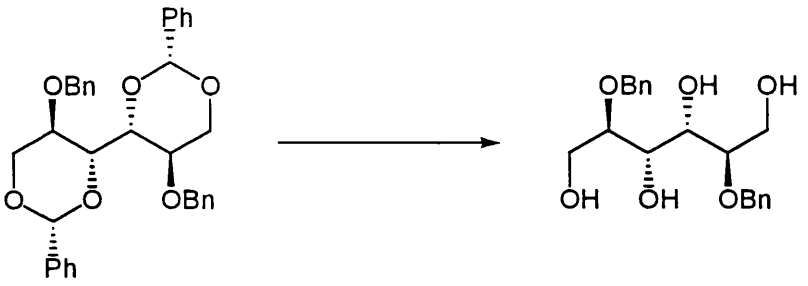
Preparation of 2,5-di-O-benzyl-1,3:4,6-di-O-benzylidene-D-mannitol (230)[166]



(200) **(230)**

1,3:4,6-di-O-benzylidene-D-mannitol (**200**) (10g, 28mmol) dissolved in DMF (100mL) was added dropwise to a solution of sodium hydride (60% dispersion in mineral oil, 5g, 125mmol) in DMF (50mL) over a period of 20min. Benzyl bromide (8.3mL, 70mmol) was added to the reaction over 10min. The reaction was stirred for a further 30min and was quenched with MeOH. Partition with ether/H_2O, the organic layer was separated. The aqueous layer was extracted with ether (2x200mL). The combined organic extracts were washed with water (200mL) and brine (200mL). The ether extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Recrystallisation with ether/PE 30-40 afforded *2,5-di-O-benzyl-1,3:4,6-di-O-benzylidene-D-mannitol* (**230**) (11.5g, 72%) as white crystalline solids; **m.p.** 99-104°C, lit.,[166] 102-103°C; $[\alpha]_D^{23}$=–46.6°, (c=1, acetone), lit.,[166] $[\alpha]_D^{23}$=–36.6° (c=1, $CHCl_3$); **IR** (KBr disc/cm^{-1}): $\tilde{\nu}_{max}$ 3036.8, 2919.2, 2872.1, 1496.2, 1456.3, 1420.8, 1373.3, 1317.0, 1277.7, 1255.0, 1172.1, 1099.9, 1026.5, 914.1, 746.1, 697.6, 604.2; **^{1}H NMR** (400MHz, $CDCl_3$): δ 3.63-3.68(2H, dd, *J* 10Hz, 1-$H_{(cis)}$ and 6-$H_{(cis)}$), 3.95-4.01(2H, ddd, *J* 5, 10Hz, 2-H and 5-H), 4.05-4.06(2H, d, *J* 9Hz, 3-H and 4-H), 4.31-4.35(2H, dd, *J* 5, 10Hz, 1-$H_{(trans)}$ and 6-$H_{(trans)}$), 4.53-4.60(4H, AB dd, J_{AB} 12Hz, 2xCH_2), 5.39(2H, s, 2xCHPh), 7.20-7.25(10H, m, 2xPh), 7.32-7.35(6H, m, Ph), 7.41-7.45(4H, m, Ph); **^{13}C NMR** (100MHz, $CDCl_3$): δ 66.7, 69.6, 72.6, 77.2, 100.9, 126.2 (Ph), 127.9 (Ph), 128.0 (Ph), 128.1 (Ph), 128.4 (Ph), 128.8 (Ph), 137.6 (Ph), 137.8 (Ph); ***m/z*** (FAB): 539 (MH^+, 14%); **HRMS** (FAB) for $C_{34}H_{35}O_6$: Requires 539.2434, Found 539.2450.

Preparation of 2,5-di-O-benzyl-D-mannitol (198)[167]



(230) **(198)**

1,3:4,6-di-O-benzylidene-2,5-di-O-benzyl-D-mannitol (**230**) (8g, 14.9mmol) in EtOH (55mL) and H_2O (65mL) was added HCl (9.5mL). The mixture was heated to reflux at 100°C for 8h. The reaction was quenched with $NaHCO_{3(sat.)}$ and extracted with EtOAc (3x150mL). The organic extracts were washed with brine (200mL) and dried over $MgSO_4$. The organic phase was concentrated *in vacuo* and recrystallised from MeOH/PE 30-40 to afford *2,5-di-O-benzyl-D-mannitol* (**198**) (3.96g, 74%) as a white solid; **m.p.** 112-115°C, lit.,[167] 119-120°C; $[\alpha]_D^{23}$ =–26.7°, (c=1, acetone), lit.,[167] $[\alpha]_D^{23}$ =–7.7° (c=1.4, EtOH); **IR** (KBr disc/cm^{-1}): $\tilde{\nu}_{max}$ 3471.6, 3380.0, 3271.8, 2920.0, 1452.5, 1470.1, 1307.9, 1097.8, 1025.9, 850.9, 739.4, 699.5; **^{1}H NMR** (400MHz, $CDCl_3$): δ 3.56-3.62 (2H, m, 2-H & 5-H), 3.74-3.84 (4H, m, 2x1-H & 2x6-H), 3.93-3.96 (2H, d, *J* 6Hz, 3-H & 4-H), 4.53-4.56 (2H, AB d, J_{AB} 11Hz, CH_2), 4.61-4.64 (2H, AB d, J_{AB} 11Hz, CH_2), 7.26-7.33 (10H, m, 2xPh); **^{13}C NMR** (100MHz, $CDCl_3$): δ 61.2, 69.8, 72.6, 79.6, 128.1 (Ph), 128.2 (Ph), 128.6 (Ph), 137.6 (Ph); ***m/z*** (FAB): 385 (MNa^+, 70%), 363 (MH^+, 19%); **HRMS** (FAB) for $C_{20}H_{26}O_6Na$: Requires 385.1627, Found 385.1640.

Attempted synthesis of titanium 2,5-di-O-benzyl-D-mannitol complex (205)

2,5-Di-O-benzyl-D-mannitol (**198**) (1g, 2.76mmol) in toluene (15mL) and hexane (15mL) was refluxed at 100°C. Titanium(IV) isopropoxide (0.82mL, 2.76mmol) was added and the reaction was refluxed for 4h. The reaction was left to cool to room temperature overnight and the solvent was removed *in vacuo*. The residue was taken up in DCM and any insoluble species was filtered off. The resultant solution was concentrated *in vacuo*. The product was precipitated out using ether, as a white solid. The off-white solids were filtered and washed with ether several times to afford an off-white amorphous solid (0.97g) (**113**); ^{1}**H NMR** (400MHz, $CDCl_3$): a series of broad signals were observed at 3.50 to 5.00ppm and 7.00 to 7.50ppm; ***m/z*** (FAB): did not reveal any discrete molecular ions between 200 to 2000. From the recorded data, a polymeric material may have formed and no conclusive structural information could therefore be dedicated with the *titanium 2,5-di-O-benzyl-D-mannitol complex* (**205**)

Attempted reduction of Acetophenone (206)

Titanium 2,5-di-O-benzyl-D-mannitol complex (**205**) (98mg, 0.08mmol) in DCM (10mL) was cooled to –20°C. Acetophenone (59μL, 0.5mmol) was added followed by catecholborane (70μL, 0.55mmol). The reaction was monitored using TLC. The reaction was stopped after 18h and quenched with 1N HCl (5mL). The mixture was extracted with ethyl acetate (3x10mL) and washed 1N NaOH (3x10mL). The organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was filtered through a pad of silica with ether and analysed; **Chiral GC**: Only starting material detected.

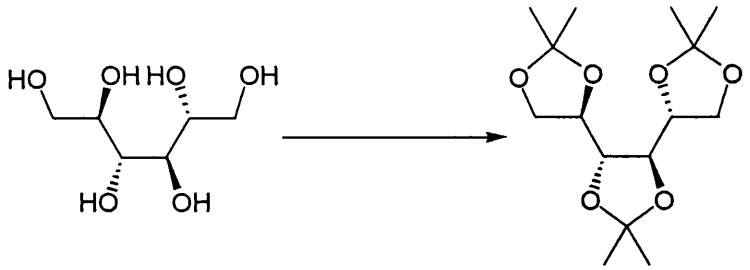
Attempted synthesis of titanium 1,3:4:6-di-O-benzylidene-D-mannitol complex (207)

1,3:4,6-Di-O-benzylidene-D-mannitol (**200**) (0.72g, 2mmol) in toluene (2mL) was added titanium(IV) isopropoxide (1mmol, 0.34mL). The slurry was refluxed for 3h. The reaction was cooled to room temperature and concentrated *in vacuo*. The residue was taken up in DCM, any insoluble species was filtered off. The resultant solution was concentrated *in vacuo*. The product was precipitated out using ether. The off-white solids were filtered and washed several times with ether to afford an off-white amorphous solid (0.45g) (**207**); **^{1}H NMR** (400MHz, $CDCl_3$): δ 3.61-3.66 (2H, dd, *J* 11Hz, 1-$H_{(cis)}$ and 6-$H_{(cis)}$), 4.12-4.15 (2H, d, *J* 9Hz, 3-H and 4-H), 4.15-4.21(2H, m, 2-H and 5-H), 4.35-4.39 (2H, dd, *J* 5, 11Hz, 1-$H_{(trans)}$ and 6-$H_{(trans)}$), 5.49 (2H, s, 2xCHPh), 7.35-7.38 (6H, m, Ph), 7.43-7.46 (4H, m, Ph); **^{13}C NMR** (100MHz, $CDCl_3$): δ 61.5, 70.5, 80.4, 101.5, 125.9 (Ph), 128.4 (Ph), 129.3 (Ph), 136.9 (Ph). From the recorded data, starting material may still be present, therefore no conclusive structural information could be dedicated with the *titanium bis-2,5-di-O-benzyl-D-mannitol complex* (**114**).

Attempted reduction of Acetophenone (208)

Titanium bis-1,3:4,6-di-O-benzylidene-D-mannitol complex (**207**) (76mg, 0.1mmol) in DCM (5mL) was cooled to –20°C. Acetophenone (59μL, 0.5mmol) was added followed by catecholborane (70μL, 0.55mmol). The reaction was monitored using TLC. The reaction was stirred overnight and quenched with 1N HCl (5mL). The mixture was extracted with ethyl acetate (3x10mL) and washed 1N NaOH (3x10mL). The organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was filtered through a pad of silica with ether and analysed; **Chiral GC**: trace amounts of racemic product detected.

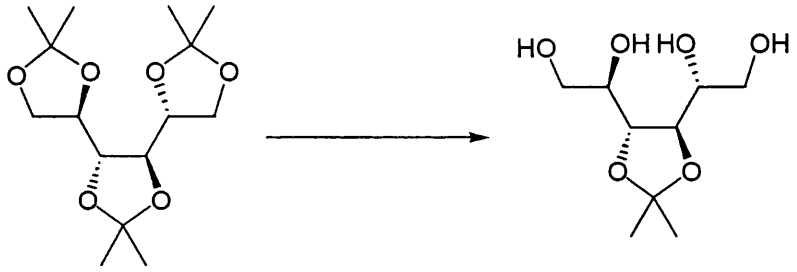
Preparation of 1,2:3,4:5,6-tri-O-isopropylidene-D-mannitol (201)[168]



(201)

D-Mannitol (20g, 0.11mol) in freshly distilled acetone (250mL) was stirred with sulfuric acid (96%) (2mL) for 24hr. The reaction was neutralised with 33% NH_4OH (7mL) and Na_2CO_3 (12.5g). The mixture was filtered and concentrated *in vacuo* afforded a white solid. Recrystallisation from ethanol gave *1,2:3:4,5,6-tri-O-isopropylidene-D-mannitol* (**201**) (8.4g, 26%) as a white solid; **m.p.** 65-68°C, lit.,[168]. 69°C; $[\alpha]_D^{23}$ =+13.1°, (c=1, acetone), lit.,[168] +13.6°, (c=1, CH_2Cl_2); **IR** (KBr disc/cm^{-1}): $\tilde{\nu}_{max}$; **^{1}H NMR** (400MHz, $CDCl_3$): δ 1.33(6H, s, 2xCH_3), 1.37(6H, s, 2xCH_3), 1.40(6H, s, 2xCH_3), 3.92-3.94(2H, dd, *J* 2, 4Hz, 3-H and 4-H), 3.95-3.98(2H, dd, *J* 6, 8Hz, 1-$H_{(cis)}$ and 6-$H_{(cis)}$), 4.04-4.08(2H, dd, *J* 6, 8Hz, 1-$H_{(trans)}$ and 6-$H_{(trans)}$), 4.15-4.20(2H, m, 2-H and 5-H); **^{13}C NMR** (75.4MHz, $CDCl_3$): δ 26.2 (CH_3), 27.4 (CH_3), 28.4 (CH_3), 67.2, 77.2, 80.3, 110.5 (CMe_2), 111.1 (CMe_2); ***m/z*** (FAB): 303 (MH^+, 23%), 287 ($[M-CH_3]^+$, 100%).

Preparation of 3,4-O-isopropylidene-D-mannitol (202)[169]

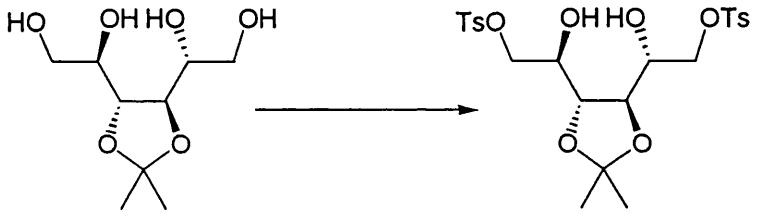


(201) **(202)**

1,2:3:4,5,6-Tri-O-isopropylidene-D-mannitol (**201**) (7.24g, mmol) was stirred in 70% acetic acid (145mL) at 40°C for 1.5hr. The acetic acid was rapidly removed using high vacuum attached to a rotary evaporator at 40°C. Traces of acetic acid was removed by formation

of an azeotrope with cyclohexane. Recrystallisation from acetone afforded *3,4-O-isopropylidene-D-mannitol* (**202**) (3.5g, 79%) as a white solid; **m.p.** 84-87°C, lit.,[169] 90°C; **^{1}H NMR** (400MHz, $CDCl_3$): δ 1.36 (6H, s, 2xCH3), 2.86 (4H, br.s, 4xOH), 3.69-3.73 (4H, m, 2x1-H and 2x6-H), 3.79-3.91 (4H, m, 2-H 3-H 4-H 5-H); **^{13}C NMR** (100MHz, $CDCl_3$): δ 26.8 (Me), 63.9, 72.9, 79.7, 109.6 (CMe_2); ***m/z*** (FAB): 245 (MNa^+, 100%).

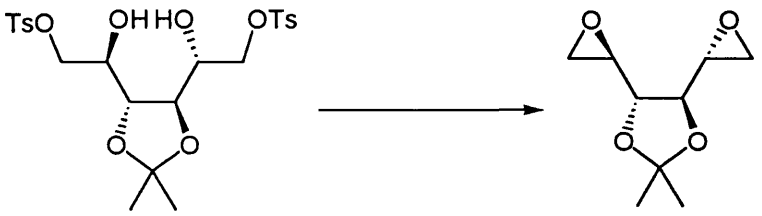
Preparation of 1,6-di-O-tosyl-3,4-O-isopropylidene-D-mannitol (203)[168]



(202) **(203)**

3,4-O-isopropylidene-D-mannitol (**202**) (0.5g, 2.25mmol) in pyridine (7.2mL, 89mmol) was cooled to 0°C. Tosyl chloride (0.88g, 4.62mmol) was added portionwise to the reaction and the stirred for 3.75hr. The reaction was poured into a solution of 6M HCl (29mL) in Et_2O (13.5mL). Excess acid was neutralised with 3% sodium bicarbonate solution (18mL). The mixture was extracted with ether (3x50mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed (SiO_2, ether) to afford *1,6-di-O-tosyl-3,4-O-isopropylidene-D-mannitol* (**203**) (0.56g, 47%) as a white solid; **m.p.** 83-85°C, lit.,[168] 86°C; $[\alpha]_D^{23}$ =+27°, (c=1, $CHCl_3$), lit.,[168] $[\alpha]_D^{23}$ =+24° (c=2.58, CH_2Cl_2); **IR** (KBr disc/cm^{-1}): $\tilde{\nu}_{max}$; **^{1}H NMR** (400MHz, $CDCl_3$): δ 1.23 (6H, s, 2xCH_3), 2.42 (6H, s, 2xCH_3 (Tolyl), 3.72-3.78 (4H, m, 2x1-H and 2x2-H), 4.02-4.06 (2H, dd, *J* 6, 11Hz, 2-H and 5-H), 4.26-4.29 (2H, dd, *J* 2, 8Hz, 3-H and 4-H), 7.31-7.33 (2H, d, *J* 8Hz, *p*-tolyl), 7.76-7.78 (2H, d, *J* 8Hz, *p*-tolyl); **^{13}C NMR** (100MHz, $CDCl_3$): δ ; ***m/z*** (FAB): 553 (MNa^+, 87%), 531 (MH^+, 100%), 515 ($[M-CH_3]^+$, 19%), 265 ($[M/2]^+$, 83%).

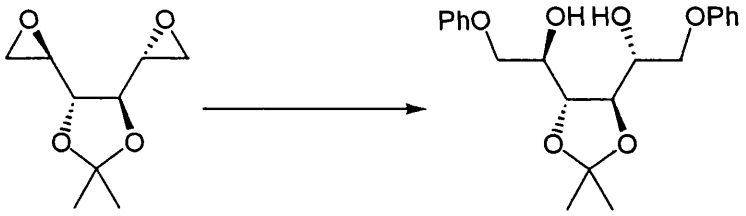
Preparation of 1,2,5,6-di-O-anhydro-3,4-O-isopropylidene-D-mannitol (204)[168]



(203) **(204)**

1,6-Di-O-tosyl-3,4-O-isopropylidene-D-mannitol (**203**) (8.5g, 16mmol) in MeOH (100mL) was added K_2CO_3. The reaction was stirred for 2.5hr. The mixture was diluted with water and extracted with DCM. Washing of extracts with $NH_4Cl_{(sat)}$, drying ($MgSO_4$) and evaporation afforded a syrup. The residue was chromatographed (SiO_2, Et_2O) to afford *1,2,5,6-di-O-anhydro-3,4-O-isopropylidene-D-mannitol* (**204**) (1.6g, 54%) as a colourless oil; $[\alpha]_D^{23}$ =–1.9°, (c=1, $CHCl_3$), lit.[168] $[\alpha]_D^{23}$ =–2.3° (c=2.8, $CHCl_3$); **^{1}H NMR** (400MHz, $CDCl_3$): δ 1.41(6H, s, 2xCH_3), 2.68-2.71(2H, dd, *J* 3, 5Hz, 1-$H_{(trans)}$ and 6-$H_{(trans)}$), 2.80-2.83(2H, dd, *J* 1, 5Hz, 1-$H_{(cis)}$ and 6-$H_{(cis)}$), 3.08-3.11(2H, m, 2-H and 5-H), 3.81-3.81(2H, dd, *J* 1, 3Hz, 3-H and 4-H); **^{13}C NMR** (100MHz, $CDCl_3$): δ 26.5 (Me), 45.0, 51.3, 78.1, 110.2 (CMe_2) ; ***m/z*** (FAB): 187 (MH^+, 23%), 171 ($[M\text{-}CH_3]^+$, 100%).

Preparation of 1,6-di-O-phenyl-3,4-O-isopropylidene-D-mannitol (199)[170]



(204) **(199)**

Phenol (2g, 21.25mmol) in benzene (50mL) was added sodium (0.5g, 21.74mmol) in small lumps, the reaction was stirred until no effervescence. *1,2,5,6-Di-O-anhydro-3,4-O-isopropylidene-D-mannitol* (**204**) (1.6g, 8.6mmol) was added portionwise to the reaction. The reaction was stirred for 18hr and quenched with MeOH. The mixture was diluted in water and extracted with DCM. Washing of extracts with 1N NaOH and water, drying ($MgSO_4$) afforded an off-white solid. The crude mixture was chromatographed (SiO_2,

ether) to afford *1,6-di-O-phenyl-3,4-O-isopropylidene-D-mannitol* (**199**) (2.9g, 90%) as a white solid; **m.p.** 112-113°C, lit.,[170]115°C; $[\alpha]_D^{23}$ =–35.8°, (c=1, $CHCl_3$), lit.,[193] $[\alpha]_D^{23}$ =–44.9° (c=1.52, $CHCl_3$); **^{1}H NMR** (400MHz, $CDCl_3$): δ 1.27(6H, s, 2xCH_3), 3.51(2H, br.s, 2xOH), 3.93-3.97(6H, m, 2x1-H and 2x6-H, 2-H and 5-H), 4.09-4.11(2H,d, *J* 9Hz, 3-H and 4-H), 6.82-6.86(6H, m, 2xPh), 7.13-7.19(4H, m, 2xPh); **^{13}C NMR** (75.4MHz, $CDCl_3$): δ 27.3 (CH_3), 69.8, 72.1, 80.1, 110.3 (CMe_2), 115.1 (Ph), 121.5 (Ph), 129.9 (Ph), 158.9 (Ph); ***m/z*** (FAB): 397 (MNa^+, 13%), 374 (M^+, 27%), 359 ($[M-CH_3]^+$, 18%).

Attempted synthesis of titanium complex from 1,6-di-O-phenyl-3,4-O-isopropylidene-D-mannitol (209)

1,6-di-O-phenyl-3,4-O-isopropylidene-D-mannitol (**199**) (1g, 2.67mmol) in hexane (30mL) and toluene (20mL) was added titanium(IV) isopropoxide (0.8mL. 2.67mmol). The reaction was refluxed for 4h. The mixture was cooled and evaporated to dryness for analysis; **^{1}H** and **^{13}C NMR** revealed that only starting material is present (broad baseline); ***m/z*** (FAB): 1364 (41%), 437 (90%). From the recorded data, starting material may still be present, therefore no conclusive structural information could be dedicated with the *titanium 1,6-di-O-phenyl-3,4-O-isopropylidene-D-mannitol complex* (**209**).

Attempted diethylzinc addition to benzaldehyde (210)[60]

To a stirred solution of *titanium 1,6-di-O-phenyl-3,4-O-isopropylidene-D-mannitol complex* (**209**) (583mg, 1mmol) and titanium(IV) isopropoxide (1.79mL, 6mmol) in toluene (20mL) was added benzaldehyde (0.51mL, 5mmol). The resultant yellow solution was cooled to –25°C, diethylzinc (1M in hexanes, 9mL, 9mmol) was added dropwise to the reaction. The reaction was stirred for 24h and quenched with $NH_4Cl_{(sat)}$ (15mL). The mixture was extracted with ether (3x20mL) and washed with brine. The combined organic extracts was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed (SiO_2, 40% ether in PE 40-60) to afford *1-phenyl-1-propanol* (**165**) (320mg, 59%); See (**152**) for NMR data; Chiral GC: racemic product detected.

Attempted reduction of Acetophenone (211)

Titanium 1,6-di-O-phenyl-3,4-O-isopropylidene-D-mannitol complex (**209**) (63mg, 0.08mmol) in DCM (10mL) was cooled to –20°C. Acetophenone (59μL, 0.5mmol) was added followed by catecholborane (70μL, 0.55mmol). The reaction was monitored using TLC. The reaction was stirred overnight and quenched with 1N HCl (5mL). The mixture was extracted with ethyl acetate (3x10mL) and washed 1N NaOH (3x10mL). The organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was filtered through a pad of silica with ether and analysed; **Chiral GC**: trace amounts of racemic product detected.

Attempted synthesis of lanthanum alkoxide complex from 1,6-di-O-phenyl-3,4-O-isopropylidene-D-mannitol (212)

1,6-di-O-phenyl-3,4-O-isopropylidene-D-mannitol (**199**) (562mg, 1.5mmol) in THF (10mL) was cooled to –78°C. *n*-BuLi (2.47M in hexanes, 1.22mL, 3mmol) was added to the solution and stirred for 30min. A solution of anhydrous lanthanum(III) chloride (123mg, 0.5mmol) in THF (10mL) was added to the lithium alkoxide. The reaction was warmed to room temperature and stirred for 18h. The reaction was concentrated *in vacuo* and analysed using NMR and mass spectrometry; **^{1}H NMR** (400MHz, $CDCl_3$): δ 0.68(br.s), 0.85(br.s), 3.27-3.37(br.m), 4.01(br.s), 4.23-4.33(br.m), 6.78-7.08(m, Ar) (broad peaks); **^{13}C NMR** (75.4MHz, $CDCl_3$): δ 26.0, 27.2, 68.4, 71.7, 78.4, 109.7, 114.8, 122.1, 130.5, 158.9 (fat baseline); ***m/z*** (FAB): .1552 ({4x[M-2H+2Li]+Li}$^+$, 23%), 1166 ({3x[M-2H+2Li]+Li}$^+$, 100%), 779({2x[M-2H+2Li]+Li}$^+$, 12%).

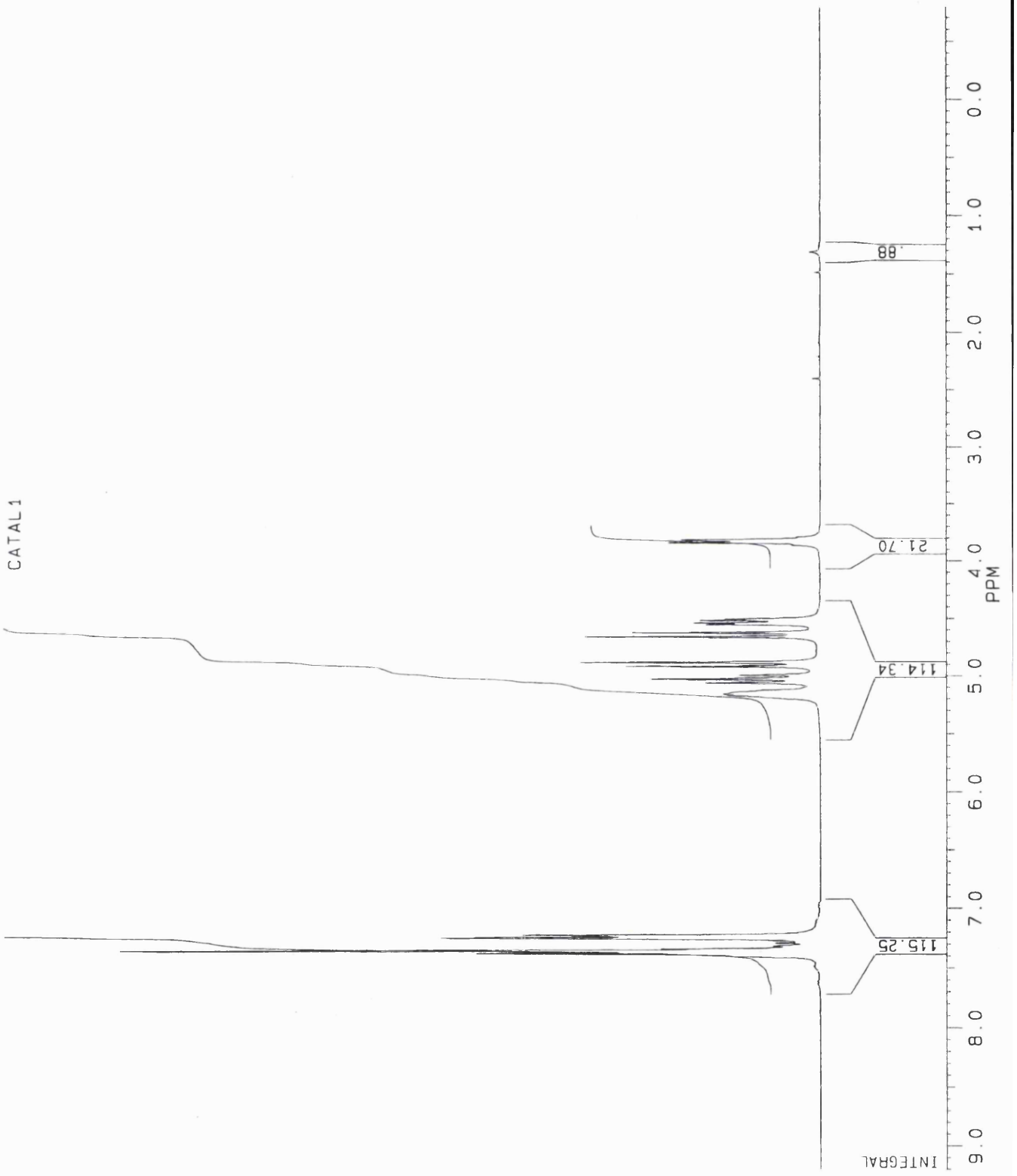
Attempted dimethyl phosphite addition to benzaldehyde using lanthanum alkoxide (213)

Lanthanum 1,6-di-O-phenyl-3,4-O-isopropylidene-D-mannitol complex (**212**) (125mg) in DCM (20mL) was cooled to –20°C. Dimethyl phosphite (0.2mL, 2.2mmol) was added. The reaction was stirred for 30min, then benzaldehyde (0.2mL, 2mmol) was added. The mixture was stirred for 15h and quenched with $NaHCO_{3(sat)}$ (20mL) and the mixture was extracted with DCM (3x40mL). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed (SiO_2, ethyl acetate) to afford *dimethyl hydroxy (phenyl) methyl phosphonate* (**178**) (241mg, 56%) as a white solid; $[\alpha]_D^{23}$ =–5.6° (c=1, $CHCl_3$); **GC:** Mosher's ester derivatisation gave 4%de.

Attempted dimethyl phosphite addition to benzaldehyde using lanthanum alkoxide (214)

Trimethylsilyl chloride (0.26mL, 2.2mmol) was added to a stirred solution of dimethyl phosphite (0.2mL, 2.2mmol) and triethylamine (0.3mL, 2.2mmol) in DCM (10mL) maintained at 0°C. After 10min, *Lanthanum (1,6-di-O-phenyl-3,4-O-isopropylidene-D-mannitol) complex* (**212**) (125mg) in DCM (10mL) was added to the dimethyl phosphite mixture. The reaction was stirred for 30min and the solution was cooled to –20°C. Benzaldehyde (0.2mL, 2mmol) was added. The reaction was stirred overnight and quenched distilled water (30mL) and the mixture was extracted with DCM (3x60mL). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed (SiO_2, ethyl acetate) to afford *dimethyl hydroxy (phenyl) methyl phosphonate* (**178**) (77mg, 18%) as a white solid; $[\alpha]_D^{23}$ =–2.1° (c=1, $CHCl_3$); **GC:** Mosher's ester derivatisation gave 2%de.

APPENDIX A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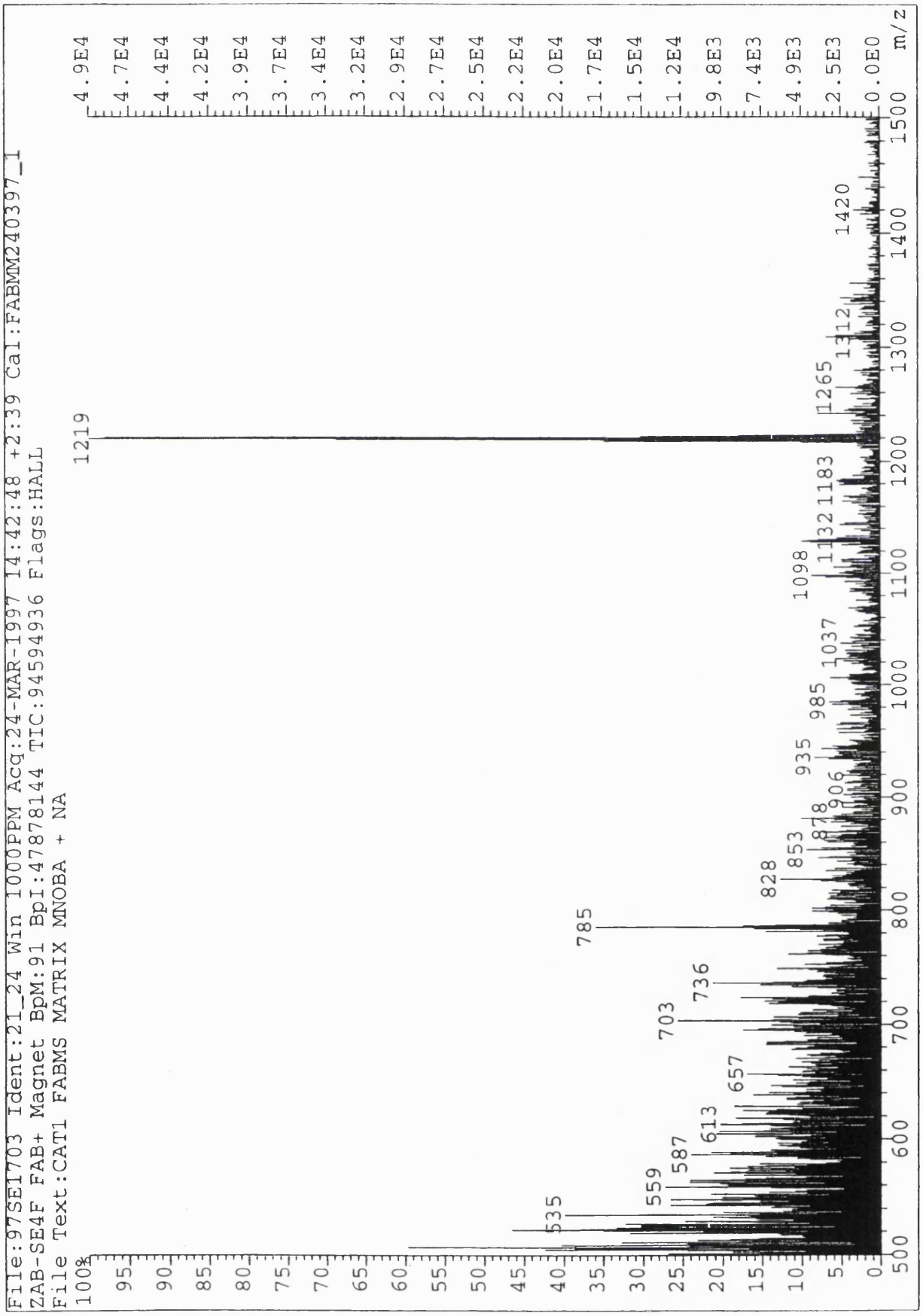
PPM

APPENDIX B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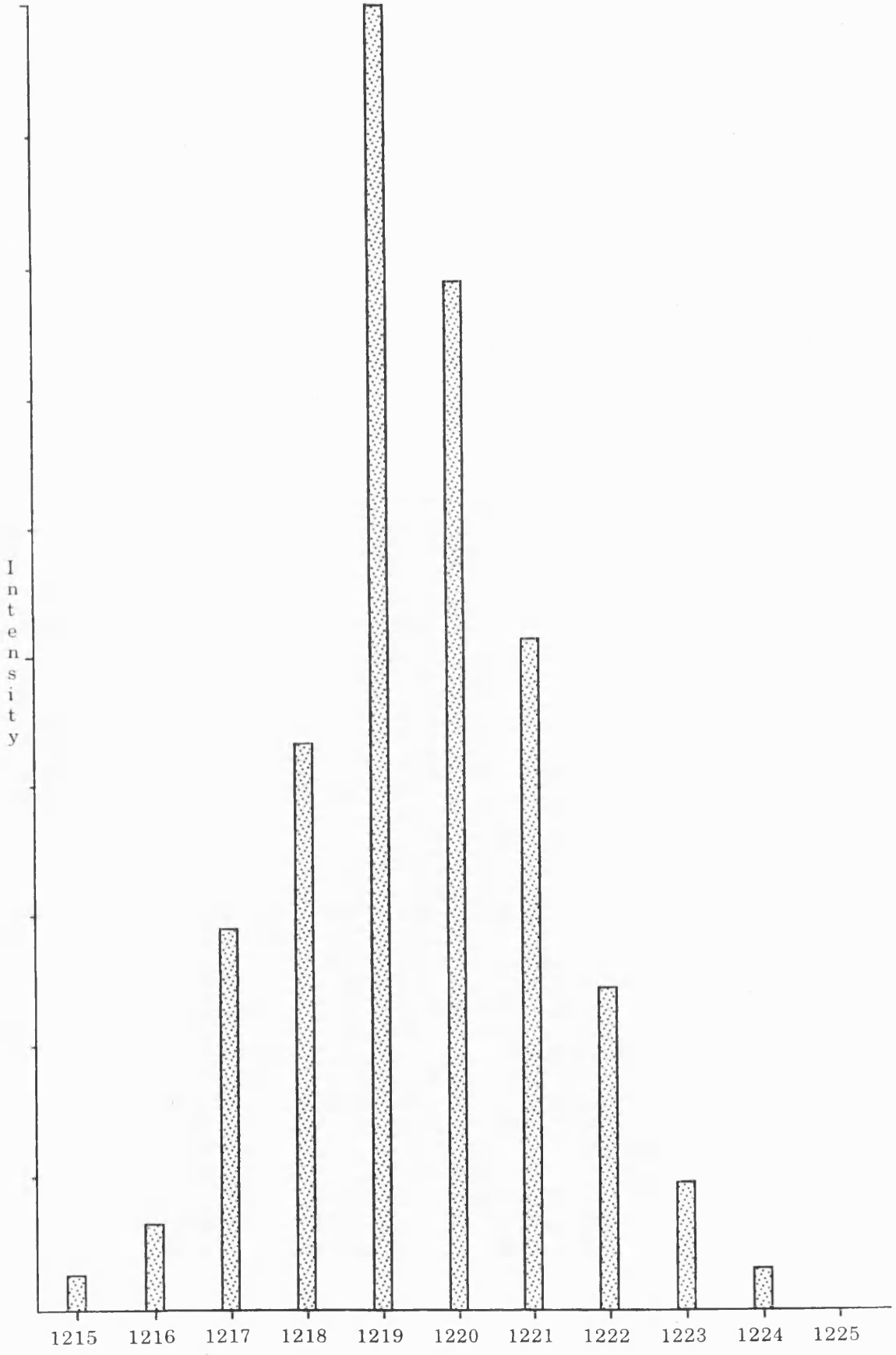
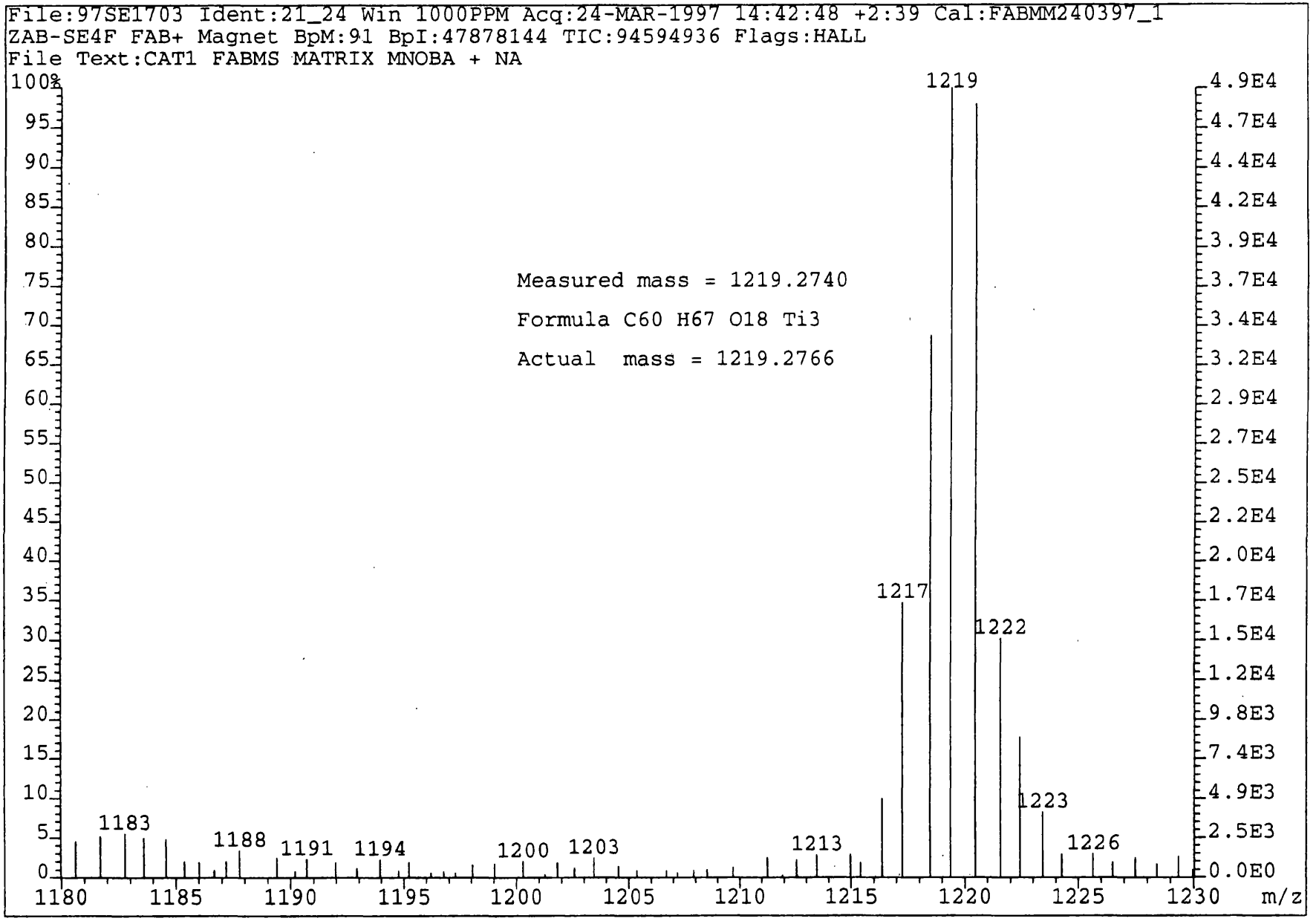
APPENDIX C

C60H67O18Ti3

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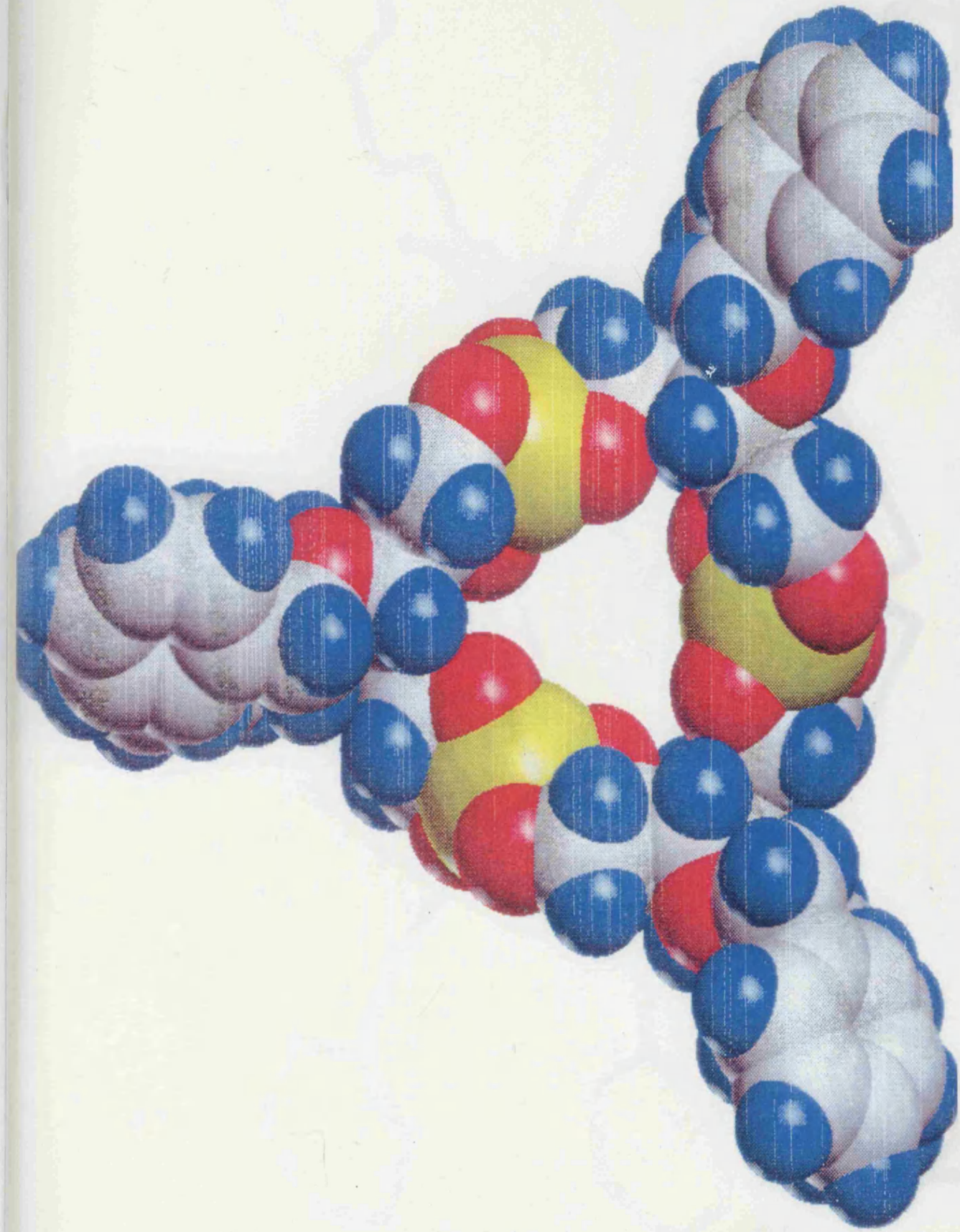
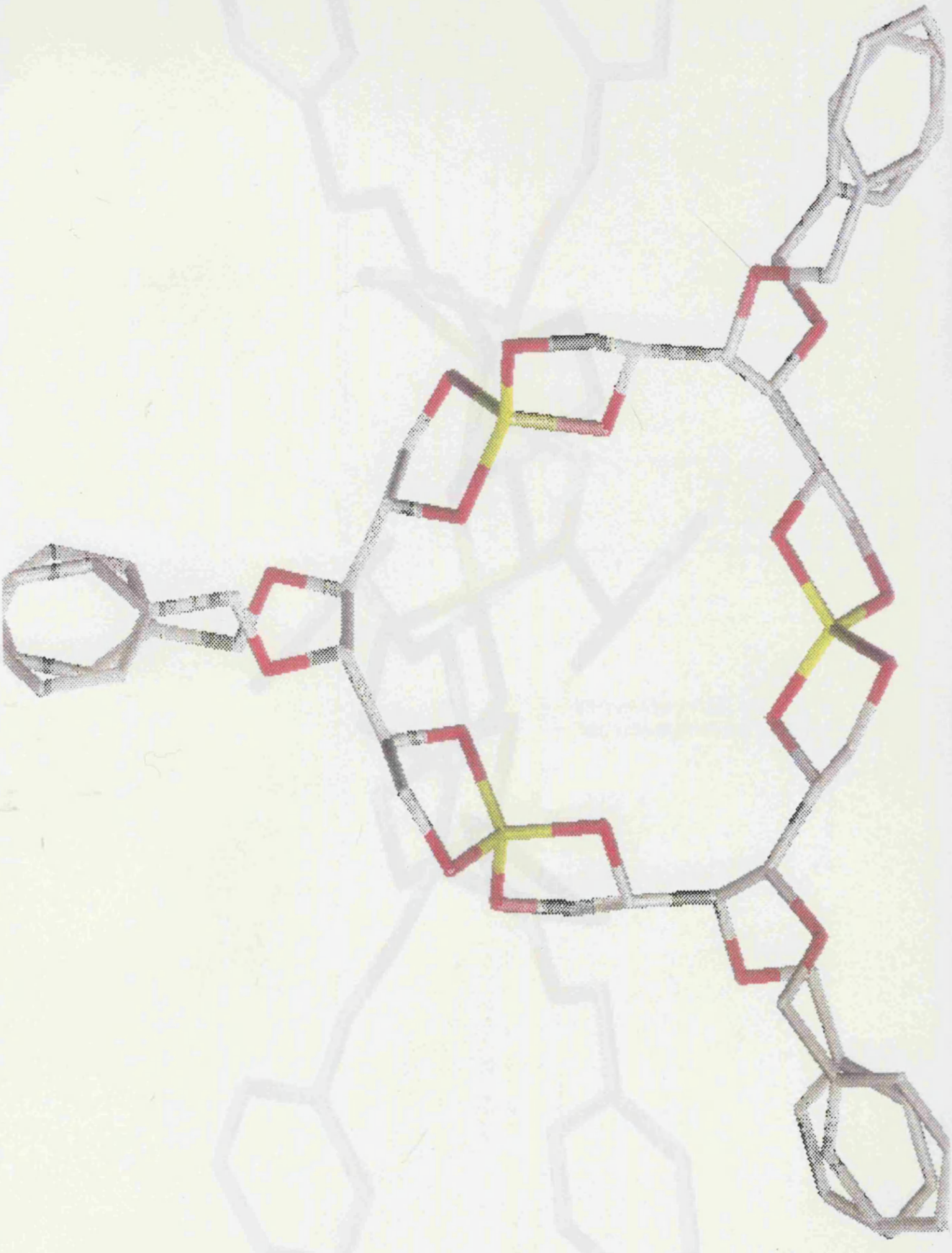
m/z

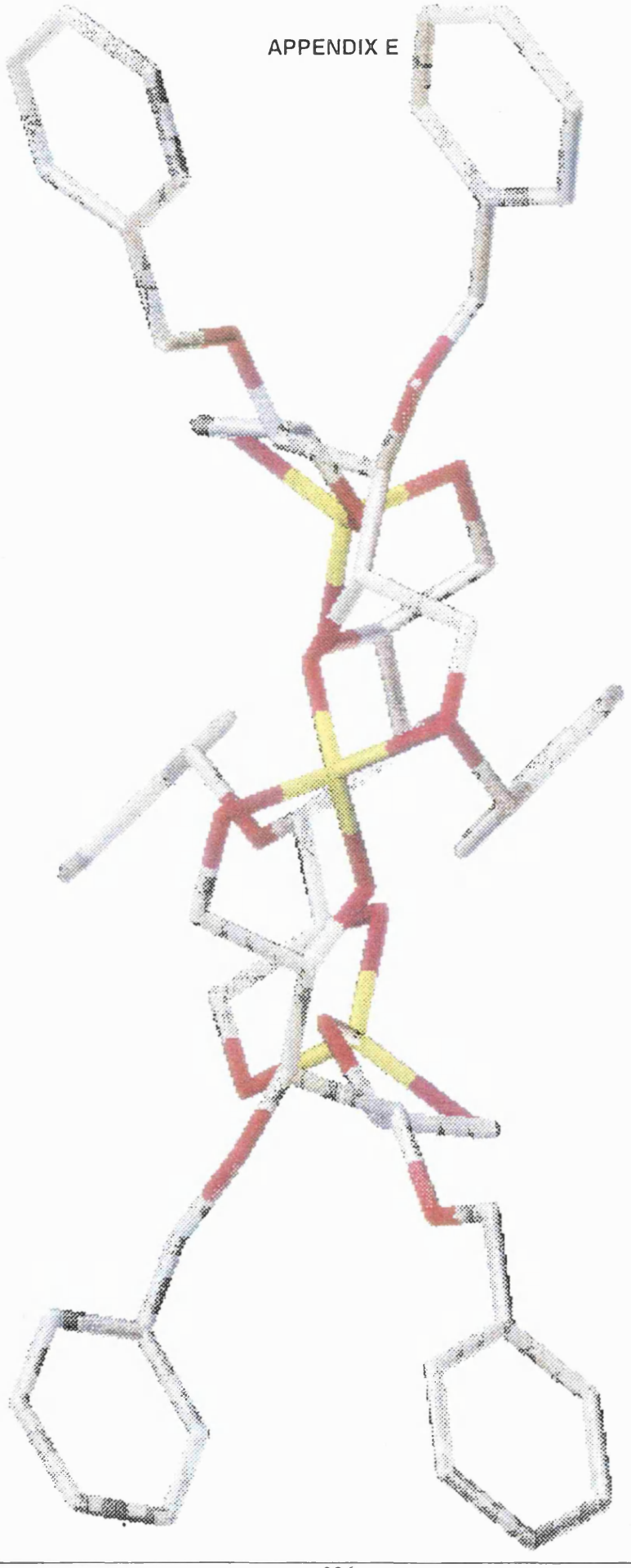
APPENDIX E



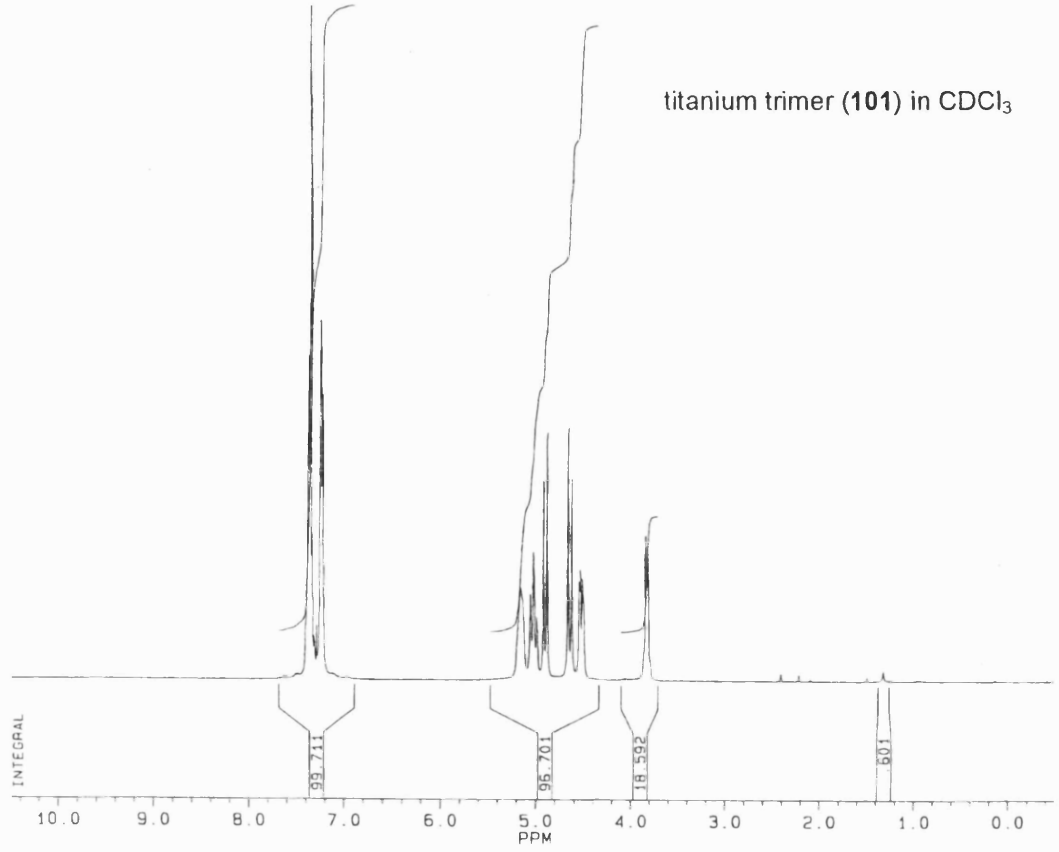
APPENDIX E



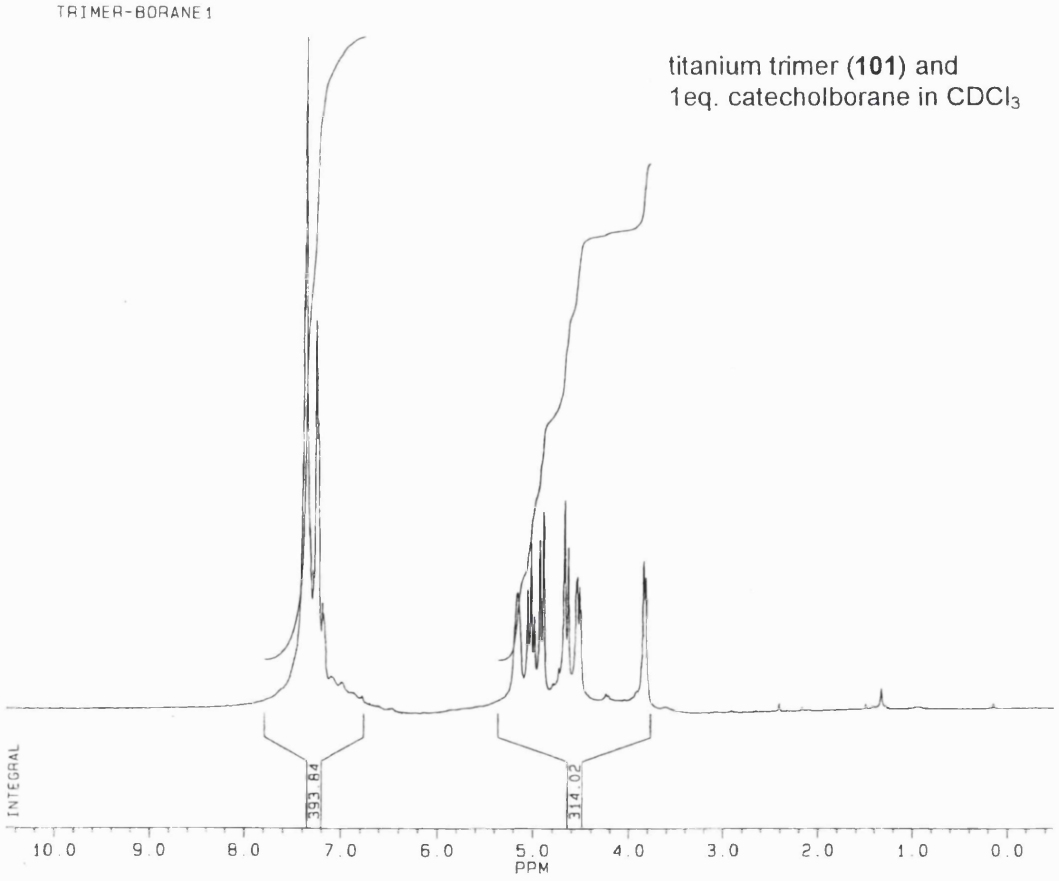
APPENDIX E



APPENDIX F

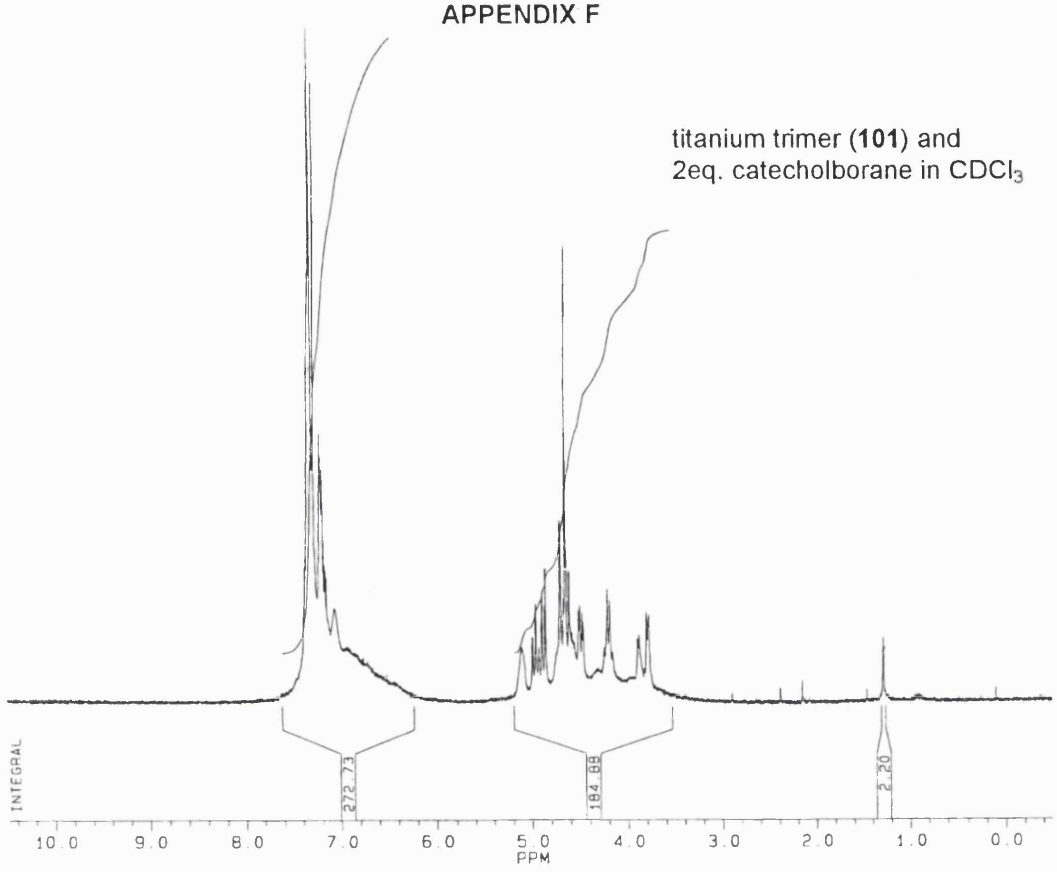


titanium trimer (**101**) in $CDCl_3$

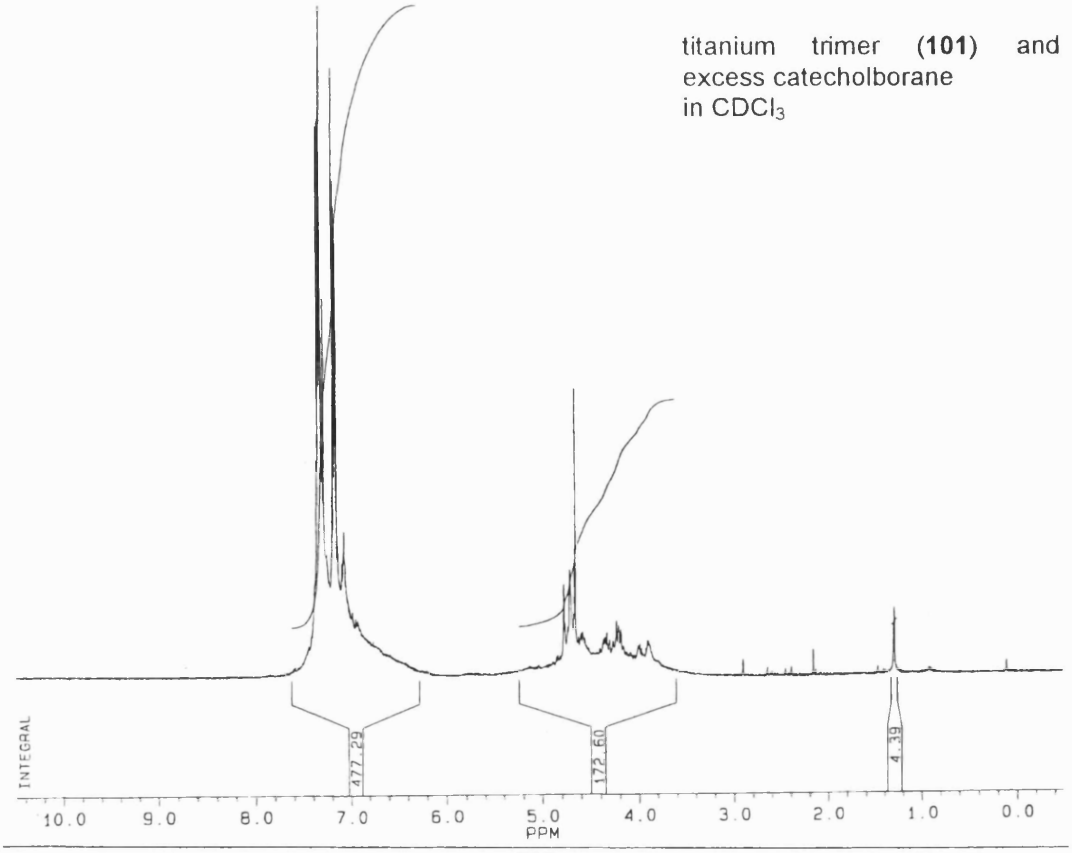


titanium trimer (**101**) and
1eq. catecholborane in $CDCl_3$

APPENDIX F



titanium trimer (**101**) and
2eq. catecholborane in $CDCl_3$



titanium trimer (**101**) and
excess catecholborane
in $CDCl_3$

References

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