

# Asymmetric Catalysis Using Niobium and Tantalum Complexes

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At Dublin City University, School of Chemical Sciences under  
the  
supervision of Dr. Joshua Howarth

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## DECLARATION

I hereby certify that this material, which I now submit on the programme of study leading to the award of Ph.D., is entirely my own work and has not been taken from the work of others save and to the extent that such work has been cited and acknowledged within the text of my work

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## ABBREVIATIONS

Aq	aqueous
Ar	Aryl
Binap	Bi-2-naphthol
Bu	Butyl
<i>t</i> -Bu	<i>iso</i> -Butyl
<i>n</i> -Bu	<i>normal</i> -Butyl
<i>t</i> -Bu	<i>tertiary</i> -Butyl
Cat	Catalyst
CDI	Carbonyl diimidazole
Conc	Concentrated
Cp	Cyclopentadienyl
Cp'	Methyl cyclopentadienyl
Cp*	Pentamethyl cyclopentadienyl
<i>d</i>	Dispersity
D	Deuterium
DAST	Diethylaminosulphurtrifluoride
DCM	Dichloromethane
de	Diastereomeric excess
DEE	Diethyl ether
DIPP	Diisopropyl phenoxy
DME	Dimethoxy ethane
DMF	Dimethyl formamide
DMSO	Dimethyl sulphoxide
DIBAL-H	Diisobutyl aluminum hydride
EA	Ethyl acetate
ee	Enantiomeric excess
Et	Ethyl
EtOH	Ethanol
GC	Gas Chromatography
h	Hour(s)
HPLC	High Performance Liquid Chromatography
ht	Head to tail

IR	Infra-red spectroscopy
L	Ligand
LA	Lewis Acid
$\text{LiAlH}_4$	Lithium aluminium hydride
M	Metal
MAO	Methylalumoxane
Me	Methyl
MeCN	Acetonitrile
MeOH	Methanol
min	Minute(s)
$M_n$	Average molecular weight
m s.	Molecular sieves
Ms	Methylsulphonyl
$\text{NaBH}_4$	Sodium borohydride
Naph	Naphthyl
NBE	Norbornene
NBS	<i>N</i> -Bromosuccinimide
NMR	Nuclear magnetic resonance spectroscopy
Np	Neopentyl
PE	Petroleum ether (40–60°)
Ph	Phenyl
Pr	Propyl
<i>n</i> -Pr	<i>normal</i> -Propyl
<i>i</i> -Pr	<i>iso</i> -Propyl
Pyr	Pyridine
r.t.	Room temperature
S	Solvent
Tf	Trifluoromethylsulphonate
THF	Tetrahydrofuran
TBDMS	<i>t</i> -Butyldimethylsilyl
TLC	Thin-layer chromatography
TMS	Trimethylsilyl
Ts	<i>p</i> -Toluenesulphonyl
UV	Ultraviolet



## PUBLICATIONS

The following papers were published as part of the work contained within this thesis:

(1) Joshua Howarth and Kevin Gillespie, *Tetrahedron Lett* , **1996**, *37*, 6019.

(2) Joshua Howarth and Kevin Gillespie; *Tetrahedron: Asymmetry*, **1998**,  
submitted for publication.

## ABSTRACT

### Asymmetric Catalysis using Niobium and Tantalum Complexes

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Niobium and tantalum have been used for a number of catalytic reactions. These include carbon monoxide reduction, dimerisation and polymerisation of olefins, oligomerisation and polymerisation of acetylenes, nucleophilic Wittig-type reactions, hydrogenation of arenes and aryl phosphines, hydrodenitrogenation and hydroboration reactions.

In this work their potential as enantioselective catalysts was investigated. The metal chlorides displayed Lewis-acid activity and they were used, in conjunction with a number of chiral ligands, in the catalysis of the Diels–Alder reaction between cyclopentadiene and either crotonaldehyde or methacrolein. A number of amino acids were investigated and, although Lewis-acid activity was evident from the yield at low temperature and from the *endo.exo* ratios, no chiral induction was achieved. When C<sub>2</sub>-symmetrical tartrate esters were used ee's of 22 and 40% in the presence of niobium pentachloride were achieved for the ethyl and *i*-propyl esters respectively. Chiral Schiff bases were synthesised by a condensation reaction between salicylaldehyde or *t*-butyl salicylaldehyde and a number of amino alcohols. The complexes formed between these compounds and either niobium pentachloride or niobium penta*isopropoxide* failed to give enantiomeric excess in the test reaction. Pyridine-*bis*-oxazoline (Pybox) ligands were synthesised and, along with the Jacobsen ligand, complexes were formed with niobium and tantalum pentachloride. One such complex, that between NbCl<sub>5</sub> and *R, R*-Jacobsen ligand was isolated and characterised. These complexes did provide enantiomeric excess in the test reaction. The extent of the ee was dependent on the ligand used, whether co-catalyst was added and whether 4Å molecular sieves were included. The best results achieved were with the Jacobsen ligand where up to 52% ee was achieved.

In a second part of the work an attempt was made to design a catalytic system whereby the effects of central, planar and helical chirality in the catalyst could be compared. The enantioselective epoxidation of olefins was chosen as the test reaction and *bis* sandwich complexes of niobium and tantalum as the test catalysts. Attempts were made to synthesise unsymmetrical sandwich complexes containing cyclopentadienyl and indenyl ligands, leading to the formation of peroxometallic species. These were, however, unsuccessful. An attempt was made to synthesise a heptahelicene with terminal five-membered rings. A literature method was first used. This proved to be difficult to emulate and thus a different method was devised. However this also proved to be unsuccessful. It was not possible to perform the chirality comparison experiments.

## **CHAPTER 1**

### **SURVEY OF THE LITERATURE**

## 1.1 BACKGROUND

The history and chemistry of niobium and tantalum share the fact that, as with their discovery, their chemistry has shown many parallels. A mineral sample found in New England, early in the 19th century, and initially called columbium and one found in Scandinavia and called tantalum were believed to be one and the same. It was nearly 50 years later that the metals were shown to be different, though generally found together, and were thus named niobium and tantalum. Their co-occurrence is significant in terms of their separation which is quite a difficult process because of the chemical similarity of the two metals and, in terms of classical separation techniques, their size. The atomic radii of these second and third row metals is identical at 1.47 Å despite the larger number of electrons in tantalum. This is a feature of lanthanide contraction whereby, due to the shape of the f orbitals, the shielding of f electrons is quite poor and they experience a higher effective nuclear charge as atomic number increases. Thus there is a contraction in the atomic radius. The atoms subsequent to the lanthanides in the table of the elements, including tantalum are profoundly affected.

Niobium and tantalum differ from vanadium significantly. Principally this is characterised by the relative instability of the lower oxidation states, their failure to form ionic species and the inertness of their pentoxides. Of the pentahalides only vanadium (V) fluoride is known, whereas all those of niobium and tantalum are accessible. It seems likely that the small atomic radius of vanadium is a contributory factor as only the tetrachloro compound is known with bromine and iodine forming  $\text{VBr}_3$  and  $\text{VI}_3$  respectively. The catalytic work described in this thesis involves the use of niobium (V) chloride and tantalum (V) chloride.

The organometallic chemistry and inorganic chemistry of niobium and tantalum is extensive. However, this literature survey will be confined mostly to the uses of the metals and the various organometallic complexes thereof in the catalysis of organic reactions. This area has received much less attention over the years and perhaps warrants further examination. Compared to other metals, the relative lack of work using niobium and tantalum can be explained in terms of their relative lack of abundance although the cost of  $\text{NbCl}_5$  is quite low. As early transition metals, their compounds are highly electropositive, forming strong metal–oxygen bonds and are thus water and oxygen sensitive. Their early group status also means that they contribute

few electrons to potential complexes and thus there are fewer possible combinations of ligands providing 18 electron systems. The manipulation of sensitive compounds has, however, improved greatly over the past 20 to 30 years due to the development of suitable handling techniques and equipment.

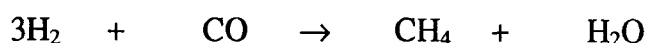
## 1.2 ORGANOMETALLIC CHEMISTRY

The first organometallic species of niobium and tantalum were reported in 1928 as being the metal aryls  $\text{TaCl}_4(\text{C}_6\text{H}_5)$  and  $\text{NbCl}_4(\text{C}_{10}\text{H}_7)$  although there was doubt about the structure.<sup>1,2</sup> Simple reactions with phenyl and ethyl Grignards were also attempted but no characterisation was achieved.<sup>3</sup> The first well-characterised organometallic species were reported by Wilkinson and Birmingham and these were sandwich complexes of the type  $\text{Cp}_2\text{MBr}_3$  (Cp = cyclopentadienyl, M = Nb, Ta)<sup>4</sup>. The complexes were formed by the addition of solutions of  $\text{CpMgBr}$  or  $\text{NaCp}$  to the metal halide. The ease of synthesis and relative stability (they will, however, hydrolyse in moist air or water) of the compounds makes it unsurprising that *bis* sandwich complexes have been comprehensively investigated.

There are a number of common themes in catalytic reactions involving Nb and Ta. These features relate to the traditional transition metal catalytic systems and to the specific nature of the group V metals. These reaction types are outlined below.

### 1.2.1 Carbon Monoxide Reduction

A great deal of attention has been paid to attempts to reduce carbon monoxide to methanol or some other synthetically useful organic compound or fuel. There have been numerous examples of such successful reactions using other metal systems<sup>5,6</sup>. Thus a synthesis gas of 3:1  $\text{H}_2:\text{CO}$  could yield methane:-

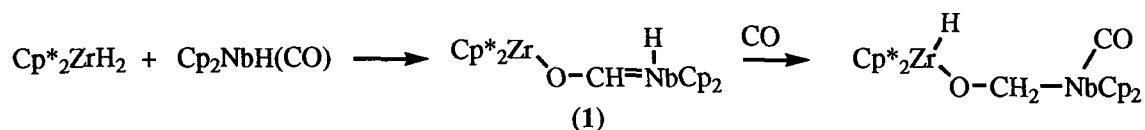


The criteria for a good catalyst capable of effecting such a reduction would be one which could effectively lower the carbon-oxygen bond order leading to facile C-O cleavage and which could facilitate hydride transfer to the carbon and oxygen atoms. It



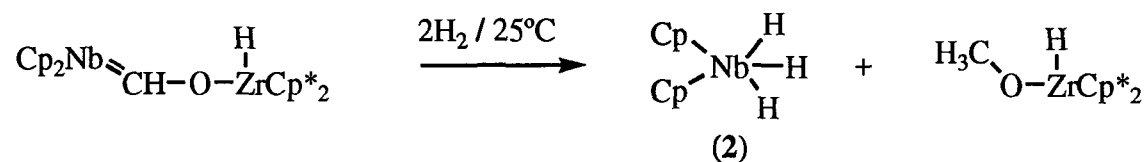
has been shown that the hydrides of these metals tend to be more nucleophilic than those of the later transition metals which would enhance this potential

The idea of using mixed metal systems, *i.e.* the metal carbonyl of one metal and the metal hydride of another has been attempted and a zirconium hydride/niobium carbonyl system yielded a plausible methanol precursor:<sup>7</sup>



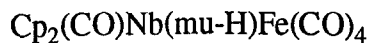
Scheme 1

Structure (1) above is tautomeric with the alkyl structure and is actually trapped by the addition of CO. The fact that addition of H<sub>2</sub> to (1) at room temperature leads to the stable niobium hydride (2) and a zirconium complex suggests that the potential of this system is limited.



Scheme 2

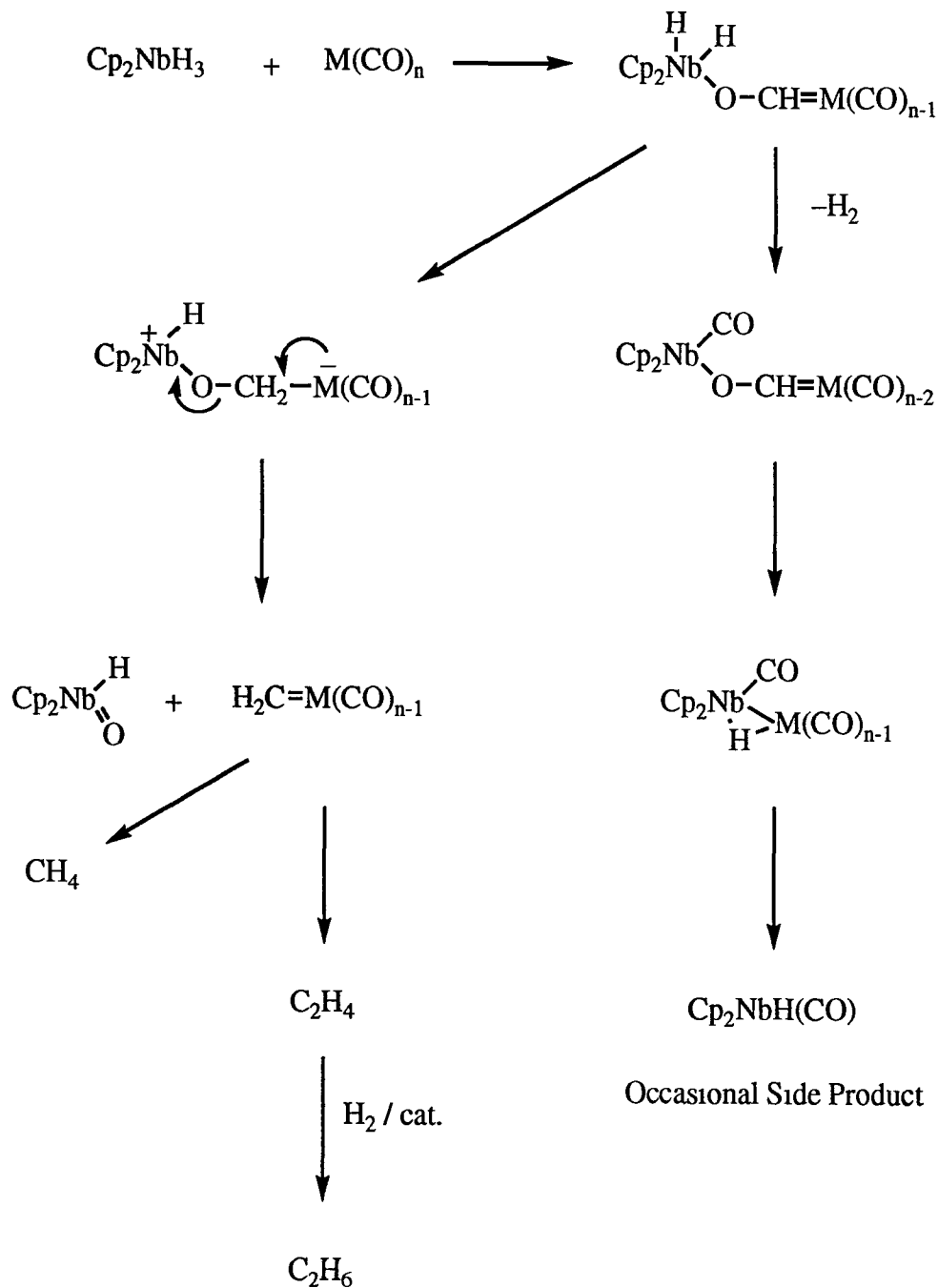
It was shown that metallocenes and tantalocenes were not susceptible to the migratory insertion of CO into the M–H bond.<sup>8a</sup> However reduction of CO to methanol using Cp<sub>2</sub>Ti(CO)<sub>2</sub> had proved successful although the complex was hydrolysed by the alcohols to form a six-centred cluster<sup>8b</sup> It was with this in mind and with the knowledge that both Cp<sub>2</sub>NbH<sub>3</sub> and Cp<sub>2</sub>NbH(CO) are stable to water and ethanol at room temperature, that CO reduction by these complexes was attempted.<sup>9</sup> Formation of the C–H bond appears to be the key step here *i.e.* hydride attack on electrophilic CO, as CO insertion into the M–H bond seems unlikely. Thus Cp<sub>2</sub>NbH(CO) was reacted at 140°C in the presence of H<sub>2</sub> with evolution of CH<sub>4</sub> in the gas phase along with higher alkanes. Methane and ethane were produced in 2–5% yield relative to Nb. Labelling studies showed that D<sub>2</sub> usage produced CH<sub>4</sub> and CDH<sub>3</sub> in roughly equal amounts and the use of Cp<sub>2</sub>NbH(<sup>13</sup>CO) gave <sup>13</sup>CH<sub>4</sub> but no label inclusion for the higher alkanes, suggesting that they were formed by degradation of the complex. The hydridic character of NbH is low compared to that of the group IV metals and furthermore ν<sub>CO</sub> is 1900 cm<sup>-1</sup> in Cp<sub>2</sub>NbH(CO) suggesting that CO lacks the electrophilic character required for the reductive process. Thus Cp<sub>2</sub>NbH<sub>3</sub> was reacted with Fe(CO)<sub>5</sub>, rapidly, at room temperature. <sup>1</sup>H NMR monitoring of the reaction suggested a transient formyl species with the isolated product being (3)



(3)

**Figure 1**

Reaction with other metal carbonyls led to much more promising results<sup>10</sup> When  $\text{Cr}(\text{CO})_6$  was employed ethane was produced selectively using  $\text{Cp}_2\text{NbH}_3$  in benzene in a  $\text{H}_2$  atmosphere. The fact that the ethene:ethane ratio drops dramatically over the reaction period suggests that the former is initially formed and then reduced. A mechanism for the reaction has been proposed.-



**Scheme 3**

From this system it can be seen that metal oxides are formed as opposed to H<sub>2</sub>O and this fact along with the formation of unreactive Cp<sub>2</sub>NbH(CO) precludes potential catalysis. The strong M=O bond formation is a feature of group V chemistry. Schrock and Wood reported the reduction of CO via an  $\eta^2$ -acetone intermediate<sup>11</sup>. Indeed, this intermediate could be supported by the fact that a different structure, Cp<sub>2</sub>NbH<sub>3</sub>, reduces acetone or trifluoroacetone to the corresponding alcohol<sup>12</sup>. The half sandwich complex CpTaMe<sub>4</sub> was reacted with CO in ether at -78°C. There was spectroscopic evidence of an intermediate of the structure (4)

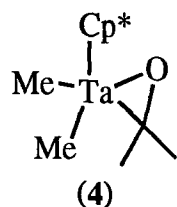
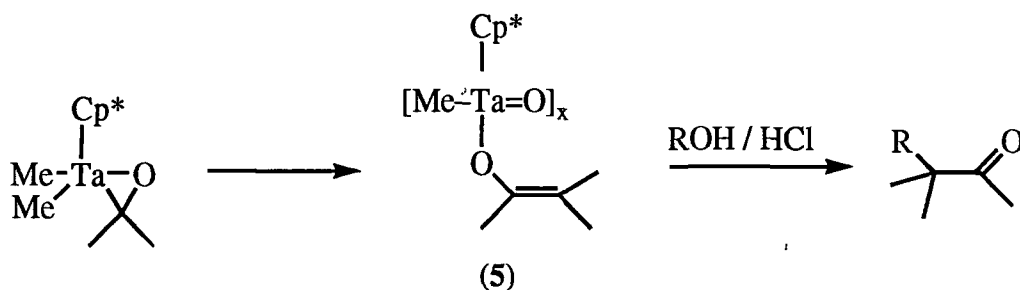


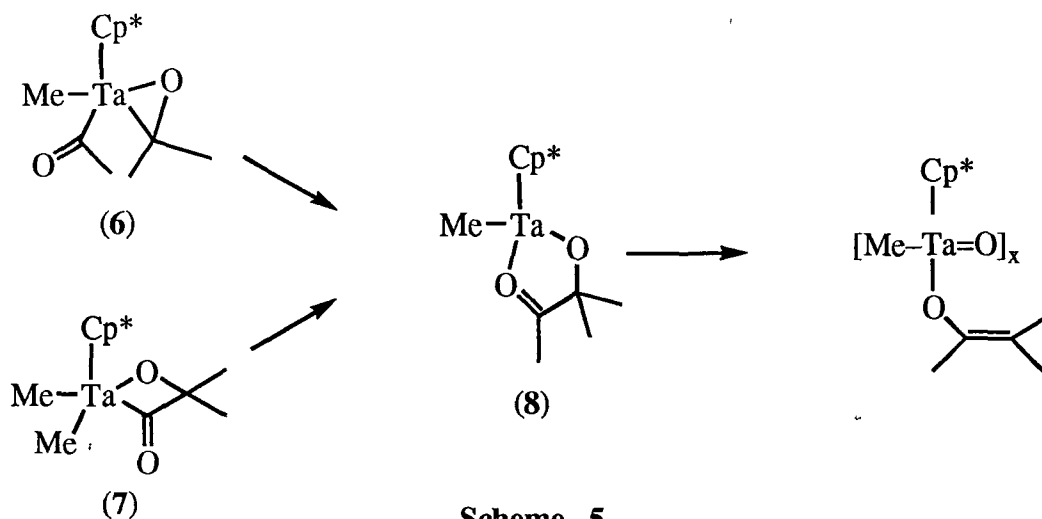
Figure 2

Further reaction of this species involved attempted exchange with acetone-*d*<sup>6</sup> which was unsuccessful, reaction with O<sub>2</sub> to produce acetone and with water to yield propanol. Compound (4) can absorb a further equivalent of CO to form an enolate which can then be hydrolysed

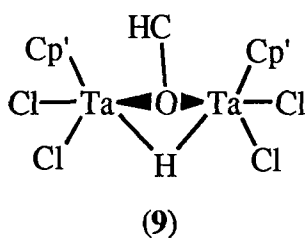


Scheme 4

A 1:1 mixture of deuterated and non-deuterated Cp\*Ta(CH(D)<sub>3</sub>)<sub>4</sub> was reacted with two equivalents of CO producing 54% (CH<sub>3</sub>)<sub>2</sub>HCC(O)CH<sub>3</sub> and 43% (CD<sub>3</sub>)<sub>2</sub>HCC(O)CD<sub>3</sub> demonstrating that the reaction is essentially intramolecular. The second step of the reaction is proposed as either (6) or (7) rearranging to (8) which gives (5)



A bimolecular tantalum hydride complex was used to reduce CO to methane or methanol<sup>13</sup> Initially  $[\text{TaCp}'\text{Cl}_2\text{H}]_2$  ( $\text{Cp}' = \text{C}_5\text{Me}_4\text{Et}$ ) was reacted with one equivalent of CO to give crystalline  $\text{Ta}_2\text{Cp}'_2\text{Cl}_4(\text{H})(\text{CHO})$  (9)



**Figure 3**

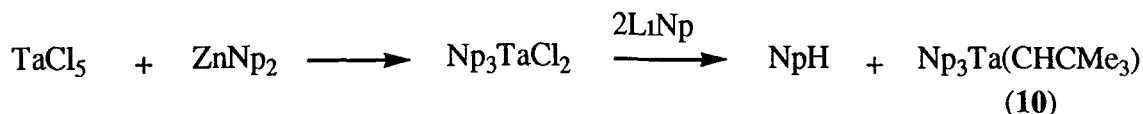
Treatment of this complex with  $\text{AlCl}_3$  yields methane (30%), but this rises to 70% if the reaction is performed under  $\text{H}_2$ . In  $\text{D}_2$  a 2:3 mixture of  $\text{CH}_4$  and  $\text{CH}_3\text{D}$  is observed. Hydrolysing the complex with aq HCl in propanol yields MeOH. When HCl gas in aprotic solvent is used, no MeOH is observed.

No catalytic CO reduction has been achieved and the high affinity of the metals for oxygen may well preclude this possibility. However it is an area that could benefit from greater attention.

## 1.2.2 Reactions with Olefins

### 1.2.2.1 Dimerisation

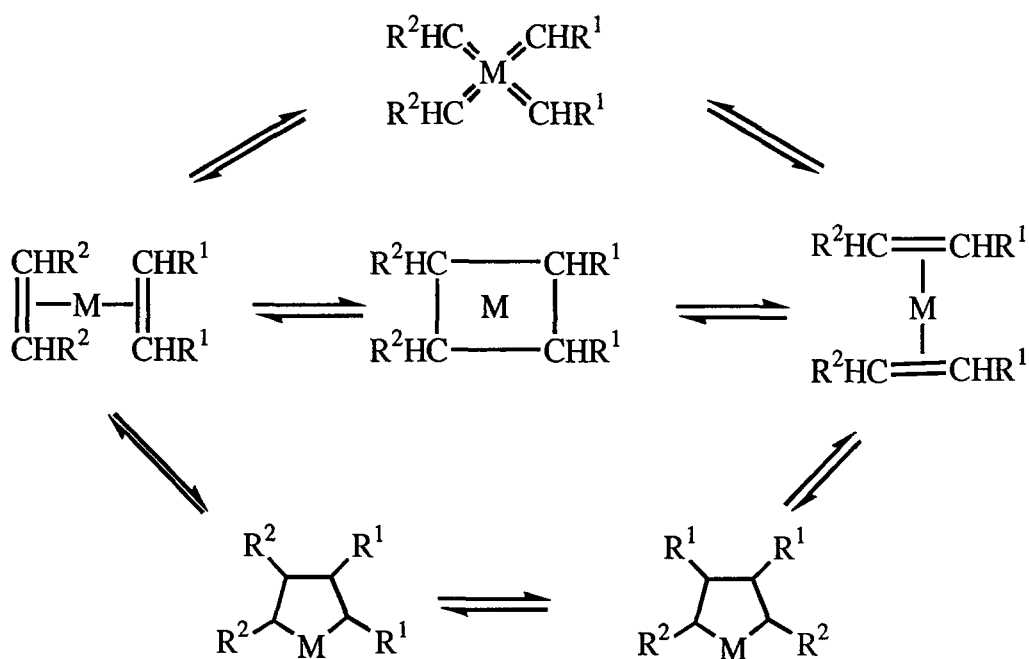
Schrock synthesised the first stable alkylidene complex in a serendipitous reaction in which he was attempting to make a penta-alkyltantalum compound<sup>14</sup>



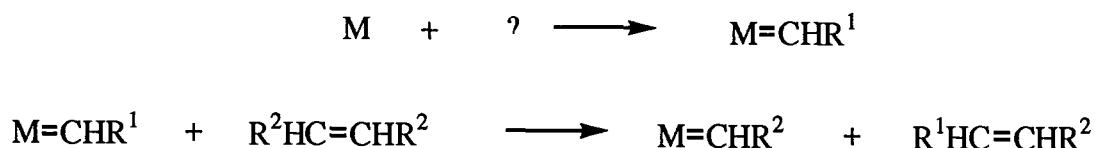
Scheme 6

This resulted from an  $\alpha$ -elimination reaction. Given the generally accepted mechanism for metathesis in the non-pairwise fashion (see below), it seemed likely that this would provide a useful entry point for the group V metals into olefin metathesis. The earlier suggestion of a pairwise mechanism,<sup>15</sup> whereby the products of the metathesis of  $\text{CHR}^1=\text{CHR}^1$  and  $\text{CHR}^2=\text{CHR}^2$  were  $2\text{CHR}^1=\text{CHR}^2$  was shown to be flawed as a statistical distribution of products frequently resulted in systems where fixed or cyclic olefins were used, this being more consistent with a non-pairwise mechanism.

Pairwise

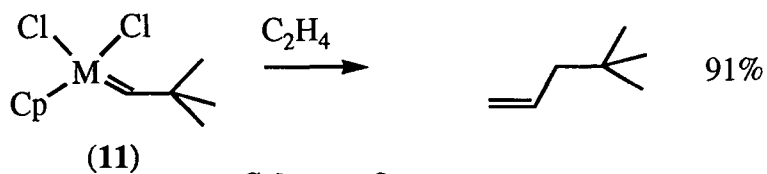


Non-Pairwise



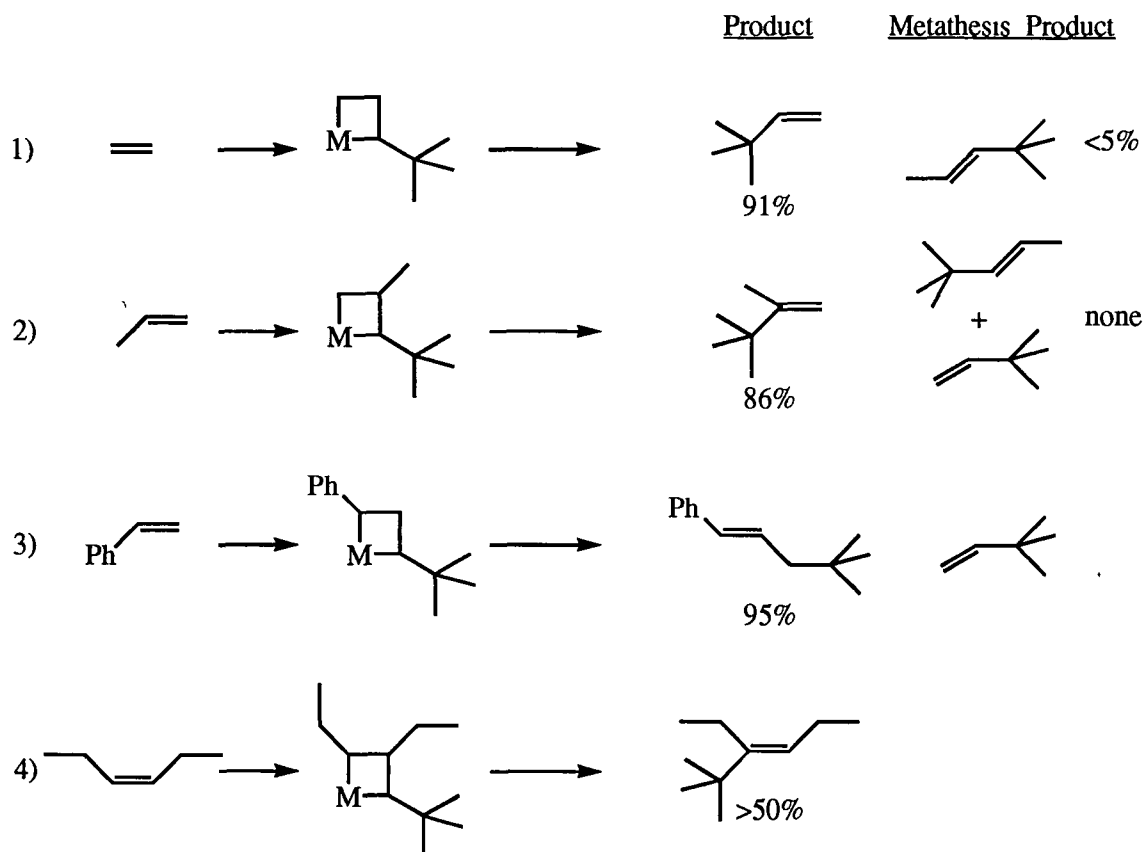
Scheme 7

Schrock later used a related system to attempt metathesis, but instead yielded a product consistent with insertion of ethylene into the alkylidene bond<sup>16</sup>



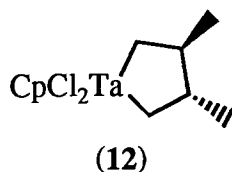
Scheme 8

This situation is consistent with the formation of a metallacyclobutane ring as an intermediate but this was not isolable (This type of structure was not properly characterised until 1988, see below). A number of reactions were carried out using this system with ethylene, styrene, propene and *cis* 3-hexene. Scheme 9 shows the isolated hydrocarbons, the proposed intermediates and the expected metathesis products.



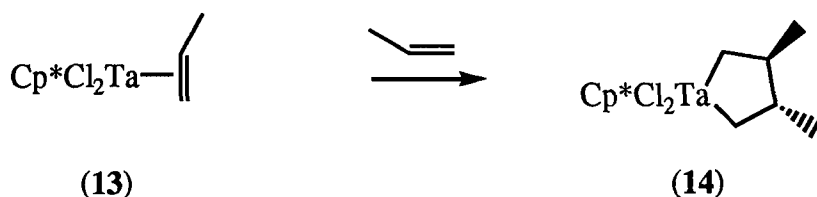
Scheme 9

The products result from the transfer of a  $\beta$ -hydrogen atom selectively to the substituted  $\alpha$ -carbon in the intermediate four-membered ring. The reaction with niobium was appreciably slower than that of tantalum. This mechanism led to the proposal of a selective catalyst for the dimerisation of ethylene to but-1-ene<sup>17</sup> and established the basis for a successful system. In an analogous reaction (12) was allowed to decompose to give 2,3-dimethyl but-1-ene. In the presence of propylene the product is formed catalytically and at the same rate as the stoichiometric reaction.



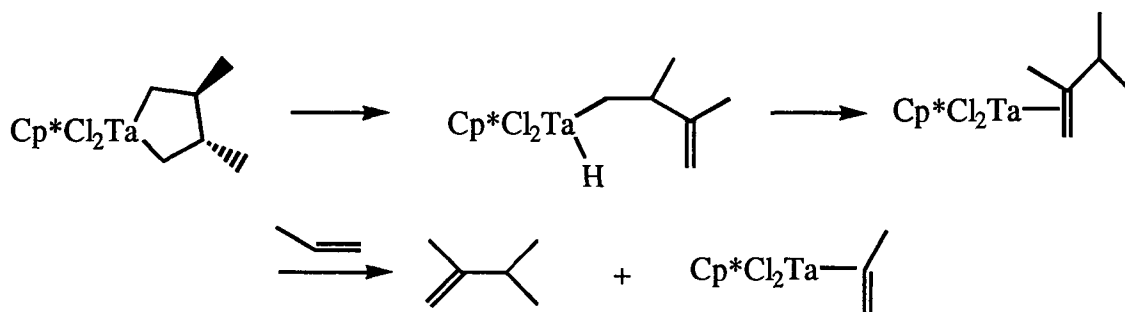
**Figure 4**

The mechanism of olefin dimerisation was thoroughly investigated using an homologous series of olefins as well as deuterated varieties.<sup>18</sup> In the simplest possible scheme for this system a metallacyclopentane is formed by the insertion of a second molecule of olefin into structure (13) to give (14).-



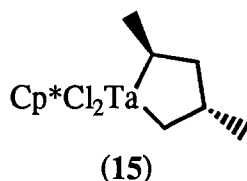
**Scheme 10**

This involves a formal increase in the oxidation number of Ta, a situation which the early transition group V metals favour. The species (14) is isolable and has been characterised<sup>17</sup>. A shift of the H atom on the  $\beta$ -carbon to the metal and then to the (formerly)  $\alpha$ -carbon can ensue



**Scheme 11**

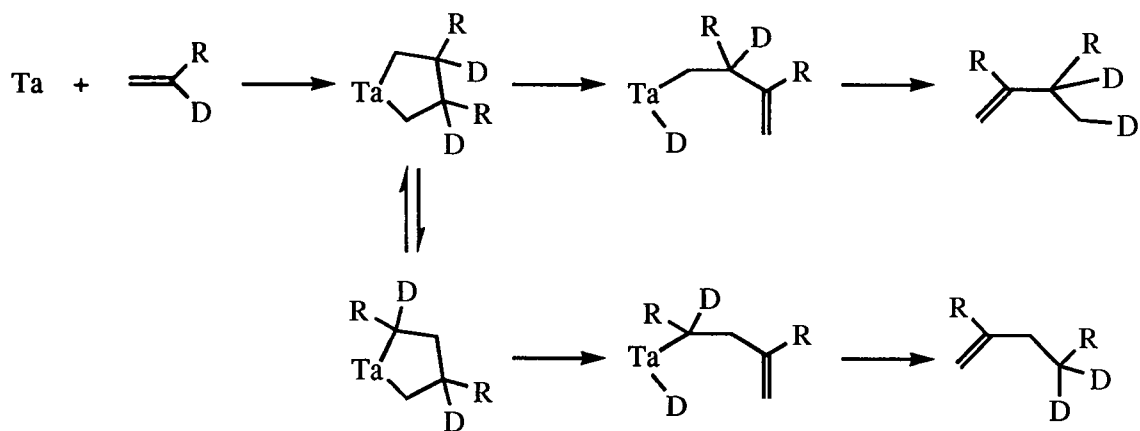
The difficulty with this mechanism is that there are two metallacyclopentane ring possibilities, (14) and (15)



**Figure 5**

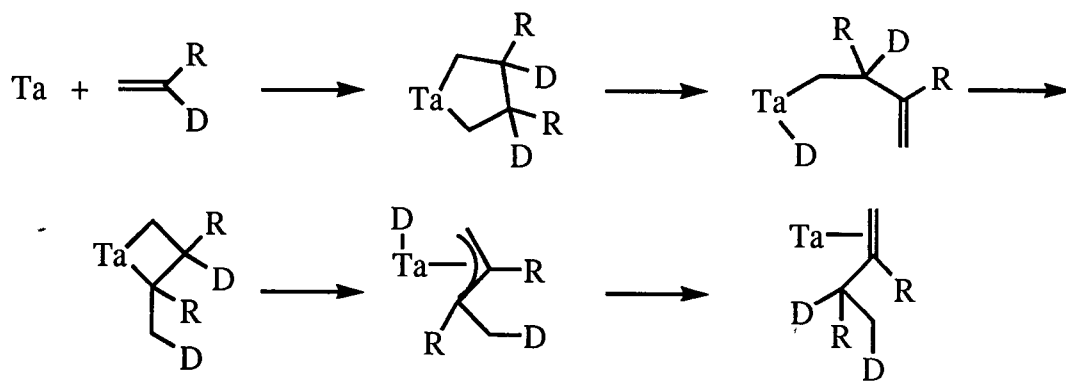
However, it would appear that these two species are in equilibrium. The former leads to the head to tail (ht) dimer and the latter to the tail to tail (tt) dimer. The structure of the former is strongly favoured but the latter decomposes more rapidly leading to

formation of the tt dimer. This situation predominates as the size of the substituent (Me in (14) and (15)) increases. Thus if ethylene is used the ht dimer is formed exclusively but if 1-neoheptene is used the tt dimer is exclusively formed. Deuterium labelling studies were used to establish the route.



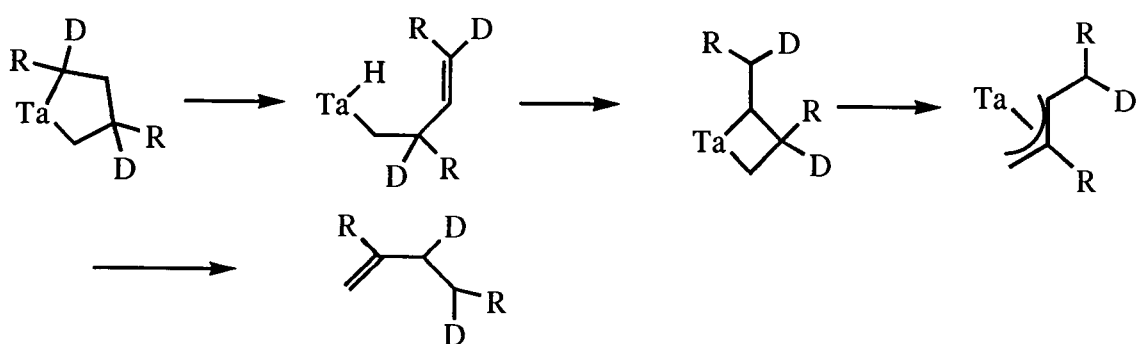
Scheme 12

Thus a route via metallacyclobutane was proposed which would give the experimentally found deuterated tt dimer.



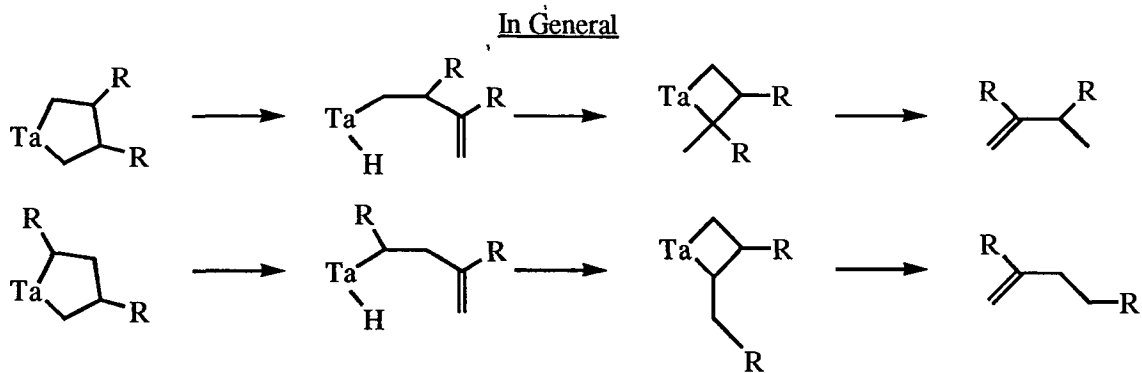
Scheme 13

and,



Scheme 14





Scheme 15

In the case where Cp\* (C<sub>5</sub>Me<sub>5</sub>) is used, no internal alkene is seen and a selective system for producing terminal alkenes with high catalytic turnover is achieved. Interestingly, in a mixed system where two different alkenes are used to make the metallacyclopentane (*i.e.* ethylene and one other) to yield (16), this structure decomposes to yield the two symmetrical ring structures (17) and (18).

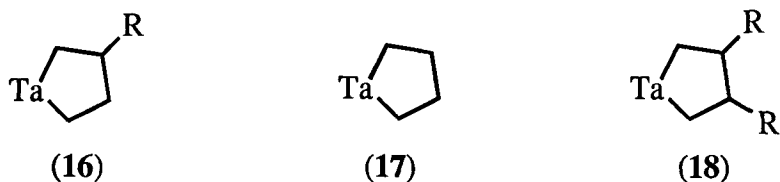
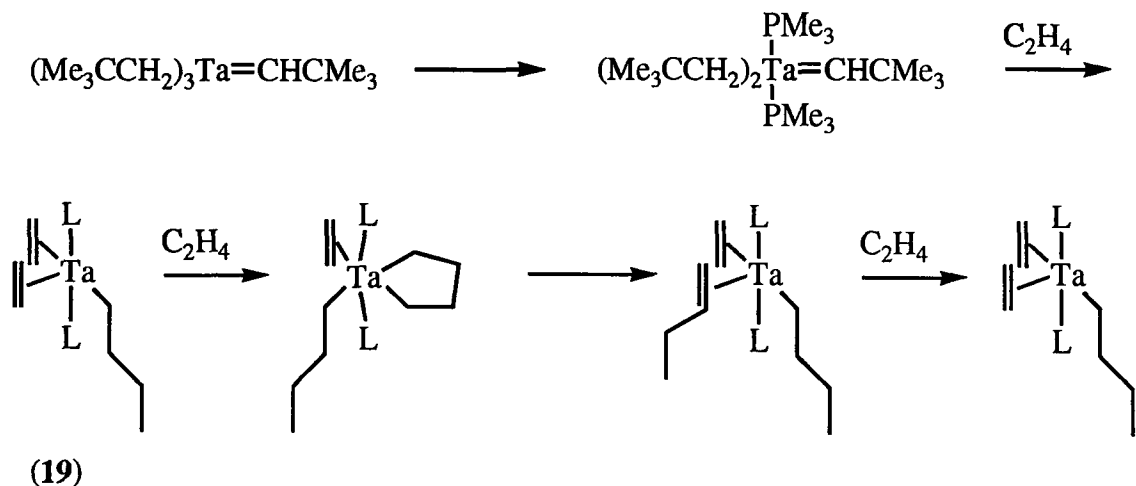


Figure 6

This indicates that the metallacyclopentane, though isolable, is an equilibrium structure in solution. It is believed that the driving force for this transformation is the greater stability of unsubstituted (17).<sup>19</sup>

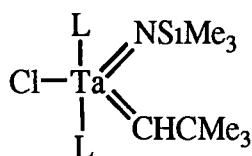
A similar structure bearing no Cp\* ring has been used for ethylene dimerisation. The authors proposed the following mechanism:-



Scheme 16

The process produced 0.5 turnovers/metal/min at 0°C.<sup>20</sup> One of the differences between this mechanism and that of the system containing the Cp\* ligand is that the

hydride elimination step and the ring contraction from metallacyclopentane to metallacyclobutane (the former being the rate limiting step) are absent.<sup>21a</sup> The analogous niobium system produces no catalysis and it is postulated that this is due to the unreadiness of Nb to form metallacyclopentanes. Metathesis was attempted using the imido structure (20) but again it was the rearrangement products which were produced in the reaction with ethylene<sup>21b</sup>

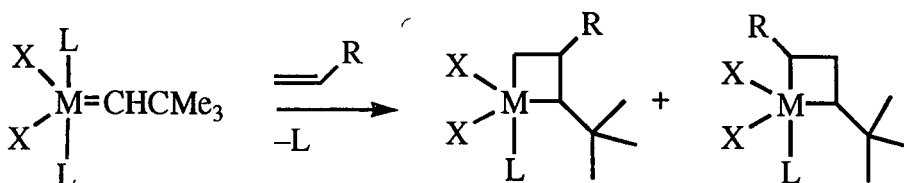


(20)

Figure 7

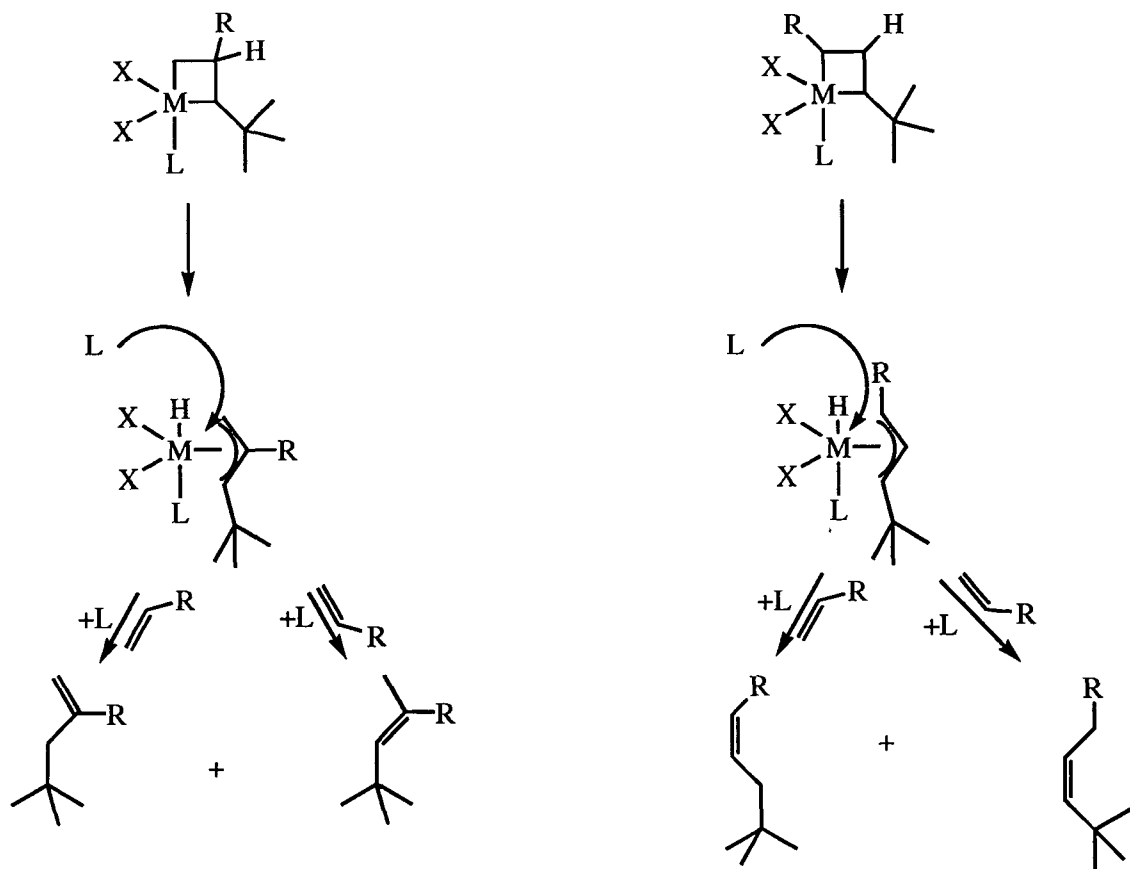
### 1.2.2.2 Metathesis

Although alkene metathesis was envisaged as being a useful outcome of the development of alkylidene complexes of Nb and Ta, this was proving not to be the case. The reaction of an olefin with the alkylidene complex was surmised to produce a metallacyclobutane

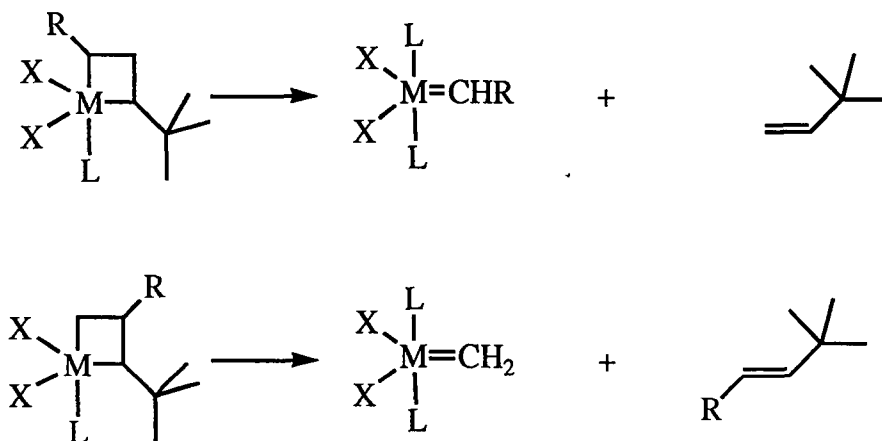


Scheme 17

There are two competing processes for the decomposition of this four-membered ring, namely,  $\beta$ -hydrogen shift to form a new olefin (Scheme 18) and metathesis (Scheme 19)



Scheme 18



Scheme 19

In some cases the rearrangement/elimination products were exclusively formed but a degree of metathesis production was eventually achieved<sup>22</sup> Neopentylidene-type complexes which had been used for dimerisation<sup>20,21</sup> were modified such that the rate of rearrangement was slowed relative to that of metathesis. The original complexes were of the formula Ta(CHCMe<sub>3</sub>)(PMe<sub>3</sub>)Cl<sub>2</sub> and these were modified by replacing the phosphine ligands with THF or pyridine with limited success. However the

replacement of the Cl ligands with one, two or three <sup>t</sup>Bu-O groups had a more pronounced effect. With one alkoxy ligand rearrangement still prevailed and with three ligands only 13% of the products were those of metathesis. However, with the dialkoxy complex only metathesis products were seen in the reaction with ethylene. This was true also of the reaction with 1-butene and in the case of 1-pentene the chloro-THF complex Ta(CHCMe<sub>3</sub>)(THF)<sub>2</sub>Cl<sub>3</sub> gave a substantial amount of metathesis product. One of the catalysts used, Nb(CHCMe<sub>3</sub>)(O<sup>t</sup>Bu)<sub>2</sub>(PMe<sub>3</sub>)Cl, gave a turnover rate of 35 while most of the other complexes that functioned as true catalysts gave turnovers of 5–6.

This poor level of catalysis is unsurprising considering the potential termination steps, namely -

- bimolecular decomposition of alkylidene complexes
- rearrangement of metallacyclobutane rings to olefins
- rearrangement of alkylidene ligands to olefins

Where an aryloxy ligand is used metathesis may also be successful. Thus the substitution of alkoxy ligands for chloride was important in slowing down the rate of rearrangement. This has been ascribed to the ability of alkoxy ligands to stabilise a d<sup>0</sup> metal centre. As described above the rearrangement of metallacycles to olefins involves the reduction of the metal to a d<sup>2</sup> olefin complex. The alkoxy ligand stabilises against this making the metathesis pathway more favoured.

### 1.2.2.3 Polymerisation

Schrock's group noted the production of uncharacterised high-boiling organic compounds rather than metathesis or rearrangement products when ethylene was reacted with (21).<sup>22</sup>

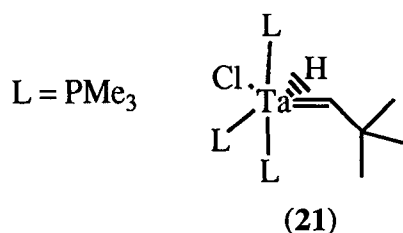
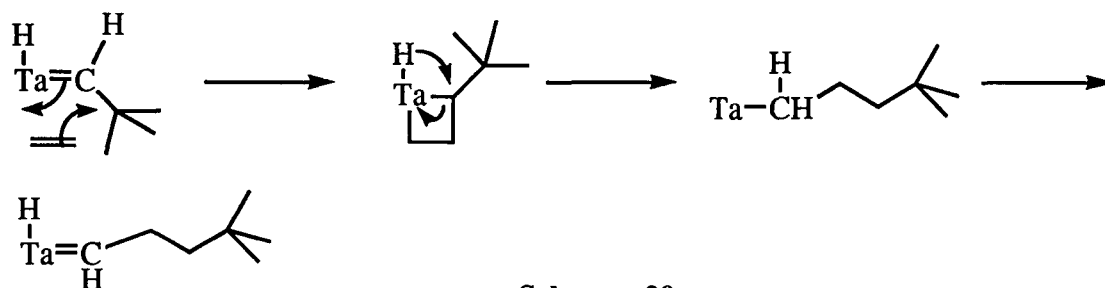


Figure 8

Encouraged by this, they modified the system until they developed a polymerisation catalyst for ethylene, Ta(CHCMe<sub>3</sub>)(H)(L)<sub>3</sub>(Cl)<sub>2</sub>, which gave defined products reproducibly.<sup>23</sup> On termination the polymer could be recovered and resuspended in fresh solvent under ethylene whereby it continued to take up ethylene but at a significantly lower rate. This was suggestive of the formation of a living polymer. There was evidence of a good deal of chain transfer. The proposed mechanism was *via* a metallacyclobutane hydride intermediate.



It was believed that the alkylidene hydride complex could be a catalyst for the stereospecific polymerisation of propylene.<sup>24</sup> Studies of this and related compounds suggested structures (22) and (23).<sup>25</sup>

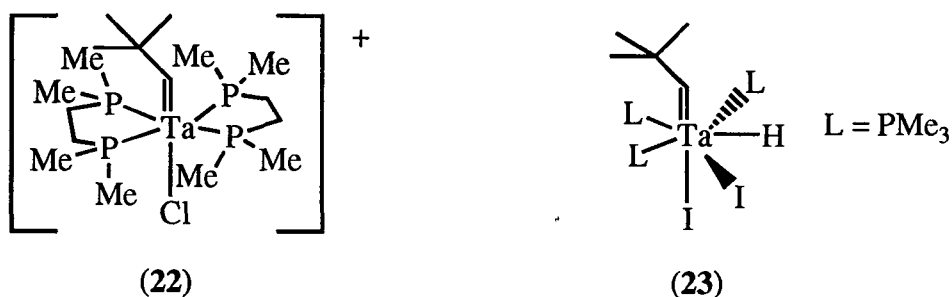
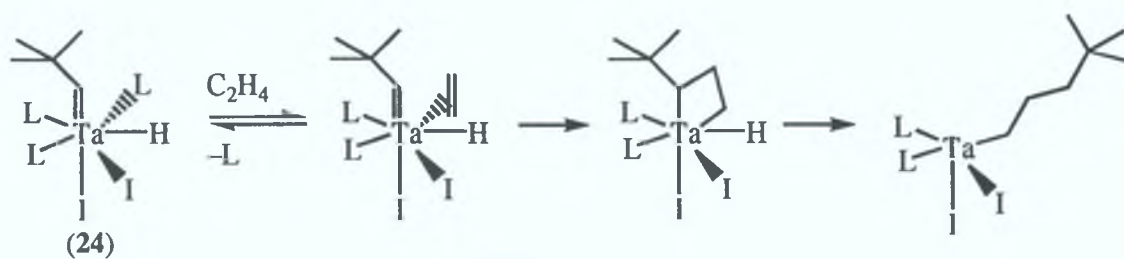


Figure 9

This led to the proposed detailed mechanism which depends on the lability of the ligand L (L = PMe<sub>3</sub>) (Scheme 21).<sup>26</sup> The labile ligand is assumed to be that nearest the

hydride. As such, when excess  $\text{PMe}_3$  is added, the reaction proceeds much more slowly indicating that this is the rate limiting step.



Scheme 21

As stated above, the tantalacyclobutane intermediate (25) was often postulated but was not isolated and characterised until 1988.<sup>27</sup>

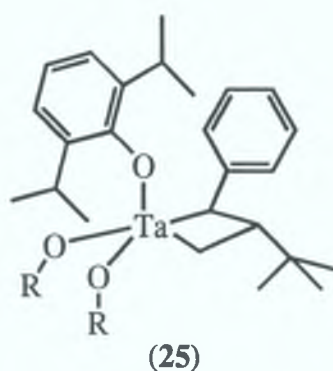
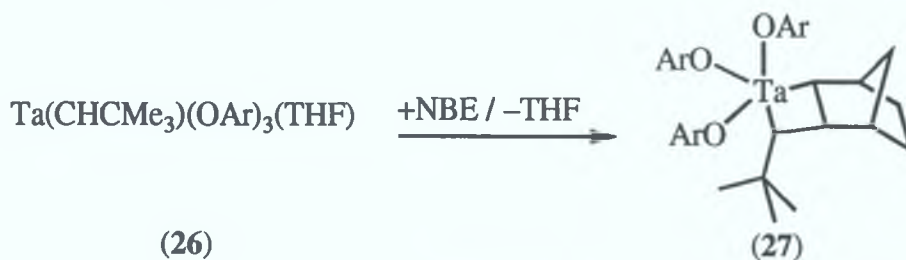


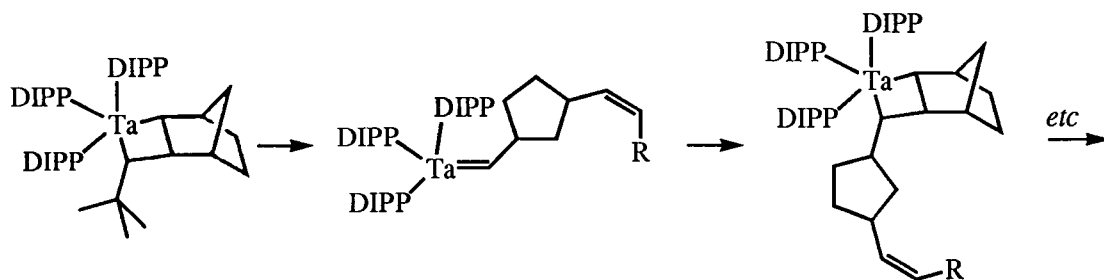
Figure 10

The structure is half-way between a square pyramid and a trigonal bipyramid and was achieved by reacting  $\text{Ta}(\text{CHCMe}_3)(\text{DIPP})_3(\text{THF})$  (26) (where DIPP = diisopropyl phenoxy) with styrene. Another tantalacycle was achieved by reacting (26) with norbornene (NBE) to give (27).<sup>28</sup>



Scheme 22

In the presence of excess norbornene, polymerisation is observed with the collapsing of the tantalacyclobutane as the rate limiting step for the complex containing DIPP.



Scheme 23

When DIPP is exchanged for 2,4,6 trisopropyl benzene thiolate (TIPT) giving structure (28) (not shown) a different picture emerges. The reaction does not progress at room temperature in THF. Similarly when the catalyst is co-ordinated with pyridine no reaction is observed at room temperature. At elevated temperatures where the base-free compound becomes available an amount of norbornene is consumed. Again by adding pyridine the rate reduces. This suggests that the rate limiting step is the loss of coordinating base. However, the catalyst (28) (where base = THF or pyridine) gives a polynorbornene polymer with low molecular weight dispersion ( $M_n=59000$ ,  $d=1.05$ ) compared with (26) ( $M_n=146000$ ,  $d=4.41$ ) under the same conditions. The fact that (28) is a poor metathesis catalyst and (26) is quite good is one explanation for the different polymerisation activities of the two complexes.

Although niobocene and tantalocene dichlorides were found to be inactive as polymerisation catalysts in the presence of MAO (methylalumoxane), analogues in which one Cp ligand was replaced with  $\eta^4$ -butadiene were found to be effective.<sup>29</sup> Dialkyl analogues were investigated and the catalysts (29–31) were synthesised.

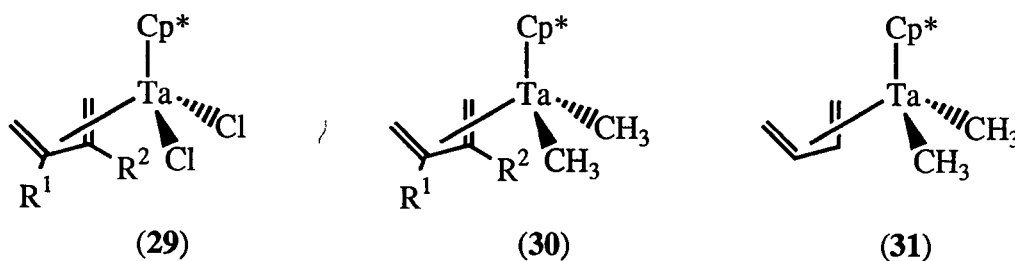
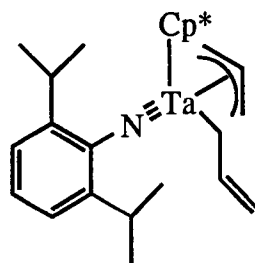


Figure 11

The tantalum species with the smaller Cp ligand was more active at  $-20^\circ\text{C}$ , acting as a living polymer. That with niobium was even more active

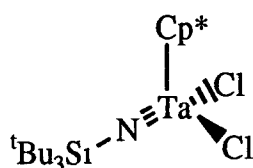
Half-sandwich complexes were used for the polymerisation of ethylene<sup>30</sup> The report cited a related vanadium system but found activity with allyl imido complex (32) in the absence of MAO.



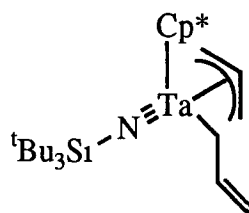
(32)

Figure 12

The reaction takes place in fluorobenzene with (32) and a salt of  $B(C_6F_5)_4^-$  Another complex (33) was active in the presence of MAO but (34) was inactive



(33)



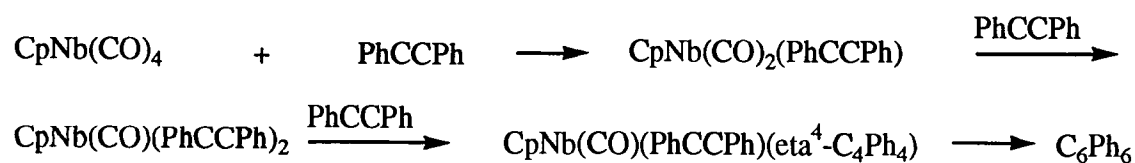
(34)

Figure 13

The bulky  $tBu_3Si$  group is believed to shield the low co-ordinate metal centre, preventing dimerisation to an inactive catalyst, but allowing co-ordination of the alkene. It may also prevent MAO from attacking the basic N atom

#### 1.2.2.4 Alkynes

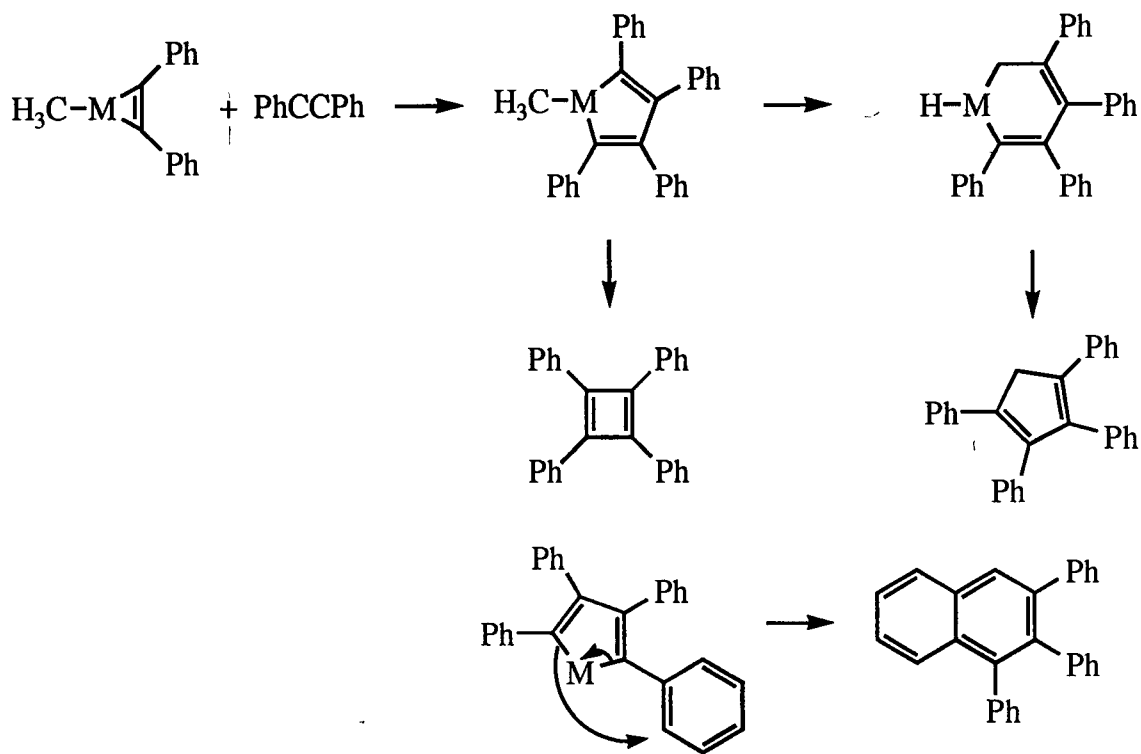
Cyclotrimerisation of alkynes and their polymerisation have proved to be successful A Russian group used a CO complex of Nb to achieve this<sup>2</sup>



Scheme 24



In the reaction of diphenylacetylene with  $\text{NbCl}_5$  some polymeric products, 1,2,3-triphenylnaphthalene, 1,2,3,4-tetraphenyl cyclopentadiene and 1,2,3,4-tetraphenylcyclobutadiene were detected<sup>31</sup> The proposed mechanisms are shown below.-

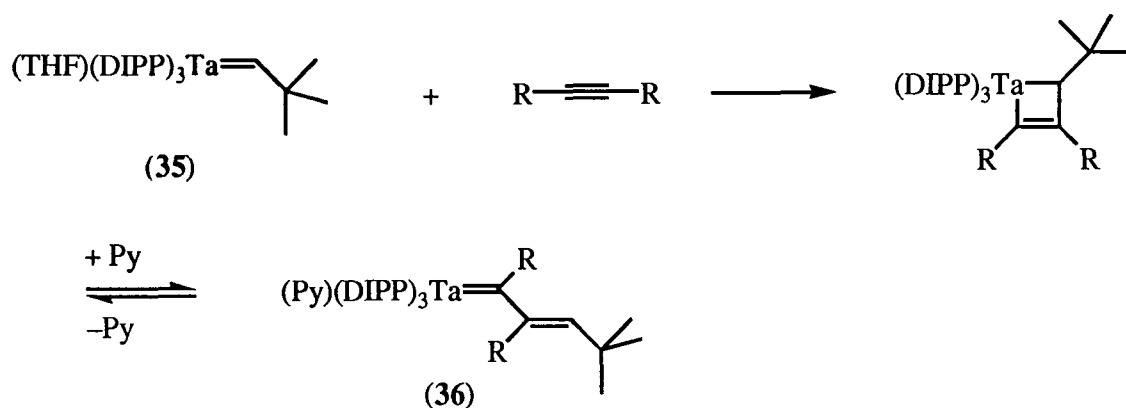


Scheme 25

A variety of alkynes were reacted in the presence of  $\text{NbCl}_5$  and it was found that the product depended on whether terminal or internal alkynes were used. Phenylacetylene trimerised, internal alkynes polymerised and 1,7-octadiyne underwent intramolecular ring closure to form 1,4 *bis* tetralin butane<sup>32</sup> The polymerisation of 1-trimethylsilyl, 2-methyl acetylene was catalysed by  $\text{NbCl}_5$  to give a polymer with a narrow weight dispersion ( $d=1.2$ ). The polymer weight could be controlled by varying the catalyst:monomer ratio. This is an example of Lewis-acid catalysis with  $\text{NbCl}_5$ .<sup>33</sup>

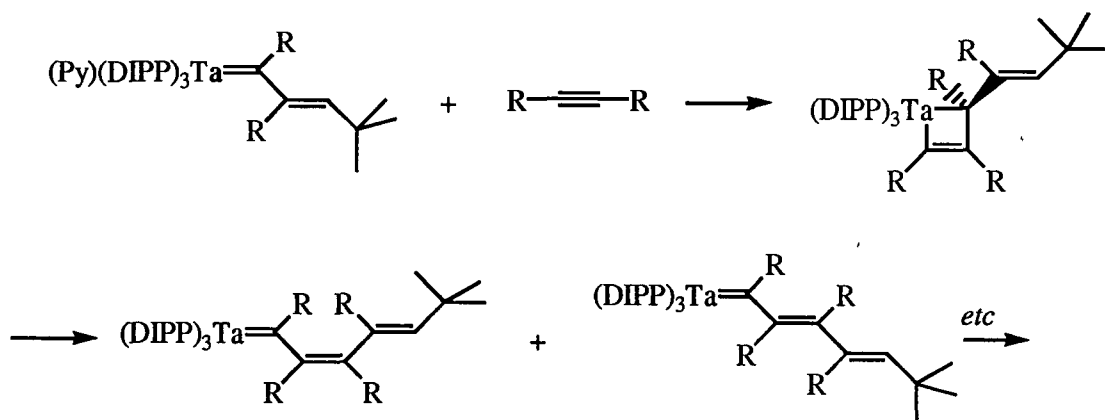
Schrock's group developed a catalyst for polymerising acetylene.<sup>34</sup> They cite the benefits of polyacetylene as being a good conductor when doped and as having properties which make it useful for selective membranes for gases and liquids. The same catalyst as that used for norbornene polymerisation<sup>28</sup> was employed. One of the important features of the initiation is the formation of the metallacyclobutane ring by

elimination of the co-ordinating solvent. In the presence of base the metallacyclobutene is in equilibrium with the alkylidene structure



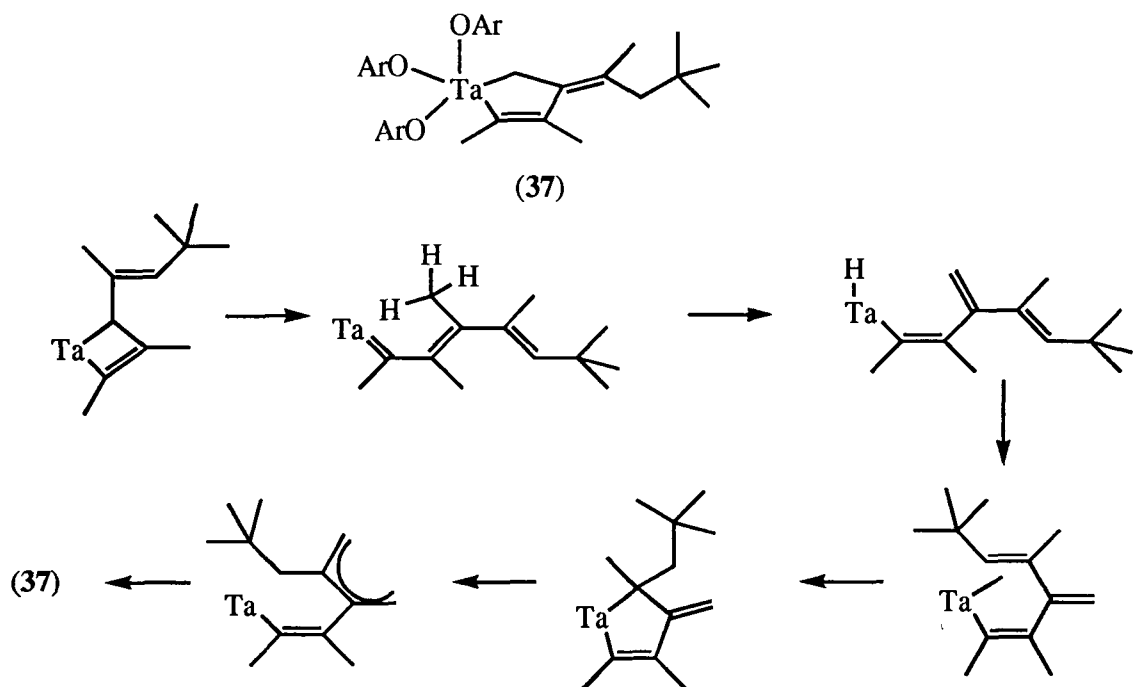
Scheme 26

The polymerisation can continue via (36)



Scheme 27

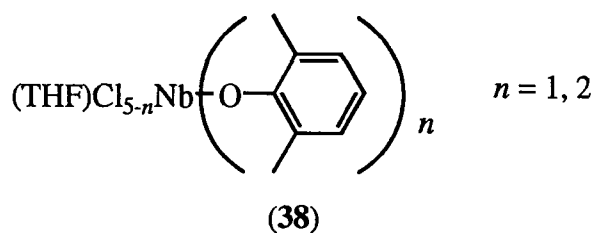
The reaction of one equivalent of 1,2-dimethyl acetylene gives an unexpected structure (37) and the proposed mechanism for its formation is shown below



**Scheme 28**

This polymerisation resulted in a polymer which was monodisperse and increased in molecular weight in proportion to the amount of monomer added. This was described as being indicative of a living polymerisation *via* a single mechanism and an initiation rate that is greater than or equal to the rate of propagation. The thiolate structure (28) gave a poorly defined polymer with high dispersity.

A Japanese group reported that compounds of type (38) can polymerise alkynes in the presence of a Grignard reagent or an alkyl aluminium.<sup>35</sup>

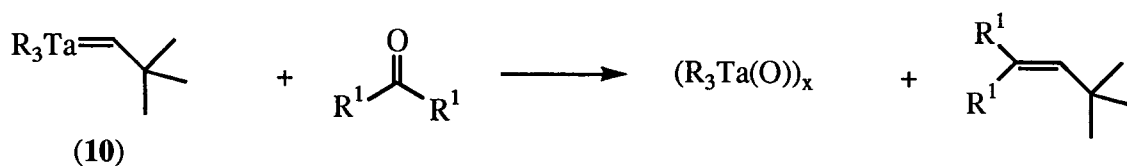


**Figure 14**

Unlike  $\text{NbCl}_5$ , in the catalysis of 1,2-di-*tert*-butylacetylene, (38) afforded polymers of molecular weight *circa*  $2 \times 10^6$  as opposed to trimers. When a less bulky alkyne like the 1, 2-diethyl was used only cyclotrimers were produced. It is believed that the ligand acts sterically to block the co-ordination site for trimers.

### 1.2.3 Nucleophilic Reactions

Nucleophilic reactions involving group V metal complexes were first described by Schrock<sup>36</sup>. The major difference between the group V alkylidenes and the carbenes of later transition metals is that the former are nucleophilic whilst the latter are electrophilic. The group used neopentylidene complex (10)<sup>14</sup> in reactions with carbonyl bearing compounds to yield products analogous to those from the Wittig reaction. Schrock tentatively proposed the metallabuta-oxirane (39) as an intermediate.



Scheme 29

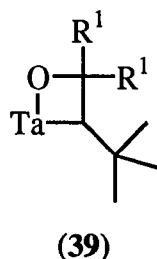

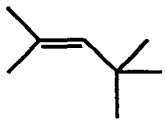
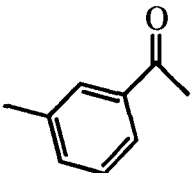
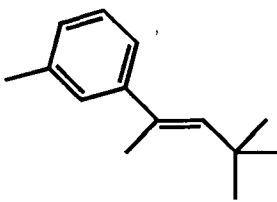
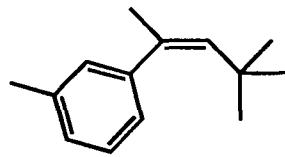
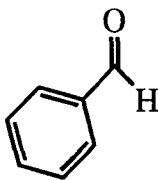
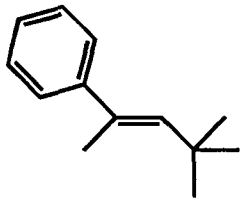
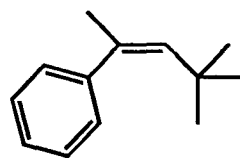
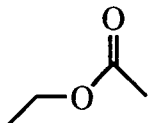
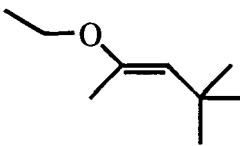
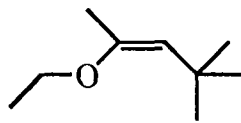
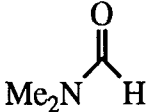
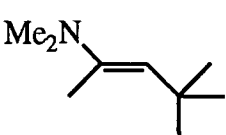
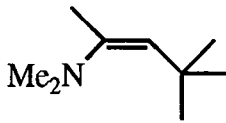
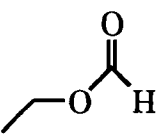
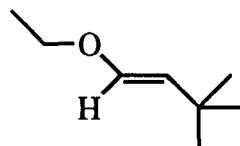
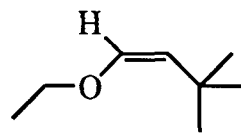


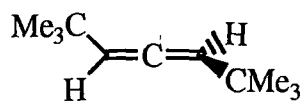
Figure 15

The reaction with acetone gave a very high yield of alkene and a number of other reactants were examined. The results can be seen in Table I.

Table I

Compound	Product	Yield
		80%
	 + 	90%
	35	65
	 + 	90%
	35	65
	 + 	60%
	2	1
	 + 	77%
	95	5
	 + 	90%
	1	1

In general esters and amides reacted more slowly than aldehydes and ketones with highly substituted compounds also reacting more slowly than those with a more exposed carbonyl functionality. The *E:Z* selectivity varied widely as can be seen in the results. This system allowed reaction with carbonyl compounds not easily coupled *via* a standard Wittig. Interestingly, the alkylidene (**10**) reacts instantly with CO<sub>2</sub> to form the allene (**40**).



(40)

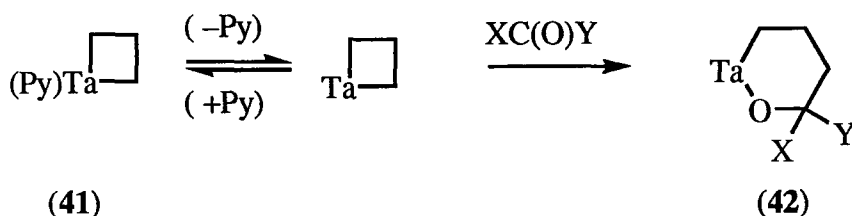
Figure 16

These reactions were extended later to other complexes (26) and (28)<sup>28</sup> The result of these reactions are presented in Table II.

Table II

<u>Complex</u>	<u>Compound</u>	<u>Product</u>	<u>Yield</u>	<u>Cis:Trans</u>
26			95%	
26	PhCHO		96%	1 2
26	Ph <sub>2</sub> CO		88%	
26	DMF		95%	100% <i>trans</i>
28	PhCHO		82%	1 1

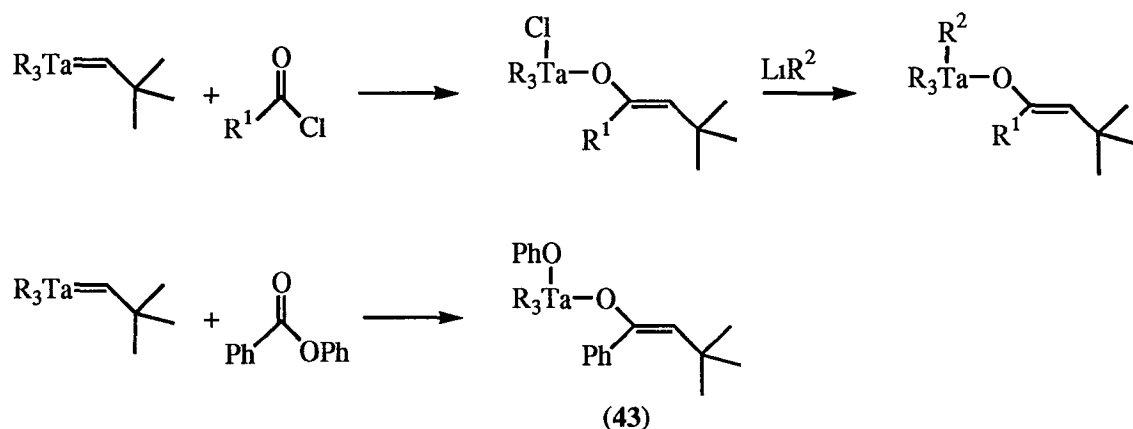
Metallacycles like (41) also react directly to give products similar to those above indicating that the four-membered ring is a viable intermediate structure. However in some cases the organic carbonyl inserts into the Ta–C bond to give an oxyantalacyclohexane(42)

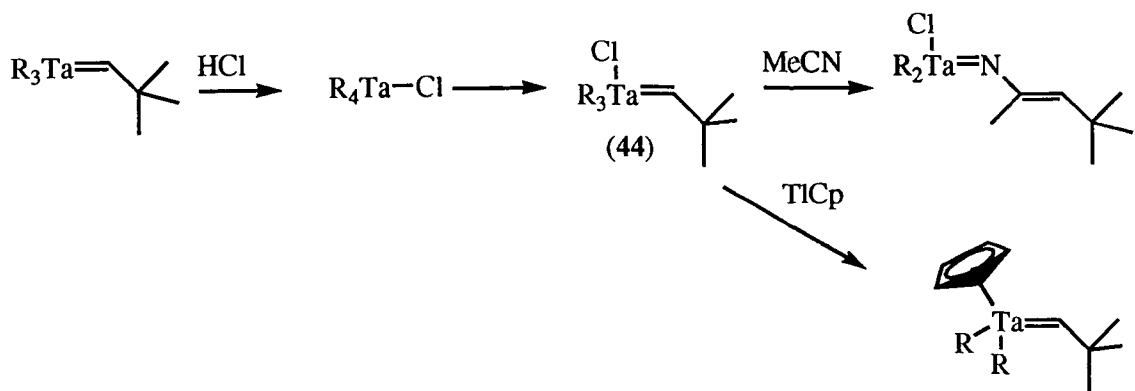


Scheme 30

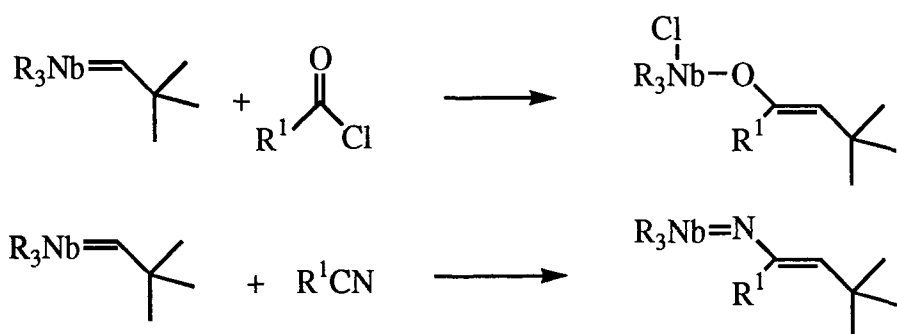
The proportion of insertion to Wittig-type product is dependent on the substitution of the tantalacyclobutane ring, the carbonyl compound and the temperature.<sup>28</sup>

Schrock demonstrated a number of other nucleophilic reactions of the neopentylidene complex in reactions with acyl halides, nitriles, esters and HCl<sup>37</sup> Reactions were performed with tantalum and niobium





Scheme 31

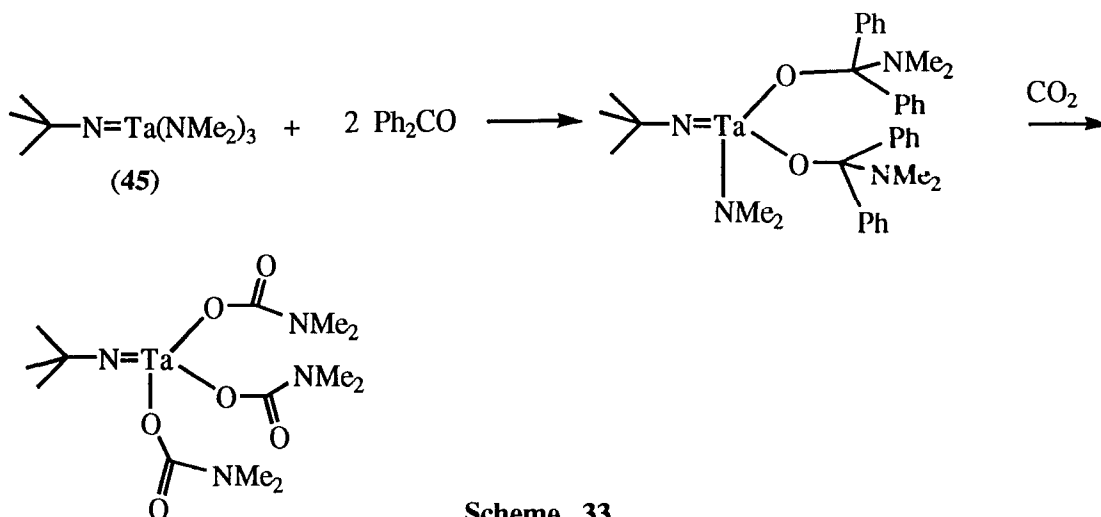


Scheme 32

The formation of (43) is anomalous considering other ester reactions<sup>36</sup> and the structure (44) is unverified but assumed given the products of its reactions with TICp or MeCN. The reactions involving Nb are limited only by the availability of the alkylidene and the other reactions are assumed to be just as feasible.

A butylimido complex of tantalum (45) was found to react with benzophenone<sup>38</sup> When two equivalents of benzaldehyde are used an insertion reaction occurs (Scheme 33) and the benzophenone is displaced leaving the carbamate. Reaction of (45) with benzaldehyde yields the imine PhCH=N<sup>t</sup>Bu (46) However, it was pointed out that this could arise from free <sup>t</sup>BuNH<sub>2</sub> present as a result of catalytic amounts of H<sup>+</sup>.





Scheme 33

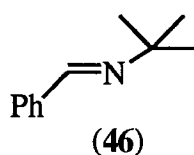
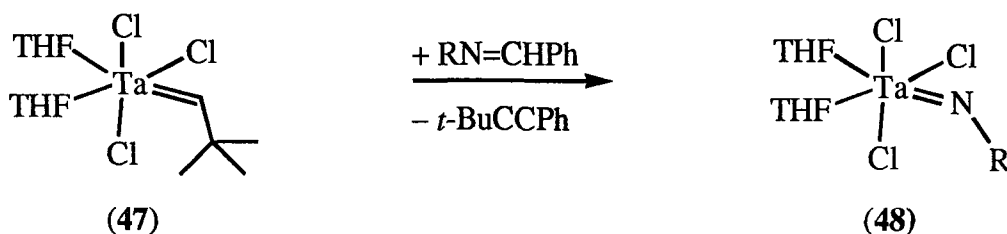


Figure 16

A neopentylidene ligand was reacted with a Schiff base to give an alkene and a tantalum imido complex<sup>39</sup>

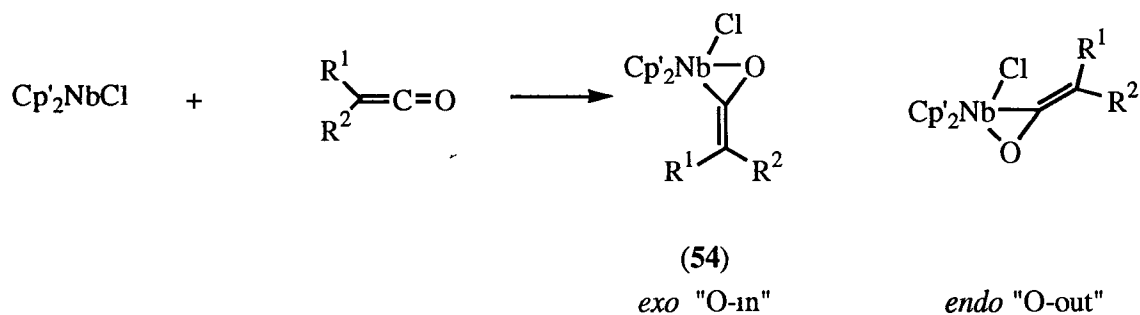


Scheme 34

The Ta=N-R angle is almost 180°, *i.e.* Ta=N is closer to a triple bond making this transformation plausible, the strength of the bond formed being the driving force. More complexes of this type were formed by replacing THF with PMe<sub>3</sub> to give (49), reduction of (49) with Na/Hg amalgam in the presence of PMe<sub>3</sub> to give (50) and addition of an alkene ligand to give (51).



Bruno's group have been studying the synthesis and reactivity of niobocene ketene complexes. Using  $\text{Cp}'_2\text{NbCl}$  and a number of ketenes they formed the complexes regioselectively in the *exo* (O-in) conformation<sup>41</sup>



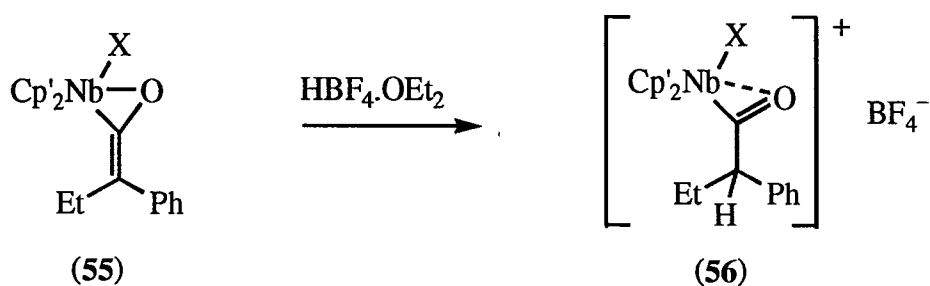
Scheme 38

Where  $\text{R}^1 = \text{Me}$  and  $\text{R}^2 = \text{Ph}$  (*i.e.* unequal) the *E/Z* ratio was 81:19.



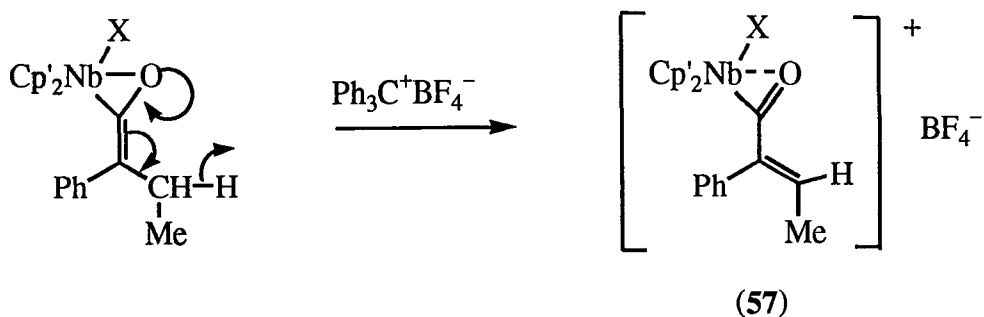
Figure 17

Compound (54) was reduced to the hydride using a Na/EtOH/Na cycle. It was further possible to protonate both the chloride and the hydride and study the enolisation of the complexes. They proved to be a great deal more acidic than comparable ketones<sup>42</sup>



Scheme 39

Conversely, by using triphenyl carbenium tetrafluoroborate a  $\gamma$ -hydride abstraction can be effected from the chloro compound with stereospecific formation of the *E*-enaclyls<sup>43</sup>



Scheme 40

Further treatment of (57) with  $\text{KOtBu}$  yielded the vinyl ketene (58).<sup>44</sup>

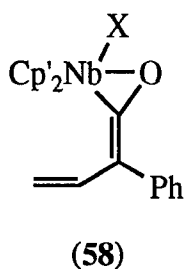
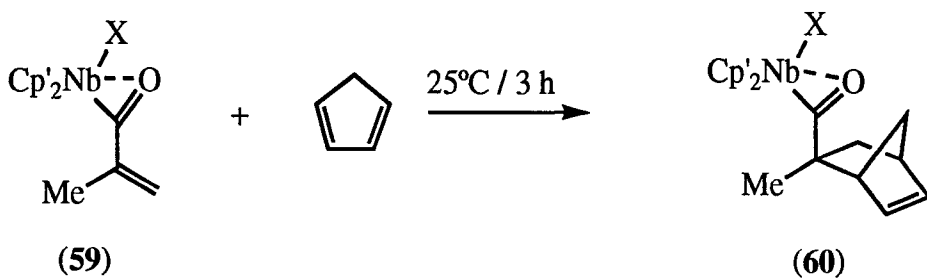


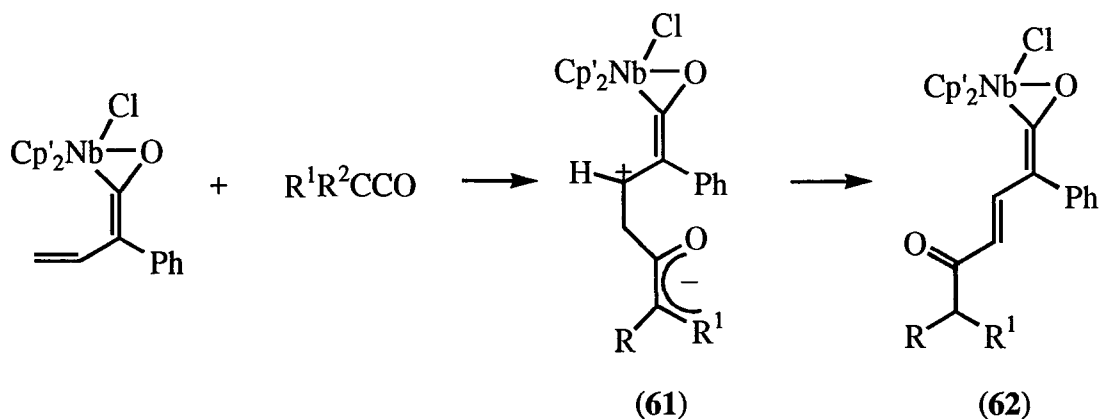
Figure 18

Compound (59) underwent a Diels-Alder type addition with cyclopentadiene to yield the *exo* product (60) only.



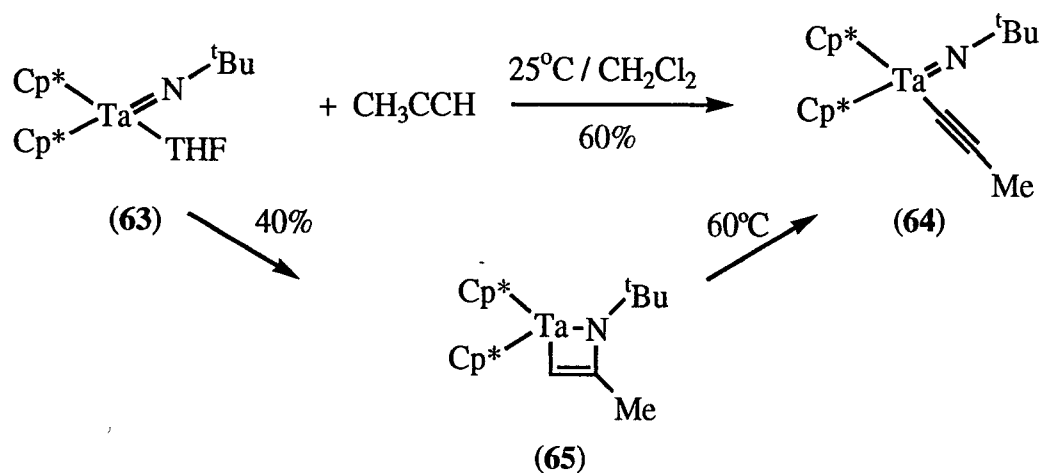
Scheme 41

However vinyl ketenes failed to undergo a similar reaction. Instead they reacted with free ketene. The organic ligand can be isolated by mild oxidation of the complex.<sup>43</sup>



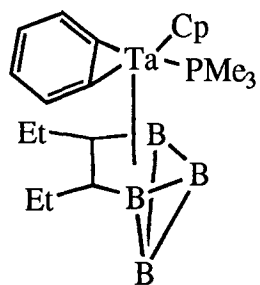
Scheme 42

The reaction of a tantalum imido complex provides an example of an  $\alpha$ -H abstraction where no  $\beta$ -H is available<sup>45</sup>. There were two products of the complex in its reaction with methyl acetylene but on heating compound (65) reverted to (64) presumably by the mechanism shown



Scheme 43

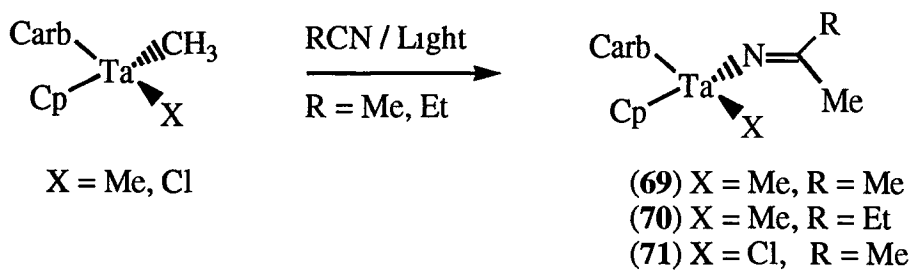
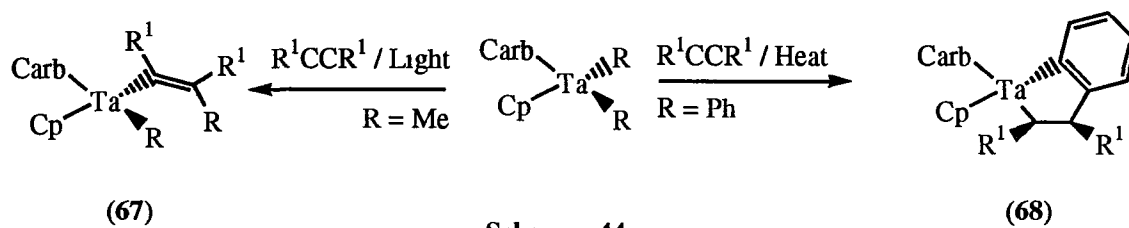
Carborane substituted complexes are more stabilised at the metal centre than their *bis* Cp analogues and thus complexes with a benzyne ligand are possible (66).<sup>46</sup>



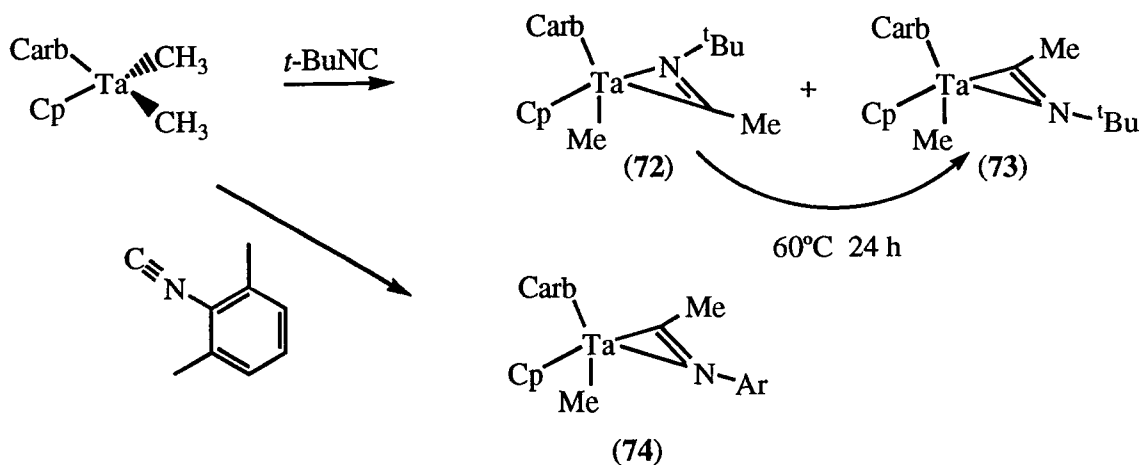
(66)

Figure 19

Related phenyl and methyl complexes undergo reactions with alkynes and nitriles slowly and rapidly with isocyanides (Schemes 44–46).<sup>47</sup>



Scheme 45

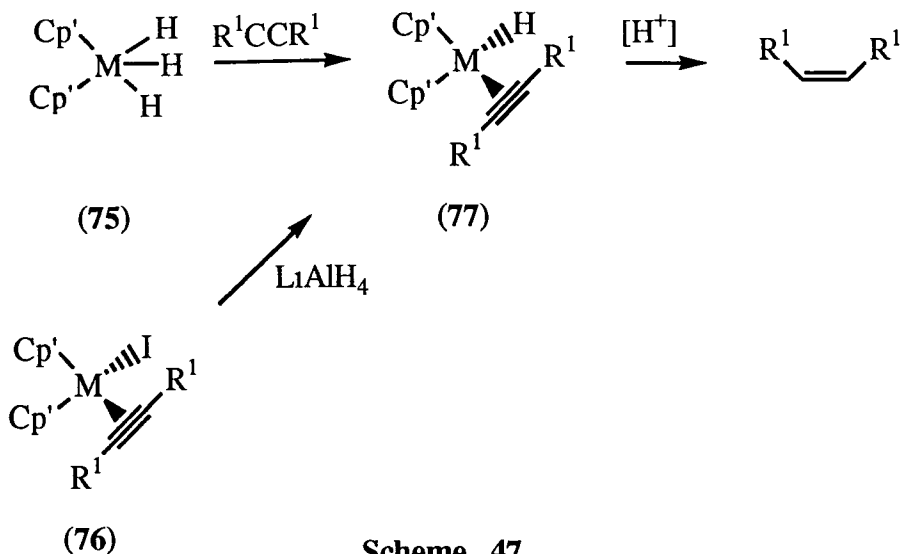


**Scheme 46**

It was suggested that in the reaction between the carborane compound and *t*-butyl isocyanide that (72) (*N-out*) was the kinetic product and (73) the thermodynamic product. Hence (72) could be converted to (73). The potential for ligand isolation was not discussed.

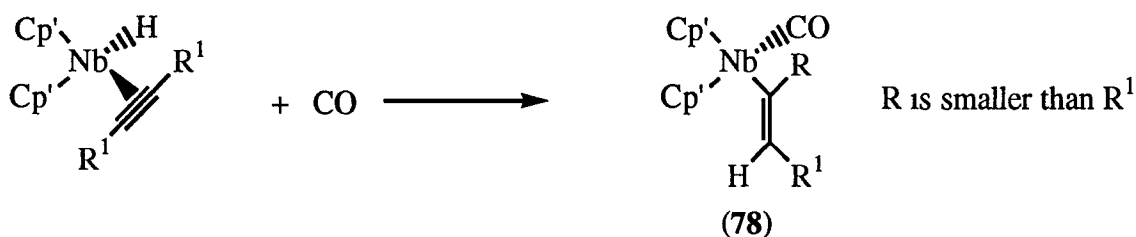
### 1.2.4 Hydrogenation

The use of niobium and tantalum compounds as reduction catalysts has received greater attention in recent years. An early example involved the hydrogenation of alkynes to yield the *cis* alkene. The hydridoalkene could be made by direct reaction with  $\text{Cp}'_2\text{TaH}_3$  or by reducing  $\text{Cp}'_2\text{TaI}(\text{CR}'\equiv\text{CR})$  with  $\text{LiAlH}_4$ . Treatment of the complex with acid yielded the alkene.<sup>48</sup>



**Scheme 47**

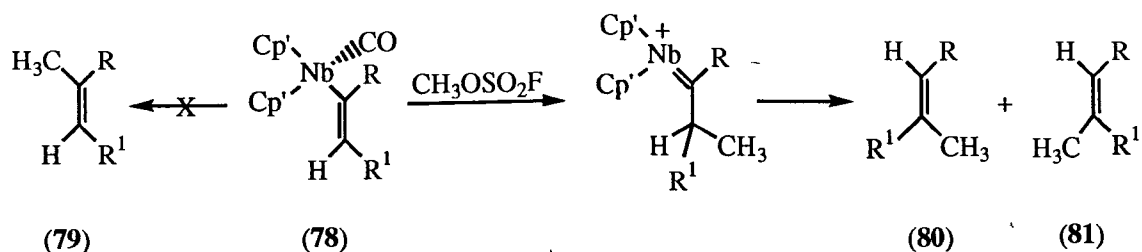
As regards the orientation of the acetylene group, it was found that the sterically less bulky R group tended to be in proximity with the hydride on the metal. The acetylene hydride complexes of Nb behave in a similar manner.<sup>49</sup> Attempts to methylate acetylene by treatment of (77) with methylfluorosulphonate failed, with evolution of methane and acetylene being the result. It was believed that methylation and protonation both occur at the metal centre prior to transfer to acetylene, but that reductive elimination of CH<sub>4</sub> was too fast to allow acetylene insertion into the Nb–H bond to compete. By reacting (77) with CO, the carbonyl (78) is formed. There is a high regioselectivity of insertion with Nb going to the carbon with the smallest substituent



**Scheme 48**

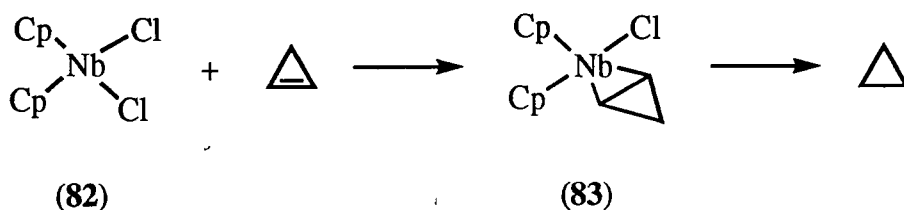
Again (78) will react with acid to give the *cis* olefin but reaction with methylsulphonate does not give the expected olefin (79) via insertion. Rather methylation occurs “allylically” at the β vinyl carbon giving both isomers.





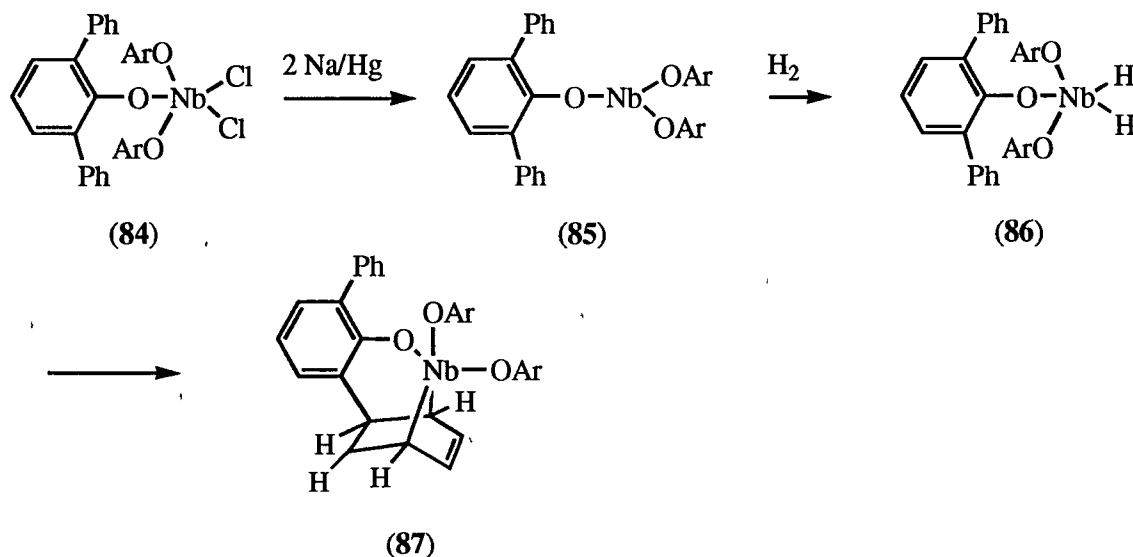
**Scheme 49**

Cyclopropene was reduced to cyclopropane *via* initial complexation to  $\text{Cp}_2\text{NbCl}_2$  and treating this complex with  $\text{HCl}$ .<sup>50</sup>



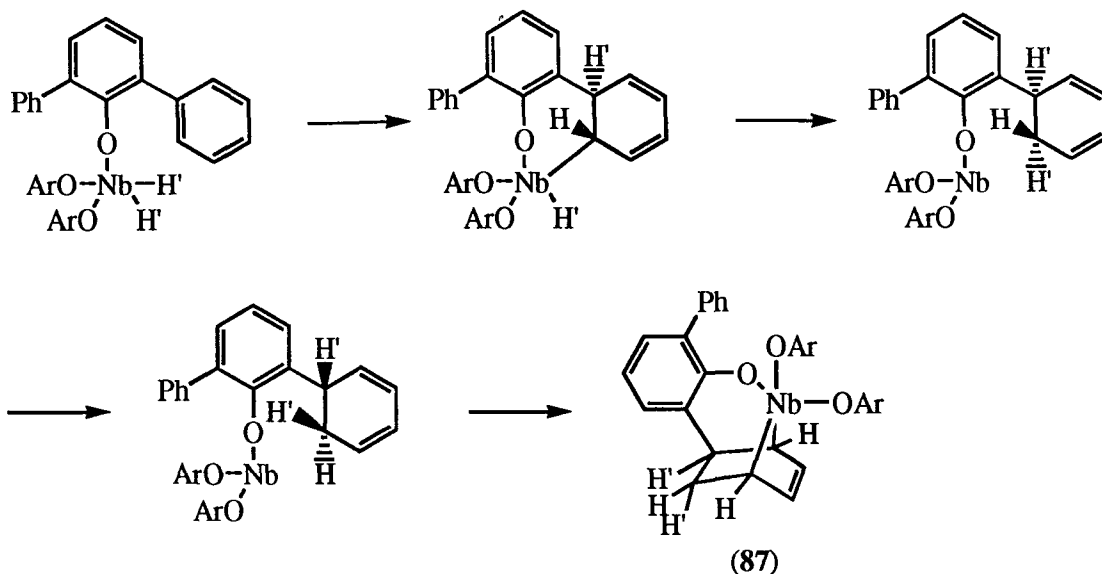
**Scheme 50**

Rothwell's group describe an intramolecular hydrogenation in niobium aryloxy complexes.<sup>51</sup> When the aryloxy group is 2,6-diphenyl phenol, one of the substituent phenyl groups can be reduced and then co-ordinates to the metal in the manner of 1,3-cyclohexadiene.



**Scheme 51**

Because the two hydrogen atoms introduced to the ring are mutually *cis* and because their position is opposite the side of the ring to which the metal is bound, the following mechanism was proposed:-



Scheme 52

The exact positions of the added H atoms were elucidated by deuterium labelling. Although there were no organic products from this work, it paved the way for a good deal of catalytic work. Complete hydrogenation of the phenyl substituents of the OAr group was achieved and following hydrolysis of the products, dicyclohexyl phenol was recovered.<sup>52</sup> However, with 2,4,6-triphenylphenol only the phenyls in the 2 and 6 positions were hydrogenated. This lent more evidence to the mechanism described above and strongly suggested a niobium-hydride intermediate. Further, a deuterium labelling study found that the cyclohexyl ring was of the form (88).

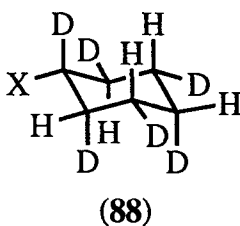
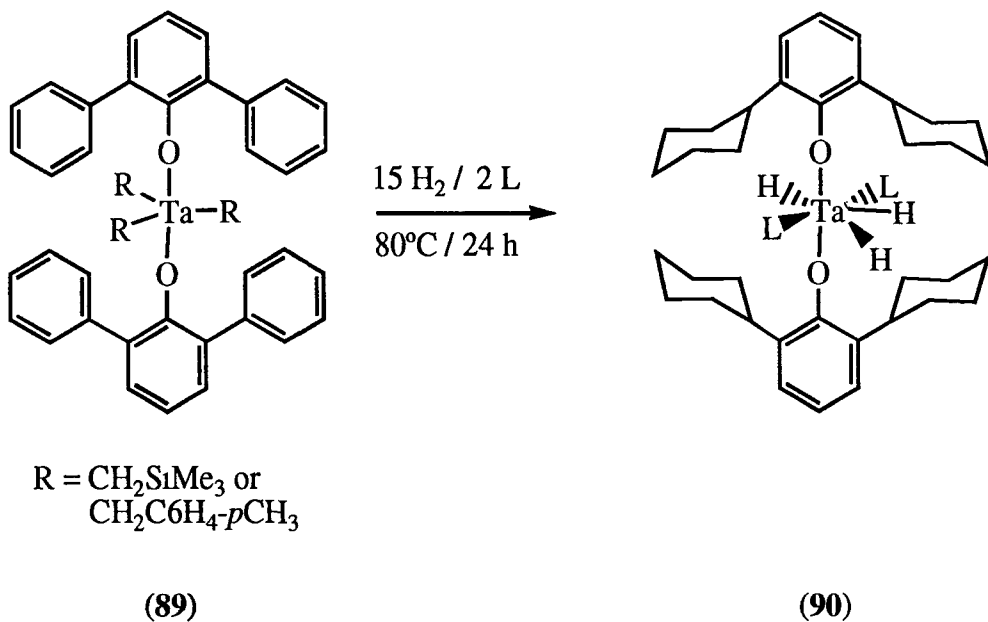






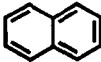
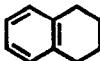
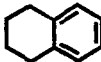
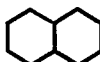
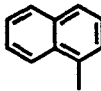
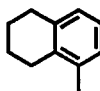
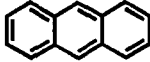
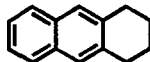
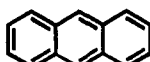
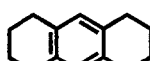
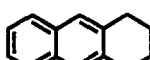
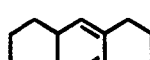
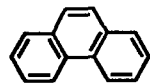
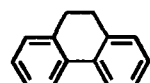
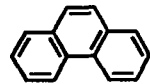
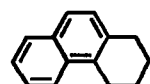
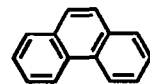
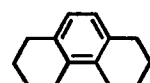
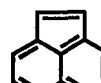
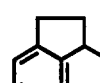
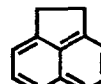
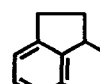


Figure 20

There are two D atoms on one face and four on the other. This suggests that the initial two D atoms are incorporated leading to (87), and from there the complex is deuterated on the face close to the metal. Related hydride complexes were isolated and applied to arene hydrogenation.<sup>53</sup> The complexes were derived from tantalum alkyl aryloxy compounds which were hydrogenated in the presence of basic ligands.



**Scheme 53**

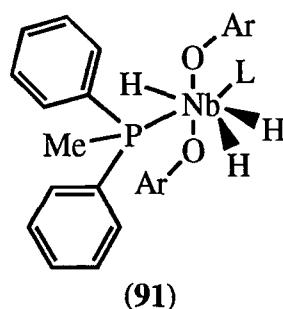
As might be expected, in the case where the aryloxy substituents possess phenyl rings in the *ortho* position, these were reduced to cyclohexyls. A 5 mol% solution of (90) in hexane effected a 60% conversion of naphthalene to tetralin. The structure of the compound was found to be pentagonal bipyramidal<sup>54</sup> and that under certain conditions phosphine ligands bearing phenyl rings were hydrogenated.<sup>55</sup> The application of the catalyst to arene hydrogenation was extended and some results are shown in Table III<sup>65,57</sup>

<u>Starting Material</u>	<u>Product</u>	<u>Conditions</u>
		100°C / 1200 psi H <sub>2</sub> 1 h / 0 25% cat
		100°C / 1200 psi H <sub>2</sub> 1 h / 0 50% cat
		100°C / 1200 psi H <sub>2</sub> 6 h / 5% cat
		80°C / 1200 psi H <sub>2</sub> 24 h / 0 25% cat
		80°C / 1200 psi H <sub>2</sub> 24 h / 0 25% cat
		100°C / 1200 psi H <sub>2</sub> 6 h / 5% cat
		100°C / 1200 psi H <sub>2</sub> 6 h / 5% cat
		100°C / 1200 psi H <sub>2</sub> 6 h / 5% cat
		100°C / 1200 psi H <sub>2</sub> 6 h / 5% cat
		100°C / 1200 psi H <sub>2</sub> 6 h / 5% cat
		100°C / 1200 psi H <sub>2</sub> 6 h / 5% cat
		80°C / 1200 psi H <sub>2</sub> 24 h / 0 25% cat
		80°C / 1200 psi H <sub>2</sub> 24 h / 0 25% cat
		80°C / 1200 psi H <sub>2</sub> 24 h / 0 25% cat

The hydrogenation proceeds in a regiospecific manner providing all *cis* hydrogenation. In the case of fused rings, these species hydrogenate at a rate considerably faster than benzene and thus the hydrogenation of naphthalene can be effected in benzene solution. Where one of the fused rings is substituted, it is the unsubstituted ring which is

preferentially hydrogenated. The niobium version of the catalyst has much the same activity.

The fact that aromatic phosphine ligands (mentioned above) may be hydrogenated has been exploited.<sup>57,58</sup> Although a large number of heterogeneous hydrogenation catalysts bear phosphine ligands this is the only example of their phenyl substituents being hydrogenated. The niobium hydride (**91**) exhibits much greater activity than the tantalum variety. An intermediate with partial saturation of the phenyl ring has never been detected



**Figure 21**

Despite the fact that cyclohexylphosphines are more basic and might be expected to bind more tightly than the substrate to the metal centre, the reaction is catalytic. The other substituents on the metal probably inhibit the ability of the product phosphine to bind. A number of phosphines which have been reduced are outlined in Table IV. Among some of the interesting ones are those in which only one cyclohexyl ring has been formed. These ligands are chiral due to the barrier to pyramidal inversion in P atoms. This well-characterised system has been patented.

Table IV

Substrate	Product		
			Both Diastereomers

Structures related to (87), *ie* cyclohexadiene co-ordinated to tantalum and niobium compounds were synthesised <sup>59</sup>

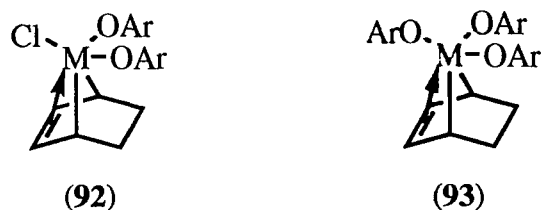


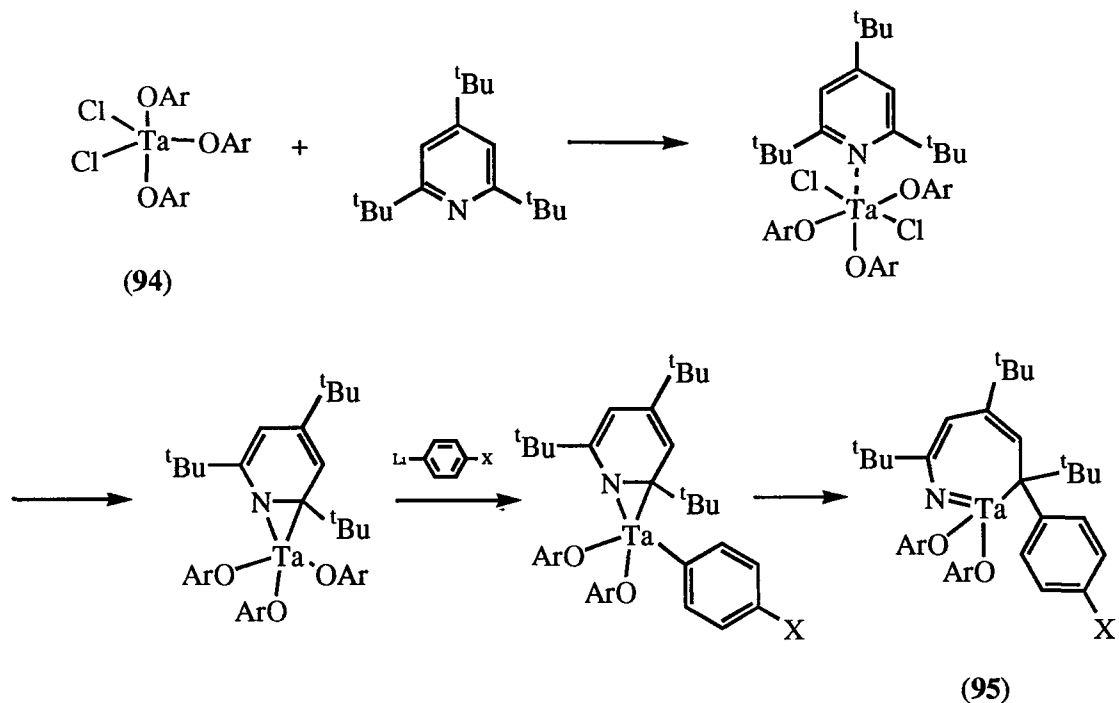
Figure 22

Compound (93) catalyses the disproportionation of 1,3-cyclohexadiene into cyclohexene and benzene as well as the hydrogenation of cyclohexadiene and cyclohexene into cyclohexane. However cyclohexene is not released during this conversion. The hydrogenation of 1,3-cyclohexadiene by (92) goes stepwise via the intermediate cyclohexene. No cyclohexene is hydrogenated until all the diene has been consumed.

## 1.2.5 Other Reactions

### 1.2.5.1 Hydrodenitrogenation

Hydrodenitrogenation is the process whereby nitrogen containing compounds are broken down in petroleum feedstocks, thereby improving the quality of the hydrocarbons. This is usually achieved using heterogeneous catalysts such as sulphided CoMo/Al<sub>2</sub>O<sub>3</sub> or NiMo/Al<sub>2</sub>O<sub>3</sub> under conditions which remove nitrogen as NH<sub>3</sub>. A tantalum complex has been used as a model to investigate the mechanism of the process.<sup>60</sup> The cleavage of the strong C–N bond is crucial to the process and in this system the aromatic N-containing compound co-ordinates in an  $\eta^2$ -C, N fashion. The metal centre is attacked by a nucleophile, followed by migration to the  $\alpha$ -C inducing ring opening.



Scheme 54

### 1.2.5.2 Hydroboration

Finally, a solution of (96) was described as catalysing olefin hydroboration in the presence of catechol borane.<sup>61</sup>

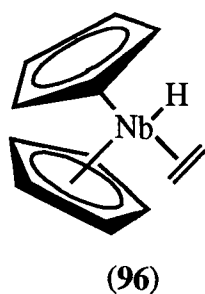


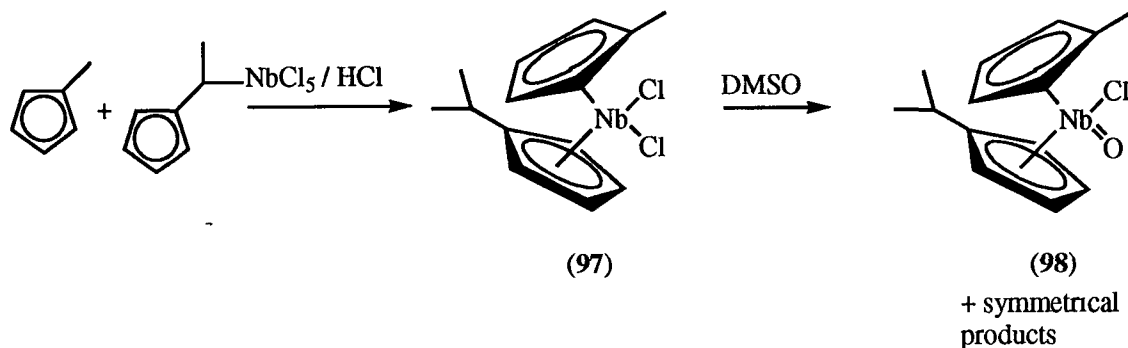
Figure 23

### 1.2.6 Stereochemical Considerations

Molecules containing niobium and tantalum with chirality at the metal centre are rare and those which have been applied catalytically are even less common. A number of these molecules will be examined and speculation as to their catalytic utility will be made.

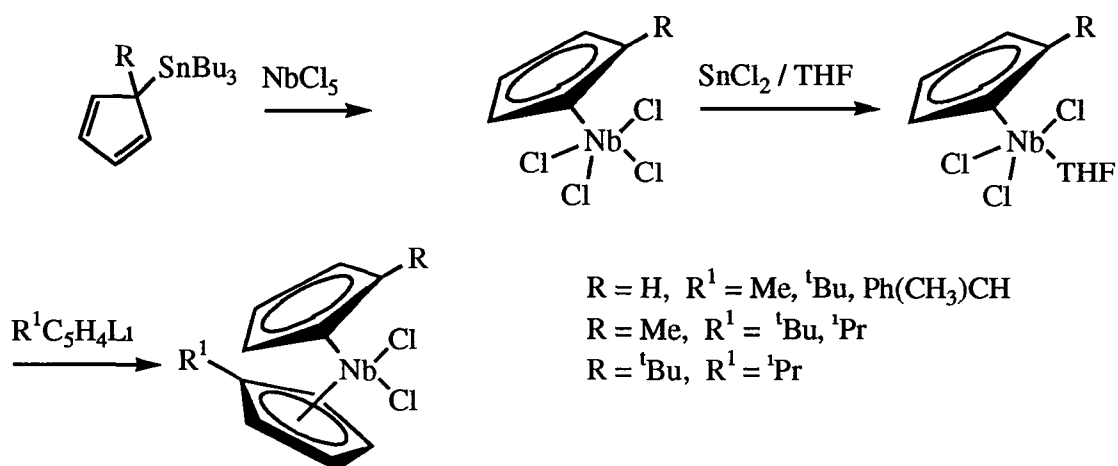


The first group V chiral molecule mentioned in the literature was by Broussier *et al.* whereby one equivalent of each of two different cyclopentadienyl anions were reacted to give an unsymmetrical (prochiral) niobocene dichloride (**97**). They further reacted this molecule with DMSO which oxidised the niobium (IV) complex to the niobium (V) species (**98**). This molecule is chiral<sup>62</sup>



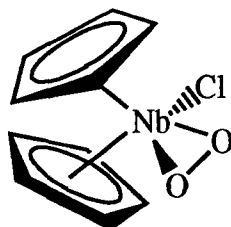
Scheme 55

Making chiral species in a more efficient sequential manner bears the difficulty that simple addition of cyclopentadienyl anion in a 1:1 manner with  $\text{NbCl}_5$  leads to half an equivalent each of  $\text{Cp}_2\text{NbCl}_2$  and  $\text{NbCl}_5$ . Several milder methods for making the monocyclopentadienyl derivatives became available, however.<sup>63</sup> These involve transmetallation from Sn, Mg or Si. Thus Broussier *et al.* refined their method for the synthesis of chiral niobium complexes and were able to do so without the need to separate out the symmetrical species (Scheme 56).<sup>64</sup> It was also possible to achieve the target compound without the reduction step.



Scheme 56

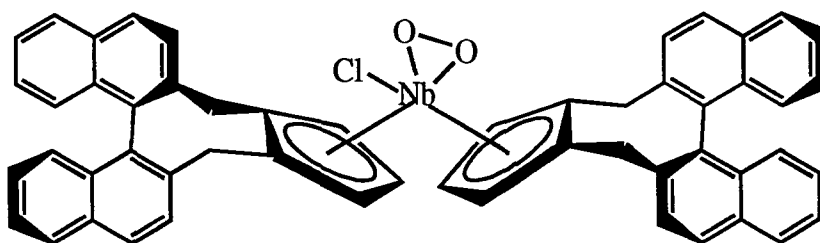
The discovery of a related complex made the catalytic potential of this series more obvious. Sala-Pala *et al* oxidised niobocene dichloride with hydrogen peroxide to give the peroxo species (99)



(99)

Figure 24

This complex catalysed the epoxidation of cyclohexene<sup>65</sup> The potential for chiral catalysis was realised in this series by Haltermann He synthesised a group of Nb and Ti catalysts specifically directed at the epoxidation of *trans* olefins Compound (100) catalyses the epoxidation of cyclohexene giving 35 turnovers and an ee of 10%.



(100)

Figure 25

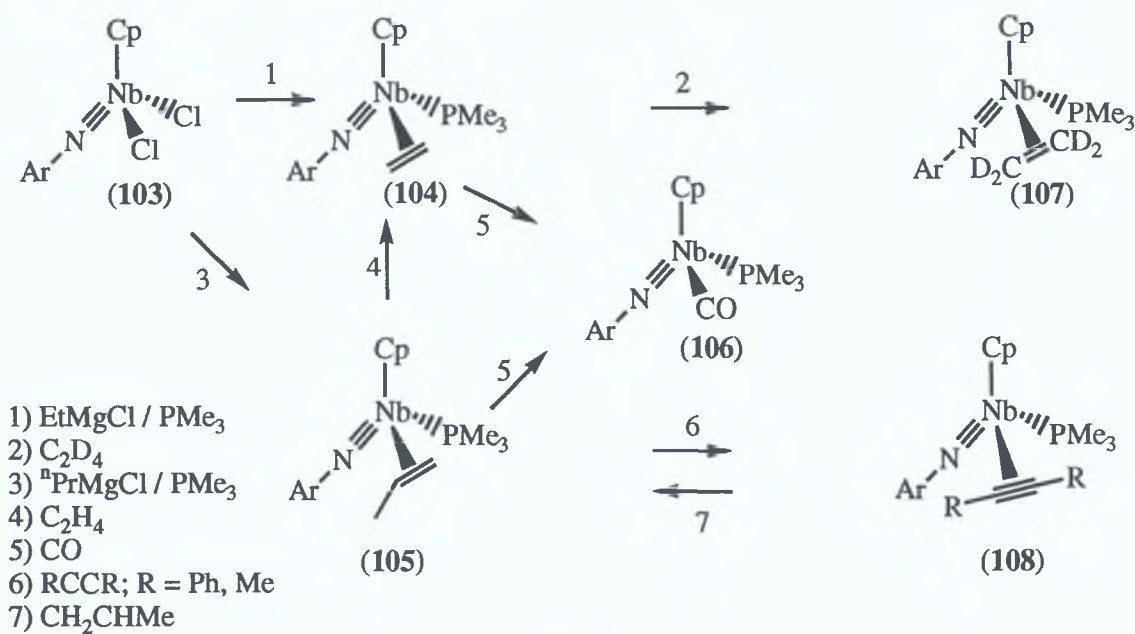
The yield and e e are disappointing and in fact the complex *bis* indenyl oxoniobium chloride, the parent compound, displayed even poorer yield. However the potential for chiral catalysis was demonstrated and this work is discussed in more detail in Chapter 5

The related chalcogen structure (101) has been oxidised to give chiral complex (102) (Scheme 46). Although the *anti* version of (102) was a theoretical possibility, only one isomer was detected using Pirkle alcohol as a shift reagent. This compound bears both niobium-centred and sulphur-centred chirality.



Scheme 57

Half-sandwich complexes of niobium and tantalum bearing an imido ligand have been synthesised.<sup>68</sup> Starting from the dichloro compound (103) the addition of ligand and base leads to structures which are tetrahedral (104–108).



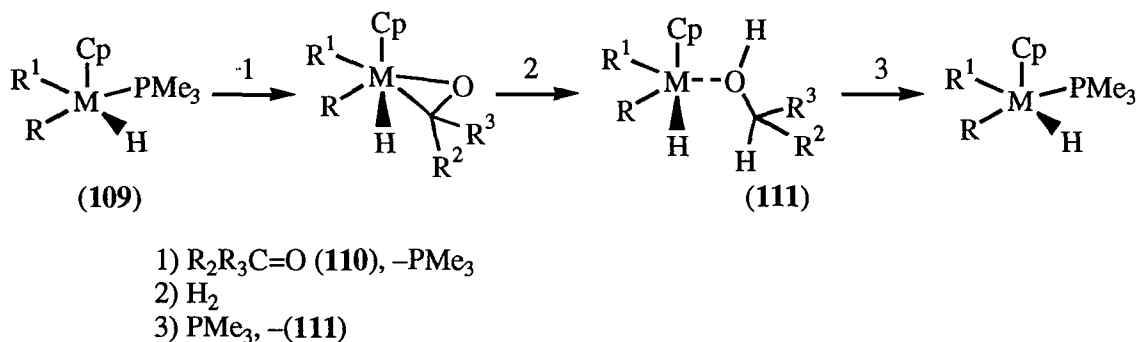
Scheme 58

Of the various possible orientations of (105), *i.e.* where the position of the propylene ligand varies, only the one with the methyl oriented towards the aryl and away from the cyclopentadienyl and the PMe<sub>3</sub> ligand is observed, though obviously as both enantiomers.

### 1.2.7 Potential in Stereoselective Synthesis

Many of the molecules described bear four or more ligands and as such have the potential to be unsymmetrical. Reduction of CO yielded very little catalytic potential

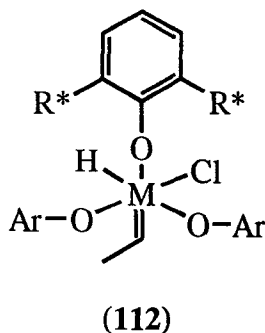
but reduction of ketones proved more useful. Given that this probably occurs through metal-hydride transfer to a co-ordinated carbonyl, by moulding the reaction centre, it might be possible to achieve a chirally enhanced result. Like the alkylidenes which bear nucleophilic character, the group V metal hydrides bear a great deal of hydridic as opposed to acidic character and as early transition metals, Nb and Ta might be made to effect a synthetically useful reduction given the right circumstances. For instance if hypothetical molecule (109) were to bear a weak base  $\text{PR}_3$ , which could be displaced by the prochiral substrate (110) then alcohol (111) could result.



**Scheme 59**

Much more likely would be the potential control of olefin reactions to give selected metathesis products, dimers or polymers. It has already been seen that in the case of the dimerisation of olefins the substituents determine whether it is the head to tail or tail to tail dimer which is formed (Scheme 11–15). Should the Cp ligand in compound (109) bear a bulky chiral group perhaps this could be controlled even further. The alkylidene complexes could also be adjusted in this manner.

Alkene metathesis was best achieved using alkoxy ligands instead of phosphine bases. Stereocontrol of these large ligands might yield a complex which selects for the formation of desired metathesis products

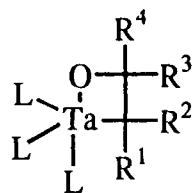


**Figure 26**

This would most likely have to be balanced with an inevitably slower rate of reaction. Metathesis, polymerisation and dimerisation have in common the proposed metallacyclobutane such as (25). Obviously when the four-membered ring bears a

large group, this enhances the possibility of stereocontrol. However, if the ligands are very large, non-bonding interactions with even small groups on the intermediate (and hence the substrate) could influence the products of catalysis.

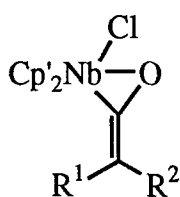
The nucleophilic reactions of Schrock's group seem likely to proceed *via* a four-membered ring-structure such as (113)



(113)

Figure 27

Again the ligand sizes and structures could be investigated for the potential for producing unsymmetrical alkenes selectively. These reactions are, however, likely to be stoichiometric and hence expensive. The singularly *exo* formation of ketene complex as evidenced by Bruno's group (*eg* compound (54)) and the fact that it is largely in the *E* conformation has obvious consequences for its selectivity.



(54)

*exo* "O-in"

Figure 28

Selective hydrogenation of alkynes to the *cis* configuration has been seen and in terms of the binding of the alkynes to the metal, this seems logical. However, the hydrogenation of arenes by Rothwell's group would seem to have great potential. The mechanism is well characterised to give all *cis* hydrogenation. Were substituted arenes to be used (though electron-withdrawing or deactivating substituents might be necessary) the potential for creating synthetically versatile chiral molecules from inexpensive commercially available substrates could be great.

The group V metals are stable with four or five ligands and can also accommodate a number of bases in addition. This gives them enough ligands to bear metal-centred chirality and potentially enough crowding to make them effective as chiral catalysts.

## 1.3 CHIRALITY AND ASYMMETRIC SYNTHESIS

The history of chiral chemistry started in earnest with the work of Pasteur in the 1840's when he separated enantiomers of sodium ammonium tartrate by crystallisation and painstakingly differentiating between the two types of crystals formed. Fischer performed ground-breaking experiments in the field when he converted sugars to the next highest homologues using the hydrocyanation reaction<sup>69,70</sup>. A true understanding of the nature of chirality and the development of theories of stereochemical control based on steric and electronic factors did not come about until the 1940's and 1950's. Around this time, chirally enhanced products were achieved in the reaction of ketones and optically active aluminium alcoholates<sup>71,72</sup> and the Grignard reduction of a ketone to produce optically active alcohols was achieved.<sup>73,74</sup> The outcome of these reactions was given some rationale by Cram.<sup>75</sup> Initially considered somewhat of esoteric and of mechanistic interest only, the discovery of the economic and sometimes tragic biochemical and biomedical implications of enantiomeric purity and impurity has made asymmetric synthesis one of the foremost pursuits of organic chemistry.

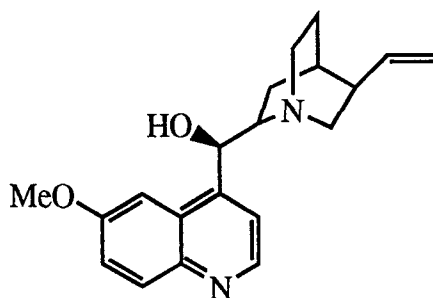
### 1.3.1 Separation in Asymmetric Synthesis<sup>76</sup>

In order to achieve an optically pure or at least an optically enriched end product, a number of strategies have been employed. Of the separative methods, some are physical and others are chemical.

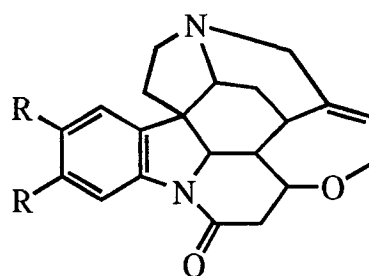
### 1.3.1.1 Physical Separation

The main physical methods of separation are crystallisation and chromatography. In order to separate crystals they must form as conglomerates as opposed to racemic crystals. This was the case, rather fortuitously, in Pasteur's separation of tartrate salts. Only a small number of molecules such as helices form this type of crystal so in general, it is not possible to achieve separation by this method directly. When it is possible, the separations often require manual operation with determination of the optical rotation of each individual crystal. This is obviously laborious and time-consuming.

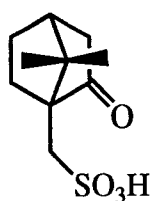
By adding an optically pure acid or base, however, bases or acids can be respectively crystallised as the salt even from racemic crystal formers. One enantiomer will form a salt at a faster rate than the other. Bases (114–116) and acids (117) and (118) are often used.



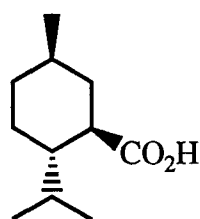
(114) Quinine



(115) R = H Strychnine  
(116) R = OMe Brucine



(117) Camphorsulphonic acid



(118) Menthyloxyacetic acid

Figure 29

Chromatography on chiral separating materials is possible. The most common of these for HPLC have been the Pirkle columns which are formed using aromatic fluoro alcohols<sup>77</sup> and  $\alpha$ ,  $\beta$  and  $\gamma$  cyclodextrins containing six, seven or eight glucose units

respectively. These molecules are shaped as hollow cones with primary hydroxyl groups at the narrow end and secondary hydroxyls on the wider side. Molecules are separated on the basis of selective inclusion into the cavities. Unfortunately, such chromatography is difficult to perform above the semi-preparative scale and is thus of limited commercial synthetic value.

### 1.3.1.2 Chemical Separation

Chemical separation can be achieved through either thermodynamic or kinetic methods. Thermodynamic separation is rare but one example is the treatment of the ketone (119) with optically active brucine (116) which leads to enolisation and the formation of a single enantiomer of ketone in 90% yield.

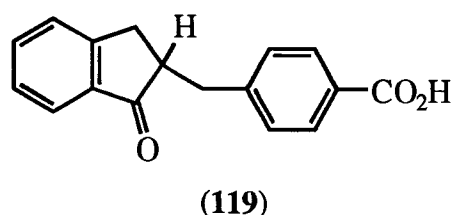
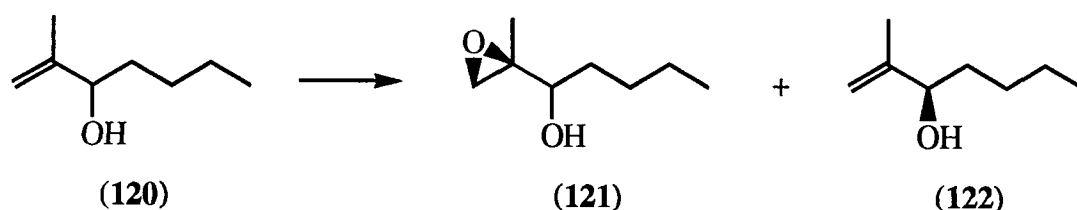


Figure 30

Kinetic resolution relies on the fact that of two enantiomers, one will react more rapidly in a chiral environment and thus the product will be chemically different to the remaining unreacted (or partially reacted) enantiomer. These different molecules can be more easily separated. This system can be applied to an unwanted enantiomer leaving the more useful enantiomer unchanged or the desired enantiomer can be selectively reacted. An example of this is the epoxidation of the allylic alcohol (120) with only the *R* enantiomer being formed.<sup>78</sup>



Scheme 60

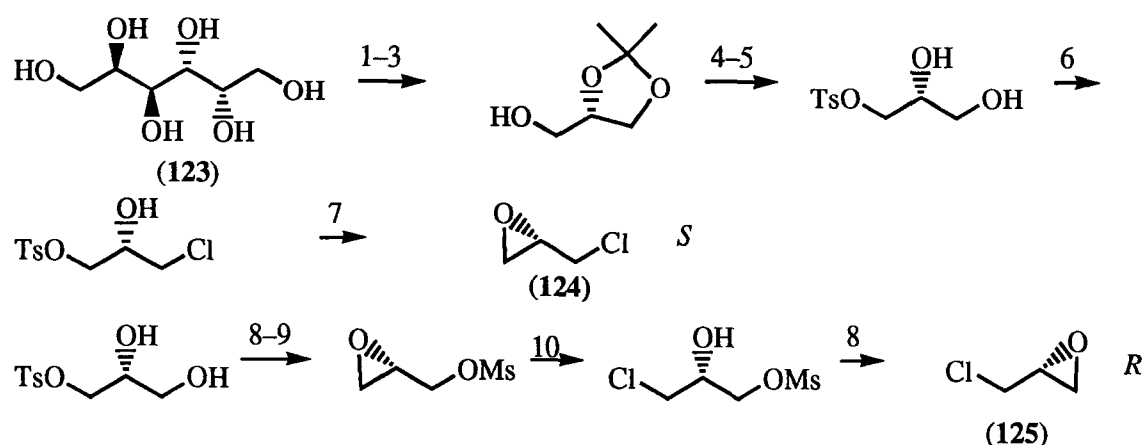


Similarly biochemical separations can be achieved using enzymes. The difficulty with separative methods is that they display poor atom efficiency. In general 50% of the product of the original reaction is unwanted.

## 1.3.2 Asymmetric Synthesis

### 1.3.2.1 Chiral Templates

There is an abundance of optically pure molecules available for the chemist to manipulate. Such naturally occurring molecules as amino acids, hydroxy acids, terpenes and carbohydrates have been exploited.<sup>79</sup> These compounds provide functionalised, optically active building blocks which can be used, especially in natural product synthesis. A recent example of this can be seen in Chida and Ogawa.<sup>80</sup> The key to their use has been described as “disconnection of strategic bonds with minimum perturbation of chiral centres”.<sup>79</sup> The synthesis of *R* and *S* epichlorohydrin from D-mannitol can be seen in scheme 61.

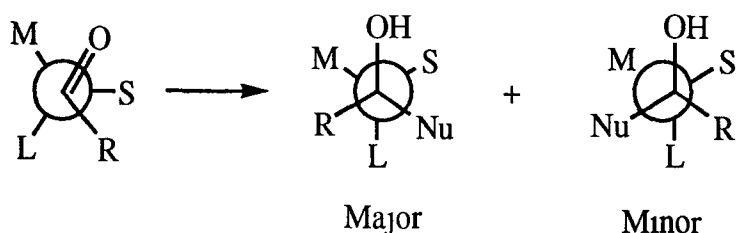


- 1) Acetone,  $H^+$ , 2)  $Pb(OAc)_4$ , 3)  $NaBH_4$ ,
- 4)  $TsCl$ , pyridine, 5) aq  $HCl$ , 6)  $Ph_3P$ ,  $CCl_4$ ;
- 7)  $(CH_2OH)_2$ ,  $Na$ , 8)  $NaOMe$ ,  $MeOH$ ,
- 9)  $MsCl$ , pyridine, 10) Conc  $HCl$

Scheme 61

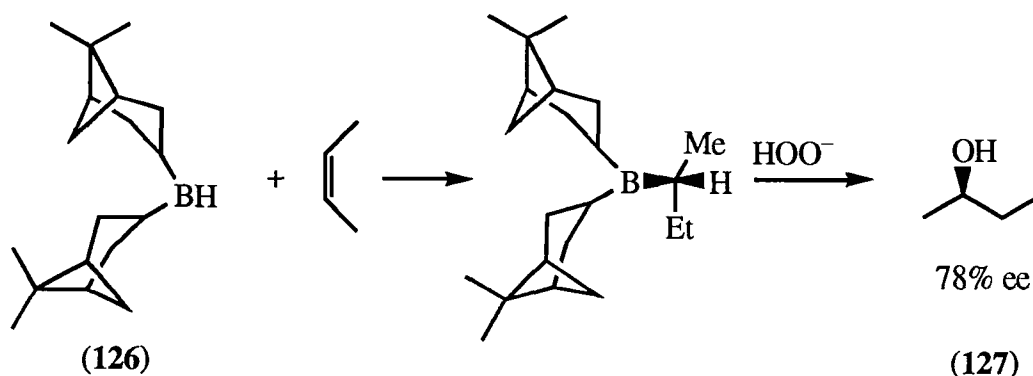
### 1.3.2.2 Synthesis of New Chiral Centres

The synthesis of new chiral centres provides an important challenge for the synthetic chemist. The reduction of an unsymmetrical ketone, for example will produce a chiral alcohol. If the ketone has a chiral centre  $\alpha$  to the carbonyl, then the reduction will proceed through two different diastereomeric transition states. It is conceivable that these two transition states will have different activation energies and that this difference will cause the formation of one product diastereomer in preference to the other. The major product is predicted by Cram's rule whereby the oxygen of the carbonyl orients itself between the small (S) and the medium (M) substituents on the  $\alpha$  carbon and preferential attack will take place on the face opposite the large (L) group.



Scheme 62

In the case where there is no chiral centre on the substrate an enantiomerically enriched product can be achieved by using chiral auxiliaries as in the hydroboration below (Scheme 63) where *d*<sub>1</sub>-3-pinanylborane was used<sup>81</sup>



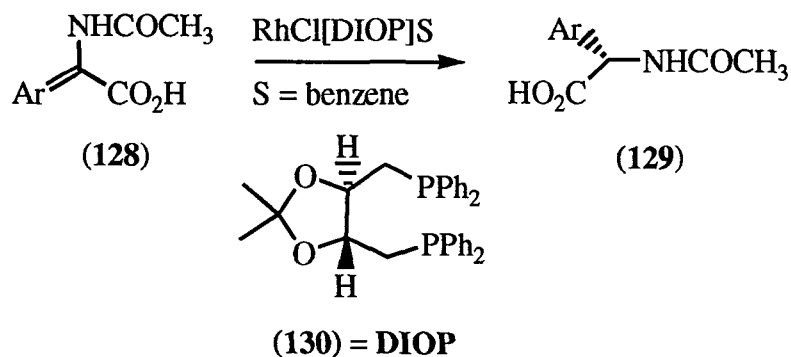
Scheme 63

### 1.3.3 Catalytic Asymmetric Synthesis

Catalytic asymmetric synthesis affords the possibility of adding an achiral reagent to an achiral substrate to realise a chiral addition compound. It is the catalyst which provides the chiral environment and binds to the substrate “blocking” one face and allowing the reagent to attack at the other face. Ideally the product will have a lower binding constant for the catalyst than the substrate and can be displaced by more substrate. When this process occurs efficiently a low amount of catalyst is needed. However, where it is inefficient, sometimes stoichiometric amounts of catalyst are needed.<sup>82</sup> There are many examples of such catalysis.

#### 1.3.3.1 Hydrogenation

Homogeneous hydrogenation catalysis was first developed in the 1960's with the introduction of rhodium complexes bearing chiral phosphine ligands.<sup>83</sup> Kagan achieved over 80% ee in the reduction of dehydro *N*-acyl amino acids such as (128) using a rhodium DIOP system.<sup>84</sup>



Scheme 64

### 1.3.3.2 Epoxidation of Olefins

Porphyrins and salen ligands have been widely used in the epoxidation of unfunctionalised olefins with selectivity and reactivity being greater in the case of *cis* examples. Porphyrins are natural products being a constituent part of cytochrome *P*-450. The first porphyrin system epoxidised *p*-chlorostyrene in 51% ee using iodosyl mesitylene as oxidant. The chiral substituents were (132) or (133).

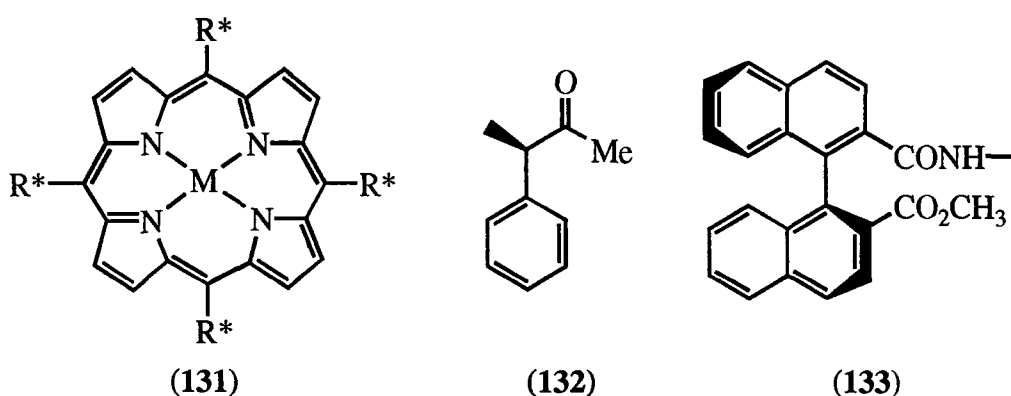


Figure 31

The Jacobsen catalyst (134) has been successfully used in the epoxidation of unfunctionalised olefins. A large number of ligand substituents and substrates were examined.<sup>82</sup>

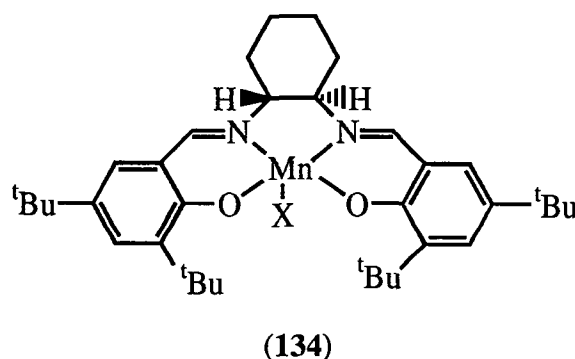
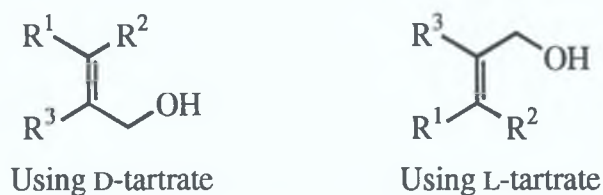


Figure 32

### 1.3.3.3 Epoxidation of Allylic Alcohols

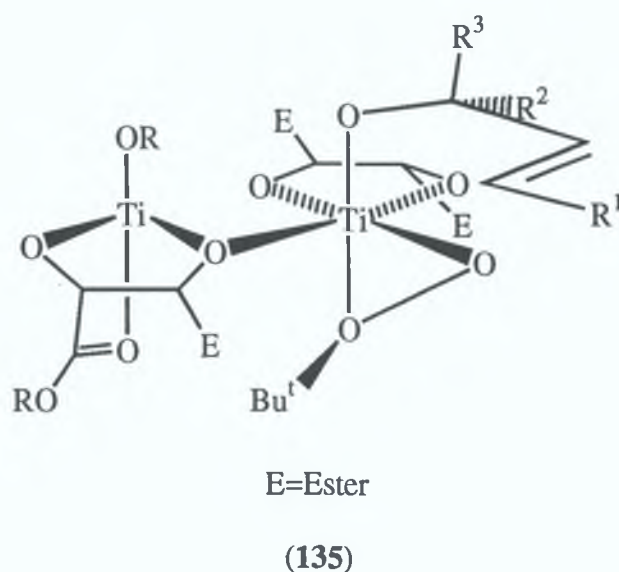
The epoxidation of allylic alcohols has been dominated by the Sharpless system which allows the selective epoxidation to either enantiomer of virtually all allylic alcohols.<sup>85</sup> The catalyst is formed by pre-mixing titanium isopropoxide (usually) with L- or D-

tartrate ester, depending on the enantiomer required. This is followed by the addition of oxidant, usually <sup>t</sup>BuOOH. The facial selectivity is shown below:-



**Figure 33**

The catalyst is believed to have structure (135) in solution.



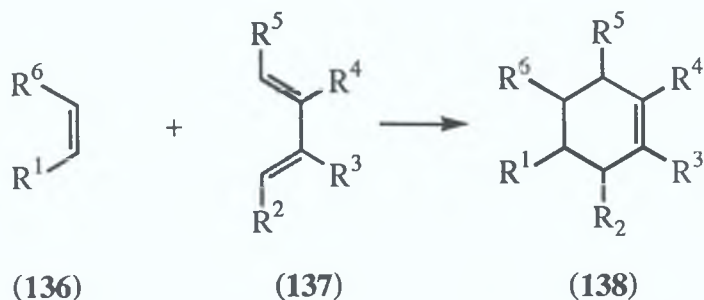
**Figure 34**

#### 1.3.3.4 Lewis Acid Catalysis

Lewis acids have been used to promote a variety of carbon-carbon bond forming reactions. Thus a single catalytic system could be conceivably applied to a number of reactions.

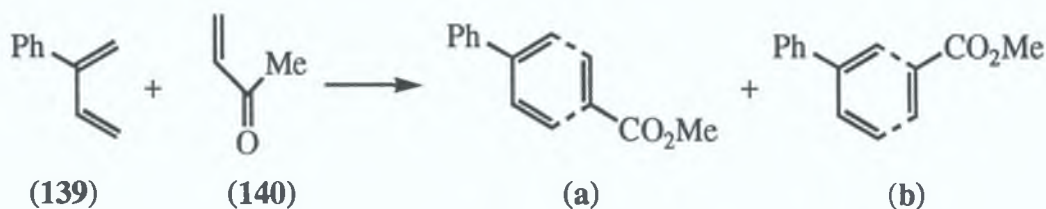
#### The Diels-Alder Reaction

This reaction was discovered in 1928<sup>86</sup> and is one of the most important C-C forming reactions in chemistry. It involves the [4πs + 2πs] cycloaddition of a diene (136) and a dienophile (137) to give the adduct(138).



Scheme 65

As can be seen, up to four new stereocentres may be formed so stereocontrol of this reaction is very important. Two new  $\sigma$  bonds are formed at the expense of two  $\pi$  bonds which is a significant driving force. The reaction usually proceeds in a kinetically controlled irreversible manner. Frontier molecular orbital theory has been used to explain several aspects of the Diels–Alder reaction,<sup>87</sup> including its reactivity, regioselectivity and its catalysis by Lewis acids. In the “normal” reaction the dienophile bears electron-withdrawing groups and the diene bears electron-donating groups. The LUMO of the dienophile is thus lowered in energy and the energy of the HOMO of the diene is raised leading to more effective overlap and thus faster reaction. Where there is an unsymmetrical diene as with (139) below, generally a regioselective addition occurs. This is because the carbon with the closest matching atomic orbital co-efficients tend to bond. Thus the approach of the dienophile is as (a) instead of (b).

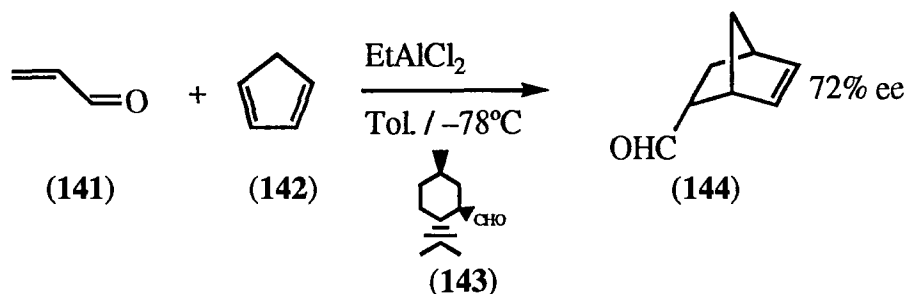


Scheme 66

The stereochemical situation is simplified by the “*cis* principle” which states that the relative stereochemistry of the reactants is preserved in the adduct. Achieving overall enantioselectivity, therefore, requires merely  $\pi$ -facial control.

Both the reactivity and selectivity of the Diels–Alder reaction are improved by the use of a Lewis acid catalyst. This was first observed by Yates and Eaton in 1960,<sup>88</sup> whereby they reacted anthracene and maleic anhydride in the presence of  $\text{AlCl}_3$  to yield a complete reaction in minutes. They predicted 4800 h for the uncatalysed reaction at room temperature. Thus the Lewis acid lowers the energy of the LUMO of the dienophile (which must bear a functional group to which the Lewis acid may co-

ordinate) still further, providing improved overlap of the molecular orbitals. In addition, the atomic orbital co-efficient of the carbon  $\alpha$  to the electron-withdrawing group is lowered making the reaction more selective. The earliest examples of chiral catalysis in the Diels–Alder reaction were in the 1970's.<sup>89,90</sup>



Scheme 67

Chiral binaphthol (145) and the so-called Narasaka catalyst (146) have been used<sup>91</sup>

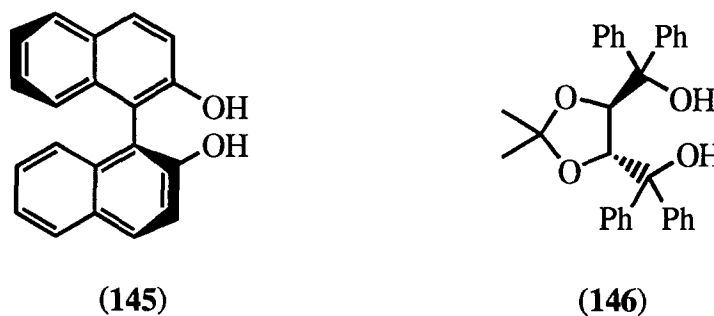
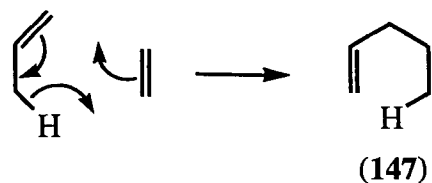


Figure 35

The vast majority of reactions have been catalysed by boron, titanium or aluminium<sup>92</sup>

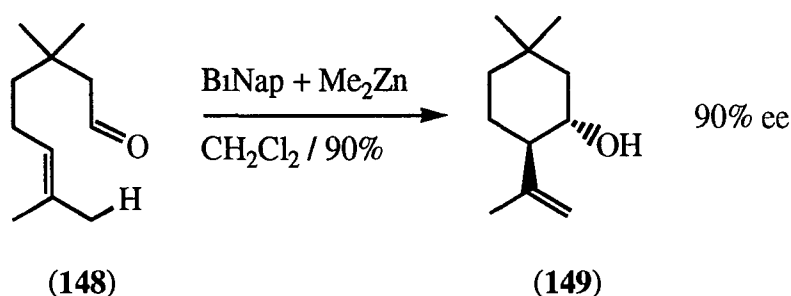
### The Ene Reaction

In this reaction an alkene bearing an allylic hydrogen atom reacts with an enophile. A  $\sigma$ -bond forms with the terminal allyl carbon and a 1,5 migration of the allylic hydrogen atom occurs in addition to a change in the position of the double-bond.



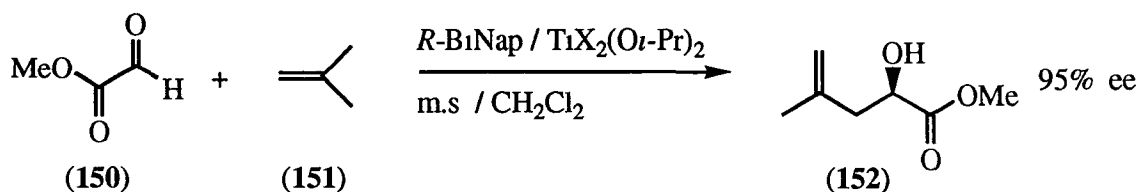
**Scheme 68**

Because large activation energies and high temperatures are required, this reaction often benefits from Lewis acid catalysis when there is heteroatom substitution. There is a preference for *cis* addition and the formation of *endo* products. An example of this reaction involving a heteroatom enophile and an intramolecular reaction is seen in the ring closure of (148)<sup>93</sup>



**Scheme 69**

A common reaction involves the use of glyoxalate esters such as (150) with dimethylethylene as in scheme 70.<sup>94</sup>

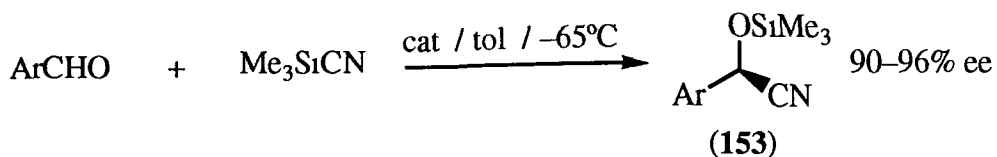


**Scheme 70**

### Hydrocyanation of Aldehydes

This is an important synthetic reaction and was used by Emil Fischer as mentioned above. The Narasaka catalyst (146) in the presence of  $\text{TiCl}_2(\text{O}^i\text{Pr})_2$  was used in the hydrocyanation of both aryl and alkyl aldehydes in high ee<sup>95</sup>

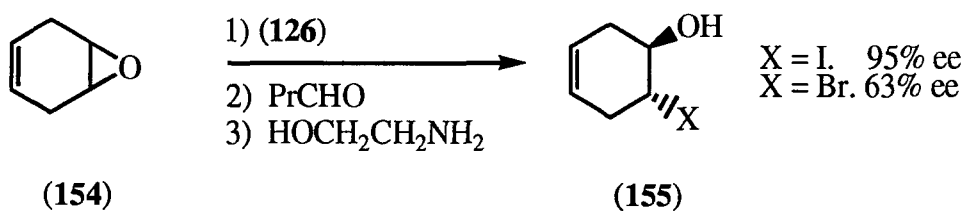




Scheme 71

### Ring Opening of Epoxides

Nucleophilic ring opening of epoxides is assisted by the presence of a Lewis acid. Thus, using camphenyl borane *meso* epoxides were selectively opened to the halohydrin<sup>96</sup>



Scheme 72

### Aldol Reaction

The aldol reaction can be quite useful synthetically in the formation of hydroxy carbonyl compounds. Along with the related Mukaiyama reaction, which involves the use of silyl enol ethers, this reaction has been frequently subjected to chiral catalysis. Thus *p*-nitrobenzaldehyde and acetone were reacted using Zn(II) complexed with two equivalents of (156):<sup>97</sup>

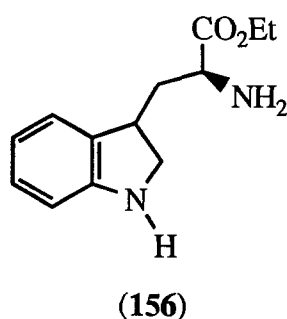
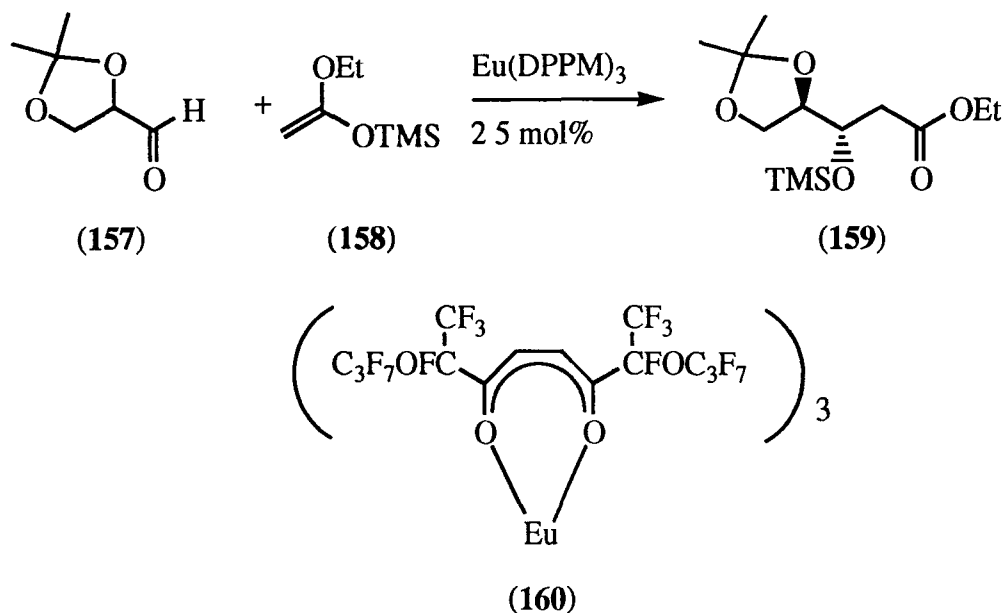


Figure 36

The Mukaiyama-type reaction between ketene silyl acetal (**158**) and aldehyde (**157**) was catalysed by the chiral Lewis acid  $\text{Eu}(\text{DPPM})_3$  (**160**).<sup>98</sup>



Scheme 71

Thus catalysis plays a hugely important role in asymmetric synthesis. The ability to use a small amount of chiral material to treat a large amount of achiral substrate makes these processes economically viable. Commercially, chemists are required to provide materials, which are essentially enantiopure, at low cost. Catalysis provides the possibility of achieving this. However, the nature of enantioselectivity and of individual catalytic systems requires further study and the number of catalysts and the scope of reactions catalysed can be extended. With this in mind the catalytic properties of niobium and tantalum have been investigated.

## **CHAPTER 2**

### **THE USE OF AMINO ACIDS AND C<sub>2</sub>-SYMMETRICAL DIOLS IN THE LEWIS-ACID CATALYSED DIELS- ALDER REACTION**

## 2.1 INTRODUCTION

An investigation into the Lewis-acid properties of niobium and tantalum halides was undertaken with a view to determining whether catalytic enantioselective reactions could be achieved. In general, enantioselective reactions of this nature have been achieved by reacting starting materials in the presence of a Lewis acid and a chiral ligand. In this chapter the use of amino acids, hydroxy acid esters and alcohols such as threotols (161) and binaphthol (162) will be examined.

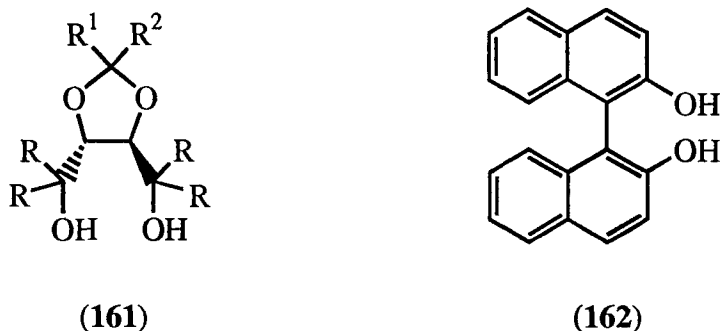


Figure 37

### 2.1.1 Chiral Ligands in Lewis-Acid Catalysis

A large number of ligands have been used in chiral Lewis-acid reactions. Described here are those which relate to the work in this chapter

#### 2.1.1.1 Amino Acids

Amino acids are inexpensive and widely available in the L- or S form. It is not surprising therefore that they, or rather their derivatives have been much applied as ligands in Lewis-acid reactions. Helmchen<sup>91,99,100</sup> and Yamamoto<sup>101</sup> simultaneously published work involving the use of *N*-sulphonyl amino acids in the presence of boron, aluminium or titanium. Boron catalysed reactions achieved the most impressive results. The sulphonyl group appears to be necessary in the case of boron as it delocalises the nitrogen lone pair thus allowing boron to act as a Lewis acid. Helmchen proposed a transition state for co-ordination with acrolein in the Diels-Alder reaction

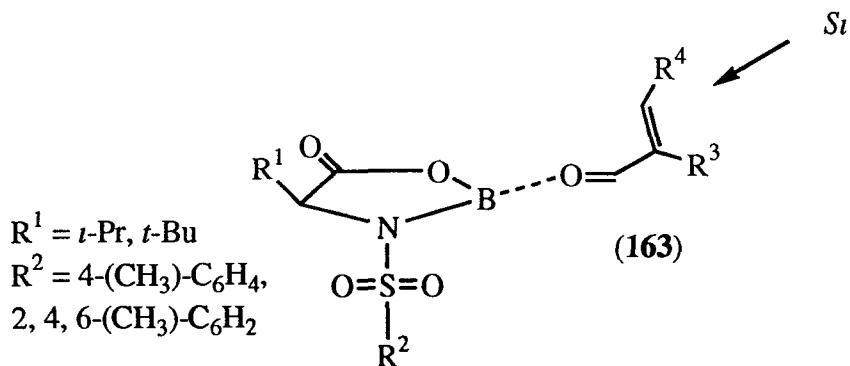
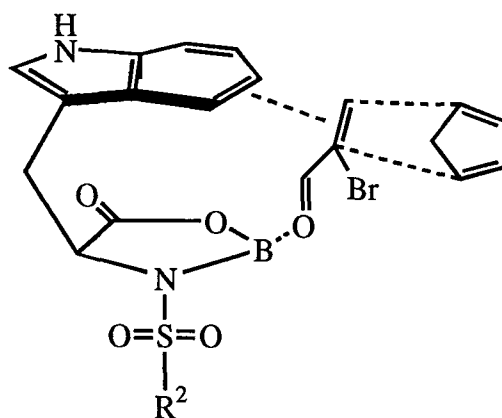


Figure 38

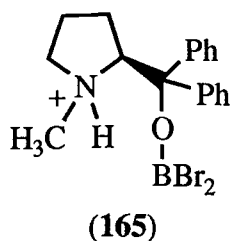
In this reaction, where cyclopentadiene was used as the diene, up to 82% ee was achieved. Several other reactions were catalysed using this system including an aldol condensation and the related Mukaiyama reaction.<sup>102</sup> Corey's group used a similar catalyst based on tryptophan (**164**) to achieve very high ee's in the reaction between cyclopentadiene and  $\alpha$ -bromoacrolein.<sup>103</sup> The ee appears to have been enhanced by  $\pi$ -acid to  $\pi$ -base interaction between the acrolein double-bond and the indoyl group. This was evidenced by a lower selectivity when the indoyl group was replaced by a cyclohexyl or a cyclopropyl group



(164)

Figure 39

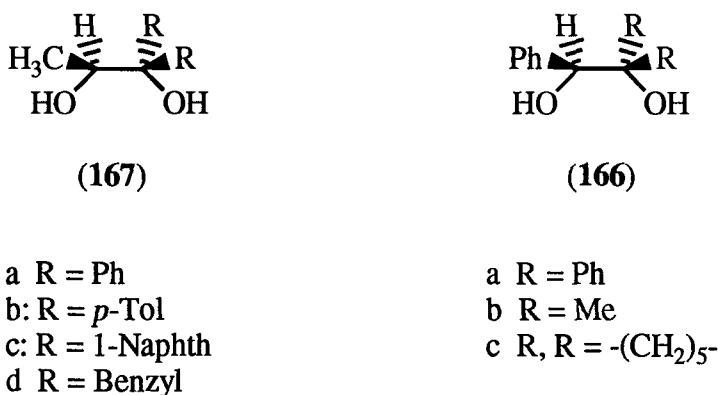
Mukaiyama applied the use of amino alcohols to the Diels–Alder reaction in the presence of boron. The *exo* product of the reaction between methacrolein and cyclopentadiene was formed almost exclusively and in 97% ee at  $-78^\circ\text{C}$  in the presence of catalyst (**165**).<sup>104</sup>



**Figure 40**

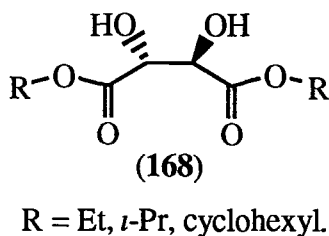
### 2.1.1.2 Tartrates and their Derivatives

Chiral diols have been applied as ligands with varied success. Those derived from *S*-ethyl mandelate (166) or *S*-ethyl lactate (167) were used to achieve modest ee's in the Diels–Alder reaction of methacrolein and cyclopentadiene in the presence of EtAlCl<sub>2</sub> ranging from 0–73%.<sup>105</sup>



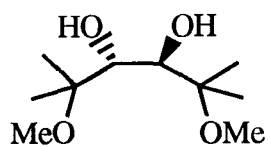
**Figure 41**

Tartrate esters (168) were used as chiral ligands in the presence of Al-*t*-Bu<sub>2</sub>Cl in the reaction between methyl acrylate and cyclopentadiene<sup>106</sup>



**Figure 42**

Diols derived from the reduction of tartrate esters (169 and 170) were used by Chapuis's group in the presence of EtAlCl<sub>2</sub>. However stoichiometric amounts of catalyst were required<sup>107</sup>



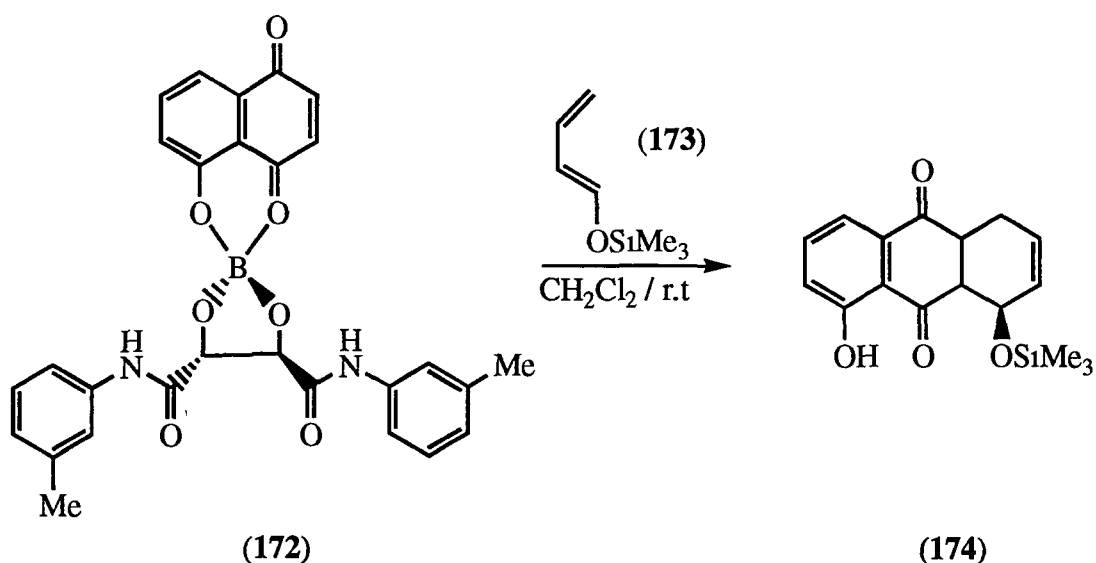
(169)



(170)

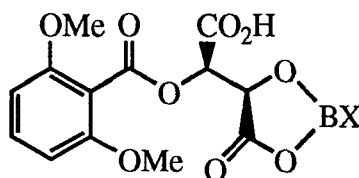
Figure 43

Boron reagents using tartrate ligands have been used to react juglone with *O*-silyl butadiene with the product being completely regioselective and highly enantioselective<sup>108</sup>



Scheme 72

The so-called Yamamoto catalyst is a boron reagent with an ester of tartaric acid as ligand (175). In its use in the catalysis of the reaction between methacrolein and cyclopentadiene, 96% ee was achieved.<sup>109</sup>



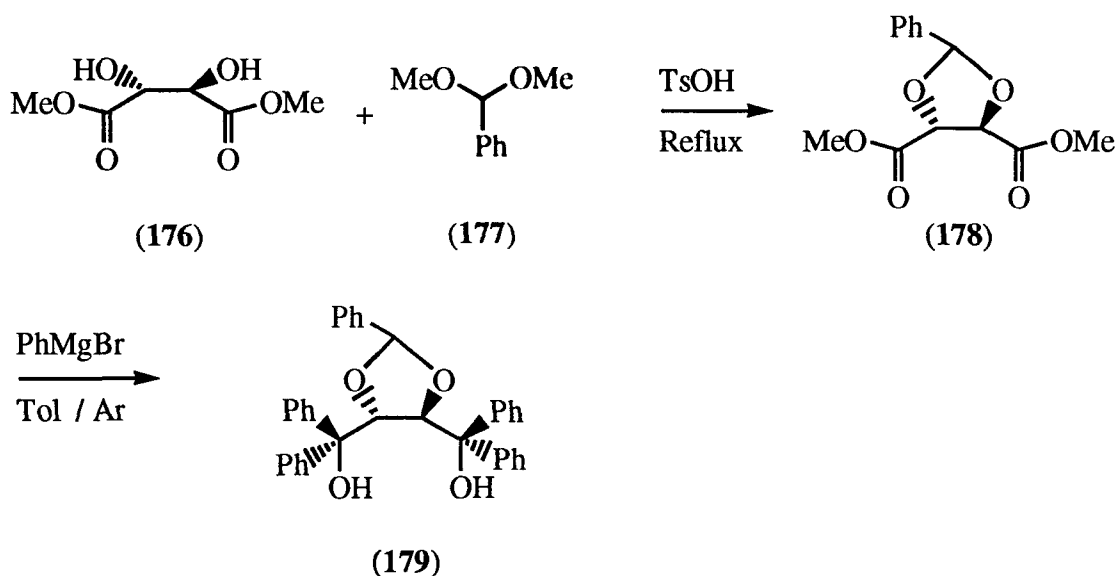
(175)

Figure 44

This catalyst was used in a variety of Diels–Alder reactions, the Mukaiyama reaction and the Sakurai–Hosomi allylation of aldehydes<sup>102</sup>

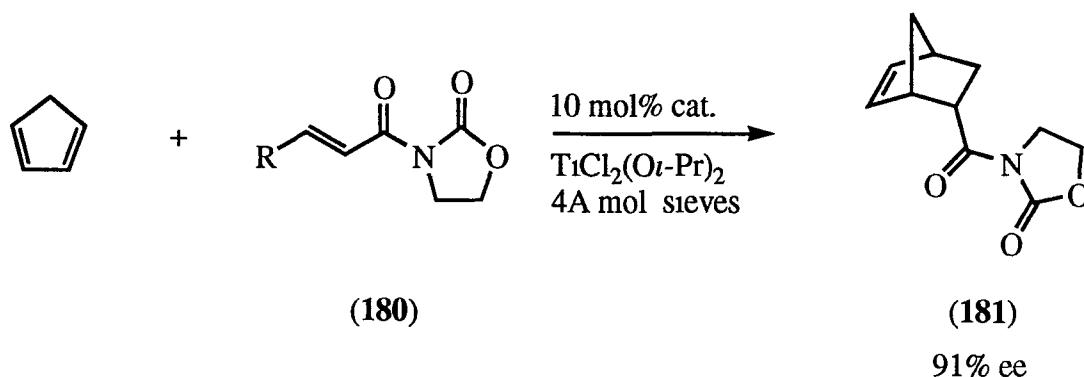
### 2.1.1.3 Threitols

Threitols, or butane tetrols are derived from tartaric acid esters and have been applied as catalysts in the Diels–Alder reaction. An example of their synthesis is shown in Scheme 73.<sup>110</sup>



Scheme 73

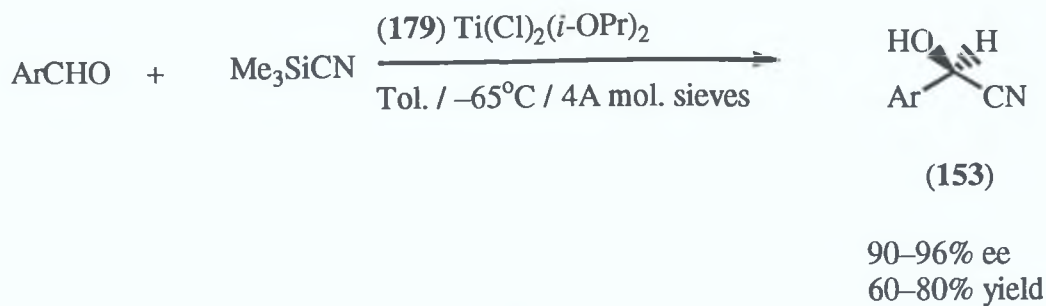
In the reaction of 3-acyl, 1,3-oxazolidin-2-ones (**180**) with cyclopentadiene 90–95% ee was achieved in the stoichiometric reaction. By addition of 4Å molecular sieves, substoichiometric amounts of catalyst could be used to achieve the same ee. The authors ascribed this effect to the removal of adventitious water. They also found enhancement with 1,3,5 trialkyl benzenes as solvents<sup>110</sup>



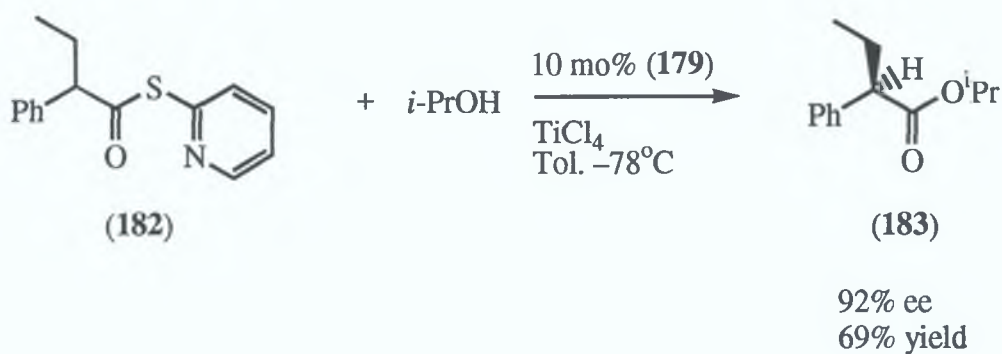
Scheme 74

The catalyst has been applied to the hydrocyanation of aldehydes, asymmetric solvolysis of racemic *S*-(2-pyridyl) thioesters and asymmetric 2+2 cycloadditions Scheme 75–77).<sup>102</sup>

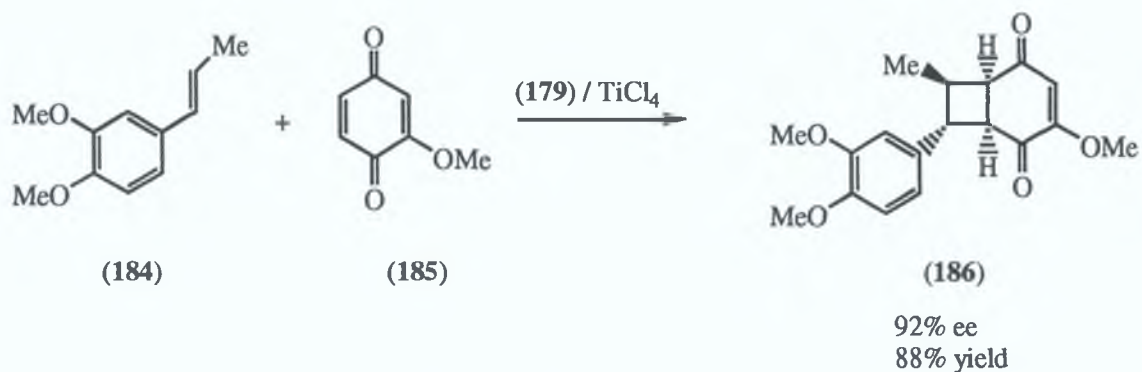




Scheme 75



Scheme 76

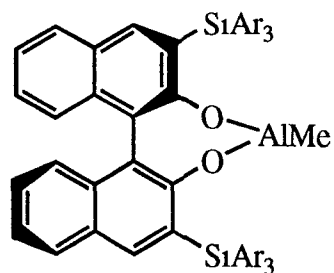


Scheme 77

#### 2.1.1.4 Binols

Binaphthol compounds such as (162) are chiral because of restricted rotation about the 2–2' bond between the aryl groups.

They have been used with boron, aluminium and titanium as ligands in chiral Lewis-acid catalysis.<sup>106,107</sup> The binol-derived catalyst (188) has been used for hetero Diels–Alder reactions, the ene reaction<sup>111</sup> and in an asymmetric Claisen rearrangement.<sup>112</sup>

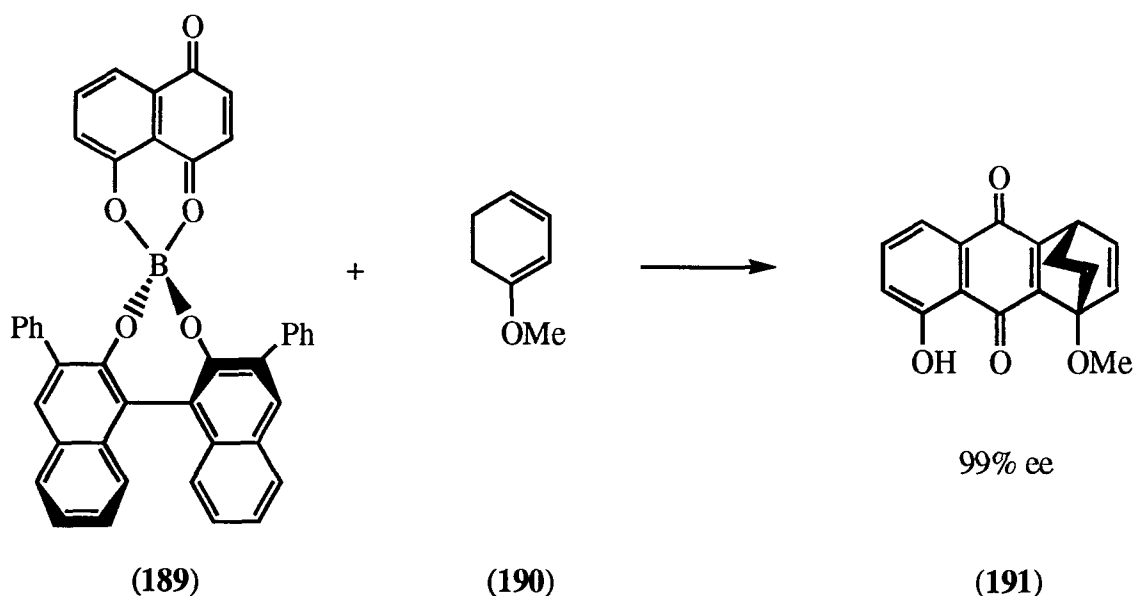


Ar = Ph, 3,5-xylyl.

(188)

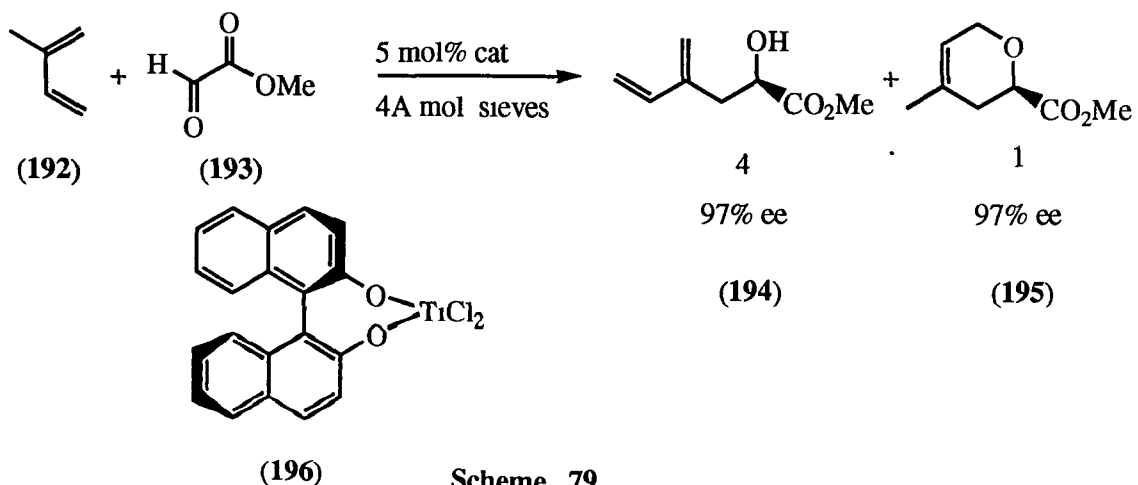
**Figure 46**

A Diels–Alder reaction using boron as the Lewis acid, binol (**189**) as the ligand with juglone as dienophile and diene (**190**) gave adduct (**191**) in 99% ee.



**Scheme 78**

In the case of titanium an ene product and a hetero Diels–Alder product of the reaction between isoprene and glyoxalate were observed, both in high ee.



**Scheme 79**

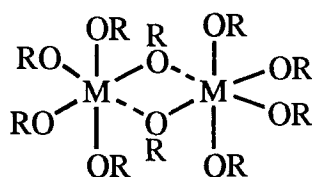
These are some of the ways in which these ligands were used to promote enantioselectivity in Lewis-acid catalysed reactions

## 2.1.2 Reactions between the Group V metals and Related Ligands

Although reaction of group V metals with amino acids has not been attempted up to now, complexes with amines, acids, alcohols and diols have all been synthesized. Some of this work is described below.

### 2.1.2.1 Alcohols

Reactions of niobium and tantalum halides with primary alcohols to produce alkoxides are possible. Partial substitution of the halides generally occurs. However in the presence of a proton acceptor, such as ammonia, the reaction will go to completion<sup>113</sup>. The volatility of these alkoxides increases with extension of the alkyl chain, because of a reduction in the tendency to form dimers. The ground state configuration of the metals (Nb =  $4d^4 5s^1$ ; Ta =  $5d^3 6s^2$ ) allows the formation of  $d^2sp^3$  hybridised orbitals leading to octahedral dimeric configuration (197).



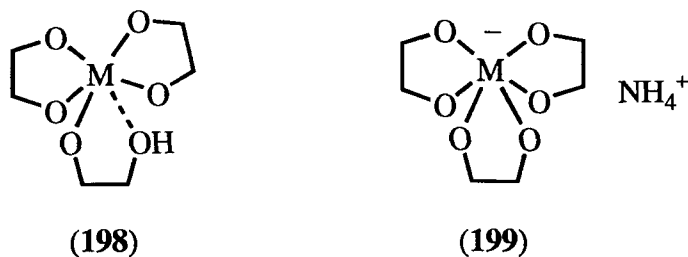
(197)

Figure 48

Alkoxides from phenol and naphthol have also been synthesized.<sup>113</sup>

### 2.1.2.2 Diols

A number of different groups have been used in the reaction of diols such as ethylene glycol, propane 1,2-diol, propane 1,3-diol, butane 2,3-diol, butane 1,4-diol, pentane 1,5-diol, hexane glycol, pinacol and catechol. The reactions were performed with niobic and tantallic acids,<sup>113</sup> niobium alkoxides,<sup>115</sup> and tantalum alkoxides.<sup>116</sup> One, two or three equivalents of the diols could be chelated. In the case of three equivalents of the diol, one of the alcohol groups forms a dative bond with the metal atom (198). On addition of a stream of ammonia, the salt (199) forms.



**Figure 49**

Similar complexation patterns were seen with catechol.

The cases of aryl (fused ring) and biaryl diols such as 2,3-dihydroxy naphthalene, 1,8-dihydroxy naphthalene, 2, 2'-dihydroxy biphenyl and 2, 2'-dihydroxy binaphthyl are interesting.<sup>117</sup> These molecules form  $HML_3$  systems where the metal is hexacoordinated in five-, six-, and seven-membered rings. The ligand 2,2'-dihydroxy binaphthyl has been used in experimentation for this chapter.

### 2.1.2.3 Acids and Hydroxy Acids

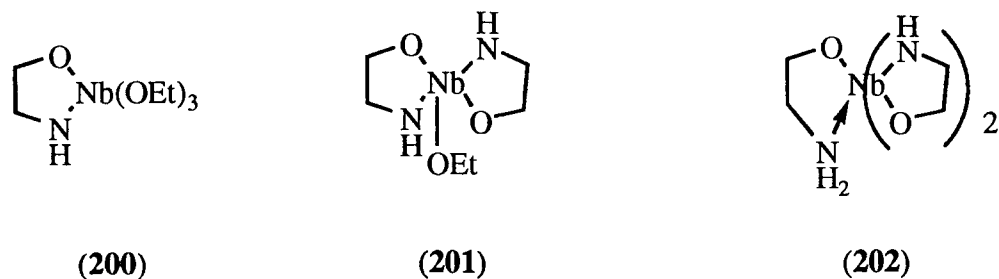
Niobium and tantalum pentachlorides form basic acetates with acetic acid. Higher molecular weight acids add 4:1 when reacted with the metal alkoxides. Lower molecular weight acids add 5:1.<sup>113</sup> Hydroxy acids, such as  $\alpha$ -hydroxy acids or salicylic acid, add in the ratio 2:1 to pentaethoxides.<sup>113</sup>

### 2.1.2.4 Amines

The metal halides react with primary, secondary and tertiary amines.<sup>113</sup> Higher primary amines form complexes of the type  $MX_3(NHR)_2 \cdot NH_2R$ . The lower amines such as  $MeNH_2$  and  $EtNH_2$  form  $MX_2(NHMe)_3$  and  $MX_2(NHEt)_3$  complexes. Secondary amines form complexes of the form  $MX_3(NR_2) \cdot NR_2$ . Tertiary amines form insoluble adducts of the form  $MX_5 \cdot NR_3$ . On this basis it is reasonable to assume that  $\alpha$ -amino acids could form similar compounds.

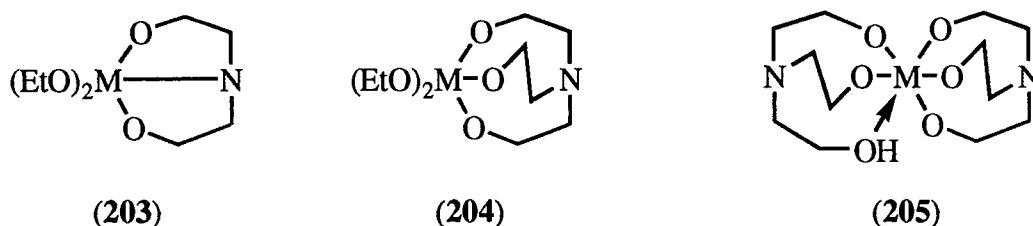
### 2.1.2.5 Amino Alcohols

Niobium and tantalum ethoxides were reacted with mono, di, and triethanolamines.<sup>118</sup> In the case of monoethanolamines one two or three equivalents of ligand were used. Where three equivalents were used, three oxygens are bonded to the metal along with two nitrogens with a further nitrogen forming a dative bond.



**Figure 50**

Diethanolamine bonded to the metal gave (203) and one equivalent of triethanolamine gave complex (204) while two equivalents gave complex (205).



**Figure 51**

Thus a number of ligands have been reacted with niobium and tantalum to give the above-mentioned complexes. However none of these compounds were used for any catalytic applications. Thus it was undertaken to investigate the potential of these and related complexes as Lewis-acid catalysts

## 2.2 RESULTS AND DISCUSSION

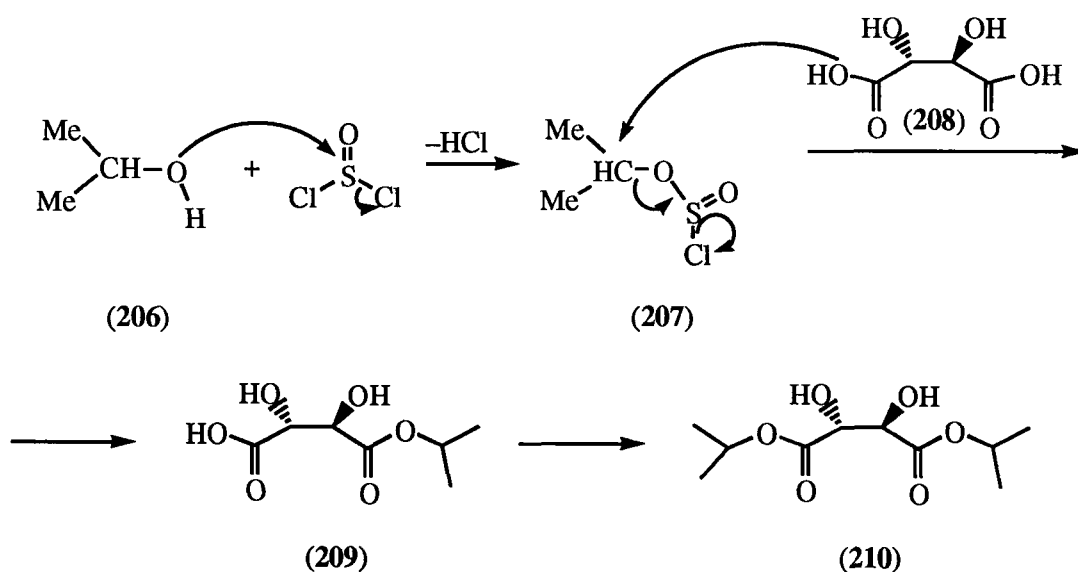
### 2.2.1 Ligand Synthesis

#### 2.2.1.1 Diisopropyl Tartrate

The majority of the ligands used in this section were commercially available and were purchased. However, the propyl ester of tartaric acid was synthesized. Initial attempts at forming the ester by mixing the alcohol and acid in benzene and azeotropically removing water using Dean and Stark apparatus were unsuccessful. However by dissolving the acid in propanol and cooling to 0°C followed by addition of 2.01 equivalents of thionyl chloride under a N<sub>2</sub> atmosphere, reaction was observed. Following removal of excess thionyl chloride and the solvent alcohol, a crude oil was generally obtained. This was purified by distillation or *via* dry flash chromatography. The former method led to significant loss of yield and thus the chromatographic method was preferred. Because of the large amount of oil (5 g) being purified, dry

flash silica gel chromatography was employed. This was possible because of the high  $R_f$  of the ester on TLC (0.6 m in a mobile phase of petroleum ether (PE):ethyl acetate (EA) in the ratio 50:50) with the only other impurities being on the baseline

The mechanism of formation of the ester might be as shown in Scheme 80. Because the solvent is the alcohol and because electrophilic attack on alcohols by thionyl chloride is much faster than that on carboxylic acids, it seems likely that the alkyl sulphonyl chloride (**207**) forms first. Subsequent nucleophilic attack by the carboxylic acid ensues. The relative lack of abundance of the tartaric acid compared to the alcohol prevents its forming an alkyl sulphonyl chloride. The electron-withdrawing carboxyl groups which are adjacent cause attack by the tartrate alcohols on the alkyl sulphonyl chloride to be disfavoured. The formation of (**207**) involves the generation of acid which may explain why the remaining alcohol does not display nucleophilicity towards the intermediate



Scheme 80

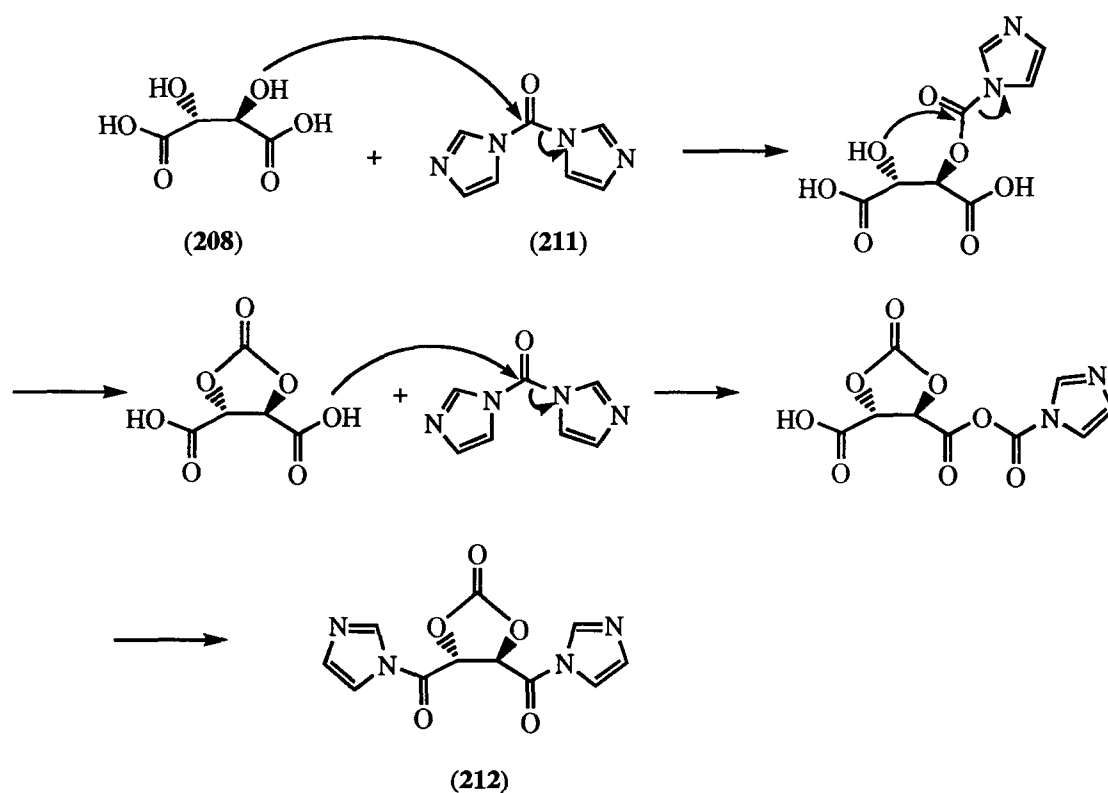
Yields of the reaction were very high even following purification demonstrating that alternative reaction pathways were not followed. Duration of reaction was found to be important. Yield was poor in reactions which were carried out for only 3 h, but in those where reaction was carried on for 24–72 h, an almost quantitative yield was achieved.

### 2.2.1.2 Benzyl and Butyl Esters

Because of the relative success with the tartrate esters in inducing stereoselectivity in the chiral Diels–Alder reaction (see below), further synthesis of these esters was attempted

The reaction was initially attempted in the same manner as described for the propyl ester. Thionyl chloride was added to a solution of tartaric acid in benzyl or *t*-butyl alcohol. However TLC analysis seemed to indicate that little or no reaction was taking place. Finally the reaction was stopped and solvent removed to reveal a white solid. Melting point and the  $^1\text{H}$  NMR spectrum in  $\text{D}_2\text{O}$  revealed this to be unreacted tartaric acid in the case of both alcohols.

A further esterification method was attempted using carbonyl diimidazole (CDI) as a coupling agent. An excess of CDI and tartaric acid were dissolved in DMF and stirred for several hours. A TLC of the reaction mixture revealed that the three equivalents of CDI had been consumed. The reaction of CDI with the acid is possibly as follows -



Scheme 81

Two equivalents of *t*-butyl alcohol and a catalytic amount of NaH were mixed in dry THF and stirred until all the NaH was consumed. Thus butoxy anion was available for attack on (212). This solution was then added to the main reaction and allowed to stir for 24 h. However when the material from the reaction was worked up and purified on a dry flash column, none of the desired ester was recovered. Instead, what appeared to be imidazole, from TLC and  $^1\text{H}$  NMR, was the only product.

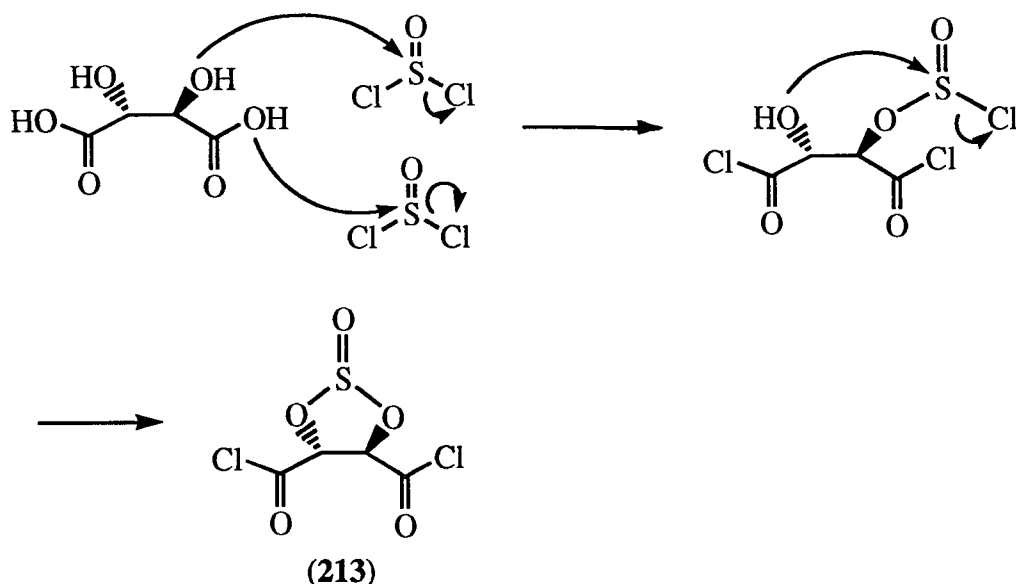
A variation of the original method was attempted for the synthesis of the benzyl ester whereby benzyl alcohol was added to dry DCM and cooled to 0°C. Thionyl chloride was added and the solution stirred for several hours. The required amount of tartaric acid was then added and the solution allowed to warm to room temperature. A suspension resulted. This was filtered and the recovered solid was found to be tartaric acid. The solvent was evaporated and an oil was recovered. This was weighed as crude and then purified before analysis by NMR. It seems likely that the original oil was the benzyl oxy sulphonyl chloride formed in the reaction between thionyl chloride and the alcohol. The final product was benzyl chloride, presumably from hydrolysis on silica gel.

Similarly, the above reaction was attempted using *t*-butyl alcohol and 1,4-dioxane as the solvent. However the result was the same in that starting material was recovered. In addition, 1.5 g of a poorly soluble material was present. TLC analysis showed that it was not tartaric acid as it had an  $R_f$  of 0.9 in PE:EA (80:20). Identification of the compound proved elusive save for the fact that NMR revealed that it did not contain a *t*-butyl group.

The reaction with benzyl alcohol was attempted in 1,4-dioxane. No reaction occurred until the solvent was heated under reflux. TLC analysis displayed a spot at 0.8 (PE:EA (75:25)) which was recovered and purified using dry flash chromatography. NMR of the product suggested that the benzyl ester was not present. This led the method to be abandoned.

A final method was attempted in which the tartaric acid was stirred in neat distilled thionyl chloride. The likely product of this is shown in Scheme 82.





Scheme 82

The thionyl chloride was distilled off to reveal a yellow–white powder to which dry DCM, a catalytic amount of *N,N*-dimethyl 4-aminopyridine (DMAP) and pyridine were added. On addition of DMAP a yellow colour immediately appeared. The reaction was cooled to  $-80^{\circ}\text{C}$  and two equivalents of benzyl alcohol were added. The crude reaction mixture showed one spot on TLC which may have been pyridine. Following work-up there were a large number visible. Thus the attempted synthesis of these esters was discontinued.

### 2.2.1.3 Threitol Type Ligands

The Narasaka ligand involved the formation of an isopropylidene threitol type system using tartaric acid esters as precursor. The ligand has the structure (178). The synthesis of similar ligands was undertaken. The first step is the formation of the ketal or acetal *via* protection of the diol function. This was attempted by dissolving the ethyl ester of tartaric acid in acetone and ten equivalents of dimethoxy propane with addition of a small amount of pyridinium *p*-toluenesulphonic acid as catalyst. The reaction was attempted on several occasions at various temperatures ranging from room temperature to heating under reflux. At the reflux temperature, a small amount of the desired material was recovered and this was reduced in a Grignard reaction with ethyl magnesium bromide, with subsequent heating of the ether solution under reflux for 2 h. The reaction mixture was cooled to  $0^{\circ}\text{C}$  and the diester added slowly. Upon complete addition the mixture was heated under reflux for several more hours. The crude material was worked up and recrystallised from DCM. The yield was extremely small, corresponding to only a few percent. Spectroscopy confirmed that it was the desired

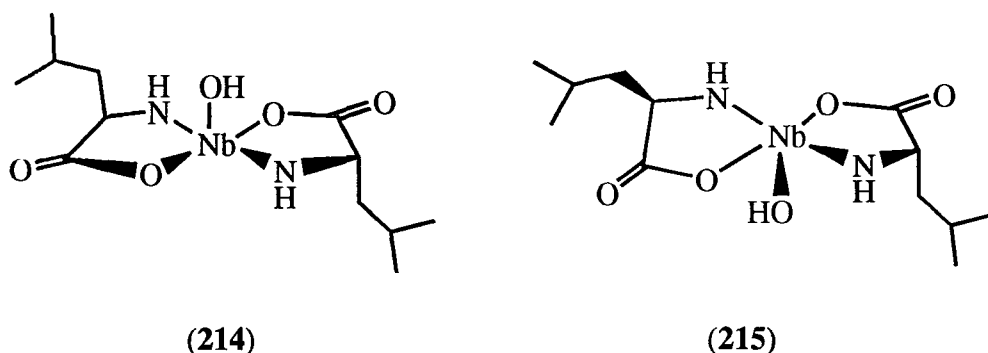
material. However it later proved possible to purchase the ligands from a commercial source and this line of synthesis was discontinued

## 2.2.2 Formation of Catalysts

### 2.2.2.1 Amino Acids

In the initial stages of experimentation formation of the catalysts was attempted in order to perform spectroscopic analysis followed by their application as Lewis acids. It was hoped to determine the structure and thus have a rational basis for describing their catalytic activity. Initially some amino acids were reacted with niobium pentachloride for several hours followed by quenching of the reaction with one equivalent of water. Prior to quenching the catalysts were coloured materials whereas following addition of water the products were white powders. They were insoluble in any solvent and any attempt to perform solution-state analysis, such as UV or NMR spectroscopy proved fruitless. However, limited success was achieved in the case of IR analysis. A comparison of the IR of phenylalanine with that of the complex formed when two equivalents of phenylalanine were reacted with  $\text{NbCl}_5$  and quenched with water reveals several marked differences. In the amino acid a peak at  $3200\text{ cm}^{-1}$  is visible, that of the N–H stretch. There is also a broad band at  $3000\text{ cm}^{-1}$  for O–H. There is a broad band between  $1500$  and  $1650\text{ cm}^{-1}$  for the carbonyl reflecting the fact that the acid does not possess a discrete C=O group. In the case of the metal complex of phenylalanine the peak at  $3200\text{ cm}^{-1}$  is a shoulder of the peak at  $3000\text{ cm}^{-1}$  (probably due to Nb–OH). In the literature an amine bound to a Nb atom was seen to have an IR stretch at  $3150\text{ cm}^{-1}$ .<sup>117</sup> Most striking, however is the presence of a sharp single carbonyl peak at  $1720\text{ cm}^{-1}$ , reflecting a discrete carbonyl and possibly the presence of an Nb–O–C(O)R system. Significant peaks were also seen at  $1490\text{ cm}^{-1}$  and  $1215\text{ cm}^{-1}$ .

The IR of the L-leucine complex with  $\text{NbCl}_5$  which was formed in the same manner as the phenylalanine adduct displayed a similar IR spectrum with N–H at  $3400\text{ cm}^{-1}$ , O–H at  $2963\text{ cm}^{-1}$ , carbonyl at  $1740\text{ cm}^{-1}$  and large peaks at  $1491$  and  $1215\text{ cm}^{-1}$ . Notably only a single carbonyl peak can be seen in the IR spectrum of the complexes. There are several ways in which the complex could form including square pyramidal (**214**) and trigonal bipyramidal (**215**).



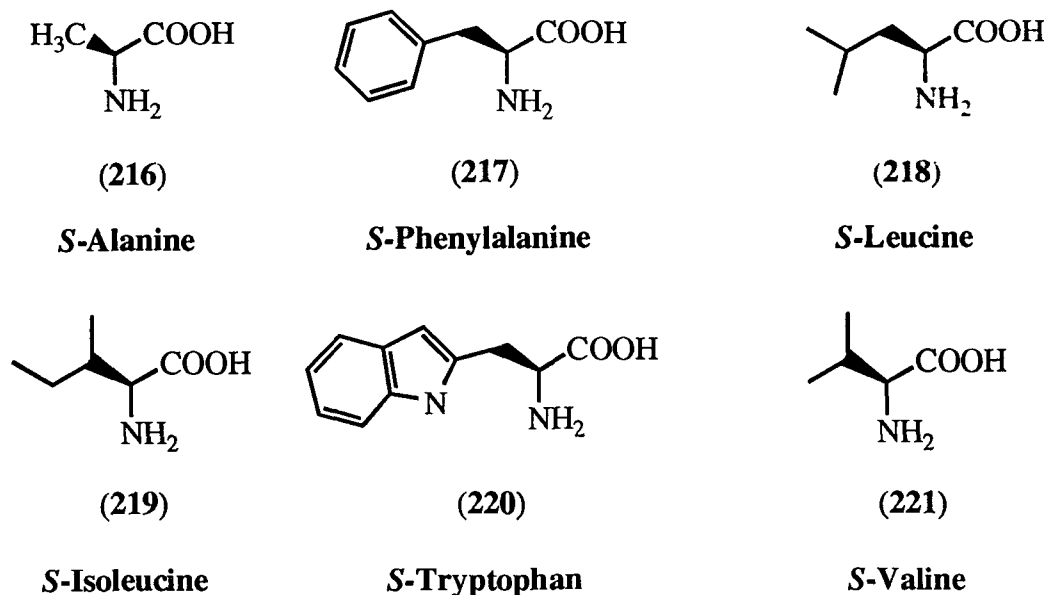
**Figure 52**

The fact that only one carbonyl stretch is present suggests that only one of these forms is present although there are several isomers of each possible. It is also possible that the stretches from a variety of isomers might have very similar values. At any rate it is difficult to glean large amounts of structural data from IR spectroscopy.

A significant feature of the reaction between the amino acids and the metal halides was colour change. In the standard reaction, prior to use as a catalyst, the metal halide was placed in a round-bottom flask (rbf) with DCM or ether and stirred under nitrogen or argon. The solid amino acid was generally added portion-wise with continuous purging with the inert gas. Depending on the ligand used, significant change of colour could be observed. The reaction was generally allowed to proceed for up to 24 h before solvent was removed and the catalyst redissolved in fresh solvent (DCM).

<b>Ligand</b>	<b>Colour of complex solution</b>
Alanine	Yellow
Valine	Yellow
Leucine	Orange/brown
Isoleucine	Orange
Phenylalanine	Brown
Tryptophan	Deep red

The colour of the complex is presented as evidence that reaction between the metal halide and the amino acid did occur. The most dramatic of these was in the case of tryptophan where the colour change was instantaneous. The extent of the change may be due to co-ordination of the nitrogen atom in the indoyl substituent to the metal. The structures of the amino acids used are shown below.



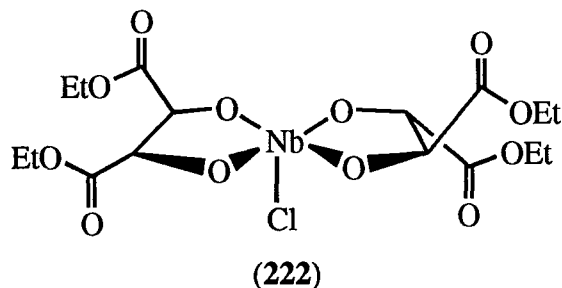
**Figure 53**

### 2.2.2.2 Diols

Chiral diols were chosen as ligands because of the possibility of  $C_2$  symmetry. Thus, no matter which way the ligand bonded to the metal, the configuration would be the same. This was done because of the difficulties in achieving ee's with the amino acid ligands (see below). The simplest and most accessible of these were the tartrate esters and initial reactions were attempted with the diethyl and diisopropyl esters of 2*R*, 3*R* tartaric acid. When the oily ester was syringed into the round-bottom flask containing a suspension of  $NbCl_5$  in DCM, an instantaneous colour change from yellow to off-white was observed. Significantly, the catalyst presented as a solution in DCM, *ie* totally dissolved, unlike the amino acid catalysts which were as suspensions or partially dissolved solids. It was possible to recover the catalyst as a gum following removal of solvent. IR revealed peaks at 1728 and 1621  $cm^{-1}$  showing two distinct carbonyls present.

It was possible to dissolve the catalyst in MeOD and run an NMR spectrum, with  $^1H$ ,  $^{13}C$  and COSY-90 being performed. The results of this analysis show two distinct ethyl groups in the proton NMR with the correct splitting. These are matched by two separate carbonyl peaks at 172.5 and 173.0 ppm in the  $^{13}C$  NMR. In the proton the difference in shift of the methyl peaks is small (2.12 vs 2.25 ppm) whereas that of the methylene groups is much larger (4.57 vs 5.19 ppm). Two peaks for C-H are visible at 5.50 ppm. There are significant differences between the free tartrate and the complex

Firstly, only one peak is seen for each of the methyl, methylene and methine protons. Secondly there is large shift in their values. Methyl in diethyl tartrate is seen at 1.27 ppm, methylene at 4.20 ppm and methine at 4.50 ppm. The difference in  $J$  values for the ester chain are 7.4 Hz and 5.8 Hz for the complex and 6.9 Hz for the free ligand. What this evidence points to is a square-pyramidal structure such as (222).

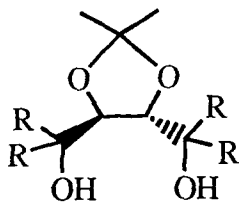


**Figure 54**

Although the tartrate complex is symmetrical, the complex as shown in Figure 54 has each of the significant protons on functional groups above and below the plane leading to a doubling of the number of signals in proton NMR and of the carbonyls on IR. The four carbons on the backbone remain in the plane and thus give a single signal in  $^{13}\text{C}$ . This leads to the notion that the square-pyramidal structure is more plausible than a trigonal bipyramid.

A stability experiment on the niobium diethyl tartrate catalyst was performed. This was done by taking one portion and placing it in a desiccator (sample A), placing a further portion and placing it on the open bench (sample B) and leaving a further sample under inert gas in a dry atmosphere (sample C). Observation and  $^1\text{H}$  NMR analysis of the compounds after three days revealed that there was no significant degradation of sample A (kept in dry air) with respect to sample C, but that sample B had significantly decomposed such that it would no longer dissolve in MeOD. It had also taken on a powdery appearance. This experiment suggested that the catalyst was moisture sensitive but relatively oxygen stable.

The series of alcohols based on threitol were used as ligands and were reacted with niobium and tantalum pentachloride. The three compounds used were the analogues of (223).

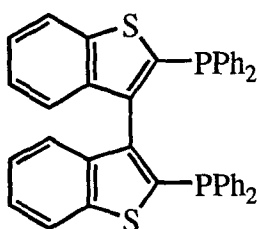


R = H, Ph, Naphth

(223)

**Figure 55**

For the complexes formed where R = H no significant colour was observed, just the formation of an off-white powder. In the cases of R = phenyl or R = naphthyl, only the Ta compound was formed. This was because no catalytic reaction was observed in the case of the Nb compound where R = H. On formation of the complex between TaCl<sub>5</sub> and (223), (R = Ph, Naph) a red colour was observed. On stirring for 24 h the solution had turned yellow. However when the solvent was removed and fresh solvent added, the red colour was again observed. It seems likely that HCl, formed when the complexation occurred, was itself associating with the complex affecting the colour. *R*-Binaphthol has chirality based on restricted rotation about the bond between the two fused-ring groups. Complexes were formed between this ligand and NbCl<sub>5</sub> and TaCl<sub>5</sub> respectively. Experiments using both one and two equivalents of ligand were attempted. The niobium complex thus formed was red and the tantalum complex was yellow. Finally a ligand with structural similarity to binol was used (224).<sup>119</sup> The resulting solution was brown.



(224)

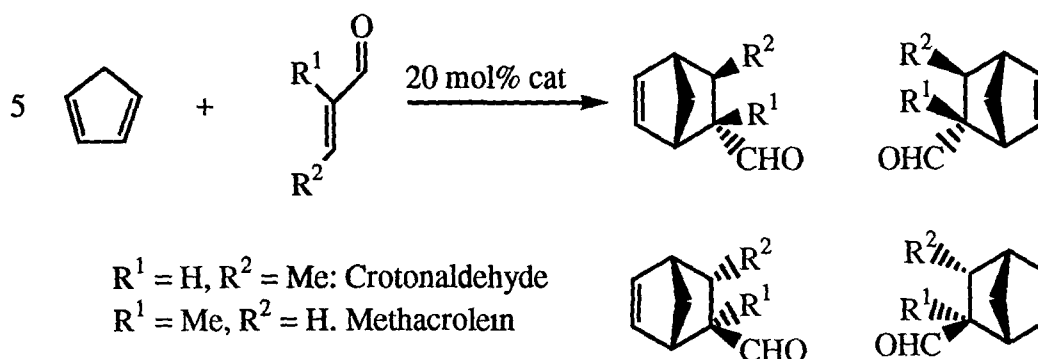
**Figure 56**

Bmol, threitol and the above thiophene-based ligand were available in very small quantities. Thus detailed structural analysis was not performed on the complexes and the material was used only as catalyst ligand.

## 2.2.3 The Diels–Alder Reaction

### 2.2.3.1 Selectivity

The Diels–Alder reaction between cyclopentadiene and either crotonaldehyde or methacrolein was used as the test reaction to determine both the Lewis-acid activity and the chiral induction capabilities of the catalytic systems



Scheme 83

Thus there are four possible products for each reaction, the *endo* and *exo* regioisomers and the *S* and *R* stereoisomers of the  $\alpha$ -carbon. The *endo*/*exo* ratio in the thermal, uncatalysed reaction is such that there is an excess of the *endo* isomer when crotonaldehyde is used as the dienophile and an excess of the *exo* isomer when methacrolein is used as the dienophile. An examination of the transition states explains this phenomenon. The most significant overlap is between the HOMO of the diene and the LUMO of the dienophile in terms of frontier molecular orbitals. This interaction, in the case of crotonaldehyde is illustrated in Figure 57

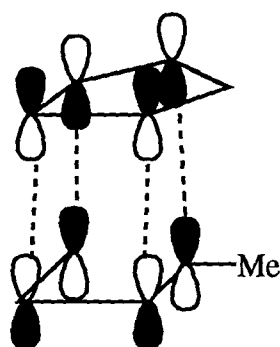


Figure 57

The overlap of the bonding orbitals is such that the addition proceeds smoothly for the thermal reaction. However, there is a secondary overlap between the carbonyl on the dienophile and the orbitals on the diene not directly involved in bonding. Thus, this transition state is highly favoured and leads to the *endo* product

In the case of methacrolein, Figure 58 shows the transition state possibilities for the *endo* and *exo* products. There is a substantial steric interaction between the methyl group and the methylene group on the diene in the case where the *endo* product is formed making this transition state highly disfavoured

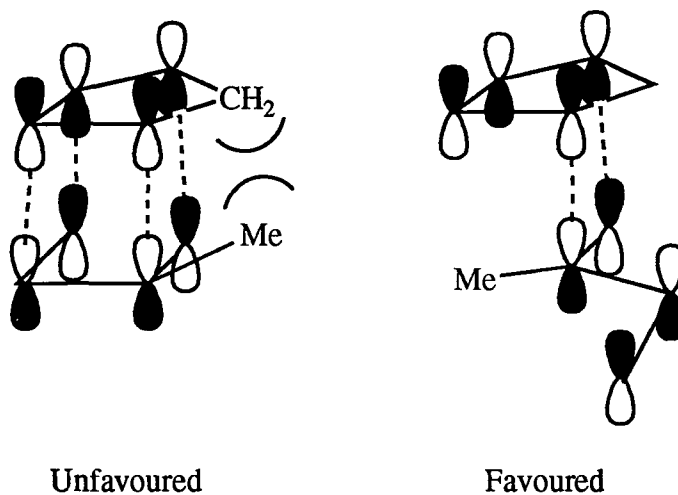


Figure 58

The co-ordination of a Lewis acid to the carbonyl group lowers the energy of the LUMO making overlap more favoured and speeding up the reaction. It also affects the atomic orbital coefficients of the atoms which in the case of an unsymmetrical diene leads to increased regioselectivity. In the case of crotonaldehyde it causes secondary overlap to be more favoured, increasing the proportion of the *endo* product. In the case of methacrolein the *endo* transition state still suffers from steric inhibition despite the Lewis-acid co-ordination. The *exo* transition state has no such inhibition and the rate being enhanced by catalysis, yields product faster leading to consumption of the dienophile in favour of the *exo* product.

In terms of stereoselectivity the aim is to design a catalyst which blocks one face of the dienophile substrate in the transition state, leaving only one face for the reagent diene to attack. Figure 59 illustrates this.



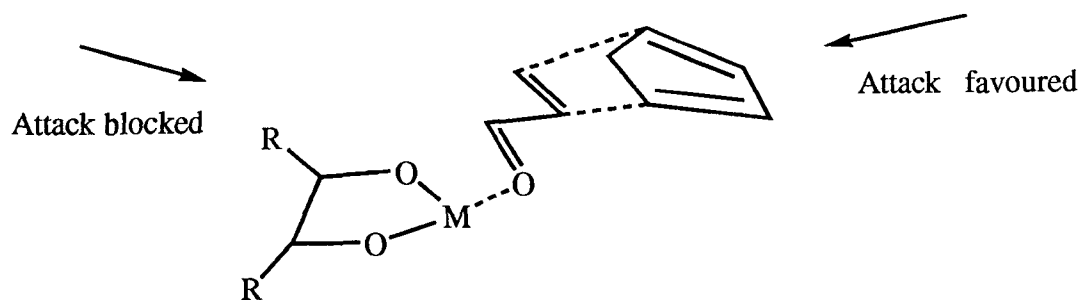


Figure 59

### 2.2.3.2 General Procedure

The use of the cyclopentadiene–methacrolein/crotonaldehyde system yields a product which is easily recovered from the reaction mixture and analysed by NMR. Generally the material could be seen on TLC by developing in PE.DCM (50:50) and visualising by exposure of the plate to a solution of phosphomolybdic acid in methanol as the product norbornene aldehyde is barely visible using UV absorption. Various methods can be used to separate the adduct from the reaction mixture. Initially water was used to quench the reaction whereby the catalyst turned to a white powder and could be filtered out. The solvent was then removed and the concentrate separated by silica gel flash chromatography. At later stages the quenching step with water was removed from the procedure and no significant difference was noticed. The reaction was removed from the freezer or cold plate and the solvent removed until only a concentrate remained. It was found that it was essential to filter out solid catalyst at this stage as not doing so blocked the column leading to poor chromatography. On the TLC system described, the crotonaldehyde adduct had an  $R_f$  of 0.65 and the methacrolein product one of 0.75. The *endo* and *exo* products were collected together and the ratio of each could be determined using  $^1\text{H}$  NMR.

The general procedure for the reaction involved formation of the catalyst in ether or dichloromethane followed by 24 h stirring. This was followed by removal of the solvent, charging with fresh DCM and separating the catalyst solution into two vessels. The vessels were then cooled to reaction temperature,  $-80^\circ\text{C}$  (if dry ice was being used) or  $-40^\circ\text{C}$  (if the cold plate was being used). The system was allowed to equilibrate for up to 1 h and then cyclopentadiene was syringed into the vessels. Finally the dienophile was added and the reaction allowed to proceed for 18–72 h.

The main reason for changing the catalyst solvent was to remove any HCl present which may have been formed during complex formation. This might catalyse condensation of the dienophiles or any other Brønsted acid catalysed reaction. One hour was judged to be sufficiently long for the catalytic system to cool to the extent that no thermal reaction could occur. In fact this was tested by mixing cyclopentadiene and crotonaldehyde in a vessel cooled to  $-80^{\circ}\text{C}$  for 1 h but which contained no catalyst. TLC analysis at 18 h and 72 h confirmed that no reaction had taken place. This was effectively the negative control.

The ratio of catalyst to dienophile to diene was 1:5:25. In this manner, it could be determined whether reactions were catalytic or stoichiometric. Furthermore there was a large excess of diene thus reducing the importance of the interaction of the reagent and the substrate-catalyst complex as a rate-limiting factor. Thus the catalyst has the greatest influence over the rate of reaction. The significance of this is in the fact that the stereochemistry will not be influenced by the availability of reagent. It is known that in several hydrogenation reactions, the amount of hydrogen available so affects the stereochemical outcome that the stereoselectivity is reversed from high to low pressure. Less dramatically, it is known that systems such as Rh[DIOP] display high selectivity at high pressure and low selectivity at low pressure. The formation of each enantiomer of a product is governed by the relative rate at which each of the diastereomeric transition states is formed. However if the rate at which the reagent and substrate-catalyst complex interact is very small then this will govern the overall rate of reaction. Any contribution to the rate made by relative facial selectivities becomes insignificant and enantioselectivity may be lost.

The temperature of the reaction was generally either  $-80^{\circ}\text{C}$  or  $-40^{\circ}\text{C}$  depending on whether it was carried out in dry ice in the freezer or on a cold plate. No significant difference was found in the ee of a given reaction depending on whether it was carried out at either of these temperatures. Neither was yield greatly affected. On certain occasions it was not possible to use 20% catalyst loading due to availability and thus 10% loading was used. A difference in ee did not result, however the yield of the reaction was adversely affected. The ee of the reaction was not affected depending on the length of reaction time, probably related to the fact that there was a large excess of reagent. However, yield was generally affected and in one case a reaction showed a

yield of 50% after 24 h and 99% after 48h Thus most parameters affected yield rather than selectivity.

### 2.2.3.3 Derivatisation and Analysis

The enantiomeric excess (ee) of the reaction was determined by derivatising the aldehyde adduct with 2*R*, 4*R* pentanediol and comparing the ratios of the diastereomeric acetal peaks This system has been used in the literature<sup>120,121</sup> and is simple and relatively sensitive In general, 10–15 mg of the adduct were mixed with an excess of diol in DCM or benzene in the presence of an acid catalyst and a drying agent. The mixture was then allowed to react for 24 h at room temperature In the case of methacrolein, *p*-toluene sulphonic acid was used as the acid catalyst because the methacrolein adduct does not possess an enolisable proton. Thus there could be no scrambling of the chiral centre in the derivatisation procedure. Initially, triethyl orthoformate was used as the drying agent to drive the reaction to completion, but it was found to interfere with the final NMR spectrum if too much was used As a replacement, an excess of anhydrous sodium sulphate was found to be adequate

The crotonaldehyde adduct does possess an enolisable proton and thus *p*-toluenesulphonic acid could not be used as a catalyst for the acetal formation Instead pyridinium *p*-toluene sulphonic acid (PTSA) was used This is a mild Lewis acid which co-ordinates to the aldehyde allowing attack by the diol without formation of the enol It has been demonstrated that there is no preference of the diol for either stereoisomer of the aldehyde, thus ruling out bias in the derivatisation procedure<sup>120</sup> This was achieved by derivatising the aldehyde sample with 2*S*, 4*S* pentanediol and comparing the result to that achieved with the 2*R*, 4*R* diol. No significant difference was observed Before NMR was performed, the mixture was evaporated to dryness and treated with ether. In the case of the crotonaldehyde solvent, this had the effect of precipitating the pyridinium *p*-toluenesulphonic acid. The ether solution was passed through a plug of silica to remove unreacted reagents The solvent was again evaporated and the residue reconstituted in CDCl<sub>3</sub> prior to analysis

### 2.2.3.4 Spectroscopic Details

NMR spectroscopy proved invaluable in the analysis of reaction mixtures and in determining the *endo exo* ratio of a given adduct. It was also useful in determining the ee as seen by the ratio of diastereomeric acetal peaks in the derivatised product

The crotonaldehyde adduct spectrum had doublets at 9.33 and 9.74 ppm for the *endo* and *exo* products respectively. There was a characteristic pair of peaks (doublet of doublets) at 6.03 and 6.27 ppm which related to the vinylic protons on the *endo* material. The corresponding *exo* peaks are at 6.10 and 6.19 ppm. The methyl peak was a doublet at 1.17 ppm. The bridgehead protons appeared at 2.30 and 0.79 ppm. The large difference can be attributed to one of the protons being shifted upfield due to the anisotropy of the carbonyl group.

In the methacrolein adduct the aldehyde peaks appeared at 9.63 and 9.34 ppm for the *exo* and *endo* products respectively. The vinylic peaks for the *exo* were at 6.05 and 6.24 ppm. The corresponding *endo* peaks were at 6.11 and 6.29 ppm. The methyl peak, a singlet, was at 0.95 ppm and the bridgehead protons could be seen at 2.19 and 0.79 ppm. In  $^{13}\text{C}$ , eight of the nine carbons in each adduct were visible, the carbonyl being visible at 204.8–206.0 ppm. The IR spectrum of each adduct was quite simple and similar with a carbonyl stretch at  $1709\text{ cm}^{-1}$ .

In the case of the derivatised acetals the important peaks were at 4.10 (*S*) and 4.15 (*R*) for the crotonaldehyde adduct. They took the form of a pair of overlapping doublets which appeared as a triplet. In the methacrolein adduct the ratio of the singlets at 4.66 (*R*) and 4.68 (*S*) ppm gave the ee. In both cases the aliphatic region was fairly complex due to the presence of the five-carbon chain which originated from the diol.

Using the above information, it was possible to determine the *endo:exo* ratio and the enantiomeric excess of the major product of each reaction with relative ease. There was generally too little of the minor product present to allow determination of its ee.

## 2.2.4 Results

### 2.2.4.1 Amino Acid Ligands

The results for the Diels–Alder reaction using niobium and an amino acid ligand with crotonaldehyde and methacrolein as the dienophiles are shown in Tables V and VI respectively.

**Table V: NbCl<sub>5</sub> as Lewis acid, amino acid as ligand and crotonaldehyde as dienophile**

<u>Ligand<sup>a</sup></u>	<u>Yield (%)</u>	<u>Endo:Exo</u>	<u>EE (%)</u>
None	12.3	94.6	N/O <sup>c</sup>
Alanine	26.8	95:5	N/O
Valine	4.7	95:5	N/O
Leucine	9.4	93:7	N/O
Isoleucine	19.9	94.6	N/O
Phenylalanine	17.5	85:25	N/O
Phenylalanine <sup>b</sup>	34.0	92.8	N/O
Tryptophan	9.6	84.16	N/O

a Two equivalents of amino acid per niobium unless otherwise stated

b One equivalent of ligand

c N/O = not observed

**Table VI: NbCl<sub>5</sub> as Lewis acid, amino acid as ligand and methacrolein as dienophile**

<u>Ligand<sup>a</sup></u>	<u>Yield (%)</u>	<u>Endo:Exo</u>	<u>EE (%)</u>
None	61.5	9:91	N/O <sup>c</sup>
Alanine	44.2	7:93	N/O
Valine	57.2	13:87	N/O
Leucine	26.6	13.87	N/O
Isoleucine	39.5	8.92	N/O
Phenylalanine	42.2	25.75	N/O
Phenylalanine <sup>b</sup>	63.8	7.93	7.0 (S)
Tryptophan	57.2	22.78	N/O

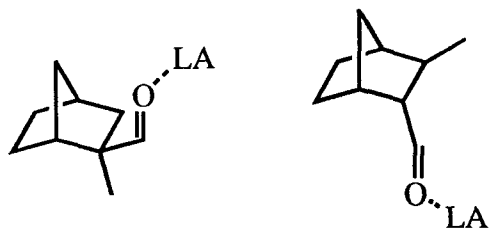
Notes as per Table V

From Table V it can be seen that in general, yields were low and *endo:exo* ratios were high ranging from 85.15 to 95:5 which compares well with 66:34 for the thermal reaction. In contrast the results from Table VI show much higher yields but poorer *endo:exo* ratios ranging from 25.75 to 7.93 for the methacrolein adduct. The lower end of this scale is quite poor and only marginally higher than the corresponding thermal reaction.

In terms of yield difference it is obvious that, in the methacrolein based reaction,  $\text{NbCl}_5$ , whether co-ordinated by an amino acid or not, is functioning as a true catalyst. The lowest observed yield was 26.6% which is higher than the 20% catalyst loading. Thus there has been at least some turnover during the reaction. Yields as high as 62–64% were observed here. Significantly these yields were seen in the reactions with theoretically the least crowding about the catalyst centre, *ie* where there was no ligand attached and where only one phenylalanine ligand was present. One could surmise that with a smaller number of ligands around the metal, any interaction between the catalyst and the substrate was more likely to lead to co-ordination rather than to repulsion.

In the case of the crotonaldehyde reaction only two catalytic results were observed. The reaction involving no ligand did not produce a catalytic result. However, that involving one equivalent of phenylalanine gave a yield of 34%, demonstrating turnover. The reaction involving alanine, the smallest amino acid used, gave a yield of approximately 27%. Thus it seems that the steric crowding at the metal centre has an influence on the yield in these reactions.

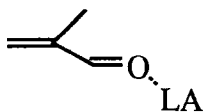
Why there should be such a large difference in yield between the use of crotonaldehyde and methacrolein is not entirely clear. Exactly the same reaction conditions and duration were used for each because in an experiment with a given catalyst, the reactions with crotonaldehyde and methacrolein were performed simultaneously. It is probable that the yield difference is a function of product binding. For any catalytic reaction, in order to achieve good catalytic turnover, the binding constant between the catalyst and the substrate should be much greater than that between the catalyst and the product. In Figure 60, possible interactions between a catalyst and the norbornene aldehyde product are depicted.



**Figure 60**

The crotonaldehyde product is almost exclusively *endo* (for reasons described in section 2.2.3.1). It can be seen that the likely binding position of the Lewis acid with the *endo* product leaves a very small interaction between the bicyclic ring system and the Lewis-acid ligand. Very little repulsion occurs, relatively speaking, and the catalyst may remain bound to the ligand. If the Lewis acid is more exposed, however, a molecule of substrate could interact with another face of the catalyst displacing the product and leading to higher turnover. This, of course, does not seem to occur where no ligand was present, though, this may be because there is no secondary repulsive interaction between ligand and product.

In the case of methacrolein the initial interaction between the Lewis acid and the carbonyl of the substrate will place the Lewis acid co-ordinated to the lone pair furthest from the  $\alpha$ -methyl group as seen in Figure 61.



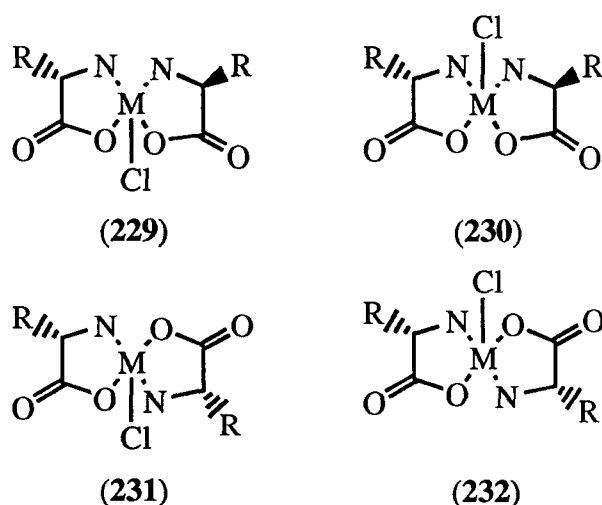
**Figure 61**

The product of the Diels–Alder reaction will be predominantly *exo* leaving the Lewis acid in the proximity of the bicyclic ring system. This will lead to a good deal of repulsion and thus the binding constant between the product and the catalyst will be relatively low. Higher turnover ensues. It is probable that the overall yield is governed both by interaction between the substrate and catalyst (“reagent side” of the reaction) and by repulsion of the catalyst by the adduct (“product side”).

The *endo:exo* ratios of the crotonaldehyde product are consistently higher than the *exo:endo* ratios for the methacrolein product. This could possibly be explained by the fact that the high *endo* selectivity in the crotonaldehyde product arises from the secondary orbital interaction between the carbonyl orbitals on the substrate and those orbitals on the diene not involved in bonding with the dienophile (see Figure 57). *Exo*

selectivity arises due to steric repulsion between the  $\alpha$ -methyl on methacrolein and the methylene group on the diene in any *endo* interaction in the transition state. The former is an attractive force whereas the latter is repulsive. Thus it possibly has greater influence over the outcome than does the non-bonding interaction which might be overcome, given sufficient energy. The *endo* interaction in the methacrolein product does involve an attractive force. However, the *endo* interaction for crotonaldehyde does not possess a corresponding repulsive force. The overall result of these relative interactions is reflected in the *endo exo* ratios.

Little or no enantiomeric excess was observed in any of the reactions attempted using amino acids save for that using one equivalent of phenylalanine as ligand. It is believed that the only significant influence on ee of the product was the shape of the catalyst (see 2.2.3.2). Two equivalents of amino acid were reacted with NbCl<sub>5</sub> leading, most likely, to a square-pyramidal-type structure. However the amino acids used were unsymmetrical and thus it is possible that a variety of different diastereomers of the metal:amino acid complex formed. It is assumed that the amine and acid moieties displace chlorine from the metal as this would be consistent with the reactions between NbCl<sub>5</sub> and either acids or amines, described in the literature.<sup>114</sup> There are four potential isomers formed.



**Figure 62**

Should these isomers be formed in roughly equal amounts, then it is likely that the products which they catalysed would be racemic. On the other hand, if only one diastereomer was formed then it is possible that the chiral centre is not sufficiently close to the metal atom to effect an ee in the product. However when one equivalent of phenylalanine was used a small ee was observed, suggesting that in the case of one



isomer some influence, however small, should be seen. What is likely is that (231) and (232) are formed in equal amounts and they have the carbonyl group more or less in the plane of the metal. Thus the remaining Cl atom does not cause a difference between them and only one C=O stretch is seen in the IR spectrum. These two catalysts will cause the formation of opposite enantiomers. The results of catalysis using amino acid ligands were disappointing and thus no reactions with TaCl<sub>5</sub> were attempted.

#### 2.2.4.2 Diol Ligands

The results for the Diels–Alder reaction between crotonaldehyde and or methacrolein and cyclopentadiene using NbCl<sub>5</sub> and a chiral diol are shown in Tables VII and VIII. Those describing the use of tantalum as Lewis acid are shown in Tables IX and X.

**Table VII: NbCl<sub>5</sub> as Lewis acid, chiral diols as ligands and crotonaldehyde as dienophile**

<u>Ligand</u>	<u>Yield (%)</u>	<u>Endo:Exo</u>	<u>EE (%)</u>
Diethyl tartrate	9.0	93:7	N/O
Diisopropyl tartrate	16.0	94:6	16(R)
Isopropylidene threitol	N/R <sup>d</sup>	–	–
Bi-2-naphthol <sup>e</sup>	N/R	–	–
Bi-2-naphthol <sup>b</sup>	28.0	85:15	N/O
Bi-2-naphthol <sup>b,g</sup>	34.0	89:11	N/O
2R, 4R pentanediol	N/R	–	–
Thiophene Ligand	N/R	–	–
Thiophene Ligand <sup>g</sup>	19.4	94:6	N/O

Notes a–c as Table V

d N/R = no reaction

e Very low amount of catalyst used

f Normal conditions

g unactivated molecular sieves added to the reaction

**Table VIII: NbCl<sub>5</sub> as Lewis acid, chiral diols as ligands and methacrolein as dienophile**

<u>Ligand</u>	<u>Yield (%)</u>	<u>Endo:Exo</u>	<u>EE (%)</u>
Diethyl tartrate	60.7	6:94	22(R)
Diisopropyl tartrate	51.8	3.97	38(R)
Isopropylidene threitol	N/R	–	–
Bi-2-naphthol <sup>e</sup>	4.4	20.80	N/O
Bi-2-naphthol <sup>b</sup>	39.0	10 90	5 0(R)
Bi-2-naphthol <sup>b,g</sup>	51.0	16.84	5.0(R)
2 <i>R</i> , 4 <i>R</i> pentanediol	N/R	–	–
Thiophene Ligand	N/R	–	–
Thiophene Ligand <sup>g</sup>	61.0	7 93	5.0(R)

Notes as Table VII

**Table IX: TaCl<sub>5</sub> as Lewis acid, chiral diols as ligands and crotonaldehyde as dienophile**

<u>Ligand</u>	<u>Yield (%)</u>	<u>Endo:Exo</u>	<u>EE (%)</u>
None	N/R	–	–
Diethyl tartate	41.7	90 10	6.0(R)
Diisopropyl tartrate	23.7	95 5	N/O
Isopropylidene threitol	14.0	99 1	N/O
Isopropylidene 1,1,4,4 tetraphenyl threitol	71.9	86.14	N/O

<b>Isopropylidene 1,1,4,4 tetranaphthyl threitol</b>	42.0	99:1	70(R)
<b>Bi-2-naphthol<sup>b</sup></b>	22.0	87:13	N/O

Notes as Table VII

**Table X: TaCl<sub>5</sub> as Lewis acid, chiral diols as ligands and methacrolein as dienophile**

<u>Ligand</u>	<u>Yield (%)</u>	<u>Endo:Exo</u>	<u>EE (%)</u>
None	N/R	–	–
Diethyl tartrate	75.0	6:94	15(R)
Diisopropyl tartrate	55.4	6:94	5(R)
Isopropylidene threitol	49.3	16:84	N/O
Isopropylidene 1,1,4,4 tetraphenyl threitol	50.2	9:91	N/O
Isopropylidene 1,1,4,4 tetranaphthyl threitol	75.0	10:90	45(R)
<b>Bi-2-naphthol<sup>b</sup></b>	35.0	20:80	N/O

Notes as Table VII

The most striking feature from these results is the superiority of the tartrate ligands in producing chiral induction with NbCl<sub>5</sub> as the Lewis acid. The structure and spectroscopic details of the complex have been discussed earlier (see section 2.2.2.2).

Thus an interaction of the dienophile, in this case methacrolein, would give  $\pi$ -facial selectivity if the complex possessed the structure postulated.

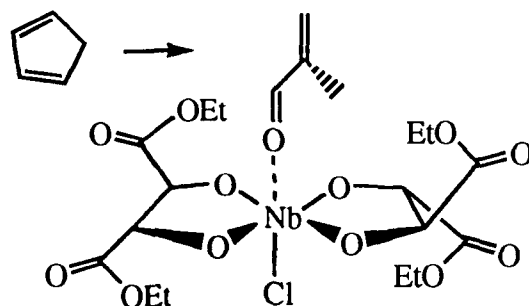
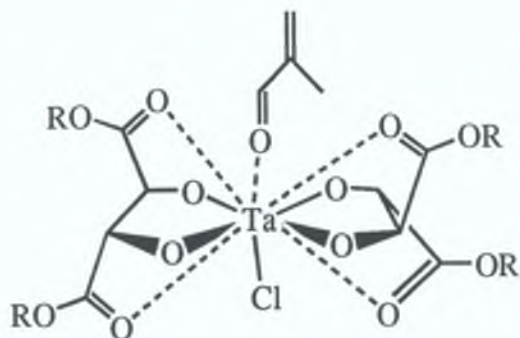


Figure 63

The  $C_2$  symmetry of the ligand is preserved in the complex. Thus only one form of the catalyst is possible leading to a stereoselective Diels–Alder reaction. The ee is, however, relatively modest being 22% in the case of the methacrolein adduct where niobium is the metal and diethyl tartrate the ligand. With crotonaldehyde as dienophile, an ee is not observed. The use of diisopropyl tartrate as ligand causes the ee to almost double giving 38% for methacrolein and in the case of crotonaldehyde, a 20% ee in the adduct is observed. Thus, although the shape of the catalyst affects the induction to some extent where Nb is the Lewis-acid centre, it does not affect it enough to produce a single enantiomer.

In the case of tantalum as the Lewis-acid centre, the inductive capability of the two ligands is reversed. Thus, for diethyl tartrate, an ee of 60% is seen where crotonaldehyde is the dienophile and 15% where methacrolein is used. For diisopropyl tartrate the result using crotonaldehyde showed no ee and that for methacrolein showed a mere 50%. Thus the tantalum complexes failed to produce the same level of chiral induction as the niobium complexes.

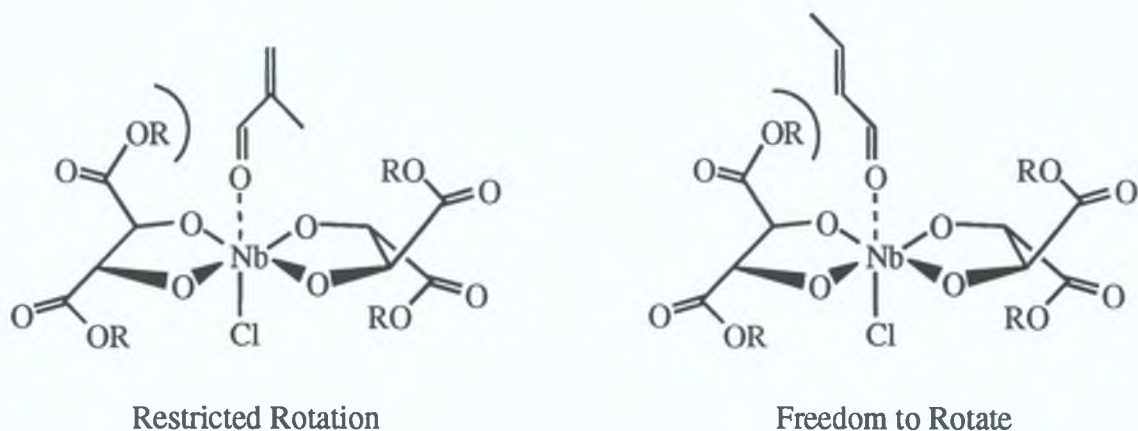
The reason for this is unlikely to be steric because both metal atoms have the same radius. However, the tantalum atom has a significantly more electropositive centre and thus may co-ordinate the carbonyl oxygens turning the “other side” of the ester group outwards and preventing steric interaction with the dienophile. The IR spectrum of the tantalum compound shows fine structure for its carbonyl peaks whereas that of the Nb compound does not. It is possible that this is due to co-ordination.



Dienophile has more freedom to rotate

Figure 64

In both cases the ee for the crotonaldehyde adduct is lower than that of methacrolein. This has been described in the literature<sup>91</sup> and it is reasonable that as an  $\alpha$ -substituent will have more influence than a  $\beta$ -substituent as greater steric interaction at a sight closer to the metal and the chiral ligands will lead to greater enantioselectivity.



Restricted Rotation

Freedom to Rotate

Figure 65

Although the structure of the tartrate catalyst in solution is not entirely certain the <sup>1</sup>H NMR data and the fact that chiral induction takes place tends to suggest a monomeric structure. It is probably not possible, however, to extend this model to make assumptions about the structure of other diol catalysts.

Several other features of the diol results are noteworthy. Again the general case that crotonaldehyde adduct is produced in lower yield is seen except for one notable exception. In the case where tantalum was used as the Lewis-acid centre and tetraphenyl threitol was used, a 71.9% yield was observed. Where methacrolein was the substrate 50.2% yield was achieved. However the crotonaldehyde reaction proceeded for 48 h as opposed to 24 h for the methacrolein. It is significant that high

catalytic turnover is seen here whereas in other cases, as little as 9.0% yield was observed

The use of  $\text{TaCl}_5$  as a Lewis acid is interesting in that in the absence of a co-ordinating ligand it fails to catalyse the Diels–Alder reaction between cyclopentadiene and either of the two dienophiles. Instead, when cyclopentadiene is added, an intractable rubbery material forms almost instantly. It is likely that  $\text{TaCl}_5$  catalyses the polymerisation of the diene and that this is the material seen. Changing the order of addition, such that the dienophile is always added first, did not change the outcome of the reaction.

Isopropylidene threitol was used as a ligand with niobium and no Diels–Alder reaction occurred. It is not entirely certain why this should be so but it is possible that the formation of a seven-membered ring does not favour catalysis with the lighter metal. Poor results were also seen with bi-2-naphthol when two equivalents of ligand were used.

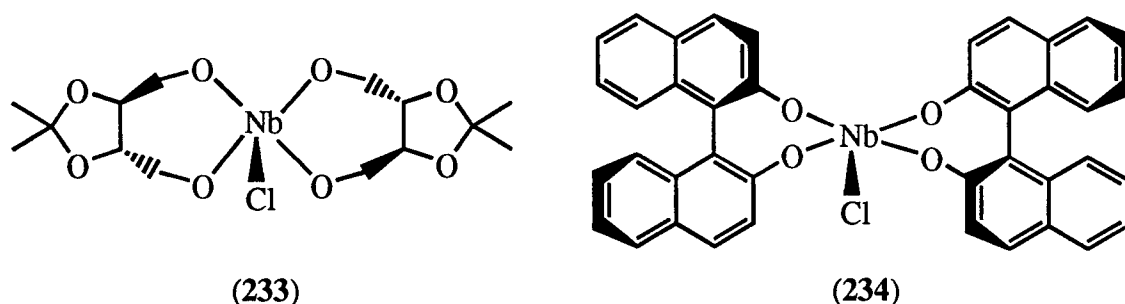
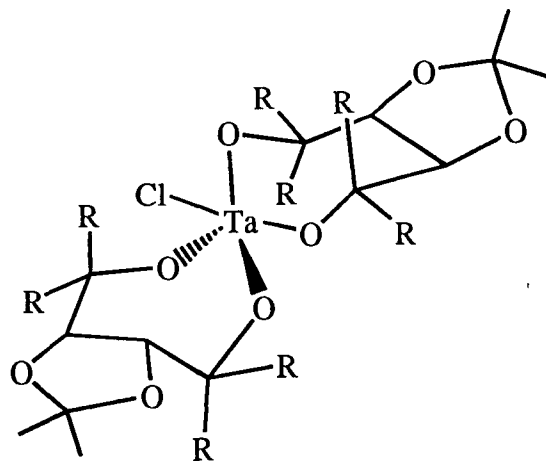


Figure 66

However all the threitols, when used with tantalum, catalysed the Diels–Alder reaction though only in the case of tetranaphthyl threitol was any ee seen. However, despite the obvious bulk of this molecule, the ee's were very modest, 7.0% in the case of crotonaldehyde and 4.5% in the case of methacrolein. It might be that such a large molecule as threitol favours a different co-ordination to the metal than does the tartrate such as a possible trigonal bipyramid structure



(235)

Figure 67

It is also possible that the diol does not achieve full co-ordination. The result is poor chiral induction by threitol.

Three other ligands were used in the case of niobium.- *2R, 4R* pentanediol, *R, R* bi-2-naphthol and the thiophene ligand (224). Although this is not a diol, it is included in this section. The initial reactions with *2R, 4R* pentanediol and bi-2-naphthol were carried out with a very small amount of catalyst and this is believed to be the reason for its failure. Also two ligands may be too many when seven-membered rings are being formed and this may have caused a problem with the bi-2-naphthol reaction. The reaction with bi-2-naphthol was repeated with both niobium and tantalum and only one equivalent of diol was used. Moderate yields and only 5.0% ee were observed with niobium as Lewis acid and methacrolein as dienophile. The low ee is curious in that this ligand has been used extensively to promote chiral induction in Lewis-acid-catalysed reactions involving other metals.<sup>91,103</sup>

A paper published in 1997 described an unusual effect with 4Å molecular sieves in a titanium-catalysed Lewis-acid reaction with bi-2-naphthol as ligand<sup>122</sup>. The authors noted the fact that highest ee was achieved using unactivated molecular sieves when compared to activated sieves or the absence of sieves. It was decided to attempt their use in the reaction catalysed by niobium using this ligand. The result was an enhancement in the yield but no change in enantiomeric excess. The paper described the existence of a  $Ti_4-O$  species in the reaction mixture which was detected using  $^{17}O$  NMR. It is probable that an analogous species does not exist in the niobium system. The yield enhancement effect was quite noticeable in the case of the thiophene ligand.

with niobium as catalyst. In the original reaction, TLC analysis demonstrated no product formation after 48 h. However, on addition of molecular sieves, the reaction went to 61% completion in a further 24 h. A small ee was observed.

In terms of *endo:exo* ratio, it was again crotonaldehyde which generally showed the higher selectivity. This was with the exception of the tartrate ligands whose methacrolein adducts had an excess of major product which was marginally higher than that of the crotonaldehyde adduct. This was true for both niobium and tantalum. When *bi*-2-naphthol was used as the ligand the *endo:exo* ratios were quite low ranging from 80:20 to, at most, 90:10. Thus the overall selectivity with this ligand and either dienophile was quite poor. The best result achieved was an *endo:exo* ratio of 99:1 when tantalum was used as the Lewis acid and complexed to either isopropylidene threitol or the tetranaphthyl analogue and crotonaldehyde was used as the ligand.

In overall terms the diols afforded better enantioselectivity than did the amino acids

## 2.3 CONCLUSIONS

In this chapter the use of chiral amino acids and chiral  $C_2$  symmetrical diols as ligands co-ordinated to niobium and tantalum was examined with respect to their ability to catalyse chiral Diels–Alder reactions. A large number of these ligands have been used previously in conjunction with different Lewis acids and it was felt that similar results might be achieved with niobium or tantalum. A number of analogous ligands such as acids, amines diols, alcohols, catechols and *bi*-2-naphthol have been previously reacted with the group V metal halides. Most of this work was performed in the 1960's and apart from the *bi*-2-naphthol, none of the ligands used were chiral. Thus there was potential for synthesising new compounds and using them as chiral catalysts

There was some difficulty in isolating the compounds in pure form and thus spectral information and detailed knowledge of the structure is limited. However it can be seen from IR that there is a limited number of forms of the amino acid complexes and the  $^1\text{H}$  NMR data for the diethyl tartrate.niobium complex suggested a square-pyramidal structure.



Both niobium and tantalum act as Lewis acids. In the absence of ligand  $\text{NbCl}_5$  catalysed the Diels–Alder reaction in a manner similar to the complexes. However,  $\text{TaCl}_5$  seems to be a very powerful catalyst for polymerisation which affects cyclopentadiene and thus the Diels–Alder reaction did not take place unless the metal was coupled to a ligand. When amino acids were used as ligands, no enantiomeric excess was achieved, suggesting that there are at least two isomers of the complex formed. When one equivalent of phenylalanine was used, however, a small ee was achieved. This supports the idea that several isomers of the two-ligand catalyst were formed.

The diol catalysts used were all  $C_2$  symmetrical; which allows only one isomer of each complex to form. One could thus expect higher enantioselectivity. This was indeed the case for tartrate esters achieving moderate ee's in the case of the niobium catalyst, though quite small ee's were observed in the case of tantalum. Yields and *endo:exo* ratios were variable with highest ratios in those experiments using crotonaldehyde as dienophile but highest yields in the case of methacrolein. Threitol did not allow catalysis in the presence of niobium but did so with tantalum, exhibiting very high *endo:exo* ratios. The bi-2-naphthol ligand, which might have been expected to perform well, did not give good ee and generally exhibited low *endo:exo* selectivity. The use of molecular sieves did not affect the ee in any reaction but did enhance the yield.

Overall, the results achieved in this chapter for the chiral catalysis of the Diels–Alder reaction were modest. Even with ligands which had displayed significant results elsewhere, high ee's were not achieved when complexed to the group V metal chlorides. Although the results were not exceptional, it was seen as a good departure point for the examination of the potential for chiral catalysis using niobium and tantalum.

## 2.4 EXPERIMENTAL

### 2.4.1 General Experimental Considerations

$^1\text{H}$  NMR spectra were measured at 400 MHz using a Bruker AM 400 spectrometer.  $^{13}\text{C}$  spectra were measured at 100 MHz using the same device. Riedel de Haen silica 60F<sub>254</sub> TLC plates were developed in the solvent systems described below. Products were detected using UV absorbance or by dipping the developed plate in a solution of

phosphomolybdc acid in MeOH and heating. Flash chromatography was performed using Riedel de Haen or Matrix silica gel 60 Diethyl ether was dried by passing through activated alumina and storing over sodium. Benzene and dichloromethane were distilled from CaH<sub>2</sub>. Toluene was purified by shaking with cold H<sub>2</sub>SO<sub>4</sub>, washing with base and brine storing over MgSO<sub>4</sub> and finally distilling from P<sub>2</sub>O<sub>5</sub> Triethylamine was distilled from KOH and pyridine was distilled from LiAlH<sub>4</sub>. THF and DMF were dried by distilling from sodium following heating under reflux for several hours. Thionyl chloride was purified by sequentially heating under reflux in sulphur and boiled linseed oil and distillation after each stage. Dicyclopentadiene was cracked every month using a *vigreux* tube at 40°C. The material was stored -18°C and distilled again before use at 40°C and atmospheric pressure using Kugelrohre apparatus. Crotonaldehyde and methacrolein were used without treatment **Niobium and tantalum compounds are suspected of being highly toxic and thus should be treated with extreme caution. Crotonaldehyde and methacrolein are extremely toxic and if inhaled will cause respiratory distress.**

## 2.4.2 Synthesis of Ligands

### Synthesis of diisopropyl-(2*R*, 3*R*)-tartrate (A)

2*R*, 3*R*-Tartaric acid (2.99 g, 0.020 mol) was placed in benzene with 1.5 equivalents of isopropyl alcohol (1.80 g, 0.030 mol) and 50 mg of *p*-toluene sulphonic acid. The mixture was heated under reflux using Dean and Stark apparatus. After 24 h the solvent was removed under vacuum and a quantity of a white solid was recovered. This was found to be tartaric acid.

### Synthesis of diisopropyl-(2*R*, 3*R*)-tartrate (B)

2*R*, 3*R*-Tartaric acid (3.01 g, 0.020 mol) was dissolved in excess isopropyl alcohol under an argon atmosphere. The solution was cooled to -6°C in an ice-salt mixture. Added to this solution were 2.01 equivalents of freshly distilled thionyl chloride (4.98 g, 0.042 mol) in a dropwise manner. The reaction was allowed to proceed for 4 days. Solvent was removed under vacuum and 4.58 g of crude material resulted. The material was purified using dry flash chromatography with a mobile phase of PE:EA

(50:50) Yield of pure material = 2.81 g (60%). Boiling point = 160°C at  $1 \times 10^{-3}$  atm.  $R_f = 0.60$  in PE EA (50:50) IR  $\nu_{\max}$  3425, 2840, 1723  $\text{cm}^{-1}$ .  $\delta_{\text{H}}[\text{MeOD}]$  includes the following signals: 1.23 (6 H, dd,  $J=6.4, 4.0$ ), 3.35 (1 H, d,  $J=7.9$ ), 4.41 (1 H, d,  $J=7.9$ ), 5.12 (1 H, m,  $J=6.4$ ).  $\delta_{\text{C}}[\text{MeOD}]$  shows the following signals 21.49, 70.16, 72.03, 171.03

#### Synthesis of di-*t*-butyl-(2*R*, 3*R*)-tartrate (A)

(2*R*, 3*R*)-Tartaric acid (3.18 g, 0.021 mol) was dissolved in approximately 150 ml of *t*-butyl alcohol and the vessel purged with argon. The mixture was cooled, with vigorous stirring to prevent the alcohol from freezing, using an ice-salt mixture. Thionyl chloride (5.26 g, 0.044 mol) was added slowly. The system was allowed to warm to room temperature and reaction was allowed to proceed for 4 days. On removal of solvent a white solid was recovered which was unreacted tartaric acid.

#### Synthesis of di-*t*-butyl-(2*R*, 3*R*)-tartrate (B)

(2*R*, 3*R*)-Tartaric acid (1.55 g, 0.010 mol) was dissolved in DMF and stirred for several hours in the presence of carbonyl diimidazole (CDI) (5.04 g, 0.030 mol). The CDI was seen to be consumed by TLC. *t*-Butyl alcohol (1.64 g, 0.022 mol) was mixed with a catalytic amount of NaH in THF. After 30 min the alcoholate-alcohol mixture was added to the original solution. The reaction was left to stir for 24 h. The solvent was removed and a black tar was recovered. Dry flash chromatography was used and a small amount of material (450 mg) was recovered. It is believed from the evidence of TLC analysis that this material was imidazole.

#### Synthesis of di-*t*-butyl-(2*R*, 3*R*)-tartrate (C)

*t*-Butyl alcohol (3.25 g, 0.043 mol) was dissolved in 1,4-dioxane and cooled to  $-6^\circ\text{C}$  using an ice-salt mixture. Thionyl chloride (5.12 g, 0.045 mol) was added slowly and the solution stirred for several hours. The mixture was again cooled and a solution of tartaric acid in 1,4-dioxane (3.05 g, 0.021 mol) was added. This reaction was allowed to proceed for 48 h and a cloudy white precipitate was observed which was shown to be tartaric acid. A further material was recovered from the filtrate but this was not identified.

### Synthesis of dibenzyl -(2*R*, 3*R*)-tartrate (A)

2*R*, 3*R*-Tartaric acid (3.14 g, 0.021 mol) was dissolved in approximately 140 ml of benzyl alcohol. The vessel was purged with argon and cooled in an ice-salt mixture, followed by addition of thionyl chloride (4.97 g, 0.042 mol). The reaction proceeded for 4 days at which time solvent was removed and a white solid recovered. This was shown to be tartaric acid.

### Synthesis of dibenzyl -(2*R*, 3*R*)-tartrate (B)

Benzyl alcohol (3.76 g, 0.035 mol) was added to a small volume of dry DCM and cooled to 0°C. Thionyl chloride (4.69 g, 0.040 mol) was added and the solution allowed to stir. 2*R*, 3*R*-Tartaric acid (2.67 g, 0.027 mol) was added portion-wise. A white suspension resulted and the solid recovered was shown to be the acid. The solvent was evaporated and the resulting oil was analysed by NMR.  $\delta_{\text{H}}[\text{CDCl}_3]$  showed the following signals:- 1.42 (1 H, s), 4.53 (2 H, s), 7.32 (5 H, m).  $\delta_{\text{C}}[\text{CDCl}_3]$  showed the following signals:- 46.16, 128.48, 128.63, 137.39. This material is benzyl alcohol.

### Synthesis of dibenzyl -(2*R*, 3*R*)-tartrate (C)

2*R*, 3*R*-Tartaric acid (2.95 g, 0.020 mol) was dissolved in 1,4-dioxane and cooled to 0°C with constant stirring. Thionyl chloride (4.79 g, 0.040 mol) was added slowly followed by addition of a large excess of triethylamine. While still cold benzyl alcohol (4.37g, 0.041 mol) was added slowly. Reaction was allowed to proceed for 20 h. Dioxane was removed under vacuum and a white solid was observed. Crude yield was 2.22 g. Material was washed in acetone whereupon the acetone was evaporated and the remaining material taken up in ethyl acetate.  $R_f=0.9$  using PE:EA (80:20). NMR contained no aromatic peaks.

### Synthesis of dibenzyl -(2*R*, 3*R*)-tartrate (D)

2*R*, 3*R*-Tartaric acid (2.99 g, 0.012 mol) was dissolved in freshly distilled thionyl chloride at -6°C in an ice-salt mixture. This was allowed to react for 20 h with warming to room temperature. Thionyl chloride was distilled off and dry DCM added. *N,N*-Dimethyl aminopyridine (DMAP) (25 mg, .0004 mol) was added and a yellow colour appeared. The reaction was cooled to -80°C and an excess of pyridine and benzyl alcohol (4.27 g, 0.040 mol) were added. The mixture was allowed to warm to room temperature and reaction took place for 20 h. TLC of the crude material showed

a spot with  $R_f=0.75$  in PE:EA (75:25). Removal of solvent and washing with water resulted in a TLC with 7 spots

### Synthesis of 1,1,4,4-tetraethyl, 2*R*, 3*R*-threitol

2*R*, 3*R*-Tartaric acid, diethyl ester (8.01 g, 0.039 mol) was dissolved in 100 ml of acetone in a 250 ml 3-neck, round-bottom flask. 2,2-Dimethoxy propane (40.45 g, 0.388 mol) and 0.50 g of pyridinium *p*-toluene sulphonic acid were added. Solvent was removed after 24 h reaction and ether added to precipitate the catalyst. The ether was removed under vacuum and a crude oil resulted. The oil was distilled at 160°C under vacuum and the yield was 6.90 g (73%). IR  $\nu_{\max}$  1732  $\text{cm}^{-1}$ .  $\delta_{\text{H}}[\text{CDCl}_3]$  showed the following signals:- 1.24 (3 H, dt,  $J=7.0, 1.9$ ), 1.41 (3 H, s), 4.20 (2 H, dd,  $J=7.0, 1.9$ ), 4.48 (2 H, s).  $\delta_{\text{C}}[\text{CDCl}_3]$  showed the following signals - 13.88, 26.13, 62.10, 71.98, 76.92, 171.39.

A solution of this material in ether (6.90 g, 0.028 mol) was added to 4.1 equivalents of ethyl magnesium bromide at 0°C. The reaction was allowed to warm following complete addition and was heated under reflux for 2 h. Water was then added followed by a solution of  $\text{NH}_4\text{Cl}$ . The water layer was extracted with ether and the organic fractions combined. The ether was evaporated to leave 2.41 g of crude material. This was recrystallised from ethyl acetate and petrol. 0.50 g of white powder was recovered (overall yield = 1.4%).  $R_f=0.80$  using PE:EA (90:10). Melting point = 89°C. IR  $\nu_{\max}$  3375  $\text{cm}^{-1}$ .  $\delta_{\text{H}}[\text{CDCl}_3]$  showed the following signals:- 0.92 (6 H, dt,  $J=7.6, 11.3$  Hz), 1.34 (3 H, s), 1.59 (4 H, dd,  $J=7.6, 11.2$  Hz), 2.81 (1 H, s), 3.98 (1 H, s).  $\delta_{\text{C}}[\text{CDCl}_3]$  showed the following signals:- 6.56, 7.16, 26.67, 27.36, 28.75, 73.08, 78.38, 106.5.

### 2.4.3 Lewis-Acid Catalysed Diels–Alder Reactions

#### None

Two vessels containing dry DCM were cooled to -80°C. Cyclopentadiene was placed in each vessel, 580.9 mg (8.782 mmol) in vessel 1 and 611.4 mg (9.247 mmol) in vessel 2. Crotonaldehyde (143.0 mg, 2.040 mmol) was added to vessel 1 and methacrolein (175.1 mg, 2.498 mmol) to vessel 2. At 24 h and 72 h TLC analysis was performed using PE:DCM (50:50). No products were detected.

## Niobium Pentachloride

Niobium pentachloride (75.7 mg, 0.280 mmol; 72.9 mg, 0.270 mmol) was added to each of two 50 ml dry round-bottom flasks. Dry DCM was added and the suspensions stirred under argon for 1 h. The vessels were then cooled on dry ice and cyclopentadiene added; 461.8 mg (6.984 mmol) to vessel 1 and 444.8 mg (6.727 mmol) to vessel 2. Crotonaldehyde (127.0 mg, 1.812 mmol) was then added to vessel 1 and methacrolein (131.4 mg, 1.875 mmol) to vessel 2. The reaction was allowed to proceed for 18 h. The product of each reaction was purified using silica gel flash chromatography with a mobile phase consisting of PE DCM (50:50).

Adduct A (from vessel 1):- Colourless oil,  $R_f=0.65$ . IR  $\nu_{\max}$  2874, 2821, 2724, 1709, 1377, 1333, 1006  $\text{cm}^{-1}$ .  $\delta_{\text{H}}[\text{CDCl}_3]$  showed the following signals:- 0.79 (1 H, dd,  $J=8.7, 6.4$  Hz), 1.14 (3 H, d,  $J=6.9$ ), 1.49 (1 H, dd,  $J=6.9$ ), 1.72–1.83 (1 H, m,  $J=4.4, 2.0$ ), 2.27–2.32 (1 H, m,  $J=3.0, 4.4$  Hz), 2.53 (1 H, s), 3.10 (1 H, d,  $J=8.7$ ), 6.03 (1 H, dd,  $J=5.4, 3.4$  Hz), 6.27 (1 H, dd,  $J=5.4, 3.4$  Hz), 9.33 (1 H, d,  $J=3.4$  Hz).  $\delta_{\text{C}}[\text{CDCl}_3]$  showed the following signals - 20.73, 36.22, 45.34, 46.11, 48.99, 61.30, 132.54, 138.93, 204.80. Yield = 30.4 mg (12.3%).

Adduct B (from vessel 2).- White low-melting solid,  $R_f=0.75$ . IR  $\nu_{\max}$  2879, 2750, 1709, 1377, 1343, 1020  $\text{cm}^{-1}$ .  $\delta_{\text{H}}[\text{CDCl}_3]$  showed the following signals:- 0.70 (1 H, d,  $J=12.4$ ), 0.95 (3 H, s), 1.34 (2 H, d,  $J=15.5$  Hz), 2.20 (1 H, dd,  $J=12.3, 3.9$ ), 2.76 (1 H, d,  $J=1$  Hz), 2.83 (1 H, s), 6.04 (1 H, dd,  $J=2.9$ ), 6.24 (1 H, dd,  $J=2.9$ ), 9.63 (1 H, s).  $\delta_{\text{C}}[\text{CDCl}_3]$  showed the following signals:- 20.03, 34.59, 43.22, 47.40, 47.61, 50.00, 133.09, 139.55, 205.79. 157.1 mg, (61.5%). The adducts were derivatised as described below to determine ee. None detected.

### General procedure for derivatisation of adduct to acetal

Adduct A (18.2 mg, 0.134 mmol) was placed in a 5-ml round-bottom flask with 1.1 equivalents of 2*R*, 4*R*-pentanediol (15.3 mg, 0.147 mmol) and 5 mg of pyridinium *p*-toluene sulphonic acid in 1 ml of dry DCM. The reaction was allowed to proceed for 24 h. The solvent was removed under vacuum and ether added whereby the catalyst was precipitated. The suspension was passed through a plug of silica gel and then the plug washed with a further 2 ml of diethyl ether. The ether fractions were combined and the solvent removed under vacuum. The residue was dissolved in  $\text{CDCl}_3$  and analysed using NMR. The ratio of the diastereomeric acetal peaks at 4.10 (*S*) and 4.15 (*R*) were used to determine the enantiomeric excess (ee).

Adduct B (11.0 mg, 0.081 mmol) was placed in a 5-ml round-bottom flask with 1.1 equivalents of 2*R*, 4*R*-pentanediol (10.3 mg, 0.099 mmol), 5 mg of *p*-toluene sulphonic acid, 2 drops of triethyl orthoformate or 20 mg of anhydrous Na<sub>2</sub>SO<sub>4</sub> and 1 ml of DCM or benzene. The reaction was allowed to proceed for 24 h. The solvent was then removed under vacuum and the residue dissolved in ether (1 ml). The solution was passed through a plug of silica followed by washing of the plug with 2 ml of ether. The ether fractions were combined and the solvent removed. The residue was dissolved in CDCl<sub>3</sub> and analysed by NMR. The diastereomeric acetal peaks at 4.66 (*S*) and 4.68 (*R*) were used to determine the ee.

#### **Niobium pentachloride and *S*-alanine**

A suspension of NbCl<sub>5</sub> (310.3 mg, 1.149 mmol) in dry diethyl ether was prepared. *S*-Alanine (204.0 mg, 2.290 mmol) was added over 30 min under a stream of argon. The suspension was stirred for several hours at which time it was divided into two round-bottom flasks by syringing from the original vessel under a stream of argon. The ether was removed under vacuum and each of the vessels charged with dry DCM and cooled to -80°C on dry ice. Cyclopentadiene was added to each vessel, 811.0 mg (12.26 mmol) to vessel 1 and 935.1 mg (14.14 mmol) to vessel 2. Crotonaldehyde (173.0 mg, 2.468 mmol) was added to vessel 1 and methacrolein (211.3 mg, 3.004 mmol) to vessel 2. Reaction was allowed to proceed for 21 h and products were separated using column chromatography (PE:DCM (50:50)). Adduct A:- yield = 39.0 mg (26.8%). Adduct B:- yield = 63.1 mg, (44.0 %). The adducts were derivatised as described above in order to determine ee. None detected.

#### **Niobium pentachloride and *S*-valine**

A suspension of NbCl<sub>5</sub> (276.9 mg, 1.025 mmol) in dry diethyl ether was prepared. *S*-Valine (244.3 mg, 2.085 mmol) was added over 30 min under a stream of argon. The suspension was stirred for several hours at which time it was divided into two round-bottom flasks by syringing from the original vessel under a stream of argon. The ether was removed under vacuum and each of the vessels charged with dry DCM and cooled to -80°C on dry ice. Cyclopentadiene was added to each vessel, 560.3 mg (8.474 mmol) to vessel 1 and 511.6 mg (7.737 mmol) to vessel 2. Crotonaldehyde (163.2 mg, 2.328 mmol) was added to vessel 1 and methacrolein (154.4 mg, 2.203 mmol) to vessel 2. Reaction was allowed to proceed for 14 h and products were separated using column chromatography (PE:DCM (50:50)). Adduct A:- yield = 15.0 mg (4.7%). Adduct B:-

yield = 164.7 mg, (57.2%) The adducts were derivatised as described above in order to determine ee. None detected.

#### **Niobium pentachloride and *S*-leucine**

A suspension of NbCl<sub>5</sub> (286.5 mg, 1.060 mmol) in dry diethyl ether was prepared. *S*-Leucine (276.8 mg, 2.102 mmol) was added over 15–20 min under a stream of argon. The suspension was stirred for several hours. A portion was removed and dried. It was found to be insoluble in any solvent but was analysed by IR. IR  $\nu_{\max}$  3400, 2963, 1740, 1491, 1215 cm<sup>-1</sup>. The remainder was divided into two round-bottom flasks by syringing from the original vessel under a stream of argon. The ether was removed under vacuum and each of the vessels charged with dry DCM and cooled to –80°C on dry ice. Cyclopentadiene was added to each vessel, 850.5 mg (12.86 mmol) to vessel 1 and 841.8 mg (12.73 mmol) to vessel 2. Crotonaldehyde (220.0 mg, 3.139 mmol) was added to vessel 1 and methacrolein (211.6 mg, 3.019 mmol) to vessel 2. Reaction was allowed to proceed for 12 h and products were separated using column chromatography (PE:DCM (50:50)). Adduct A:- yield = 40.1 mg (9.4%). Adduct B - yield = 109.4 mg, (26.6%). The adducts were derivatised as described above in order to determine ee. None detected.

#### **Niobium pentachloride and *S*-isoleucine**

A suspension of NbCl<sub>5</sub> (280.3 mg, 1.038 mmol) in dry diethyl ether was prepared. *S*-Isoleucine (275.3 mg, 2.099 mmol) was added over 25 min under a stream of argon. The suspension was stirred for several hours at which time it was divided into two round-bottom flasks by syringing from the original vessel under a stream of argon. The ether was removed under vacuum and each of the vessels charged with dry DCM and cooled to –80°C on dry ice. Cyclopentadiene was added to each vessel, 586.1 mg (8.363 mmol) to vessel 1 and 691.8 mg (10.21 mmol) to vessel 2. Crotonaldehyde (147.8 mg, 1.673 mmol) was added to vessel 1 and methacrolein (173.3 mg, 2.043 mmol) to vessel 2. Reaction was allowed to proceed for 14 h and products were separated using column chromatography (PE:DCM (50:50)). Adduct A:- yield = 45.3 mg (19.9%) Adduct B.- yield = 110.0 mg, (39.5%). The adducts were derivatised as described above in order to determine ee. None detected.



### Niobium pentachloride and *S*-phenylalanine (1)

A suspension of NbCl<sub>5</sub> (306.1 mg, 1.133 mmol) in dry diethyl ether was prepared. *S*-Phenylalanine (441.3 mg, 2.660 mmol) was added over 20 min under a stream of argon. The suspension was stirred for 2 h at which time the colour had changed from yellow to brown. A portion was removed and quenched with water whereupon it turned white. It was analysed using IR. IR  $\nu_{\max}$  3200, 3000, 1720, 1491, 1215 cm<sup>-1</sup>. The remaining suspension was divided into two round-bottom flasks by syringing from the original vessel under a stream of argon. The ether was removed under vacuum and each of the vessels charged with dry DCM and cooled to -80°C on dry ice. Cyclopentadiene was added to each vessel, 899.7 mg (13.61 mmol) to vessel 1 and 796.4 mg (12.04 mmol) to vessel 2. Crotonaldehyde (210.1 mg, 2.895 mmol) was added to vessel 1 and methacrolein (161.9 mg, 1.905 mmol) to vessel 2. Reaction was allowed to proceed for 12 h and products were separated using column chromatography (PE:DCM (50:50)). Adduct A:- yield = 57.1 mg (17.5 %) Adduct B:- yield = 137.1 mg, (42.2%). The adducts were derivatised as described above in order to determine ee. None detected.

### Niobium pentachloride and *S*-phenylalanine (2)

A suspension of NbCl<sub>5</sub> (277.1 mg, 1.026 mmol) in dry diethyl ether was prepared. One equivalent of *S*-phenylalanine (157.4 mg, 1.009 mmol) was added over 25 min under a stream of argon and the suspension allowed to stir overnight. It was then divided into two round-bottom flasks by syringing from the original vessel under a stream of argon. The ether was removed under vacuum and each of the vessels charged with dry DCM and cooled to -80°C on dry ice. Cyclopentadiene was added to each vessel, 712.2 mg (10.77 mmol) to vessel 1 and 781.4 mg (11.82 mmol) to vessel 2. Crotonaldehyde (146.1 mg, 2.350 mmol) was added to vessel 1 and methacrolein (164.7 mg, 2.350 mmol) to vessel 2. Reaction was allowed to proceed for 18 h and products were separated using column chromatography (PE:DCM (50:50)). Adduct A:- yield = 57.1 mg (17.5 %) Adduct B:- yield = 137.1 mg, (42.2%). The adducts were derivatised as described above in order to determine ee. In the case of adduct B an ee of 7.0% (*S*) was found.

### Niobium pentachloride and *S*-tryptophan

A suspension of NbCl<sub>5</sub> (275.2 mg, 1.019 mmol) in dry diethyl ether was prepared. *S*-Tryptophan (419.8 mg, 2.056 mmol) was added over 20 min under a stream of argon. The suspension was stirred for 3 h at which time it was divided into two round-bottom flasks by syringing from the original vessel under a stream of argon. The ether was removed under vacuum and each of the vessels charged with dry DCM and cooled to -80°C on dry ice. Cyclopentadiene was added to each vessel, 619.5 mg (9.372 mmol) to vessel 1 and 630.8 mg (9.540 mmol) to vessel 2. Crotonaldehyde (146.3 mg, 2.087 mmol) was added to vessel 1 and methacrolein (72.1 mg, 1.029 mmol) to vessel 2. Reaction was allowed to proceed for 20 h and products were separated using column chromatography (PE:DCM (50:50)). Adduct A - yield = 27.4 mg (9.6%). Adduct B - yield = 80.1 mg, (57.2%). The adducts were derivatised as described above in order to determine ee. None detected.

### Niobium pentachloride and -diethyl (*2R*, *3R*)-tartrate

A suspension of NbCl<sub>5</sub> (313.8 mg, 1.161 mmol) in dry diethyl ether was prepared. Diethyl (*2R*, *3R*)-tartrate (484.0 mg, 2.325 mmol) was syringed in over 20 min under a stream of argon. The solution was stirred for 24 h. A portion was removed and analysed using IR and NMR. IR  $\nu_{\max}$  3359, 2985, 1733, 1626, 1275, 1115 cm<sup>-1</sup>.  $\delta_{\text{H}}$ [MeOD] showed the following signals:- 2.14 (3 H, t,  $J=6.9$  Hz), 2.27 (3 H, t,  $J=7.4$  Hz), 4.60 (2 H, q,  $J=6.9$  Hz), 5.22 (2 H, q,  $J=7.2$  Hz), 5.53 (2 H, d,  $J=10.8$  Hz).  $\delta_{\text{C}}$ [MeOD] showed the following signals:- 14.42, 62.49, 73.64, 172.5, 173.0. It was then divided into two round-bottom flasks by syringing from the original vessel under a stream of argon. The ether was removed under vacuum and each of the vessels charged with dry DCM and cooled to -80°C on dry ice. Cyclopentadiene was added to each vessel, 532.7 mg (8.057 mmol) to vessel 1 and 534.6 mg (8.085 mmol) to vessel 2. Crotonaldehyde (111.3 mg, 1.588 mmol) was added to vessel 1 and methacrolein (144.2 mg, 2.057 mmol) to vessel 2. Reaction was allowed to proceed for 20 h and products were separated using column chromatography (PE:DCM (50:50)). Adduct A - yield = 20.4 mg (8.9%). Adduct B - yield = 170.1 mg, (60.7%). The adducts were derivatised as described above in order to determine ee. In the case of adduct B an ee of 22% (*R*) was detected.

### **Niobium pentachloride and diisopropyl (2*R*, 3*R*)-tartrate**

A suspension of NbCl<sub>5</sub> (288.8 mg, 1.069 mmol) in dry DCM was prepared. Diisopropyl (2*R*, 3*R*)-tartrate (543.5 mg, 2.323 mmol) was syringed into the vessel over 20 min under a stream of argon. The solution was stirred for 24 h at which time it was divided into two round-bottom flasks by syringing from the original vessel under a stream of argon. The DCM was removed under vacuum and each of the vessels charged with fresh dry DCM and cooled to -80°C on dry ice. Cyclopentadiene was added to each vessel, 555.8 mg (8.406 mmol) to vessel 1 and 601.0 mg (9.090 mmol) to vessel 2. Crotonaldehyde (150.4 mg, 2.142 mmol) was added to vessel 1 and methacrolein (130.3 mg, 1.859 mmol) to vessel 2. Reaction was allowed to proceed for 18 h and products were separated using column chromatography (PE:DCM (50:50)). Adduct A:- yield = 46.6 mg (15.9 %) Adduct B:- yield = 131.2 mg, (51.8%) The adducts were derivatised as described above in order to determine ee. An ee of 16% (*R*) for adduct A was observed and the ee for adduct B was 38% (*R*).

### **Niobium pentachloride and (+)-2, 3-isopropylidene-L-Threitol**

A suspension of NbCl<sub>5</sub> (286.1 mg, 1.058 mmol) in dry diethyl ether was prepared. The ligand (343.5 mg, 2.118 mmol) was added over 25 min under a stream of argon. The suspension was stirred for 24 h at which time it was divided into two round-bottom flasks by syringing from the original vessel under a stream of argon. The ether was removed under vacuum and each of the vessels charged with dry DCM and cooled to -80°C on dry ice. Cyclopentadiene was added to each vessel, 797.8 mg (12.06 mmol) to vessel 1 and 820.8 mg (12.41 mmol) to vessel 2. Crotonaldehyde (270.5 mg, 3.860 mmol) was added to vessel 1 and methacrolein (262.1 mg, 3.741 mmol) to vessel 2. Reaction was allowed to proceed for 18 h. No products were detected.

### **Niobium pentachloride and *R*-(+)-1, 1-bi-2-naphthol (1)**

Two separate suspensions of NbCl<sub>5</sub> in dry ether were prepared, 14.5 mg (0.054 mmol) in vessel 1 and 16.0 mg (0.059 mmol) in vessel 2. The ligand was added to each vessel, 32.4 mg (0.113 mmol) to vessel 1 and 36.0 mg (0.126 mmol) to vessel 2. The suspensions were stirred for 3 h. The ether was then removed and each of the vessels charged with dry DCM and cooled to -80°C on dry ice. Cyclopentadiene was added to each vessel, 108.0 mg (1.633 mmol) to vessel 1 and 109.7 mg (1.659 mmol) to vessel 2. Crotonaldehyde (25.3 mg, 0.361 mmol) was added to vessel 1 and methacrolein (22.3 mg, 0.318 mmol) to vessel 2. Reaction was allowed to proceed for 12 h and

products were separated using column chromatography (PE:DCM (50:50)). There was no reaction in vessel 1. Adduct B.- yield = 1.9 mg, (4.4 %). The adducts were derivatised as described above in order to determine ee. None detected

### **Niobium pentachloride and *R*-(+)-1, 1-bi-2-naphthol (2)**

A suspension of NbCl<sub>5</sub> (151.9 mg, 0.540 mmol) in dry diethyl ether was prepared. One equivalent of the ligand (157.4 mg, 0.553 mmol) was added over 20 min under a stream of argon. The suspension was stirred for 24 h at which time it was divided into two round-bottom flasks by syringing from the original vessel under a stream of argon. The ether was removed under vacuum and each of the vessels charged with dry DCM and cooled to -80°C on dry ice. Cyclopentadiene was added to each vessel, 758.5 mg (11.41 mmol) to vessel 1 and 769.3 mg (11.65 mmol) to vessel 2. Crotonaldehyde (116.7 mg, 1.666 mmol) was added to vessel 1 and methacrolein (185.7 mg, 2.649 mmol) to vessel 2. Reaction was allowed to proceed for 22 h and products were separated using column chromatography (PE:DCM (50:50)). Adduct A:- yield = 63.4 mg (28.0%) Adduct B.- yield = 140.5 mg, (39.0%). The adducts were derivatised as described above in order to determine ee. None detected for adduct A but adduct B showed an ee of 5% (*R*).

### **Niobium pentachloride and *R*-(+)-1, 1-bi-2-naphthol (3)**

A suspension of NbCl<sub>5</sub> (140.0 mg, 0.519 mmol) in dry DCM was prepared. One equivalent of the ligand (151 mg, 0.531 mmol) was added over 30 min under a stream of argon. The suspension was stirred for 24 h at which time it was divided into two round-bottom flasks by syringing from the original vessel under a stream of argon. The DCM was removed under vacuum and each of the vessels charged with fresh dry DCM and unactivated 4A molecular sieves and cooled to -80°C on dry ice. Cyclopentadiene was added to each vessel, 550.2 mg (8.321 mmol) to vessel 1 and 562.4 mg (8.506 mmol) to vessel 2. Crotonaldehyde (144.1 mg, 2.056 mmol) was added to vessel 1 and methacrolein (192.3 mg, 2.744 mmol) to vessel 2. Reaction was allowed to proceed for 18 h and products were separated using column chromatography (PE:DCM (50:50)). Adduct A:- yield = 95.1 mg (34.0%) Adduct B:- yield = 173.9 mg, (51.0%) The adducts were derivatised as described above in order to determine ee. None detected for adduct A but adduct B showed an ee of 5% (*R*)

### **Niobium pentachloride and 2*R*, 4*R*-pentanediol**

Two separate suspensions of NbCl<sub>5</sub> in dry ether were prepared, 16.9 mg (0.063 mmol) in vessel 1 and 13.5 mg (0.050 mmol) in vessel 2. The ligand was added to each vessel, 13.0 mg (0.125 mmol) to vessel 1 and 11.3 mg (0.109 mmol) to vessel 2. The suspensions were stirred for 3 h. The ether was then removed and each of the vessels charged with dry DCM and cooled to -80°C on dry ice. Cyclopentadiene was added to each vessel, 125.4 mg (1.897 mmol) to vessel 1 and 97.6 mg (1.476 mmol) to vessel 2. Crotonaldehyde (25.3 mg, 0.361 mmol) was added to vessel 1 and methacrolein (18.5 mg, 0.264 mmol) to vessel 2. Reaction was allowed to proceed for 12 h and products were separated using column chromatography (PE:DCM (50:50)). There was no reaction in vessel 1 or vessel 2.

### **Niobium pentachloride and thiophene ligand**

A suspension of NbCl<sub>5</sub> (136.5 mg, 0.509 mmol) in dry DCM was prepared. One equivalent of the ligand (320.6 mg, 0.521 mmol) was added over 30 min under a stream of argon. The suspension was stirred for 24 h at which time it was divided into two round-bottom flasks by syringing from the original vessel under a stream of argon. The DCM was removed under vacuum and each of the vessels charged with fresh dry DCM and cooled to -80°C on dry ice. Cyclopentadiene was added to each vessel, 610.5 mg (9.233 mmol) to vessel 1 and 604.7 mg (9.145 mmol) to vessel 2. Crotonaldehyde (110 mg, 1.569 mmol) was added to vessel 1 and methacrolein (120.4 mg, 1.718 mmol) to vessel 2. Reaction was allowed to proceed for 18 h whereupon TLC analysis showed that no reaction had taken place. Molecular sieves (4A) were added and the reaction allowed to proceed for a further 24 h. Products were separated using column chromatography (PE:DCM (50:50)). Adduct A:- yield = 43.9 mg (19.4 %). Adduct B:- yield = 150.3 mg, (61.0%). The adducts were derivatised as described above in order to determine ee. None detected for adduct A but adduct B showed an ee of 5% (*R*).

### **Tantalum pentachloride**

Tantalum pentachloride (175.2 mg, 0.490 mmol; 185.6 mg, 0.519 mmol) was added to each of two 50 ml dry round-bottom flasks. Dry diethyl ether was added and the suspensions stirred under argon for 1 h. The vessels were then cooled on dry ice and cyclopentadiene added, 809.0 mg, (12.24 mmol) to vessel 1 and (819.7 mg, 12.40 mmol) to vessel 2. Crotonaldehyde (124.2 mg, 1.772 mmol) was then added to vessel

1 and methacrolein (186.4 mg, 2.661 mmol) to vessel 2. The almost instantaneous formation of a rubber-like material was observed. The reaction was allowed to proceed and no Diels–Alder products were detected after 24 h.

#### **Tantalum pentachloride and -diethyl (2*R*, 3*R*)-tartrate**

A suspension of TaCl<sub>5</sub> (367.6 mg, 1.026 mmol) in dry diethyl ether was prepared. Diethyl (2*R*, 3*R*)-tartrate (425.1 mg, 2.062 mmol) was syringed in over 30 min under a stream of argon. The solution was stirred for 72 h. It was then divided into two round-bottom flasks by syringing from the original vessel under a stream of argon. The ether was removed under vacuum and each of the vessels charged with dry DCM and cooled to –80°C on dry ice. Cyclopentadiene was added to each vessel, 808.8 mg (12.23 mmol) to vessel 1 and 745.3 mg (11.27 mmol) to vessel 2. Crotonaldehyde (206.1 mg, 2.943 mmol) was added to vessel 1 and methacrolein (214.4 mg, 3.060 mmol) to vessel 2. Reaction was allowed to proceed for 20 h and products were separated using column chromatography (PE:DCM (50:50)). Adduct A.- yield = 166.9 mg (41.7 %) Adduct B.- yield = 327.6 mg, (75.0%) The adducts were derivatised as described above in order to determine ee. In the case of adduct A an ee of 6% (*R*) was detected. In that of adduct B an ee of 15% (*R*) was detected.

#### **Tantalum pentachloride and diisopropyl (2*R*, 3*R*)-tartrate**

A suspension of TaCl<sub>5</sub> (392.2 mg, 1.095 mmol) in dry DCM was prepared. Diisopropyl (2*R*, 3*R*)-tartrate (513.3 mg, 2.191 mmol) was syringed into the vessel over 20 min under a stream of argon. The solution was stirred for 24 h at which time it was divided into two round-bottom flasks by syringing from the original vessel under a stream of argon. The DCM was removed under vacuum and each of the vessels charged with fresh dry DCM and cooled to –80°C on dry ice. Cyclopentadiene was added to each vessel, 852.7 mg (12.90 mmol) to vessel 1 and 871.2 mg (13.18 mmol) to vessel 2. Crotonaldehyde (178.9 mg, 2.540 mmol) was added to vessel 1 and methacrolein (183.3 mg, 2.620 mmol) to vessel 2. Reaction was allowed to proceed for 24 h and products were separated using column chromatography (PE:DCM (50:50)). Adduct A:- yield = 78.5 mg (23.7 %) Adduct B:- yield = 188.8 mg, (55.4%) The adducts were derivatised as described above in order to determine ee. No ee was observed for adduct A and the ee for adduct B was 5% (*R*).

### **Tantalum pentachloride and (+)-2, 3-isopropylidene-L-Threitol**

A suspension of TaCl<sub>5</sub> (370.8 mg, 1.036 mmol) in dry diethyl ether was prepared. The ligand (337.5 mg, 2.081 mmol) was added over 25 min under a stream of argon. The suspension was stirred for 24 h at which time it was divided into two round-bottom flasks by syringing from the original vessel under a stream of argon. The ether was removed under vacuum and each of the vessels charged with dry DCM and cooled to -80°C on dry ice. Cyclopentadiene was added to each vessel, 751.5 mg (11.37 mmol) to vessel 1 and 784.6 mg (11.86 mmol) to vessel 2. Crotonaldehyde (245.4 mg, 3.500 mmol) was added to vessel 1 and methacrolein (247.3 mg, 3.530 mmol) to vessel 2. Reaction was allowed to proceed for 24 h. Products were recovered and purified by silica gel flash chromatography (Mobile phase = PE:DCM (50:50)). Adduct A:- yield = 63.8 mg (14.0%) Adduct B.- yield = 226.8 mg (49.3%) The adducts were derivatised as described above in order to determine ee. No ee was observed for either adduct

### **Tantalum pentachloride and (-)-2, 3-isopropylidene-1, 1, 4, 4-tetraphenyl-L-Threitol**

A suspension of TaCl<sub>5</sub> (176.0 mg, 0.492 mmol) in dry diethyl ether was prepared. The ligand (464.7 mg, 0.996 mmol) was added over 20 min under a stream of argon. The suspension was stirred for 24 h at which time it was divided into two round-bottom flasks by syringing from the original vessel under a stream of argon. The ether was removed under vacuum and each of the vessels charged with dry DCM and cooled to -80°C on dry ice. Cyclopentadiene was added to each vessel, 397.6 mg (6.013 mmol) to vessel 1 and 412.4 mg (6.237 mmol) to vessel 2. Crotonaldehyde (108.4 mg, 1.935 mmol) was added to vessel 1 and methacrolein (135.6 mg, 1.935 mmol) to vessel 2. Reaction was allowed to proceed for 48 h. Products were recovered and purified by silica gel flash chromatography (Mobile phase = PE:DCM (50:50)). Adduct A:- yield = 144.7 mg (71.9%). Adduct B.- yield = 126.3 mg (50.2%) The adducts were derivatised as described above in order to determine ee. No ee was observed for either adduct.

### **Tantalum pentachloride and (-)-2, 3-isopropylidene-1, 1, 4, 4-tetranaphthyl-L-Threitol**

A suspension of TaCl<sub>5</sub> (178.7 mg, 0.499 mmol) in dry diethyl ether was prepared. The ligand (668.9 mg, 1.003 mmol) was added over 10 min under a stream of argon and a

deep red colour developed. The suspension was stirred for 24 h at which time it was seen to be yellow. The suspension was divided into two round-bottom flasks by syringing from the original vessel under a stream of argon. The ether was removed under vacuum and each of the vessels charged with dry DCM and cooled to  $-80^{\circ}\text{C}$  on dry ice. The red colour returned. Cyclopentadiene was added to each vessel, 447.3 mg (6.765 mmol) to vessel 1 and 423.0 mg (6.398 mmol) to vessel 2. Crotonaldehyde (132.3 mg, 1.888 mmol) was added to vessel 1 and methacrolein (108.3 mg, 1.545 mmol) to vessel 2. Reaction was allowed to proceed for 18 h. Products were recovered and purified by silica gel flash chromatography (Mobile phase = PE:DCM (50:50)). Adduct A:- yield = 104.6 mg (42.0%) Adduct B:- yield = 150.0 mg (75.0%). The adducts were derivatised as described above in order to determine ee. Adduct A had an ee of 7.0 (*R*) and adduct B had an ee of 4.5 (*R*).

#### **Tantalum pentachloride and *R*-(+)-1,1-bi-2-naphthol**

A suspension of  $\text{TaCl}_5$  (201.6 mg, 0.560 mmol) in dry diethyl ether was prepared. One equivalent of the ligand (161.2 mg, 0.561 mmol) was added over 20 min under a stream of argon. The suspension was stirred for 24 h at which time it was divided into two round-bottom flasks by syringing from the original vessel under a stream of argon. The ether was removed under vacuum and each of the vessels charged with dry DCM and cooled to  $-80^{\circ}\text{C}$  on dry ice. Cyclopentadiene was added to each vessel, 827.7 mg (12.50 mmol) to vessel 1 and 712.4 mg (10.77 mmol) to vessel 2. Crotonaldehyde (169.0 mg, 2.411 mmol) was added to vessel 1 and methacrolein (192.0 mg, 2.739 mmol) to vessel 2. Reaction was allowed to proceed for 22 h and products were separated using column chromatography (PE:DCM (50:50)). Adduct A:- yield = 72.1 mg (22.0%). Adduct B:- yield = 130.4 mg (35.0%). The adducts were derivatised as described above in order to determine ee. None detected.



## **CHAPTER 3**

### **THE USE OF CHIRAL SCHIFF BASES IN THE LEWIS- ACID CATALYSED DIELS–ALDER REACTION**

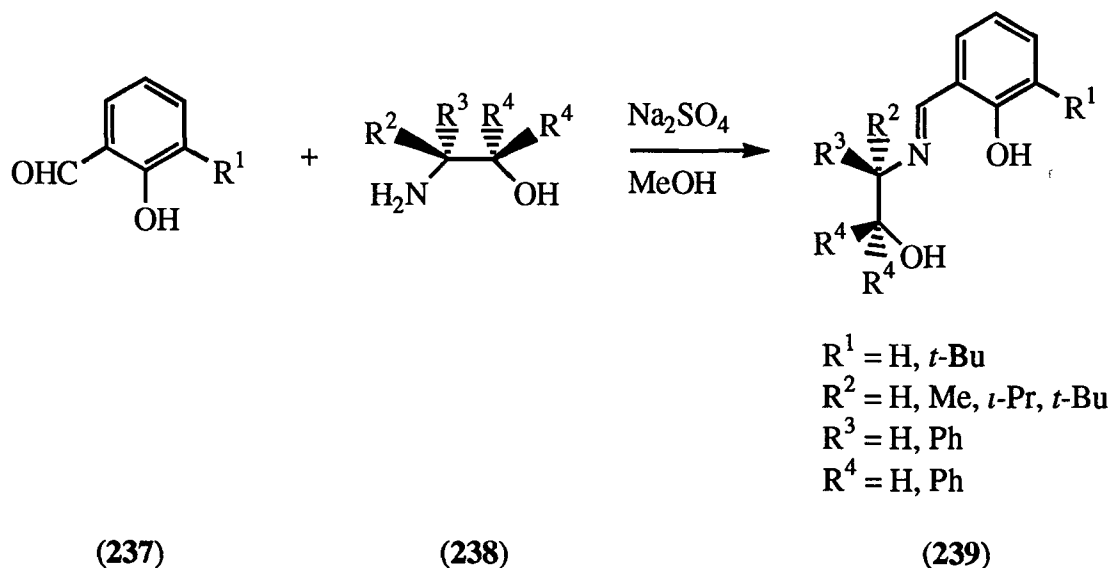
## 3.1 INTRODUCTION

In this chapter the use of complexes of niobium with chiral Schiff bases, as enantioselective Lewis acid catalysts, will be examined

### 3.1.1 The Use of Chiral Schiff Bases

#### 3.1.1.1 Titanium

Chiral Schiff bases have been used for the catalysis of the asymmetric trimethylsilylcyanation of aldehydes<sup>123,124</sup> The Lewis acid to which the ligand was coordinated was titanium isopropoxide The catalysts were formed from the condensation of amino alcohols and aromatic aldehydes, either salicylaldehyde or 3-*t*-butyl salicylaldehyde as shown in Scheme 83.



**Scheme 83**

The Schiff base thus produced was reacted with  $\text{Ti}(\text{O}^i\text{Pr})_4$  in a 1:1 molar ratio to give a catalyst which the authors characterised by  $^{13}\text{C}$  NMR spectroscopy and mass spectrometry. Their evidence pointed to a 1:1 complex as the active catalyst and was highly suggestive of the monomeric form. They further synthesised the 2:1 ligand-metal complex but found it to be catalytically inactive.

In terms of catalytic activity, the complex was used to catalyse the trimethylsilylcyanation of a number of aromatic and aliphatic aldehydes Benzaldehyde was taken as the standard material and it was found that the ligand derived from valinol and 3-*t*-butyl salicylaldehyde gave the highest ee (85%) Where the *t*-butyl group was not present,

the ee was reduced to 22% and was of the opposite configuration. Optimisation work on this system was carried out and the most promising conditions were determined. It was found that reaction temperature was highly significant with the above-mentioned reaction achieving ee's of 41% at 0°C, 67% at -30°C and 85% at -80°C. The solvent was found to have a large effect with dichloromethane proving to be optimal. Chloroform, toluene, diethyl ether and acetonitrile gave a range of yields but invariably poorer ee. The catalyst loading was set at 20% as ratios above and below this level proved to be less effective; a stoichiometric ratio of catalyst to substrate gave an ee of 22% for the standard reaction. The choice of aldehyde was important. In the case of aromatic substituents, electron-donating groups tended to improve the ee whereas electron-withdrawing groups reduced the enantioselectivity. Aliphatic aldehydes showed poorer results than aromatic varieties. One significant result noted in the system was rate-enhancement in the presence of the ligand compared to free  $\text{Ti}(\text{O}^i\text{Pr})_4$ . The Lewis acid activity demonstrated in this system led these ligands to be investigated for chiral catalysis with niobium as Lewis acid.

### 3.1.1.2 Vanadium

Two groups have recently reported the use of Schiff-base ligands in the presence of vanadium as catalysts for the enantioselective oxidation of sulphides to sulphoxides. The catalyst was ligand complexed with  $\text{VO}(\text{acac})_2$ . The earlier report of Bolm and Bienwald relied on a ligand of the form (240) and employed as little as 0.01 mol% of catalyst to achieve up to 85% ee.<sup>125</sup>

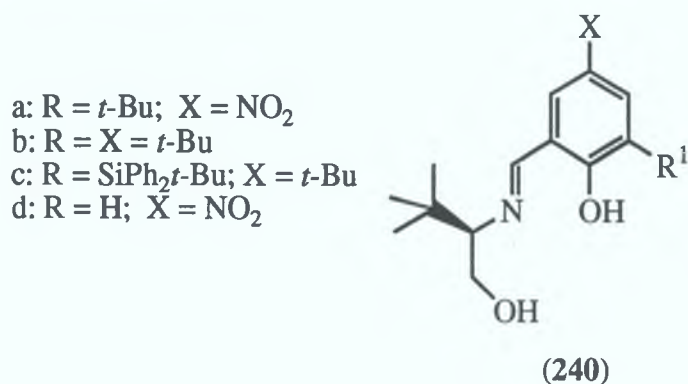
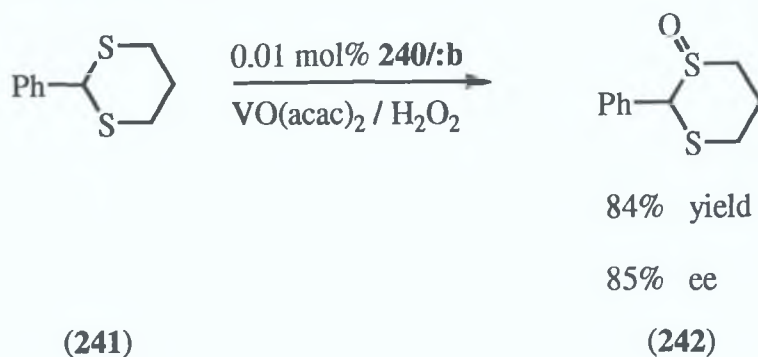


Figure 68

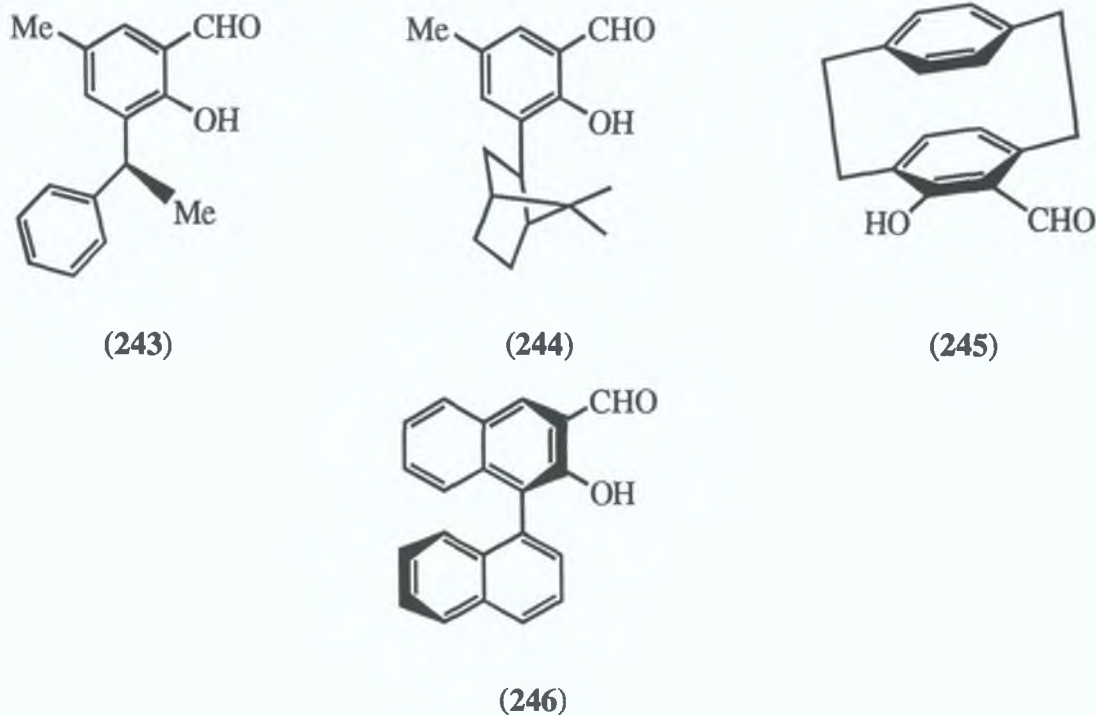
The reaction was found to be accelerated in the presence of ligand. Therefore, unbound vanadium had little or no effect on the overall result. The amino alcohol used was *t*-leucinol and it was found that for R=H, the lowest ee was achieved. This was in agreement with the trimethylsilyl cyanation reaction described above. Hydrogen peroxide was used as the oxidant, and in substrate terms, the best results were achieved

when the dithioacetal of benzaldehyde was used, resulting in (242) being formed exclusively *trans* and in 85% ee.



**Scheme 84**

Velter and Berkesel developed this idea with some novel Schiff bases which bore chirality in both the amino alcohol and the aromatic aldehyde starting materials. They used *t*-leucinol as the amino alcohol but employed chiral aldehydes (243–246) as the secondary element of chirality.<sup>126</sup>



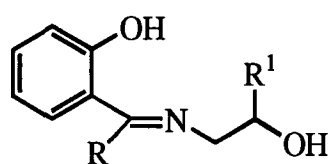
**Figure 69**

Both enantiomers of each aldehyde were used and the diastereomeric Schiff bases were separated and used as catalyst ligands. The best result was achieved using the catalyst derived from *R*-(246) (78%) with thioanisole as the substrate. The authors examined the co-operative vs. non-co-operative stereochemical enhancement of the reaction products, depending on which enantiomer of aldehyde was used. In the case of (243)

there was hardly any difference between the two results. However there was significant difference in the case of the other ligands, the “mismatched” (*i.e.* giving opposite chiral induction) Schiff base from (**245**) showing only a 2% ee. The “matched” effect was not, however, as significant. Changing the substrate to *o*-bromothioanisole resulted in a reduction in ee. The authors postulated that this was due to unfavourable non-bonding interactions between the bromine atom and the ligand.

### 3.1.2 Niobium and Tantalum Schiff Base Complexes

The first Schiff base complexes of niobium and tantalum were synthesised in 1960.<sup>127,113</sup> *Bis*-salicylidene-ethylenediamine was used and the result was [MCl(Salen)]Cl<sub>2</sub>. An Indian group synthesised a number of Schiff-base derivatives of tantalum in 1:1, 1:2 and 1:3 ratios where Ta(O<sup>*i*</sup>Pr)<sub>5</sub> was used. The ligands they employed were of the form (**247**).<sup>128</sup>

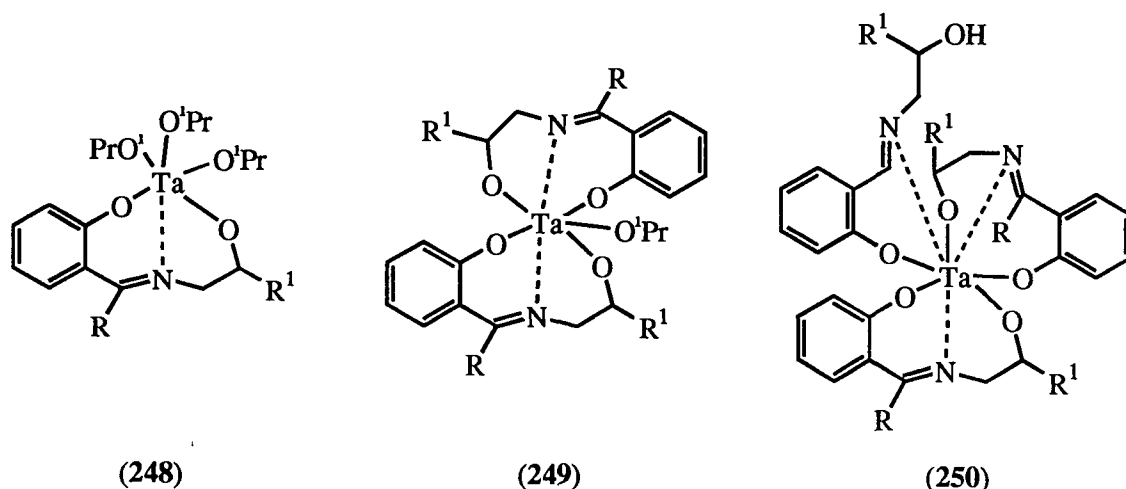


- a: R = H; R<sup>1</sup> = H
- b: R = H; R<sup>1</sup> = CH<sub>3</sub>
- c: R = CH<sub>3</sub>; R<sup>1</sup> = H
- d: R = CH<sub>3</sub>; R<sup>1</sup> = CH<sub>3</sub>

(**247**)

**Figure 70**

The structures of the metal complexes were assessed from CHN results and the amount of propanol given off as well as molecular weight determinations. They were described as being monomers of the form (**248–250**)



(**248**)

(**249**)

(**250**)

**Figure 71**

The synthesis of Schiff-base ligands and their complexes with niobium was thus undertaken to assess their usefulness in the catalysis of the Diels–Alder reaction

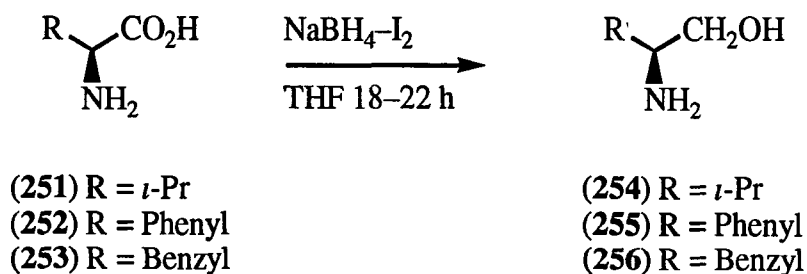
## 3.2 RESULTS AND DISCUSSION

### 3.2.1 Ligand Synthesis

The Schiff bases to be synthesised were of the type described above (3.1.1.1). Thus amino alcohols and aromatic aldehydes were required.

#### 3.2.1.1 Amino Alcohol Synthesis

Generally, amino alcohols are derived from amino acids or their esters. The earliest method involved the reaction of an amino acid ester with sodium metal in ethanol.<sup>129</sup> Other common methods include the reduction of the ester using  $\text{LiAlH}_4$ <sup>130</sup> or direct reduction of the amino acid *via* the same method<sup>131</sup> Recently, a method using sodium borohydride with  $\text{I}_2$  activation has been reported.<sup>132</sup> This method is safe and convenient, avoiding the handling problems associated with  $\text{LiAlH}_4$  and gives the amino alcohol in high yield. For the purposes of the work in this chapter, L-valine, L-phenylglycine and L-phenylalanine were reduced to valinol, phenylglycinol and phenylalaninol respectively.

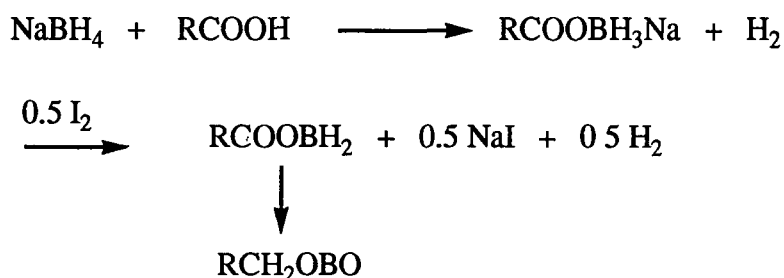


Scheme 85

The procedure involved addition of  $\text{NaBH}_4$  and amino acid in the ratio of 2.5:1 to a round-bottom flask charged with dry THF. This was flushed with argon and cooled on ice. A solution of  $\text{I}_2$  in THF was then added upon which evolution of gas ( $\text{H}_2$ ) was observed. The  $\text{I}_2$  was added slowly over about 30 min with constant stirring. It could be seen from the disappearance of the brown colour that the  $\text{I}_2$  was reduced to  $\text{I}^-$ . When the total amount of iodine (one equivalent relative to amino acid) had been added the mixture was heated under reflux. It was found that the literature procedure, which advised 18 h, gave low yield. The reaction was therefore routinely carried out for 3–4

days. At this stage, the reaction was cooled and quenched by careful addition of methanol. Removal of the solvent revealed a white solid, presumably the HI salt, which was hydrolysed by stirring the material in 20% aq KOH for several hours. The amino alcohols were then purified. Crude yields were high, 94% for valinol and 96% for phenylglycinol and phenylalaninol. However, following distillation of valinol, the yields were in the range 20–66%. The former was disappointing and an unidentified lower-boiling product was present. In the cases of phenylglycinol and phenylalaninol, the materials were recrystallised from clean dry toluene and 62.3 and 57.1% were recovered, respectively. The proton NMR showed the development of the alcohol peak at 1.78 ppm and the diastereotopic  $\alpha$ -protons at 3.27 and 3.64 ppm for valinol. The disappearance of a carbonyl peak and the sharpening of the OH stretch were also noticeable in IR.

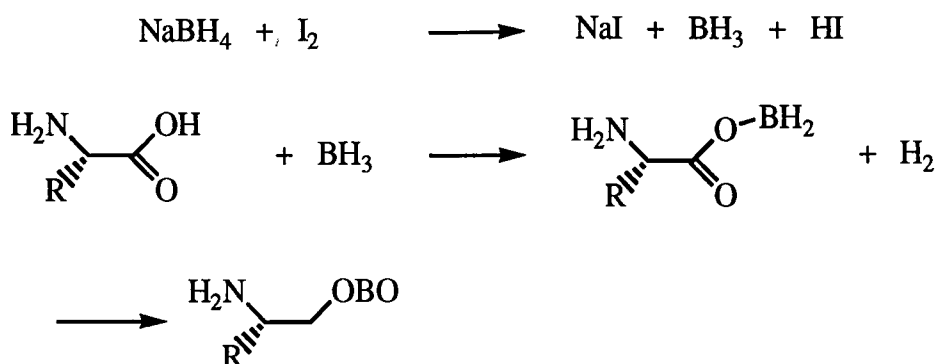
The authors of the paper on this method for amino alcohols<sup>132</sup> have not offered an explanation as to the mechanism. In the case of the original work on carboxylic acids,<sup>133</sup> the authors postulated the following mechanism.-



**Scheme 86**

However the procedure for amino acids differed in two significant respects. In the case of carboxylic acids, evolution of H<sub>2</sub> was observed when borohydride and acid were mixed. Further evolution of gas was noted when the iodine was added. This appears to support the mechanism described in Scheme 86. However, in the case of the amino acid no evolution of gas was noted by this author or by McKennon and Meyers<sup>132</sup> at this early stage. One major experimental difference was that the carboxylic acids were reacted with borohydride at room temperature, whereas amino acids were mixed with the reagent at 0°C. Although this might explain the lack of initial reaction, it does not explain the fact that 0.5 equivalents of I<sub>2</sub> were used with the acids and one equivalent was used with the amino acids. This was not an excess as the I<sub>2</sub> was completely reduced, as evidenced by the disappearance of colour in the mixture. In this case 2.5 equivalents of sodium borohydride were used as opposed to 1.2 in the case of the acid

It might be possible that at lower temperature the amino acid and NaBH<sub>4</sub> associate rather than react and that the borohydride reacts with I<sub>2</sub> to release borane which can then react with the amino acid.



**Scheme 87**

The excess of borohydride and iodine over amino alcohol causes the reaction to proceed smoothly to completion. It seems clear, though that the mechanisms for these two reactions are different.

An important consideration in the use of these procedures is the potential for racemisation. It is essential that the stereocentre remains unperturbed as this would defeat the purposes of the required amino alcohol. It has been shown in the literature, however, that the reduction procedures mentioned do not cause any significant racemisation<sup>134</sup>

### 3.2.1.2 Synthesis of *t*-Butyl Salicylaldehyde

Two different aromatic aldehydes were used for this work, salicylaldehyde, which is commercially available, and *t*-butyl salicylaldehyde which was synthesised Hayashi *et al.*,<sup>124</sup> while synthesising their ligands, made the aldehyde and they cited the work of an Italian group.<sup>135</sup> The strategy for the synthesis was to add a formyl group *ortho* to the hydroxyl of 2-*t*-butyl phenol

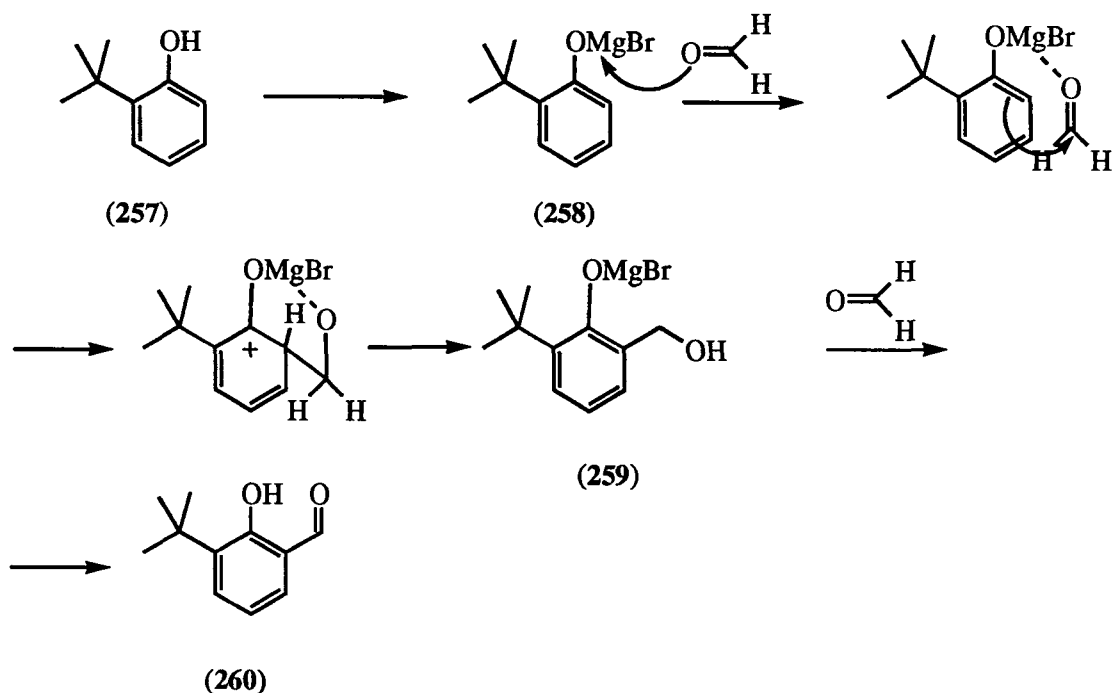
The overall procedure involved the initial formation of a Grignard reagent in THF. In this case, ethyl magnesium bromide was used. Following the usual procedure, the excess magnesium was removed and the Grignard solution cooled. Next, 2-*t*-butyl phenol was added slowly and allowed to react. The ratio of Grignard to phenol was approximately 1.5:1. When this reaction was completed, the solvent was removed and hexamethyl phosphoramide (HMPA), benzene and 2.5 equivalents of



paraformaldehyde (relative to the phenol) were added. The mixture was heated under reflux overnight.

Following an acid work-up and extraction into ether, an oily material was recovered. Distillation under vacuum was attempted and this resulted in six separate fractions, all of which were impure, containing a substantial amount of starting material. Further purification was achieved by silica-gel flash chromatography, using pentane (100%) as the solvent. Although this gave a very low  $R_f$  for the desired product, it was possible to achieve high purity.  $^1\text{H}$  NMR confirmed the purity and showed the presence of the expected aldehyde proton at 9.87 ppm. The aromatic region showed two doublets at 7.40 and 7.53 ppm and an overlapping pair of doublets at 6.95 ppm ( $J=6.9$  Hz). This is consistent with the presence of three adjacent protons. The butyl and phenol peaks were also present. The major feature of  $^{13}\text{C}$  NMR was the carbonyl peak at 197.07 ppm. In the IR spectrum the phenol OH was seen at  $3424\text{ cm}^{-1}$ , the aromatic C–H stretches at  $2961\text{ cm}^{-1}$ , the carbonyl at  $1653\text{ cm}^{-1}$  and further peaks at  $753$  and  $679\text{ cm}^{-1}$ .

<sup>1</sup> The proposed mechanism for this reaction is as shown in Scheme 88.



Scheme 88

Initial formation of the magnesium bromide salt allows co-ordination of formaldehyde, which is held in place for electrophilic attack on the aromatic ring, exclusively at the *ortho* position. An analogue of compound (259) (without the *t*-butyl group) was isolated by Casnati *et al* when performing the original work<sup>135</sup>. When this material was reacted with paraformaldehyde, both (260) and methanol were found to be produced in the reaction in the presence of HMPA. This occurs through an oxidation–

reduction process between the benzylic alcohol and formaldehyde, *via* a hydride shift. In the absence of HMPA the authors observed the formation of (261) and (262) which they postulated to occur *via* intermediate (263).

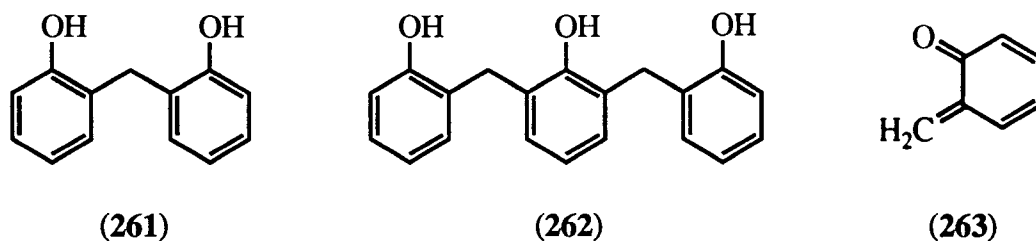


Figure 72

There were obviously several competitive processes in this reaction and it is believed that the length of reaction time, *i.e.* 20 h, was probably insufficient. The overall reaction yield was extremely small at 11%. However, sufficient material was available to synthesise the Schiff bases which were required as chiral ligands.

### 3.2.1.3 Synthesis of Schiff Bases

The Schiff bases were synthesised using salicylaldehyde, 2-*t*-butyl salicylaldehyde and the following amino acids- *S*-valinol, *S*-phenylglycinol, *S*-phenylalaninol and 2*R*, 3*S*-norephidrine.

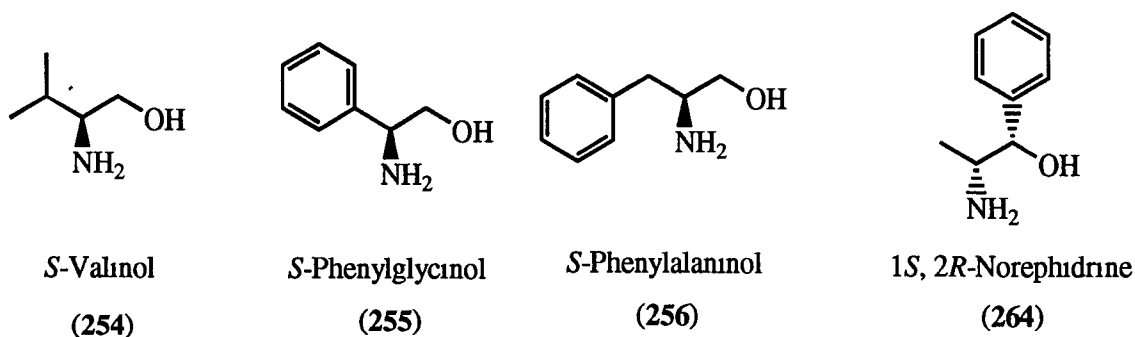
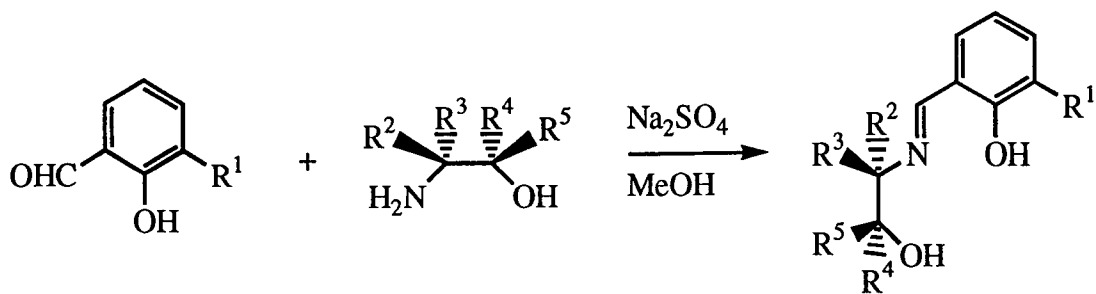


Figure 73

The synthesis involved a simple condensation under anhydrous conditions with one equivalent of aldehyde and amino alcohol, respectively, being mixed in dry methanol in the presence of an excess of anhydrous Na<sub>2</sub>SO<sub>4</sub> and heated under reflux for 24 h.



**Scheme 89**

The various compounds formed and a list of their yields and  $R_f$  values on TLC using a mobile phase of PE:EA (60:40) are shown in Table XI.

**Table XI: Schiff bases from aromatic aldehydes and chiral amino alcohols**

Ligand	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>	Yield %	$R_f$
265	H	H	<sup>t</sup> Pr	H	H	64	0.48 <sup>a</sup>
266	H	H	Phenyl	H	H	46	0.49
267	H	H	Benzyl	H	H	89	0.45
268	H	Me	H	Phenyl	H	93	0.52
269	<sup>t</sup> Bu	H	<sup>t</sup> Pr	H	H	63	0.59
270	<sup>t</sup> Bu	H	Phenyl	H	H	86	0.59
271	<sup>t</sup> Bu	H	Benzyl	H	H	82	0.59
272	<sup>t</sup> Bu	Me	H	Phenyl	H	78	0.65

<sup>a</sup> Mobile phase was PE:EA (60:40) and detection was by UV absorbance

Some of the materials were solids and others were oils which meant that the former could be purified by recrystallisation and the latter only by silica-gel flash chromatography. It was found that crystallisation led to a much greater loss in yield than the use of chromatography. This was, therefore, the preferred method of

purification. All the materials had a bright yellow or orange appearance and the solids had melting points under 100°C. The *t*-butyl compounds were oils whereas some of the butyl-free compounds were solids.

The Schiff bases shared a number of spectroscopic features. In  $^1\text{H}$  NMR the butyl salicylidene compounds had a large singlet at 1.43 ppm for the *t*-butyl group which the analogue lacked. Conversely, in the aromatic region the butyl compound displayed a simple pattern similar to that described for the parent aldehyde. The compound lacking the butyl had an extra proton visible at 6.89 ppm. The imine proton was seen between 8.25–8.62 ppm and the phenolic proton at around 13.3 ppm. The aliphatic alcohol peak could be seen generally around 4.00 ppm. The diastereotopic protons,  $\alpha$  to this functional group, generally appeared in the same region. Ligand (**272**) did not contain diastereotopic protons at this position. Instead it has a single benzylic proton which appears at 4.80 ppm.

In the  $^{13}\text{C}$  NMR spectra the imine carbon consistently appeared at 165–167 ppm. The phenyl carbon attached to the OH group was the next highest visible at 143 ppm. In the IR spectrum the OH stretches were seen between 3400 and 3420  $\text{cm}^{-1}$ . As this is a broad band, there is no splitting for the two hydroxyls present in the molecule. Aromatic and aliphatic stretches are clearly visible and C=N stretch is at 1630  $\text{cm}^{-1}$ . This is in contrast to 1652  $\text{cm}^{-1}$  for the aromatic aldehyde. There are a large number of common peaks in the fingerprint region for these compounds being within 2–4  $\text{cm}^{-1}$  of the following values. 1436, 1390, 1305, 1265, 1200, 1145, 1025, 797, 753  $\text{cm}^{-1}$ . The purity of the compounds was high and they were used as ligands for the catalysts in subsequent reactions.

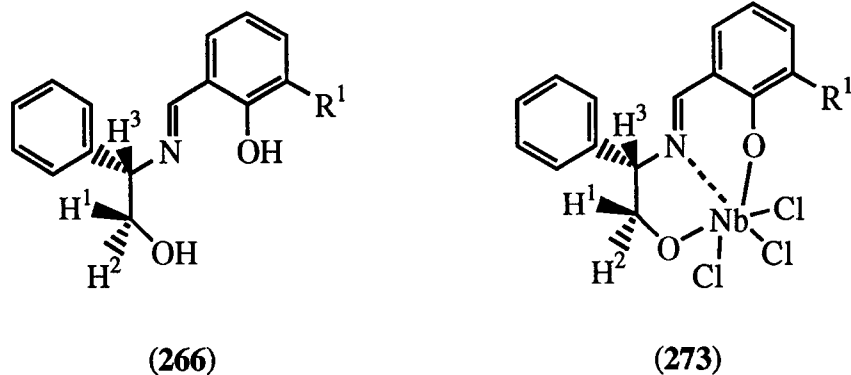
### 3.2.3 Formation of Catalysts

The original work involving titanium catalysis with the Schiff bases<sup>124</sup> used titanium in the form of  $\text{Ti}(\text{O}^i\text{Pr})_4$ . It was decided to perform this work using both  $\text{NbCl}_5$  and  $\text{Nb}(\text{O}^i\text{Pr})_5$  as the Lewis acid centres.

### Formation of niobium isopropoxide

Isopropyl alcohol was saturated with dry ammonia gas and stirred for several hours. The mixture was filtered to remove any  $\text{NH}_4\text{Cl}$  and the excess alcohol removed. The metal alkoxide was distilled. The proton NMR showed peaks at 1.22 and 4.46 ppm. The  $^{13}\text{C}$  NMR spectrum had peaks at 25.99 and 75.67 ppm. The IR peaks were at 2987, 1445 and  $1215\text{ cm}^{-1}$ . The material could not be passed through silica gel and was used as the distillate.

The formation of the metal–ligand complex was achieved by addition of equimolar amounts of  $\text{NbCl}_5$  or  $\text{Nb}(\text{O}^i\text{Pr})_5$  and ligand in dry DCM under argon. The observed result generally involved a colour change from yellow to orange. However the materials were only sparingly soluble and a precipitate generally remained. Some of the materials were subjected to  $^1\text{H}$  NMR and IR spectroscopy. However,  $^{13}\text{C}$  NMR spectroscopy failed to show any signals. This is presumably because insufficient material was dissolved to give a signal. The  $^1\text{H}$  NMR spectra showed very broad peaks and the possible presence of many species. The catalysts were not passed through silica gel before analysis was performed. They were, however, filtered to remove solids. The NMR spectroscopy was performed in acetone- $d^6$ . On standing for a few minutes a fine white/yellow precipitate appeared. Thus low concentrations of material were present in the solutions being analysed. The major features of the NMR were a shift of most peaks downfield by about 0.2 ppm, relative to the free ligand. In addition, the imine peak was shifted down by about 0.5 ppm. This larger shift can be explained by the fact that the imine N-atom will form a dative bond with the metal. Consequently, electron density will be drawn away from this functional group resulting in deshielding leading to higher ppm. The catalyst formed between (266) and  $\text{NbCl}_5$  gave a relatively clear NMR spectrum. One additional feature in this spectrum was the difference between the peaks for the protons  $\alpha$  to the aliphatic hydroxyl group in the complexed and uncomplexed material.



**Figure 74**

These protons are free to rotate in the ligand and present as a doublet at 3.87 ppm. In the complexed material the peaks can be seen at 4.15 and 4.38 ppm. They are each a doublet of doublets reflecting that each proton is now fixed in space and that H<sup>1</sup> is split by H<sup>2</sup> as well as H<sup>3</sup>. In terms of IR data, there is a marked disappearance of peaks below about 1000 cm<sup>-1</sup>. There is a broad band at 3400 cm<sup>-1</sup>, presumably due to moisture in the sample. The imine C=N stretch, seen at 1630 cm<sup>-1</sup> in the ligand is seen as two peaks at 1626 and 1660 cm<sup>-1</sup> in the complex. The peaks in the fingerprint region are much less prominent. Given that a related structure, albeit with tantalum as the central metal atom, has been described in the literature,<sup>128</sup> it seems likely that the structure of these Schiff-base complexes will be in agreement. Absolute structural confirmation has proven difficult, due to the low solubility of the materials in common solvents. Reactivity between the metals and co-ordinating solvents is a constant consideration. It may be that acetone was an unsuitable solvent for this spectroscopy. However, DMSO presents even greater difficulties with potential abstraction of S or O atoms, even under ambient conditions. Non co-ordinating solvents, such as CDCl<sub>3</sub>, tend to allow insufficient solubility and indeed this was the case for the niobium Schiff-base complexes.

### 3.2.3 Results

The results for the use of niobium pentachloride with Schiff-base ligands and crotonaldehyde and methacrolein as dienophiles are shown in Tables XII and XIII respectively.

**Table XII: Niobium pentachloride as Lewis acid catalyst of the Diels–Alder reaction between cyclopentadiene and crotonaldehyde**

<b>Ligand</b>	<b>Yield (%)</b>	<b><i>Endo:Exo</i></b>	<b>EE (%)</b>
<b>265</b>	16.0	90:10	N/O <sup>a</sup>
<b>266</b>	10.0	93:7	N/O
<b>267</b>	11.0	94:6	N/O
<b>268</b>	21.2	92:8	N/O
<b>269</b>	16.7	91:9	N/O
<b>270</b>	18.4	91:9	N/O
<b>271</b>	17.6	90:10	N/O
<b>272</b>	14.2	92:8	N/O

a N/O = not observed

**Table XIII Niobium pentachloride as Lewis acid catalyst of the Diels–Alder reaction between cyclopentadiene and methacrolein**

<b>Ligand</b>	<b>Yield (%)</b>	<b><i>Endo:Exo</i></b>	<b>EE (%)</b>
<b>265</b>	20.0	10:90	N/O
<b>266</b>	66.6	13:87	N/O
<b>267</b>	85.0	10:90	N/O

<b>268</b>	71.0	10:90	4.0 (R)
<b>269</b>	65.1	11:89	N/O
<b>270</b>	57.0	10:90	N/O
<b>271</b>	72.2	9:91	N/O
<b>272</b>	64.3	9:91	N/O

The results for the use of niobium isopropoxide with Schiff-base ligand and crotonaldehyde and methacrolein are shown in Tables XIV and XV respectively.

**Table XIV Niobium isopropoxide as Lewis acid catalyst of the Diels–Alder reaction between cyclopentadiene and crotonaldehyde**

<b>Ligand</b>	<b>Yield (%)</b>	<b><i>Endo:Exo</i></b>	<b>EE (%)</b>
<b>265</b>	16.6	98:2	N/O
<b>266</b>	18.0	97:3	N/O
<b>267</b>	15.0	95:5	N/O
<b>268</b>	11.0	95:5	N/O
<b>269</b>	8.1	91:9	N/O
<b>270</b>	4.5	93:7	N/O
<b>271</b>	17.7	92:8	N/O
<b>272</b>	10.0	90:10	N/O

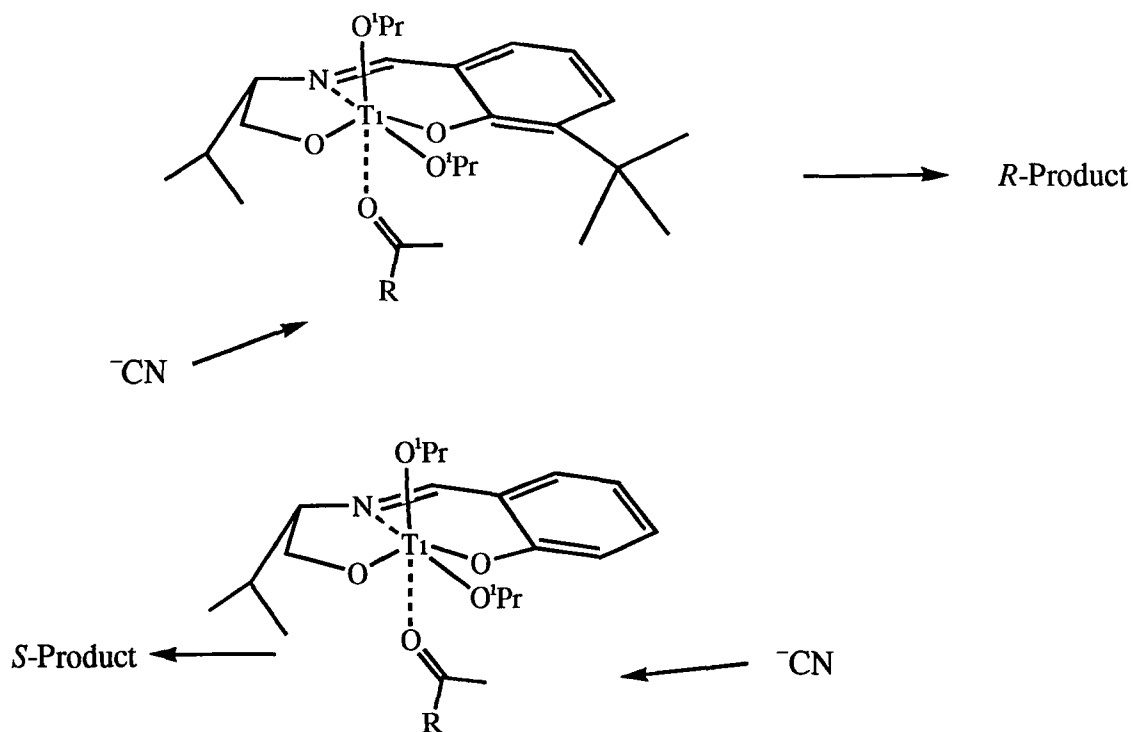


**Table XV Niobium isopropoxide as Lewis acid catalyst of the Diels–Alder reaction between cyclopentadiene and methacrolein**

<b>Ligand</b>	<b>Yield (%)</b>	<b><i>Endo:Exo</i></b>	<b>EE (%)</b>
<b>265</b>	20.0	6:94	N/O
<b>266</b>	30.0	5:95	N/O
<b>267</b>	25.0	5:95	8.0 ( <i>S</i> )
<b>268</b>	27.3	6:94	N/O
<b>269</b>	26.2	20:80	3.0 ( <i>S</i> )
<b>270</b>	8.0	9:91	N/O
<b>271</b>	33.0	6:94	N/O
<b>272</b>	18.5	3:97	N/O

The most obvious feature of the results from Tables XII–XV is that on very few occasions have ee's been achieved, and those that were, proved very small. In the use of NbCl<sub>5</sub> with ligand (**268**) which contains no butyl group and was synthesised from norephedrine, an ee of 4% (*R*) was achieved. However in the case of Nb(O<sup>*i*</sup>Pr)<sub>5</sub> and ligands (**267**) and (**269**) ee's of 8 and 3% (*S*) were achieved, respectively. This is significant in that ligands (**267**) and (**269**) have groups on the C-2 carbon and in the *S* configuration. Ligand (**268**) contains groups on C-2 and C-1 in the *R* and *S* configurations respectively. Only ligand (**269**) possesses a butyl group on the aromatic ring.

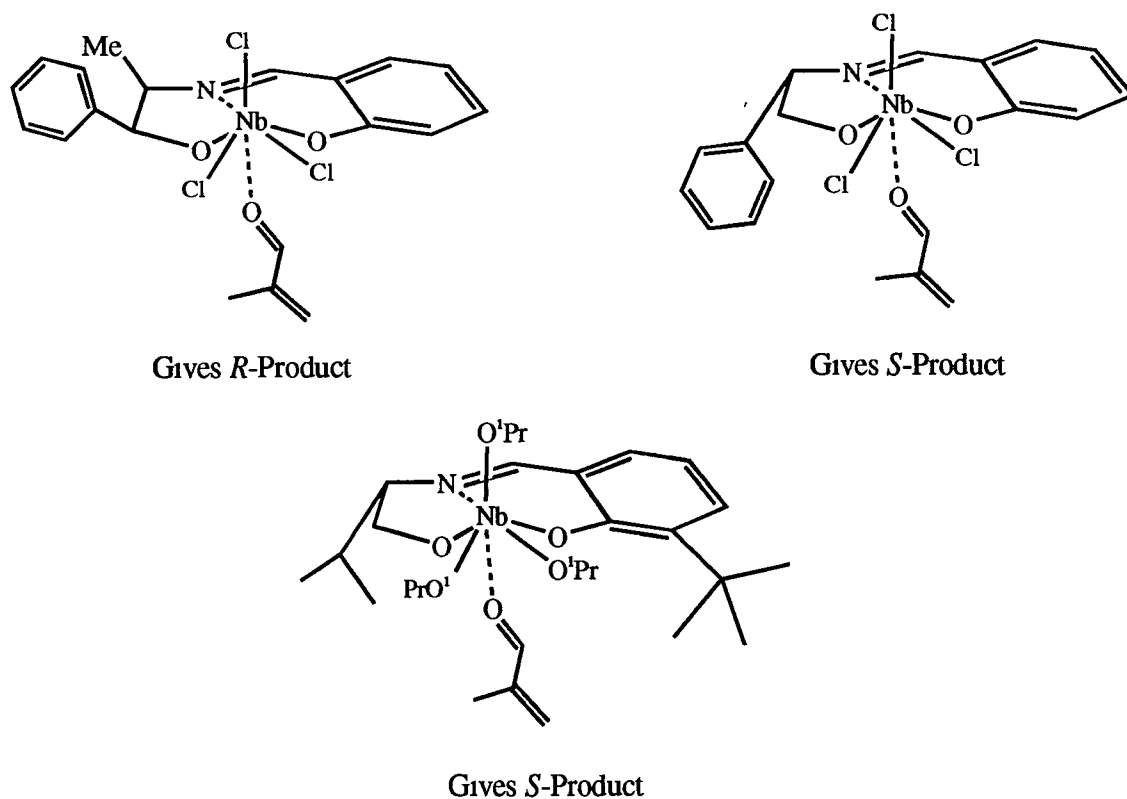
In the original work,<sup>124</sup> the authors outlined their reasoning for the development of different product orientations (*S* or *R*) based on whether a butyl group was present or not.



**Figure 75**

From Figure 75 it can be seen that, in the absence of the butyl group, it is the isopropyl group which hinders  $S_i$  attack leading to the  $S$  configuration. However, where the butyl group is present, it is more effective at hindering  $Re$  attack and thus the  $R$  configuration is favoured. The fact that the best ee achieved in the absence of the butyl group is 22% demonstrates that  $S_i$  attack is still possible in this situation, *ie* in the presence of a propyl group. Thus, the butyl group exerts a larger influence causing  $S_i$  attack despite the presence of the isopropyl group. The positioning of the isopropoxy groups on the metal is probably such that it causes least interaction with the ring substituents, thus forcing the aldehyde to co-ordinate beneath the plane, as shown.

Similar proposed structures for the complexes with  $\text{NbCl}_5$  and ligand (268) and niobium isopropoxide and ligands (267) and (269) are shown in Figure 76.



**Figure 76**

From Figure 76 it can be seen that, in the case of ligand (268), the substituents (methyl and phenyl) are above the plane. With (267) and (269) there are no substituents in the C-1 position and the substituents in the C-2 position are below the plane. This would seem to be a more important factor in directing the orientation of the product. It is not certain if the aldehyde is forced to co-ordinate below the plane in these structures as the resulting complex will not be hexaco-ordinated as with the titanium species. There will, most likely, be seven "ligands" surrounding the metal at this point. However the fact that the norephedrine-derived ligand, bearing opposite stereochemistry to the other ligands, gave a product of the opposite configuration to that achieved with the other ligands, is noteworthy. Given the evidence of Hayashi *et al.*,<sup>124</sup> it would have seemed more likely that the ligands bearing *t*-butyl groups would have given highest ee. This however was not the case. In any case, very low ee was achieved and thus it is difficult to draw conclusions on orientation based on these results. The low results are somewhat supported by the work of Bolm and Bienwald<sup>125</sup>. As mentioned above (3.1.1.2) they used a vanadium catalyst to oxidise sulphides to sulfoxides in up to 85% ee. However, when they substituted niobium for vanadium, they found only a 7% ee. It may be that the first-row metals are useful for chiral catalysis, in conjunction with these Schiff bases, but that niobium is not. This may be an atomic radius issue.

The dienophile might be capable of co-ordinating the metal centre and still have free rotation in the case of molybdenum, but be more restricted with the smaller metal

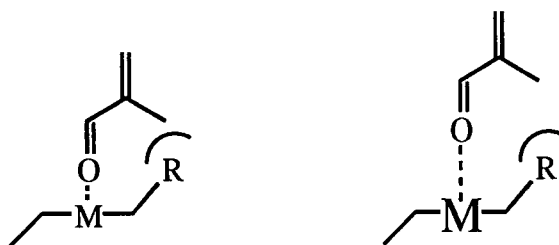


Figure 77

Overall the highest ee achieved was less than 10%.

Where  $\text{NbCl}_5$  was used, there was a clear yield difference between the adducts of crotonaldehyde and methacrolein. The crotonaldehyde results showed only one example which gave greater than stoichiometric catalysis, that with ligand (268). In the case of methacrolein, the yields varied from 20–85%. This low yield seems anomalous as all the other reactions showed substantial catalytic activity. It seems likely that the reason for the yield difference in the case of these adducts is similar to that described in Chapter 2, *i.e.* there is a large difference in the catalyst–product binding constants for the two adducts. The crotonaldehyde product has a larger binding constant, thus inhibiting further catalytic activity.

When comparing the results using  $\text{NbCl}_5$  and  $\text{Nb}(\text{O}^i\text{Pr})_5$  as catalysts, there is also a large difference in yield. Because the results for  $\text{NbCl}_5$  and crotonaldehyde were more-or-less stoichiometric, the difference with  $\text{Nb}(\text{O}^i\text{Pr})_5$  is not so pronounced. However, in the case of methacrolein adduct, most of the results for the latter are half or less of those of the former. The exception is the case of ligand (265) where both results were around 20%. This difference could be accounted for by substrate repulsion by the large isopropoxy groups surrounding the metal. A reaction using  $\text{Nb}(\text{O}^i\text{Pr})_5$  without ligand was achieved but the yield was lower than with  $\text{NbCl}_5$  (c.f. Chapter 2). It can be seen from Figure 78 that the co-ordination of the metal centre is achieved more easily with the chloro compound than with the isopropoxy.

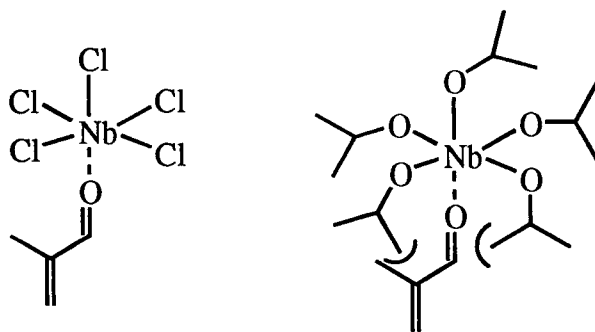


Figure 78

The substrate-binding effect is much more likely to be responsible here as there is unlikely to be a great difference in product-catalyst binding coefficients. If anything, the  $\text{Nb}(\text{O}^i\text{Pr})_5$  compound is more likely to repel the product because of the large substituents. The overall result is a significant difference in yield depending on the source of Nb used.

There is no great discernible pattern in the *endo:exo* ratios. Where  $\text{NbCl}_5$  is used, the crotonaldehyde product has an equal or larger proportion of the major product in each case. However, the difference is quite small. The highest ratio for crotonaldehyde adduct was 94:6 whereas the lowest ratio for methacrolein adduct was 13:87. The pattern is not maintained in the case of  $\text{Nb}(\text{O}^i\text{Pr})_5$ . Some of the crotonaldehyde adducts have a higher proportion of major product and with other ligands the proportion of major product is higher for the methacrolein adduct. The highest result achieved was 98% *endo* for the crotonaldehyde adduct where ligand (265) was used. In the case of methacrolein adduct, with (269) as ligand, 89% *exo* was found, which was the lowest result. Overall there was greater selectivity using  $\text{Nb}(\text{O}^i\text{Pr})_5$  than  $\text{NbCl}_5$ . This suggests that  $\text{Nb}(\text{O}^i\text{Pr})_5$  is not a weaker Lewis acid than  $\text{NbCl}_5$ . Thus the major reason for the lower yield when using the former source of Nb seems to be steric inhibition rather than any electronic effect.

The results of the experiments with niobium were disappointing in terms of chiral induction. Thus the use of tantalum was not investigated.

### 3.3 CONCLUSIONS

The chiral induction capability of niobium, as the chloride or isopropoxide, in the presence of Schiff-base ligands of the form (265–272), was examined. The Schiff bases were synthesised using a condensation reaction between two different aromatic aldehydes and four different amino alcohols. Salicylaldehyde was commercially available, but the *t*-butyl salicylaldehyde was synthesised from *t*-butyl phenol. The final yield of the pure material was 11% and thus it was believed that this synthesis could benefit from a longer reaction time. Three of the amino alcohols were synthesised by reducing the corresponding amino acids with NaBH<sub>4</sub>/I<sub>2</sub>. This is a simple, safe reaction which produces the amino alcohol in high yield offering distinct advantages over the LiAlH<sub>4</sub>-type procedures. The condensation reactions afforded the Schiff bases in 46–93% yield and in high purity. Complexation of these Schiff bases with the metal was achieved by stirring in DCM. However, spectral analysis of the compounds proved difficult.

The complexes with both NbCl<sub>5</sub> and Nb(O<sup>*i*</sup>Pr)<sub>5</sub> catalysed the Diels–Alder reaction between cyclopentadiene and either crotonaldehyde or methacrolein. Small ee's were achieved with three of the ligands. In the case of the 2*R*, 3*S*-norephedrine-based ligand, the product was 3% (*R*). In those where 2*S*-amino alcohol-derived ligands were used, the product had up to 8% (*S*) configuration. Those reactions carried out using NbCl<sub>5</sub> with methacrolein gave a much higher yield than with Nb(O<sup>*i*</sup>Pr)<sub>5</sub>. The reactions with crotonaldehyde showed little difference, possibly due to low catalytic turnover. In general, higher *endo.exo* or *exo.endo* ratios were achieved using Nb(O<sup>*i*</sup>Pr)<sub>5</sub> than NbCl<sub>5</sub> for crotonaldehyde and methacrolein adducts, respectively. The enantiomeric excesses achieved were very low and it would seem that this ligand–metal combination is not suited to high stereoselectivity in the Diels–Alder reaction.

## 3.4 EXPERIMENTAL

Experimental apparatus was described in Chapter 2. In addition methanol was purified by washing twice with water, heating a portion in magnesium, in the presence of a crystal of  $I_2$ , until magnesium methoxide had been formed, followed by heating under reflux for 3 h. The MeOH was distilled from  $P_2O_5$  and stored over 3Å molecular sieves.

### 3.4.1 Amino Alcohol Synthesis

#### Synthesis of valinol (254)

L-Valine (8.90 g, 0.076 mol) and  $NaBH_4$  (6.92 g, 0.190 mol) were placed in a three-neck round-bottom flask fitted with a condenser and stirrer. Dry THF (200 ml) was added and the vessel purged with argon and cooled to 0°C using an ice-bath. A solution of  $I_2$  (19.30 g, 0.076 mol) in 50 ml THF was added slowly over 30 min. The mixture was allowed to warm to room temperature and then heated under reflux for 72 h. The suspension was cooled on ice and MeOH (200 ml) was added. There was evolution of  $H_2$ . Solvent was removed and the resulting white solid was dissolved in 20% aq. KOH (150 ml) and stirred for 4 h. The product was extracted using DCM (5 x 200 ml). On evaporation of the solvent, a crude white solid (7.36 g, 93.4%) resulted. This material was distilled under vacuum (115°C) and the yield of pure material was 5.20 g (66.0%). IR  $\nu_{max}$  3412  $cm^{-1}$ .  $\delta_H[CDCl_3]$  showed the following signals:- 0.91 (6 H, dd,  $J=6.9$  Hz), 1.55 (1 H, m,  $J=6.9$  Hz), 1.78 (3 H, broad), 2.55 (1 H, m,  $J=8.9, 4.9$  Hz), 3.27 (1 H, dd,  $J=8.9$  Hz), 3.64 (1 H, dd,  $J=8.9$  Hz).  $\delta_C[CDCl_3]$  showed the following signals:- 18.02, 18.98, 30.49, 58.03, 64.02.

#### Synthesis of phenylglycinol (255)

L-Phenylglycine (11.50 g, 0.076 mol) was treated with  $NaBH_4$  (6.92 g, 0.190 mol) and  $I_2$  (19.30 g, 0.076 mol) as described above. Following work-up 10.10 g (94.1%) of crude material was recovered. This was recrystallised from clean dry toluene and 6.50 g (62.3%) of pure material was recovered. m.p. = 71–73°C. IR  $\nu_{max}$  3412, 2974, 753  $cm^{-1}$ .  $\delta_H[CDCl_3]$  showed the following signals:- 2.29 (3 H, br s), 3.55 (1 H, dd,  $J=8.4, 2.5$  Hz), 3.73 (1 H, dd,  $J=3.9, 6.9$  Hz), 4.04 (1 H, dd,  $J=4.4, 3.9$  Hz), 7.25–7.37 (5 H, m).  $\delta_C[CDCl_3]$  showed the following signals:- 56.88, 68.21, 126.02, 127.05, 128.16.

### Synthesis of phenylalaninol (256)

L-Phenylalanine (12.55 g, 0.076 mol) was treated with NaBH<sub>4</sub> (6.92 g, 0.190 mol) and I<sub>2</sub> (19.30 g, 0.076 mol) as described above. Following work-up 9.69 g (90.3%) of crude material was recovered. This was recrystallised from clean dry toluene and 5.88 g (62.3%) of pure material was recovered. m.p. = 89–91°C. IR  $\nu_{\max}$  3415, 2961, 755 cm<sup>-1</sup>.  $\delta_{\text{H}}[\text{CDCl}_3]$  showed the following signals: 2.49–2.54 (4 H, br m,  $J=8.9, 4.4$  Hz), 2.78 (1 H, dd,  $J=5.4, 7.9$  Hz), 3.08–3.14 (1 H, m,  $J=5.4, 3.5, 3.9, 1.5$  Hz), 3.39 (1 H, d,  $J=3.5, 7.4$  Hz), 3.62 (1 H, dd,  $J=3.9, 6.9$  Hz), 7.18–7.32 (5 H, m)  $\delta_{\text{C}}[\text{CDCl}_3]$  showed the following signals: 40.05, 53.74, 65.78, 125.95, 128.12, 128.75.

## 3.4.2 Synthesis of Aldehydes

### Synthesis of 3-*t*-butyl salicylaldehyde (260)

Magnesium (7.50 g, 0.310 mol) and ethyl bromide (29.20 g, 0.270 mol) were reacted in a three-neck round-bottom flask in dry THF (200 ml). The resulting solution was removed and the excess Mg disposed of. The THF was evaporated off and the vessel recharged with a solution of EtMgBr in 100 ml of THF. 2-*t*-Butyl phenol (26.70 g, 21.2 ml, 0.178 mol) in 50 ml THF was added dropwise at room temp. After 1 h, THF was removed and HMPA (32.94 g, 35.1 ml, 0.100 mol), paraformaldehyde (15.03 g, 0.501 mol) and benzene (1000 ml) were added. The solution was heated under reflux for 20 h. The mixture was cooled, solvent removed and acidified with 10% HCl. The aqueous layer was extracted with ether (6 x 150 ml). The organic fractions were combined and the solvent removed. Initially the oily residue was distilled and six fractions were collected. Those containing the desired product, as determined by TLC (100% pentane,  $R_f=0.1$ ), were combined and purified by silica-gel flash chromatography. Yield = 3.46 g, 11.0%. b.p. 110°C, reduced pressure. IR  $\nu_{\max}$  3424, 2961, 1652, 1613, 753, 679 cm<sup>-1</sup>.  $\delta_{\text{H}}[\text{CDCl}_3]$  showed the following signals: 1.42 (9 H, s), 6.95 (1 H, t,  $J=6.9, 7.9$  Hz), 7.40 (1 H, d,  $J=7.9$  Hz), 7.53 (1 H, d,  $J=6.9$  Hz), 9.87 (1 H, s), 11.80 (1 H, s).  $\delta_{\text{C}}[\text{CDCl}_3]$  showed the following signals: 29.14, 35.01, 119.15, 120.59, 131.93, 134.05, 138.16, 161.15, 197.10. These data match the lit. values.<sup>135</sup>



### 3.4.3 Synthesis of Schiff Bases

#### (S)-2-(N-Salicylideneamino)-3-methyl-1-butanol (265)

L-Valinol (1.21 g, 8.0 mmol) and salicylaldehyde (0.97 g, 8.0 mmol) were placed in a 50-ml round-bottom flask with 15 ml of dry methanol and five equivalents of anhydrous  $\text{Na}_2\text{SO}_4$ . The solution was heated under reflux for 18 h. It was then filtered and the MeOH removed under vacuum. The crude product was recrystallised from petroleum ether(60:40)–benzene (5:1). Yield=1.05 g (64.0%). m.p.= 98–100°C. IR  $\nu_{\text{max}}$  3315, 2965, 1630, 753, 679  $\text{cm}^{-1}$ .  $\delta_{\text{H}}[(\text{CD}_3)\text{CO}]$  showed the following signals:- 0.96 (6 H, dd,  $J=6.9$  Hz), 1.6 (1 H, br s), 1.95 (1 H, sept,  $J=6.9$  Hz), 3.12 (1 H, dd,  $J=4.0$  Hz), 3.66 (1 H, dd,  $J=4.0, 8.0$  Hz), 3.81 (1 H,  $J=4.0, 8.0$  Hz).  $\delta_{\text{C}}[(\text{CD}_3)\text{CO}]$  showed the following signals.- 18.62, 20.34, 64.57, 78.15, 119.27, 119.93, 129.84, 131.43, 166.91. These data match the lit values.<sup>124</sup>

#### (S)-2-(N-Salicylideneamino)-2-phenyl-1-ethanol (266)

L-Phenylglycinol (1.10 g, 8.0 mmol) and salicylaldehyde (0.95 g, 8.0 mmol) were reacted as described above. Crude yield = 1.94 g. This material was dissolved in a mixture of benzene–PE and purified by recrystallisation. Yield = 1.10 g (46.0%) m.p. = 84–86°C.  $[\alpha]_{\text{D}}^{25} = +125.5^\circ$ . IR  $\nu_{\text{max}}$  3410, 2957, 2880, 1630, 1437, 1265, 753, 701  $\text{cm}^{-1}$ .  $\delta_{\text{H}}[(\text{CD}_3)\text{CO}]$  showed the following signals.- 3.86 (2 H, d,  $J=6.9$  Hz), 4.22 (1 H, br s), 4.52 (1 H, t,  $J=6.9$  Hz), 6.91 (2 H, t,  $J=4.9$  Hz), 7.30–7.48 (7 H, m), 8.63, (1 H, s), 12.85, (1 H, s).  $\delta_{\text{C}}[(\text{CD}_3)\text{CO}]$  showed the following signals:-67.90, 76.90, 117.34, 119.35, 127.94, 128.24, 129.39, 132.68, 133.02, 141.36, 161.97, 166.78. Analysis: % Calculated for  $\text{C}_{15}\text{H}_{15}\text{NO}_2$ : C (74.66); H (6.28), N (5.80), Found C (74.73), H (6.34); N (5.83).

#### (S)-2-(N-Salicylideneamino)-2-benzyl-1-ethanol (267)

L-Phenylalaninol (1.14 g, 8.0 mmol) and salicylaldehyde (0.96 g, 8.0 mmol) were reacted as described above. Crude yield = 2.14 g. The yellow material was purified by silica-gel flash chromatography (PE:EA (60:40)). Yield = 1.83 g (89.4%).  $[\alpha]_{\text{D}}^{25} = -291.6^\circ$ . IR  $\nu_{\text{max}}$  3402, 2936, 2880, 1631, 1496, 1278, 756, 702  $\text{cm}^{-1}$ .  $\delta_{\text{H}}[(\text{CD}_3)\text{CO}]$  showed the following signals -2.88 (1 H, dd,  $J=5.0, 13.0$  Hz), 3.08 (1 H, dd,  $J=5.0, 13.0$

Hz), 3.60 (1 H, t,  $J=3.9$  Hz), 3.79 (1 H, br s), 4.07 (2 H, t,  $J=6.9$  Hz), 6.83 (2 H, d,  $J=8.9$  Hz), 7.14–7.32 (7 H, m), 8.25 (1 H, s), 12.50, (1H, s).  $\delta_{\text{C}}[(\text{CD}_3)\text{CO}]$  showed the following signals: -39.76, 66.04, 74.36, 117.46, 119.28, 127.07, 129.18, 130.44, 132.55, 132.93, 139.78, 166.61. Analysis. % Calculated for  $\text{C}_{16}\text{H}_{17}\text{NO}_2$ : C (75.26), H (6.72), N (5.48); Found C (75.45); H (6.82); N (5.41)

**(R)-2-(N-Salicylideneamino)-2-methyl-1-(S)-phenyl-1-ethanol (268)**

2R, 3S-Norephedrine (1.21 g, 8.0 mmol) and salicylaldehyde (0.95 g, 8.0 mmol) were reacted as described above. Crude yield = 2.25 g. The yellow material was purified by silica-gel flash chromatography (PE:EA (60:40)). Yield = 1.89 g (92.5%)  $[\alpha]_{\text{D}}^{25} = +181.4^\circ$ . IR  $\nu_{\text{max}}$  3415, 2976, 2874, 1632, 1496, 1279, 758, 704  $\text{cm}^{-1}$ .  $\delta_{\text{H}}[(\text{CD}_3)\text{CO}]$  showed the following signals: -1.32 (3 H, d,  $J=6.9$  Hz), 3.70 (1 H, q,  $J=6.9$  Hz), 4.67 (1 H, br s), 4.79 (1 H, d,  $J=6.9$  Hz), 6.83 (2 H, t,  $J=6.9$  Hz), 7.21–7.40 (7 H, m), 8.36 (1 H, s), 12.50, (1 H, s).  $\delta_{\text{C}}[(\text{CD}_3)\text{CO}]$  showed the following signals: -18.32, 70.94, 77.57, 117.09, 118.83, 127.66, 127.71, 128.30, 132.15, 132.53, 143.24, 165.43. Analysis. % Calculated for  $\text{C}_{16}\text{H}_{17}\text{NO}_2$ : C (75.26), H (6.72), N (5.48), Found C (75.11); H (6.92), N (5.22).

**(S)-2-[N-(3'-tert-Butylsalicylidene)amino]-3-methyl-1-butanol (269)**

L-Valinol (0.31 g, 3.0 mmol) and *t*-butyl salicylaldehyde (0.54 g, 3.0 mmol) were reacted as described above. The material was purified using silica-gel flash chromatography (PE:EA (60:40)). Yield = 0.70 g (92.4%) m.p. = 48–51°C. IR  $\nu_{\text{max}}$  3397, 2961, 2876, 1631, 1437, 1266, 754, 672  $\text{cm}^{-1}$ .  $\delta_{\text{H}}[(\text{CD}_3)\text{CO}]$  showed the following signals: -0.97 (6H, dd,  $J=6.9$  Hz), 1.43, (9 H, s), 2.01 (1 H, sept), 3.11 (1 H, br s), 3.67 (1 H, br s), 3.81 (1 H, br s), 3.93 (1 H, br s), 6.82 (1 H, d,  $J=7.9$  Hz), 7.25–7.32 (2 H, m), 8.47 (1 H, s), 12.96 (1 H, s).  $\delta_{\text{C}}[(\text{CD}_3)\text{CO}]$  showed the following signals: -18.62, 20.40, 64.57, 78.15, 118.67, 119.93, 127.94, 129.88, 130.92, 167.34. These data match the lit. values.<sup>124</sup>

**(S)-2-[N-(3'-tert-Butyylsalicylidene)amino] 2-phenyl-1-ethanol (270)**

L-Phenylglycinol (0.42 g, 3.0 mmol) and *t*-butyl salicylaldehyde (0.54 g, 3.0 mmol) were reacted as described above. The resulting material was purified by silica-gel flash chromatography (PE:EA (60:40)). Yield = 0.740 g (86.0%). Yellow oil. IR  $\nu_{\max}$  3400, 3068, 2960, 1629, 1440, 1265, 753, 700  $\text{cm}^{-1}$ .  $\delta_{\text{H}}[(\text{CD}_3)\text{CO}]$  showed the following signals:- 1.44 (9 H, s), 3.87 (2H, br s), 4.29 (1 H, br s), 4.52 (1 H, t,  $J=5.9$  Hz), 6.85 (1H, t,  $J=6.4$  Hz), 7.28–7.50 (7 H, m), 8.63 (1 H, s), 12.9 (1 H, s).  $\delta_{\text{C}}[(\text{CD}_3)\text{CO}]$  showed the following signals:- 22.63, 35.12, 67.68, 76.65, 118.64, 119.70, 127.82, 128.07, 129.21, 129.87, 130.89, 137.31, 141.19, 160.89, 167.31. These data match the lit values<sup>124</sup>

**(S)-2-[N-(3'-tert-Butyylsalicylidene)amino] 2-benzyl-1-ethanol (271)**

L-Phenylalaninol (0.49 g, 3.0 mmol) and *t*-butyl salicylaldehyde (0.54 g, 3.0 mmol) were reacted as described above. The yellow material was purified by silica-gel flash chromatography (PE:EA (60:40)). Yield = 0.7431 g (82.0%).  $[\alpha]_{\text{D}}^{25} = +155.5^\circ$ . IR  $\nu_{\max}$  3389, 2956, 1630, 1496, 1266, 752, 702  $\text{cm}^{-1}$ .  $\delta_{\text{H}}[(\text{CD}_3)\text{CO}]$  showed the following signals:- 1.43 (9 H, s), 2.91 (1 H, dd,  $J=7.9, 4.9$  Hz), 3.09 (1 H, dd,  $J=7.9, 4.9$  Hz), 3.59 (1 H, br s), 3.71 (1 H, br s), 4.06 (2 H, d,  $J=6.9$  Hz), 6.78 (1 H, t,  $J=7.9$  Hz), 7.11–7.32 (7 H, m), 8.27 (1 H, s), 13.50 (1 H, s).  $\delta_{\text{C}}[(\text{CD}_3)\text{CO}]$  showed the following signals:- 14.35, 20.59, 35.09, 39.44, 65.59, 73.78, 118.35, 126.74, 128.81, 129.62, 130.11, 130.58, 137.23, 139.46, 166.96. Analysis: % Calculated for  $\text{C}_{20}\text{H}_{25}\text{NO}_2$ : C (77.12), H (8.11), N (4.50); Found C (77.22), H (8.05); N (4.61).

**(R)-2-[N-(3'-tert-Butyylsalicylidene)amino] 2-methyl-1-(S)-phenyl-1-ethanol (272)**

2R, 3S-Norephedrine (0.45 g, 3.0 mmol) and *t*-butyl salicylaldehyde (0.53 g, 3.0 mmol) were reacted as described above. The yellow material was purified by silica-gel flash chromatography (PE:EA (60:40)). Yield = 0.70 g (78.3%).  $[\alpha]_{\text{D}}^{25} = -276.0^\circ$ . IR  $\nu_{\max}$  3410, 2959, 2873, 1631, 1494, 1436, 1268, 753, 703  $\text{cm}^{-1}$ .  $\delta_{\text{H}}[(\text{CD}_3)\text{CO}]$  showed the following signals:- 1.31 (3 H, d,  $J=5.9$  Hz), 1.42 (9 H, s), 3.70 (1 H, m), 4.67 (1 H, d,  $J=4.0$  Hz), 4.82 (1 H, br s), 6.77 (1 H, t,  $J=8.0$  Hz), 7.14–7.41 (7 H, m), 8.38 (1 H, s), 12.85 (1H, s).  $\delta_{\text{C}}[(\text{CD}_3)\text{CO}]$  showed the following signals:- 18.43, 23.01, 35.44, 71.11, 77.89, 118.61, 119.88, 128.06, 128.14, 128.63, 129.95, 130.92, 137.66, 143.62, 166.49. Analysis: % Calculated for  $\text{C}_{20}\text{H}_{25}\text{NO}_2$ : C (77.12); H (8.11), N (4.50), Found C (77.30); H (8.12), N (4.26).

### 3.4.4 Formation of Catalysts

Five of the catalysts formed were examined spectroscopically

#### Niobium pentachloride and ligand (265)

Niobium pentachloride (0.13 g, 0.51 mmol) was placed in a round-bottom flask with dry DCM and the vessel was purged with argon. Ligand (265) (0.10 g, 0.50 mmol) was added slowly under a stream of argon and a bright orange colour developed. The material was allowed to stir for 24 h at which time it was filtered through cotton-wool and a portion was reconstituted in acetone- $d^6$ .  $\delta_{\text{H}}[(\text{CD}_3)\text{CO}]$  showed the following signals:-1.09 (6 H, dd,  $J=7.9$  Hz), 1.29 (1 H, br s), 3.87 (1 H, br s), 4.02 (1 H, br s), 7.10–8.10 (m), 9.12 (s).

#### Niobium pentachloride and ligand (266)

Niobium pentachloride (0.14 g, 0.52 mmol) and ligand (266) (0.12 g, 0.51 mol) were treated as described above.  $\delta_{\text{H}}[(\text{CD}_3)\text{CO}]$  showed the following signals.- 3.05–3.60 (br s), 4.13 (1H, dd,  $J=3.9, 7.9$  Hz), 4.35 (1H, dd, 3.9, 7.7 Hz), 7.05 (2 H, m), 7.40–7.70 (5H, m), 8.11 (2 H, d,  $J=7.9$ ), 9.13 (1 H, s)

#### Niobium pentachloride and ligand (267)

Niobium pentachloride (0.13 g, 0.50 mmol) and ligand (267) (0.13 g, 0.51 mol) were treated as described above.  $\delta_{\text{H}}[(\text{CD}_3)\text{CO}]$  showed the following signals.- 3.07 (2 H, br s), 3.35 (1 H, dd,  $J=3.9$  Hz), 4.05 (1 H, dd,  $J=3.9$  Hz), 7.2–7.9 (7 H, m), 8.95 (1 H, s).

#### Niobium pentachloride and ligand (268)

Niobium pentachloride (0.13 g, 0.50 mmol) and ligand (268) (0.13 g, 0.51 mol) were treated as described above.  $\delta_{\text{H}}[(\text{CD}_3)\text{CO}]$  showed the following signals:- 1.10–1.44 (m), 3.41, (d), 7.16–7.03 (m), 9.13 (s).

#### Niobium pentachloride and ligand (269)

Niobium pentachloride (0.13 g, 0.50 mmol) and ligand (269) (0.13 g, 0.51 mol) were treated as described above. IR  $\nu_{\text{max}}$  3401, 2969, 2920, 1660, 1627, 1280, 1060  $\text{cm}^{-1}$ .  $\delta_{\text{H}}[(\text{CD}_3)\text{CO}]$  showed the following signals:-1.06–1.57 (m), 7.13–8.13 (m), 9.07 (s)

### 3.4.5 Lewis acid Catalysed Diels–Alder Reactions

#### Niobium pentachloride and ligand (265)

A suspension of NbCl<sub>5</sub> (270.0 mg, 1.000 mmol) in dry DCM was prepared. One equivalent of ligand (265) (206.0 mg, 1.003 mmol) was added over 25 min under a stream of argon and the suspension allowed to stir overnight. It was then divided into two round-bottom flasks by syringing from the original vessel under a stream of argon. The DCM was removed under vacuum and each of the vessels charged with dry DCM and cooled to –80°C on dry ice. Cyclopentadiene was added to each vessel, 840.0 mg (12.11 mmol) to vessel 1 and 840.0 mg (12.11 mmol) to vessel 2. Crotonaldehyde (175.0 mg, 2.500 mmol) was added to vessel 1 and methacrolein (175.0 mg, 2.500 mmol) to vessel 2. Reaction was allowed to proceed for 20 h and products were separated using column chromatography (PE:DCM (50:50)). Adduct A.- yield = 54.2 mg (16.0 %) Adduct B:- yield = 68.7 mg, (20.0%) The adducts were derivatised as described in Chapter 2 in order to determine ee. None observed

#### Niobium pentachloride and ligand (266)

A suspension of NbCl<sub>5</sub> (277.0 mg, 1.026 mmol) in dry DCM was prepared. One equivalent of ligand (266) (247.0 mg, 1.004 mmol) was added over 25 min under a stream of argon and the suspension allowed to stir overnight. It was then divided into two round-bottom flasks by syringing from the original vessel under a stream of argon. The DCM was removed under vacuum and each of the vessels charged with dry DCM and cooled to –80°C on dry ice. Cyclopentadiene was added to each vessel, 850.0 mg (12.28 mmol) to vessel 1 and 890.0 mg (13.46 mmol) to vessel 2. Crotonaldehyde (175.0 mg, 2.500 mmol) was added to vessel 1 and methacrolein (175.0 mg, 2.500 mmol) to vessel 2. Reaction was allowed to proceed for 18 h and products were separated using column chromatography (PE:DCM (50:50)). Adduct A.- yield = 35.1 mg (10.0 %) Adduct B:- yield = 226.6 mg, (66.6%) The adducts were derivatised as described in Chapter 2 in order to determine ee. None observed.

#### Niobium pentachloride and ligand (267)

A suspension of NbCl<sub>5</sub> (274.5 mg, 1.017 mmol) in dry DCM was prepared. One equivalent of ligand (267) (257.5 mg, 1.008 mmol) was added over 25 min under a stream of argon and the suspension allowed to stir overnight. It was then divided into two round-bottom flasks by syringing from the original vessel under a stream of argon.

The DCM was removed under vacuum and each of the vessels charged with dry DCM and cooled to  $-80^{\circ}\text{C}$  on dry ice. Cyclopentadiene was added to each vessel, 800.0 mg (12.12 mmol) to vessel 1 and 810.0 mg (12.27 mmol) to vessel 2. Crotonaldehyde (200.0 mg, 2.850 mmol) was added to vessel 1 and methacrolein (180.0 mg, 2.568 mmol) to vessel 2. Reaction was allowed to proceed for 16 h and products were separated using column chromatography (PE:DCM (50:50)). Adduct A:- yield = 43.0 mg (11.0 %). Adduct B:- yield = 296.5 mg, (85.0%). The adducts were derivatised as described in Chapter 2 in order to determine ee. None observed.

#### **Niobium pentachloride and ligand (268)**

A suspension of  $\text{NbCl}_5$  (270.0 mg, 1.000 mmol) in dry DCM was prepared. One equivalent of ligand (268) (260.0 mg, 1.018 mmol) was added over 15 min under a stream of argon and the suspension allowed to stir overnight. It was then divided into two round-bottom flasks by syringing from the original vessel under a stream of argon. The DCM was removed under vacuum and each of the vessels charged with dry DCM and cooled to  $-80^{\circ}\text{C}$  on dry ice. Cyclopentadiene was added to each vessel, 790.0 mg (11.97 mmol) to vessel 1 and 840.0 mg (12.73 mmol) to vessel 2. Crotonaldehyde (150.0 mg, 2.140 mmol) was added to vessel 1 and methacrolein (165.0 mg, 2.354 mmol) to vessel 2. Reaction was allowed to proceed for 18 h and products were separated using column chromatography (PE:DCM (50:50)). Adduct A:- yield = 72.2 mg (21.2 %). Adduct B:- yield = 241.1 mg, (71.0%). The adducts were derivatised as described in Chapter 2 in order to determine ee. In the case of adduct B an ee of 4% (*R*) was observed.

#### **Niobium pentachloride and ligand (269)**

A suspension of  $\text{NbCl}_5$  (270.0 mg, 1.000 mmol) in dry DCM was prepared. One equivalent of ligand (269) (254.0 mg, 1.012 mmol) was added over 20 min under a stream of argon and the suspension allowed to stir overnight. It was then divided into two round-bottom flasks by syringing from the original vessel under a stream of argon. The DCM was removed under vacuum and each of the vessels charged with dry DCM and cooled to  $-80^{\circ}\text{C}$  on dry ice. Cyclopentadiene was added to each vessel, 840.0 mg (12.73 mmol) to vessel 1 and 810.0 mg (12.27 mmol) to vessel 2. Crotonaldehyde (175.0 mg, 2.500 mmol) was added to vessel 1 and methacrolein (175.0 mg, 2.500 mmol) to vessel 2. Reaction was allowed to proceed for 18 h and products were separated using column chromatography (PE:DCM (50:50)). Adduct A - yield = 56.8

mg (16.7 %). Adduct B.- yield = 221.0 mg, (65.0%). The adducts were derivatised as described in Chapter 2 in order to determine ee. None observed.

#### **Niobium pentachloride and ligand (270)**

A suspension of NbCl<sub>5</sub> (273.0 mg, 1.011 mmol) in dry DCM was prepared. One equivalent of ligand (270) (291.0 mg, 1.021 mmol) was added over 25 min under a stream of argon and the suspension allowed to stir overnight. It was then divided into two round-bottom flasks by syringing from the original vessel under a stream of argon. The DCM was removed under vacuum and each of the vessels charged with dry DCM and cooled to -80°C on dry ice. Cyclopentadiene was added to each vessel, 780.0 mg (11.81 mmol) to vessel 1 and 790.0 mg (11.97 mmol) to vessel 2. Crotonaldehyde (205.0 mg, 2.920 mmol) was added to vessel 1 and methacrolein (155.0 mg, 2.210 mmol) to vessel 2. Reaction was allowed to proceed for 14 h and products were separated using column chromatography (PE:DCM (50:50)). Adduct A.- yield = 73.1 mg (18.4%). Adduct B.- yield = 171.3 mg, (57.0%). The adducts were derivatised as described in Chapter 2 in order to determine ee. None observed.

#### **Niobium pentachloride and ligand (271)**

A suspension of NbCl<sub>5</sub> (267.0 mg, 0.989 mmol) in dry DCM was prepared. One equivalent of ligand (271) (303.9 mg, 1.015 mmol) was added over 20 min under a stream of argon and the suspension allowed to stir overnight. It was then divided into two round-bottom flasks by syringing from the original vessel under a stream of argon. The DCM was removed under vacuum and each of the vessels charged with dry DCM and cooled to -80°C on dry ice. Cyclopentadiene was added to each vessel, 820.0 mg (12.42 mmol) to vessel 1 and 790.0 mg (11.97 mmol) to vessel 2. Crotonaldehyde (185.0 mg, 2.640 mmol) was added to vessel 1 and methacrolein (225.0 mg, 3.210 mmol) to vessel 2. Reaction was allowed to proceed for 18 h and products were separated using column chromatography (PE:DCM (50:50)). Adduct A.- yield = 62.5 mg (17.4 %). Adduct B.- yield = 327.4 mg, (72.0%). The adducts were derivatised as described in Chapter 2 in order to determine ee. None observed.

#### **Niobium pentachloride and ligand (272)**

A suspension of NbCl<sub>5</sub> (269.0 mg, 0.999 mmol) in dry DCM was prepared. One equivalent of ligand (272) (292.0 mg, 0.975 mmol) was added over 30 min under a stream of argon and the suspension allowed to stir overnight. It was then divided into

two round-bottom flasks by syringing from the original vessel under a stream of argon. The DCM was removed under vacuum and each of the vessels charged with dry DCM and cooled to  $-80^{\circ}\text{C}$  on dry ice. Cyclopentadiene was added to each vessel, 690.0 mg (10.45 mmol) to vessel 1 and 815.0 mg (12.35 mmol) to vessel 2. Crotonaldehyde (195.0 mg, 2.950 mmol) was added to vessel 1 and methacrolein (145.0 mg, 2.069 mmol) to vessel 2. Reaction was allowed to proceed for 18 h and products were separated using column chromatography (PE:DCM (50:50)). Adduct A.- yield = 57.0 mg (14.2 %) Adduct B.- yield = 180.1 mg, (64.0%). The adducts were derivatised as described in Chapter 2 in order to determine ee. None observed

### **Niobium isopropoxide without ligand**

A suspension of  $\text{Nb}(\text{O}^i\text{Pr})_5$  (395 mg, 1.026 mmol) in dry DCM was prepared. It was stirred for several hours and then divided into two round-bottom flasks by syringing from the original vessel under a stream of argon. They were then cooled to  $-80^{\circ}\text{C}$  on dry ice. Cyclopentadiene was added to each vessel, 835.0 mg (12.65 mmol) to vessel 1 and 780.0 mg (11.82 mmol) to vessel 2. Crotonaldehyde (165.0 mg, 2.350 mmol) was added to vessel 1 and methacrolein (175.0 mg, 2.500 mmol) to vessel 2. Reaction was allowed to proceed for 18 h and products were separated using column chromatography (PE:DCM (50:50)). Adduct A.- yield = 38.4 mg (12.0 %). Adduct B.- yield = 59.8 mg, (17.6%).

### **Niobium isopropoxide and ligand (265)**

A suspension of  $\text{Nb}(\text{O}^i\text{Pr})_5$  (385.0 mg, 0.997 mmol) in dry DCM was prepared. One equivalent of ligand (265) (210.0 mg, 1.014 mmol) was added over 25 min under a stream of argon and the suspension allowed to stir overnight. It was then divided into two round-bottom flasks by syringing from the original vessel under a stream of argon and cooled to  $-80^{\circ}\text{C}$  on dry ice. Cyclopentadiene was added to each vessel, 750.0 mg (11.36 mmol) to vessel 1 and 950.0 mg (14.39 mmol) to vessel 2. Crotonaldehyde (170.0 mg, 2.425 mmol) was added to vessel 1 and methacrolein (180.0 mg, 2.568 mmol) to vessel 2. Reaction was allowed to proceed for 20 h and products were separated using column chromatography (PE:DCM (50:50)). Adduct A.- yield = 54.7 mg (16.6%) Adduct B.- yield = 69.8 mg (20.0%). The adducts were derivatised as described in Chapter 2 in order to determine ee. None observed



#### Niobium isopropoxide and ligand (266)

A suspension of  $\text{Nb}(\text{O}^i\text{Pr})_5$  (377.0 mg, 0.977 mmol) in dry DCM was prepared. One equivalent of ligand (266) (244.0 mg, 1.012 mmol) was added over 20 min under a stream of argon and the suspension allowed to stir overnight. It was then divided into two round-bottom flasks by syringing from the original vessel under a stream of argon and cooled to  $-80^\circ\text{C}$  on dry ice. Cyclopentadiene was added to each vessel, 755.0 mg (11.43 mmol) to vessel 1 and 900.0 mg (13.63 mmol) to vessel 2. Crotonaldehyde (175.0 mg, 2.500 mmol) was added to vessel 1 and methacrolein (185.0 mg, 2.639 mmol) to vessel 2. Reaction was allowed to proceed for 20 h and products were separated using column chromatography (PE:DCM (50:50)). Adduct A:- yield = 61.2 mg (18.0%). Adduct B:- yield = 107.7 mg (30.0%). The adducts were derivatised as described in Chapter 2 in order to determine ee. None observed.

#### Niobium isopropoxide and ligand (267)

A suspension of  $\text{Nb}(\text{O}^i\text{Pr})_5$  (370.0 mg, 0.958 mmol) in dry DCM was prepared. One equivalent of ligand (267) (256.0 mg, 1.004 mmol) was added over 15 min under a stream of argon and the suspension allowed to stir overnight. It was then divided into two round-bottom flasks by syringing from the original vessel under a stream of argon and cooled to  $-80^\circ\text{C}$  on dry ice. Cyclopentadiene was added to each vessel, 800.0 mg (12.12 mmol) to vessel 1 and 800.0 mg (12.12 mmol) to vessel 2. Crotonaldehyde (180.0 mg, 2.568 mmol) was added to vessel 1 and methacrolein (190.0 mg, 2.711 mmol) to vessel 2. Reaction was allowed to proceed for 15 h and products were separated using column chromatography (PE:DCM (50:50)). Adduct A:- yield = 52.4 mg (15.0%). Adduct B:- yield = 92.2 mg, (25.0%). The adducts were derivatised as described in Chapter 2 in order to determine ee. Adduct B gave an ee of 8.0% (*S*).

#### Niobium isopropoxide and ligand (268)

A suspension of  $\text{Nb}(\text{O}^i\text{Pr})_5$  (392.0 mg, 1.016 mmol) in dry DCM was prepared. One equivalent of ligand (268) (256.0 mg, 1.004 mmol) was added over 30 min under a stream of argon and the suspension allowed to stir overnight. It was then divided into two round-bottom flasks by syringing from the original vessel under a stream of argon and cooled to  $-80^\circ\text{C}$  on dry ice. Cyclopentadiene was added to each vessel, 700.0 mg (10.61 mmol) to vessel 1 and 750.0 mg (11.36 mmol) to vessel 2. Crotonaldehyde

(175.0 mg, 2.500 mmol) was added to vessel 1 and methacrolein (160.0 mg, 2.283 mmol) to vessel 2. Reaction was allowed to proceed for 16 h and products were separated using column chromatography (PE:DCM (50:50)). Adduct A.- yield = 37.4 mg (11.0%). Adduct B.- yield = 84.7 mg, (27.3%). The adducts were derivatised as described in Chapter 2 in order to determine ee. None observed.

#### **Niobium isopropoxide and ligand (269)**

A suspension of Nb(O<sup>i</sup>Pr)<sub>5</sub> (370.0 mg, 0.959 mmol) in dry DCM was prepared. One equivalent of ligand (269) (257.0 mg, 1.024 mmol) was added over 25 min under a stream of argon and the suspension allowed to stir overnight. It was then divided into two round-bottom flasks by syringing from the original vessel under a stream of argon and cooled to -80°C on dry ice. Cyclopentadiene was added to each vessel, 700.0 mg (10.61 mmol) to vessel 1 and 820.0 mg (12.42 mmol) to vessel 2. Crotonaldehyde (165.0 mg, 2.354 mmol) was added to vessel 1 and methacrolein (180.0 mg, 2.568 mmol) to vessel 2. Reaction was allowed to proceed for 20 h and products were separated using column chromatography (PE:DCM (50:50)). Adduct A.- yield = 25.9 mg (8.1%). Adduct B.- yield = 91.5 mg, (26.2%). The adducts were derivatised as described in Chapter 2 in order to determine ee. An ee of 3%(*S*) was observed for adduct B.

#### **Niobium isopropoxide and ligand (270)**

A suspension of Nb(O<sup>i</sup>Pr)<sub>5</sub> (391.0 mg, 1.013 mmol) in dry DCM was prepared. One equivalent of ligand (270) (288.0 mg, 1.011 mmol) was added over 20 min under a stream of argon and the suspension allowed to stir overnight. It was then divided into two round-bottom flasks by syringing from the original vessel under a stream of argon and cooled to -80°C on dry ice. Cyclopentadiene was added to each vessel, 755.0 mg (11.40 mmol) to vessel 1 and 900.0 mg (13.64 mmol) to vessel 2. Crotonaldehyde (170.0 mg, 2.425 mmol) was added to vessel 1 and methacrolein (185.0 mg, 2.639 mmol) to vessel 2. Reaction was allowed to proceed for 20 h and products were separated using column chromatography (PE:DCM (50:50)). Adduct A.- yield = 15.7 mg (4.5%). Adduct B.- yield = 26.4 mg, (8.0%). The adducts were derivatised as described in Chapter 2 in order to determine ee. None observed.

### **Niobium isopropoxide and ligand (271)**

A suspension of Nb(O<sup>i</sup>Pr)<sub>5</sub> (390.0 mg, 1.010 mmol) in dry DCM was prepared. One equivalent of ligand (271) (300.0 mg, 1.002 mmol) was added over 25 min under a stream of argon and the suspension allowed to stir overnight. It was then divided into two round-bottom flasks by syringing from the original vessel under a stream of argon and cooled to -80°C on dry ice. Cyclopentadiene was added to each vessel, 650.0 mg (9.848 mmol) to vessel 1 and 750.0 mg (11.36 mmol) to vessel 2. Crotonaldehyde (180.0 mg, 2.568 mmol) was added to vessel 1 and methacrolein (200.0 mg, 2.853 mmol) to vessel 2. Reaction was allowed to proceed for 20 h and products were separated using column chromatography (PE:DCM (50:50)). Adduct A:- yield = 60.0 mg (17.7%). Adduct B:- yield = 110.0 mg, (33.0%) The adducts were derivatised as described in Chapter 2 in order to determine ee. None observed.

### **Niobium isopropoxide and ligand (272)**

A suspension of Nb(O<sup>i</sup>Pr)<sub>5</sub> (380.0 mg, 0.984 mmol) in dry DCM was prepared. One equivalent of ligand (272) (300.0 mg, 1.002 mmol) was added over 25 min under a stream of argon and the suspension allowed to stir overnight. It was then divided into two round-bottom flasks by syringing from the original vessel under a stream of argon and cooled to -80°C on dry ice. Cyclopentadiene was added to each vessel, 780.0 mg (11.81 mmol) to vessel 1 and 845.0 mg (12.80 mmol) to vessel 2. Crotonaldehyde (190.0 mg, 2.710 mmol) was added to vessel 1 and methacrolein (180.0 mg, 2.568 mmol) to vessel 2. Reaction was allowed to proceed for 20 h and products were separated using column chromatography (PE:DCM (50:50)). Adduct A:- yield = 36.9 mg (10.0%). Adduct B:- yield = 64.6 mg, (18.5%) The adducts were derivatised as described in Chapter 2 in order to determine ee. None observed.

## **CHAPTER 4**

### **THE USE OF PYBOX AND JACOBSEN LIGANDS IN THE LEWIS-ACID CATALYSED DIELS-ALDER REACTION**

## 4.1 INTRODUCTION

In this chapter the use of pyridine-*bis*-oxazolines (pybox) ligands, in the presence of niobium and tantalum, as chiral Lewis acid catalysts will be examined. The Jacobsen ligand was also used and compared with the pybox systems.

### 4.1.1 Development of the Pybox Ligand

The pyridine-*bis*-oxazoline (pybox) ligand possesses  $C_2$  symmetry which should make it ideal as a ligand in enantioselective reactions. The chirality is generally derived from optically active amino alcohols.

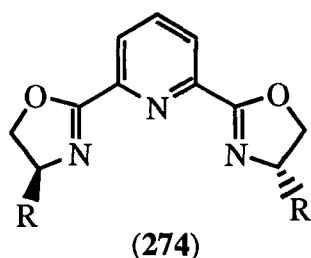
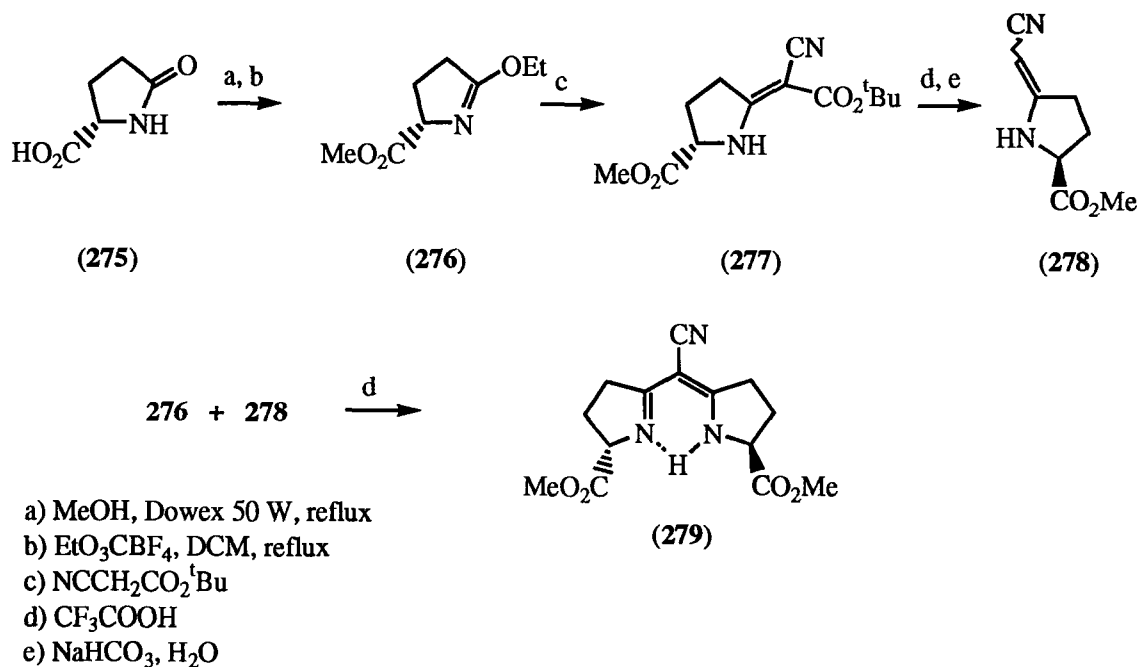


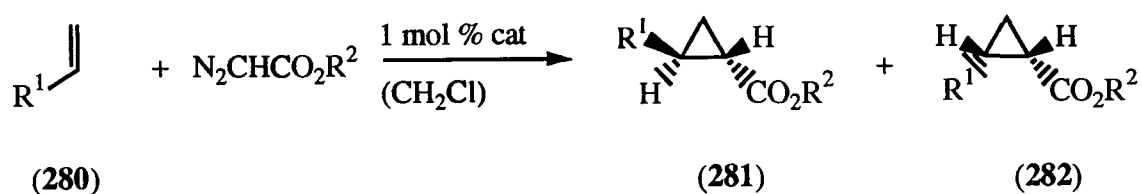
Figure 79

This class of ligand has evolved from bidentate oxazoline ligands which in turn were a progression from semicorrins.<sup>136</sup> Pfaltz introduced this class of ligand in the mid 1980's and applied it successfully to a number of transition-metal catalysed reactions. The structure of the semicorrin and a typical synthesis are shown in Scheme 90.<sup>137</sup>

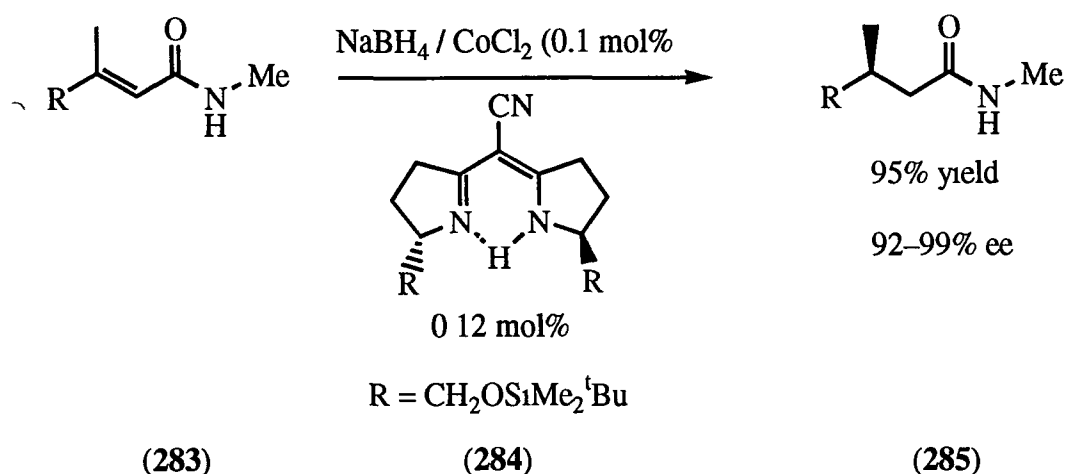


Scheme 90

Two of the major reactions to which these ligands were applied were the copper-catalysed cyclopropanation of olefins,<sup>137,138</sup> (Scheme 91) and the cobalt-catalysed conjugate reduction of  $\alpha, \beta$ -unsaturated carboxylic acid amides<sup>139</sup> (Scheme 92)



Scheme 91



Scheme 92

In 1990 Masamune *et al.* described the use of *bis*-oxazoline complexes in the Cu-catalysed asymmetric cyclopropanation of olefins with diazoacetates.<sup>140</sup> Some of the ligands used are shown in Figure 80.

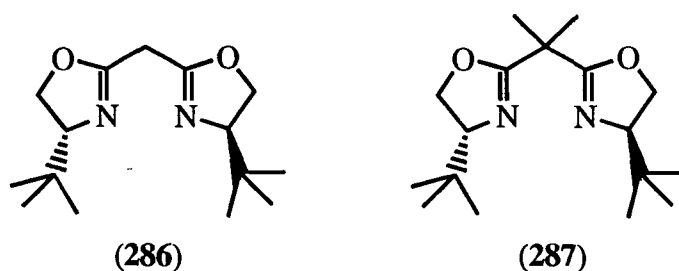
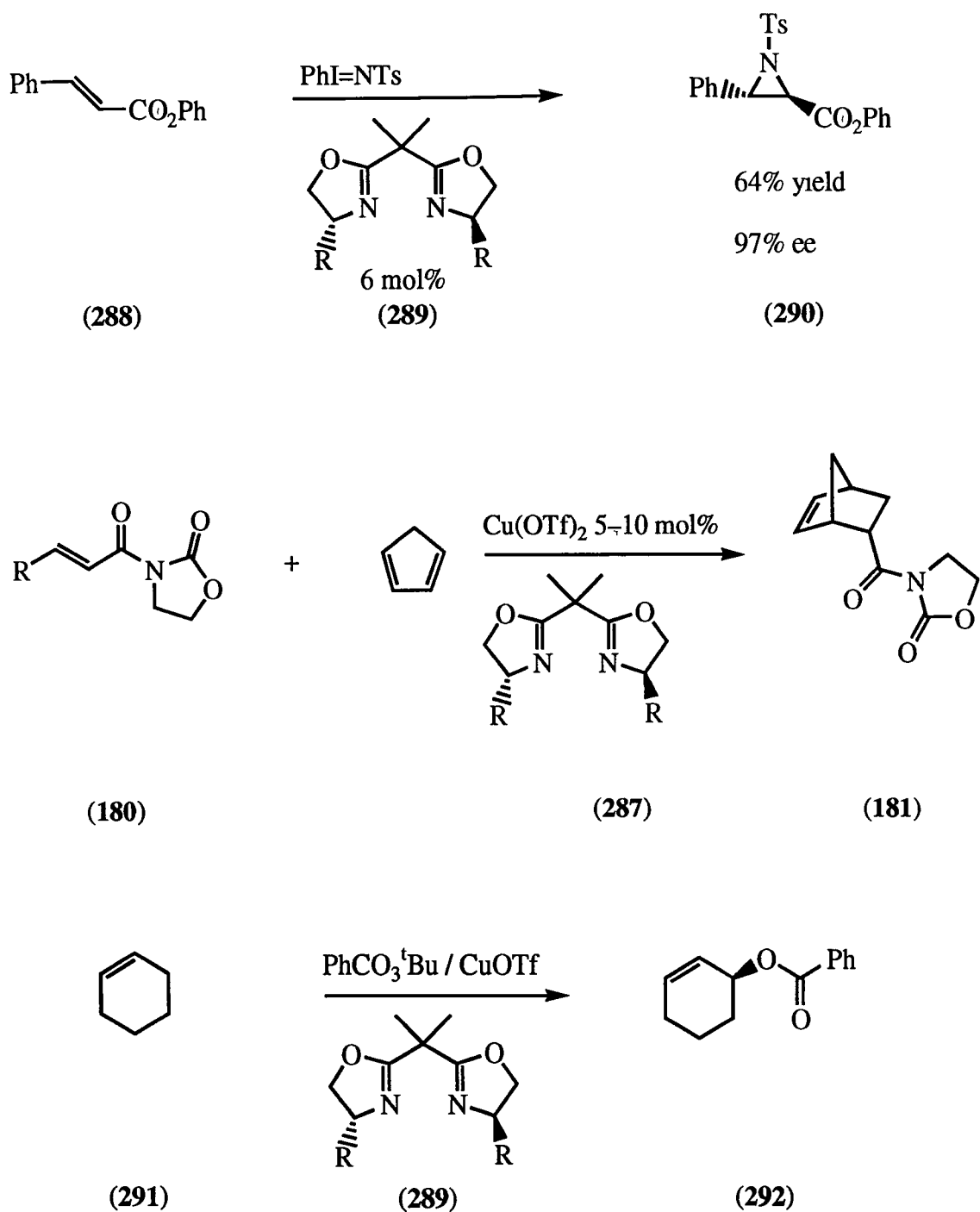


Figure 80

Since then *bis*-oxazolines have been used in a variety of reactions, including aziridinations,<sup>141</sup> Diels–Alder reactions,<sup>142</sup> and the allylic oxidation of olefins producing allylic esters<sup>143</sup>

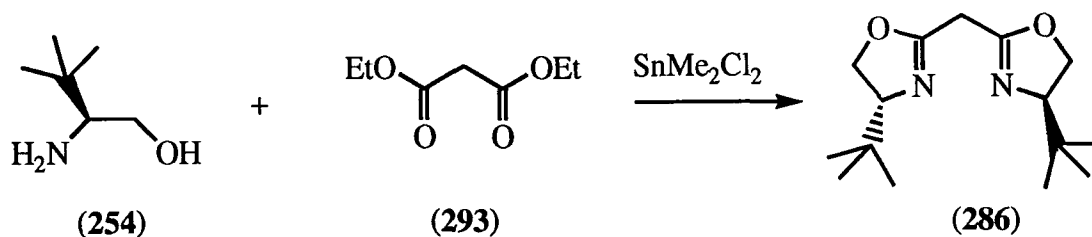


Scheme 93

Around the same time, Nishiyama *et al.* Described the synthesis of tridentate pybox ligands and their use in the enantioselective hydrosilylation of ketones.<sup>144</sup> This group, and others, have applied the ligand to a range of stereocontrolled reactions including Cu-catalysed cyclopropanation using diazoacetates,<sup>145</sup> Rh-catalysed dehydrogenative silylation of ketones using bifunctional organosilanes,<sup>146</sup> Cu-catalysed Diels–Alder reactions<sup>120</sup> and in the chirality recognition of 1,1-bi-2-naphthol.<sup>147</sup>

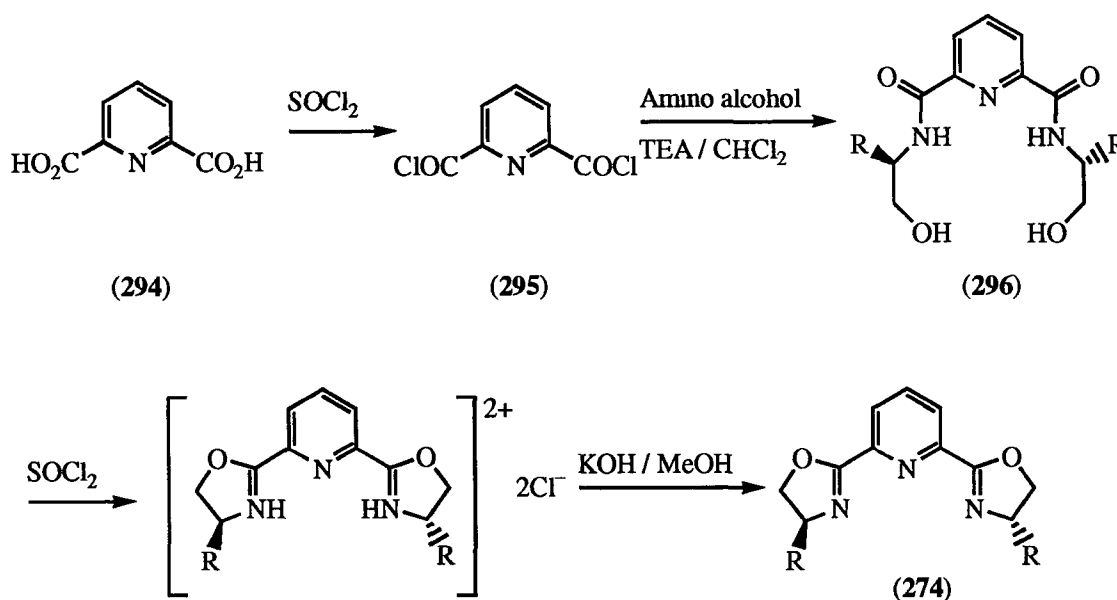
## 4.1.2 Oxazoline and Pybox Synthesis

Masamune synthesised the original *bis*-oxazoline ligands *via* the following route:-



Scheme 94

The first pybox ligands synthesised by Nishiyama *et al.* were described as being formed by the route shown in Scheme 95

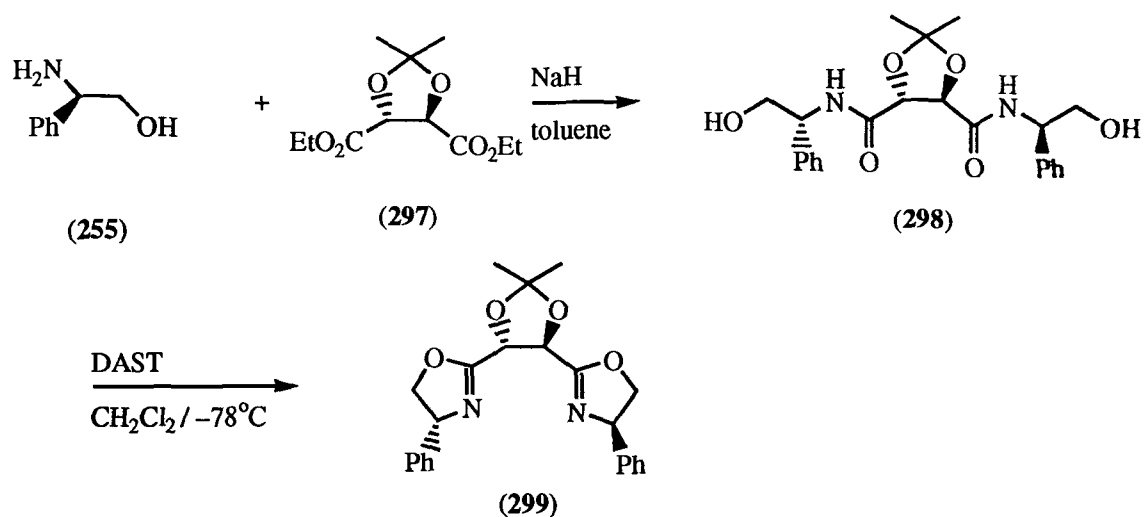


Scheme 95

This synthesis has been much used by other groups. Of those using different synthetic methods, the amido alcohol (296) is a frequent common intermediate. In a synthesis by Corey, dimethyl malonyl chloride was reacted with the desired amino alcohol and the ring closure was effected by heating in  $\text{CH}_2\text{Cl}_2$  under reflux in the presence of five equivalents of methanesulphonic acid.<sup>148</sup>

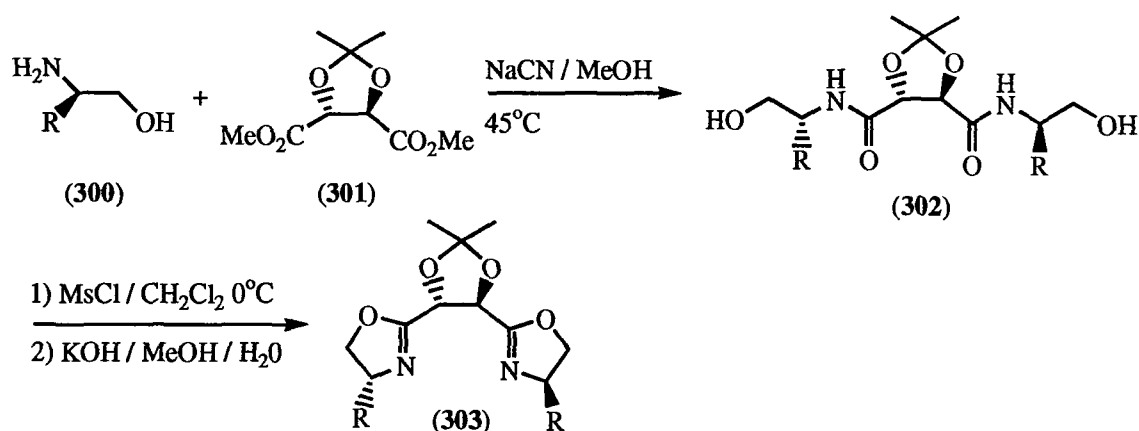
At roughly the same time, two groups published syntheses of *bis*-oxazoline ligands based on isopropylidene tartrates. Knight *et al.* used a strategy involving nucleophilic attack on a tartrate ester followed by low-temperature ring-closure of the amido alcohol using diethylammosulphurtrifluoride (DAST).<sup>149</sup>





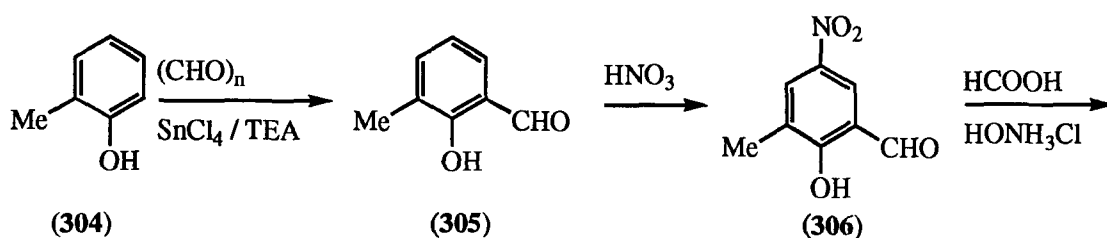
Scheme 96

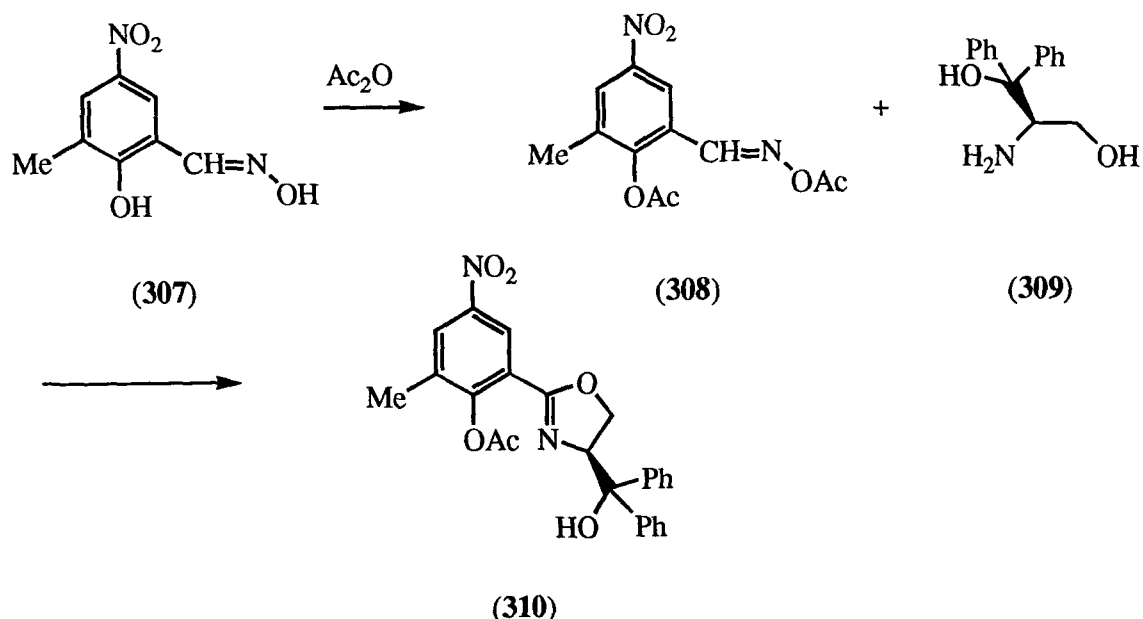
Bedeker *et al.* used a cyanide-catalysed transamination to form the amido alcohol followed by reaction with methanesulphonyl chloride (MsCl) at 0°C in the presence of base.<sup>150</sup> As with the Nishiyama method, this was followed by stirring in methanolic base. Both L- and D-tartrate were used.



Scheme 97

Salicyloxazolines were used in enantioselective Cu-catalysed cyclopropanation.<sup>151</sup> The method of formation of the oxazolme ring in this scheme was significantly different.

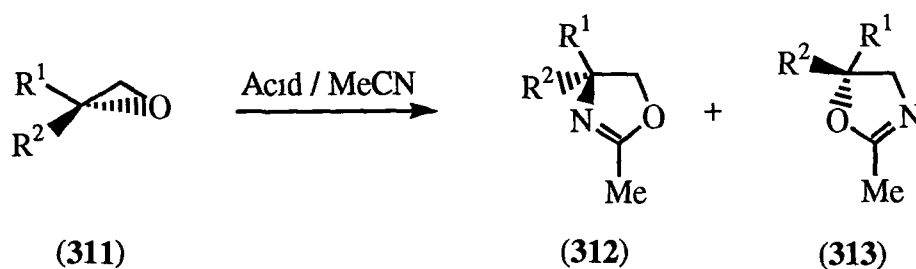




**Scheme 98**

Using a method developed by Casnati *et al*,<sup>152</sup> 2-methyl phenol was formylated, followed by nitration and formation of the oxime (307). Addition of acetic anhydride gave product (308) which was reacted with the serine derivative (309). Basic work-up yielded the desired product (310).

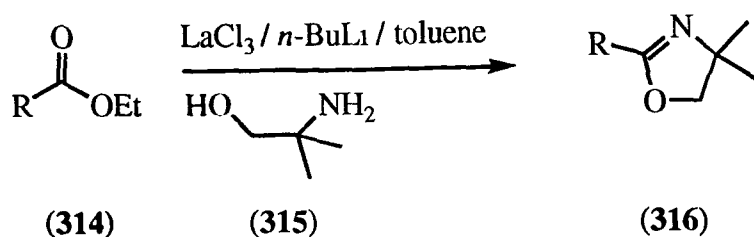
Oxazolines have been synthesised from optically active epoxides<sup>153</sup>. The procedure is very simple but not always selective. It involves an acid-catalysed reaction of the epoxide with acetonitrile.



**Scheme 99**

The nature of the substituents  $\text{R}^1$  and  $\text{R}^2$  and that of the acid greatly influenced the regioselectivity and stereoselectivity. The use of  $\text{AlCl}_3$  generally promoted high stereoselectivity when compared with protic acids. Due to poor regioselectivity, however, this method does not provide a viable alternative to other methods of oxazoline synthesis.

A direct one-pot synthesis of oxazolines from carboxylic esters, using lanthanum trichloride as catalyst, has been described<sup>154</sup>. No reaction mechanism is proposed in the communication but in two cases, an intermediate amido alcohol was isolated.



Scheme 100

There are a variety of methods available for the formation of this functionality. However, some procedures would appear to be more robust than others.

### 4.1.3 Oxazoline Ligands in Lewis-Acid Catalysed Reactions

The most common reaction in the literature, using oxazoline ligands, is the Cu-catalysed cyclopropanation of olefins. However, some Lewis-acid catalysed reactions, particularly the Diels–Alder reaction, have also been undertaken. Corey's group initially demonstrated the usefulness of the ligand in this area by catalysing the formation of (181) from (180) and cyclopentadiene in the presence of the FeI<sub>2</sub> salt (317) in 82% ee.<sup>155</sup>

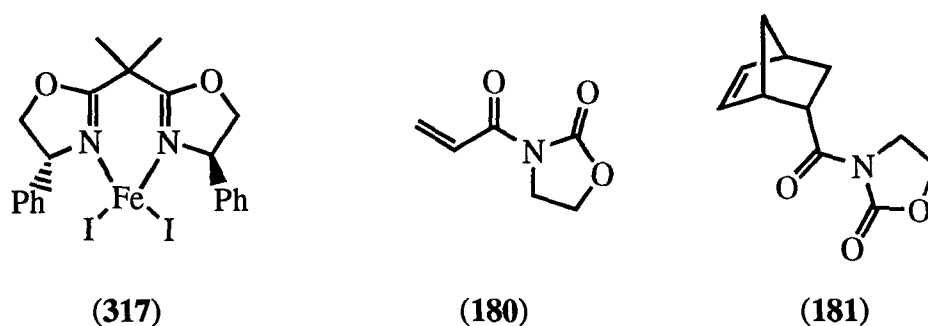
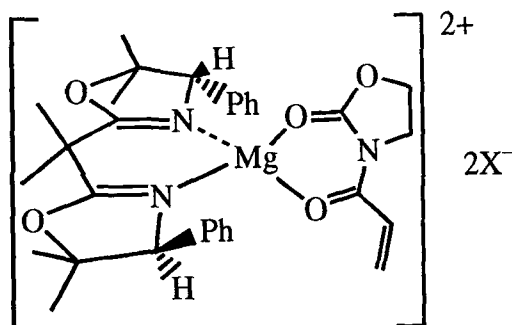


Figure 81

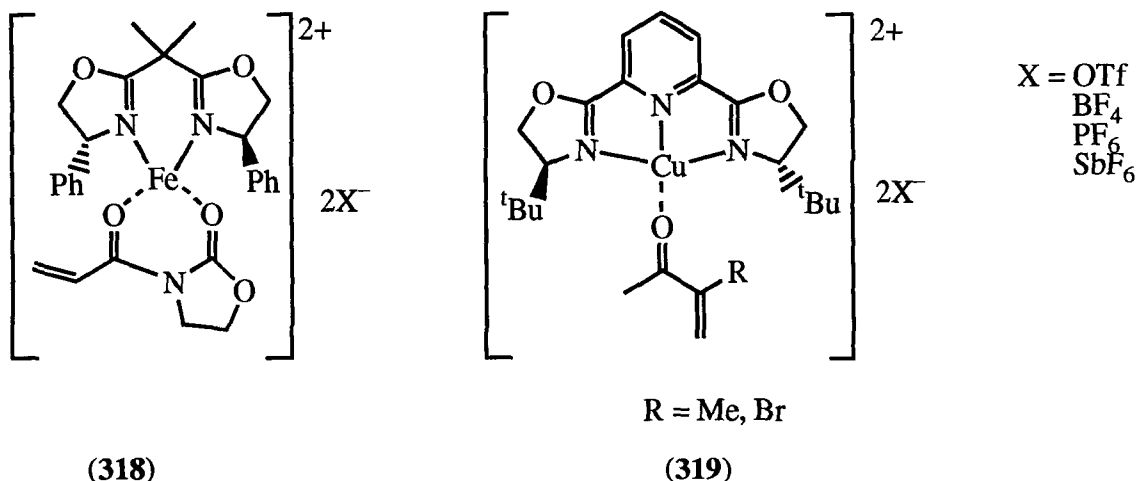
This system was further developed by employing a more rigid oxazoline ring and the use of magnesium, a weak Lewis acid. The structure below was proposed as the transition state substrate–catalyst complex.<sup>148</sup>



**Figure 82**

Iodine, sodium tetraphenylborate or silver antimony hexafluoride were used as co-catalysts and it was found that they enhanced the selectivity notably. In their presence 90, 91 and 91% ee's were achieved, respectively, compared to 80% in their absence.

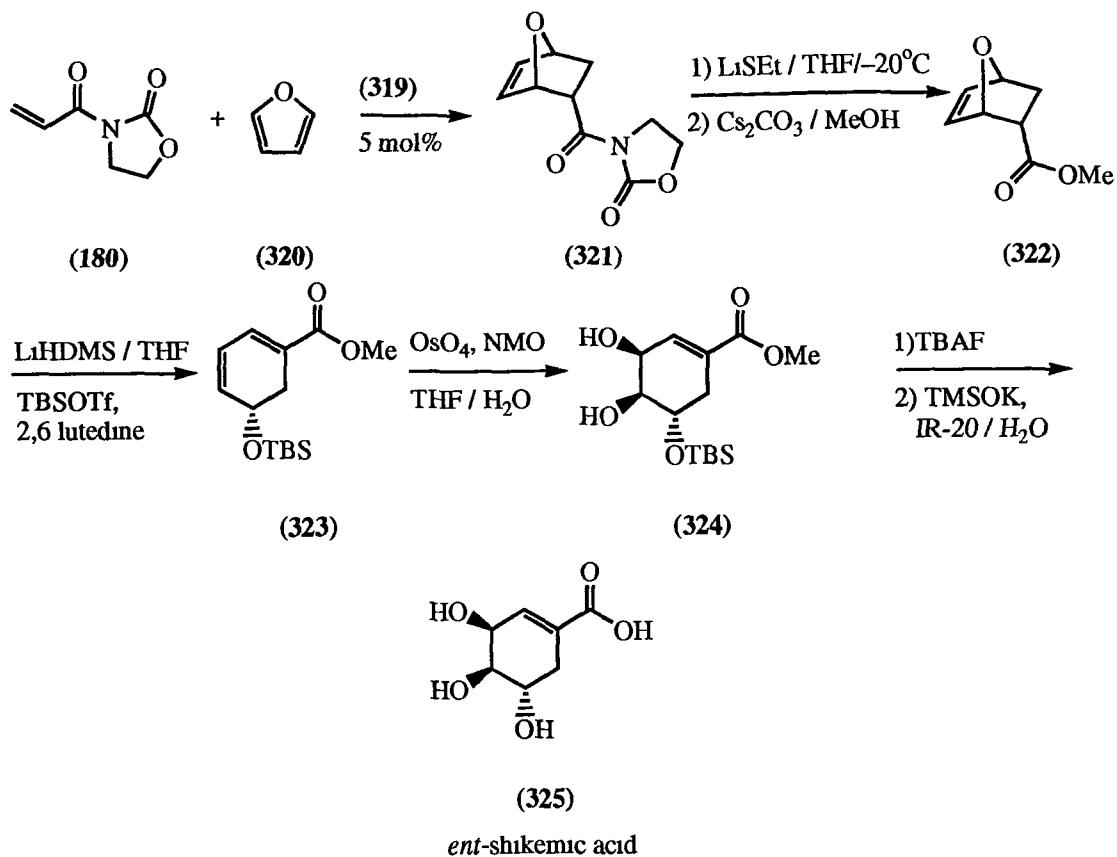
The Evans group were also involved in the promotion of the Diels–Alder reaction as described above<sup>153</sup> They developed this work using pybox ligands and also examined the effect of using various counterions.<sup>120</sup> The group proposed a square-planar coordination with either bidentate or monodentate dienophile co-ordination, depending on which substrate was used.



**Figure 83**

A rate enhancement was observed when counterions were used with SbF<sub>6</sub><sup>-</sup> giving 100% reaction in 8 h in the case of (319)

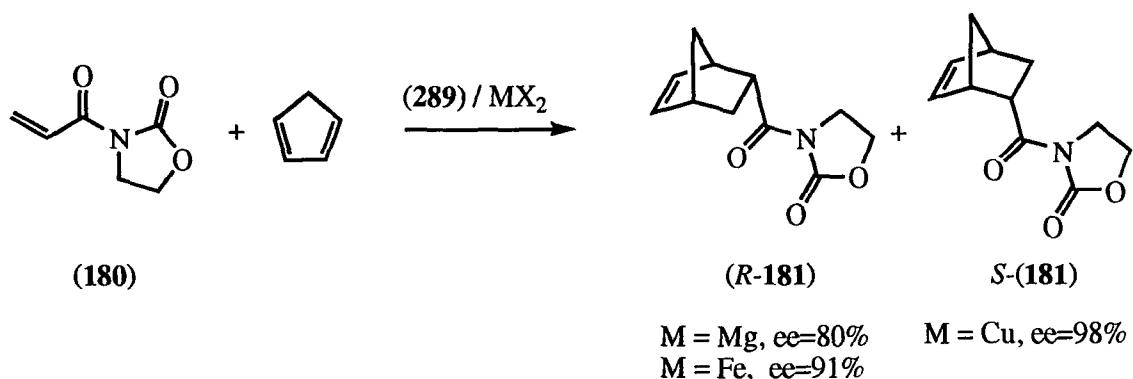
The catalyst (318), in the presence of AgSbF<sub>6</sub> was used to promote a Diels–Alder reaction between (180) and furan as an initial step in the synthesis of shikemic acid<sup>156</sup>



Scheme 101

Thus the test reaction for enantioselectivity was directly applied to a natural product synthesis.

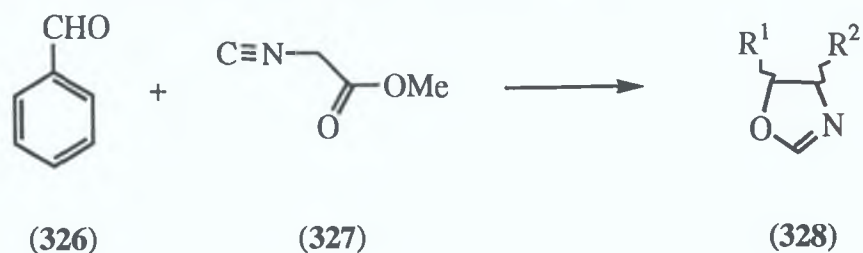
A paper from an Italian group pointed out that, in the Diels–Alder reaction between cyclopentadiene and (180), the orientation of the product could be reversed if a different metal was used, even if the same enantiomer of ligand was employed<sup>157</sup>



Scheme 102

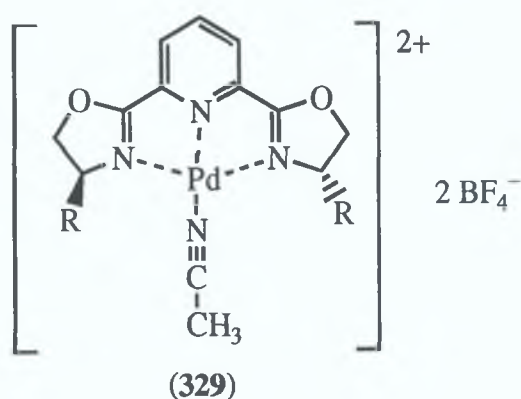
Using the substrate (180) in the presence of magnesium perchlorate they found that (*S*-181) was the major product. However, on addition of two equivalents of water to catalyst the major product was (*R*-181). This was rationalised on the basis that, in the presence of water, the initial square-planar system takes on an octahedral co-ordination, opening the *Re* face of the dienophile to attack.

Nesper *et al.* employed a dication Pd(II) species, in the presence of pybox ligand, to effect an aldol reaction between benzaldehyde and methyl isocyanoacetate.<sup>158</sup>



**Scheme 103**

Several ligands were employed, two of which were isopropyl and benzyl pybox, to give the catalyst (329).



**Figure 84**

Thus pybox and related ligands have been used in the catalysis of Lewis-acid promoted reactions and this appeared to be an interesting molecule to investigate in terms of niobium- and tantalum-catalysed Diels–Alder reactions.

## 4.2 RESULTS AND DISCUSSION

### 4.2.1 Ligand Synthesis

#### 4.2.1.1 Formation of Acid Chloride

According to the route of Nishiyama *et al.*, the acid chloride of pyridine 2, 6-dicarboxylic acid was first synthesised.<sup>144</sup> They achieved this by heating the acid under reflux in thionyl chloride for 10 h. Initially, milder conditions were favoured and the acid was stirred in chloroform in an excess of thionyl chloride. This produced no reaction. In the second attempt the acid was stirred in neat thionyl chloride at room temperature for 24 h and again no reaction occurred. A third attempt involved heating

under reflux in chloroform with an excess of thionyl chloride, and again there was no result. Finally the acid was boiled under reflux in neat thionyl chloride. An intractable black tar resulted.

The use of thionyl chloride was discontinued in favour of phosphorous pentachloride and a solid phase reaction. In this case pyridine 2,6-dicarboxylic acid was placed in a 50-ml round-bottom flask with two equivalents of  $\text{PCl}_5$ . The reactants were heated and stirred until liquefied and then heated under reflux for 30 min. The liquid  $\text{POCl}_3$  which resulted was distilled off and the remaining semi-solid left under vacuum overnight. Yield of the crude solid was high (96%), and it was easily recrystallised from benzene:PE to give the pure material in about 50% overall yield.

#### 4.2.1.2 Nishiyama Method

Initially the Nishiyama method for synthesising pybox was followed. This involved reaction of the acid chloride and amino alcohol (*S*-valinol) at  $0^\circ\text{C}$ , in the presence of base, to form the amido alcohol which was not isolated but further reacted with 10–15 equivalents of thionyl chloride, this time under reflux for 2 h. The reaction was then quenched in ice-water and worked up. The initial paper describes a white powder at this stage, however in this case a brown gum was recovered. The material was chromatographed and then stirred in methanolic NaOH for 72 h. The resulting crude material was purified by column chromatography to yield a very small amount of product (400 mg). The proton NMR of the material contained the peaks described in the literature but demonstrated that the material was not pure. The method was repeated using *S*-valinol, however, no product matching the desired compound was recovered.

The reaction was subsequently attempted using phenylglycinol and phenylalaninol as amino alcohols. There was a variation in the method used with phenylalaninol. Instead of using  $\text{SOCl}_2$  to convert the amido alcohol to the oxazoline ring, two equivalents of  $\text{PCl}_5$  were added and the solid state reaction was heated with consequent melting. The liquid was then heated under reflux. In the case of both of these reactions one major product was isolated. For phenylglycinol this was 15% yield and for phenylalaninol this was 23% yield. Comparison with literature values for spectroscopic data demonstrated that these were not the desired pybox ligands.

Reasonable purity was achieved in both cases and it could be seen from NMR that there were aromatic protons present for both the phenyl groups of the amino alcohols and the pyridine ring. Significantly absent were the expected peaks for the oxazoline ring. There were, however, peaks at 4.00 and 5.57 ppm for the phenyl compound and at 3.06 and 4.67 ppm for the benzyl compound. Possibly most striking was the difference in the carbonyl stretch in IR. The literature values were in the region of  $1630\text{ cm}^{-1}$  whereas these compounds showed stretches at  $1679$  and  $1688\text{ cm}^{-1}$ , respectively. This indicated that the amide functionality was still intact. However, it was evident from TLC that these were not the intermediate amido alcohols. A simple halogen test was performed on each, whereby a quantity of the compound was dissolved in MeOH and added dropwise to an aqueous solution of  $\text{AgNO}_3$ . The resulting cloudiness confirmed the presence of halogen and led to the conclusion that the compound recovered was (330).

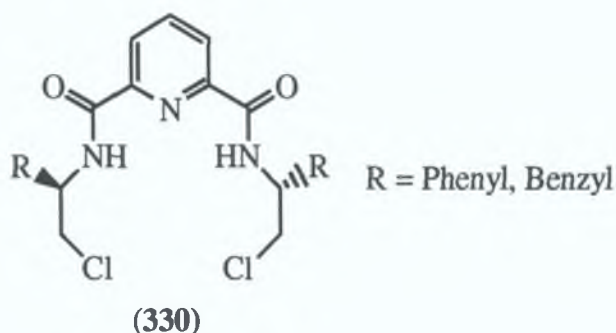


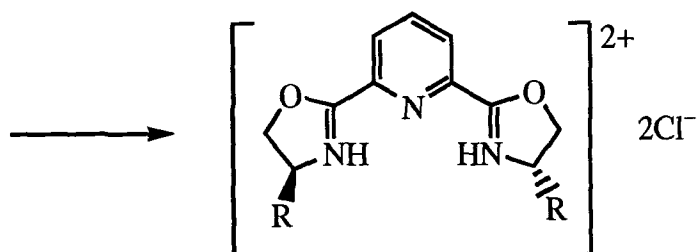
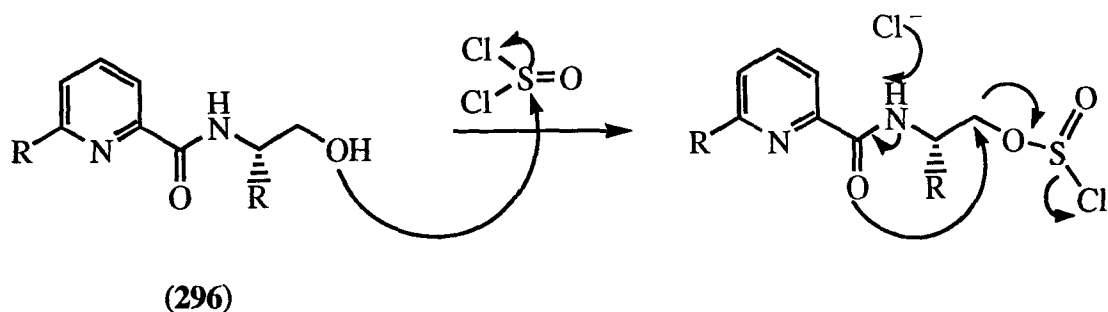
Figure 85

A ring closure of benzyl-(330) was then attempted. A small quantity of (330) was dissolved in acetone and ten equivalents of NaI were added and the solution heated under reflux for 4 h. A large excess of dry TEA was then added and heating under reflux continued for 2 days until TLC had revealed the disappearance of (330). The reaction mixture was purified by column chromatography and the major component isolated. The spectroscopic data matched the literature values for benzyl pybox.<sup>158</sup> However the overall yield of the method was very poor and not viable in view of the amount of ligand required.

The mechanism of the Nishiyama synthesis was claimed to go according to Scheme 104. This assumes that the material recovered from work-up after reflux in  $\text{SOCl}_2$  was

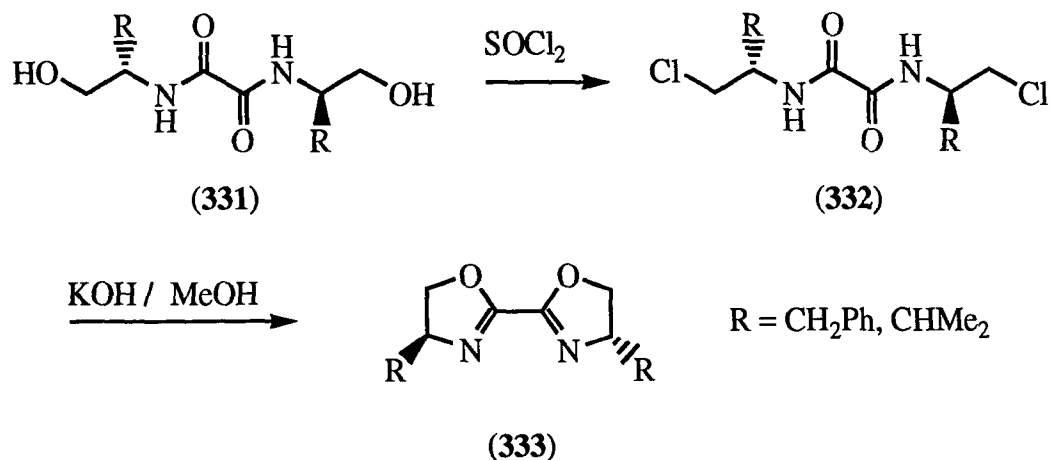


the HCl salt of the pybox ligand. There was, however, no evidence presented to support this.



Scheme 104

An obvious reaction pathway is that  $\text{Cl}^-$  will nucleophilically attack the carbon  $\alpha$  to the  $-\text{O}-\text{SOCl}$  leaving group, rather than act as a base. This is indeed what occurred in the formation of (330). Denmark *et al.* effected the ring closure of oxazoline (333) and actually recovered and characterised the chloro-amido compound (332) in so doing.<sup>159</sup>



Scheme 105

This seems a more likely mechanism as the base-catalysed removal of the N-H proton can effect ring closure more easily. Comparison of benzyl-(332) and benzyl-(330) NMR data showed some similarities. This, along with the halogen test and the ring closure reaction on (330) to form pybox ligand tends to confirm the proposed structure of the isolated material.

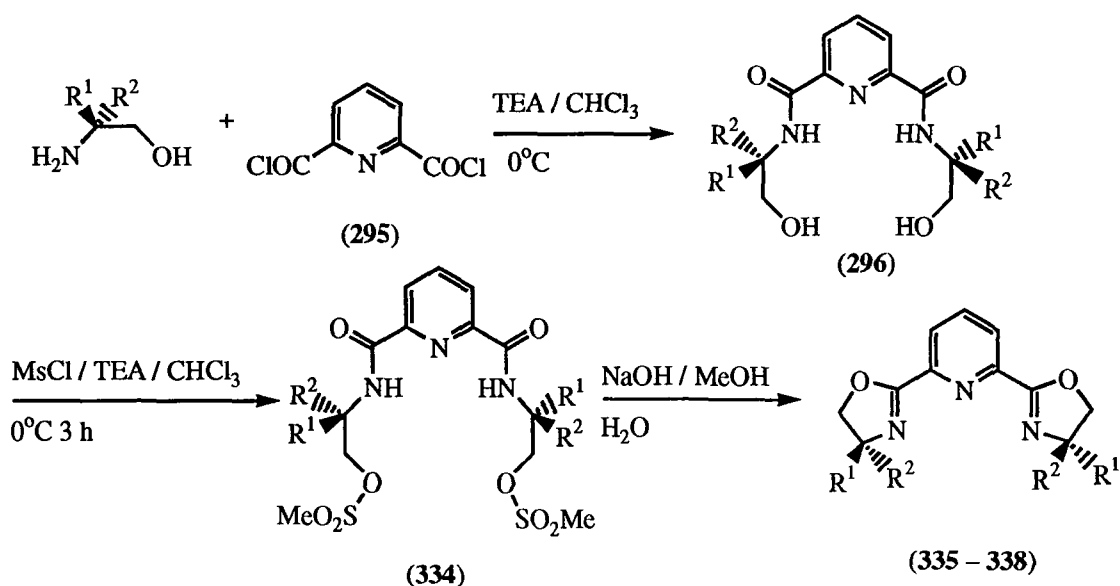
#### 4.2.1.3 One-Pot Method

A one-pot synthesis of oxazolines, described in the literature,<sup>154</sup> seemed to be an attractive alternative to the Nishiyama procedure. This method, described in Scheme 100, required the ester of pyridine 2,6-dicarboxylic acid. This was synthesised by heating the acid under reflux in toluene in the presence of 1.1 equivalents of *p*-toluenesulphonic acid and a large excess of ethanol. The crude product was a yellow oil from which crystals formed in an overall yield of about 40%.

Phenylglycinol,  $\text{LaCl}_3$  and toluene were mixed and cooled to  $0^\circ\text{C}$  and butyl lithium added. This was stirred and eventually heated to reflux whereupon the ester was added. The reaction was carried out overnight. On work-up it was found that a large number of products were formed. Although some were isolated, none could be identified. The oxazoline and the amido alcohol, both seen in the original paper, were not observed here. The method was abandoned.

#### 4.2.1.4 Mixed Synthetic Method

The synthetic difficulties in the formation of pybox ligand could be identified as a failure to effect ring closure of the amido alcohol *via* the use of  $\text{SOCl}_2$  followed by base. Thus, an alternative ring-closure method was sought as, evidently, the formation of the amido alcohol did not present any difficulties. Bedekar *et al.* used a strategy for tartrate oxazoline synthesis which involved reacting the amido alcohol with mesyl chloride in the presence of base at low temperature ( $0^\circ\text{C}$ ).<sup>152</sup> This system was employed in the synthesis and the desired pybox ligands were achieved. The overall general procedure is shown below.



Scheme 106

Purification was achieved by column chromatography in two dimensions. The first column used DCM:MeOH:TEA (95:5:3) and the second used DCM:DEE:TEA (60:40:3). An important factor in the recovery of the pybox ligands was the addition of base to the mobile phase during chromatography. Although TLC showed the desired spot, it was found that the flash-chromatography procedure gave different chromatographic behaviour. Addition of base solved this. It is possible that in the initial procedure, using the Nishiyama method, the desired pybox ligand remained on silica and was not recovered. However, the high yield of chloro amide suggests that there was also difficulty in effecting ring closure. The ligands formed were as shown in Table XVI. The amino alcohols were synthesised as described in Chapter 3 or were purchased from Aldrich.

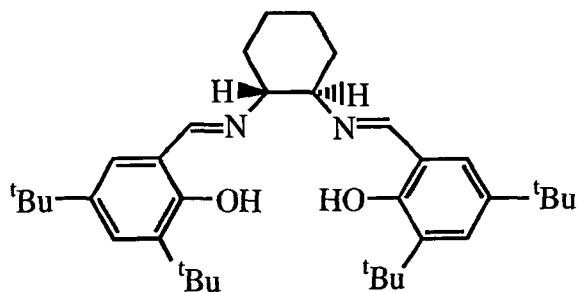
**Table XVI: Pybox ligands synthesised**

Ligand	Amino alcohol	R <sup>1</sup>	R <sup>2</sup>	Yield(%) <sup>a</sup>	R <sub>f</sub> <sup>b</sup>
(335)	S-Valinol	<i>t</i> -Pr	H	26	0.64
(336)	S-Isoleucinol	<i>t</i> -Bu	H	50	0.68
(337)	R-Phenyglycinol	H	Phenyl	47	0.75
(338)	S-Phenylalaninol	Benzyl	H	26	0.80

a Compared to amount of acid chloride

b Mobile phase = DCM:DEE:TEA (60:40:3)

The pybox ligands, along with the Jacobsen ligands (**339** and **340**), were then used as chiral directing agents in the Lewis-acid catalysed Diels–Alder reaction. The Jacobsen ligand has been used in Lewis-acid reactions, namely the Cr-catalysed ring-opening of epoxides whereby substantial ee was achieved.<sup>160</sup> It has also been used with Cr in a hetero Diels–Alder reaction<sup>161</sup> and with Al in the catalytic hydrocyanation of imines.<sup>162</sup> In addition, Bedekar *et al* have designed their tartrate ligands on the basis that the isopropylidene backbone is out of the plane (**307**) “blocking” one face of the catalyst.<sup>150</sup> It was believed that a comparison of this type of system, provided by the cyclohexyl ring of the Jacobsen ligand, with the flat pyridine ring of pybox might prove interesting.



(339 = *R, R*-Jacobsen ligand)

(340 = *S, S*-Jacobsen ligand)

Figure 86

#### 4.2.2 Synthesis of the Complexes

The pybox and Jacobsen ligands were complexed with the metal chlorides by forming a suspension of  $MCl_5$  in dry DCM under argon followed by slow addition of ligand. On addition of pybox ligand the suspension of metal chloride clarified and on continuous stirring overnight a green solution formed. It was possible to isolate some of those formed and perform some analyses. A  $^1H$  NMR spectrum of the isobutyl pybox (337) complex with  $NbCl_5$  was achieved. It was not entirely pure but there were noticeable differences between ligand and complex.

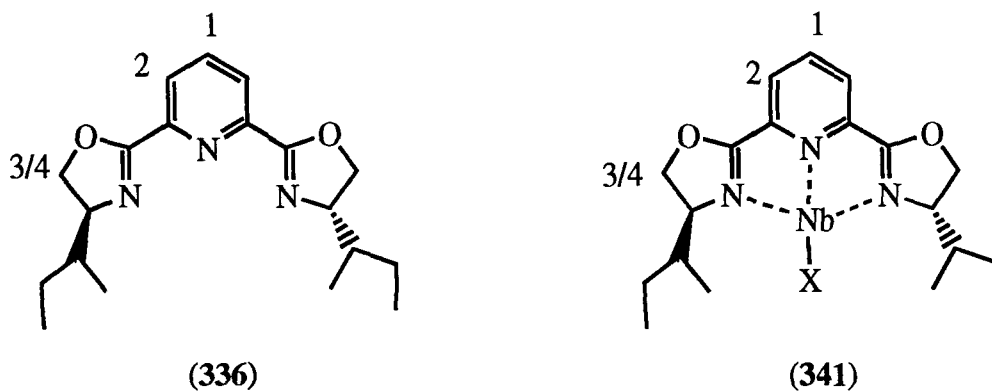


Figure 87

In the aromatic region the peak for proton 2 remains in the same position. However, in the complex, there are peaks at 8.61 and 9.61 ppm whereas the peak at 7.91 ppm in the ligand has disappeared. In the ligand the oxazoline peaks at 4.06, 4.39 and 4.57 ppm (with integration of 2 at each peak) are split into six separate peaks in the complex. There were broad singlets at 4.60, 4.75, 4.96 and 5.65 ppm and doublets of doublets at 3.73 and 3.95 ppm. The signals for the butyl side-chains showed broader peaks. The change in the oxazoline peaks was probably due to lack of free rotation of the rings. In the IR spectrum the C=N stretch at  $1638\text{ cm}^{-1}$  in the ligand was at  $1655\text{ cm}^{-1}$  in the complex, probably due to the nitrogen involvement in a dative bond with the metal.

A sample of the complex of *R, R*-Jacobsen ligand and NbCl<sub>5</sub> was recovered. The initially red solution was passed through silica whereupon an orange solution was observed. This was recrystallised from DCM whereupon yellow needles were recovered. The <sup>1</sup>H NMR of the complex differed from the ligand, mostly in the aromatic region. The peaks for the aromatic protons were at 6.99 and 7.30 ppm in the ligand and spread out between 7.16 and 8.40 ppm in the complex, presumably due to lack of free rotation. The imine proton was shifted from 8.31 ppm to 9.43 ppm and was significantly broadened. It was not integrating as 1 and therefore might be exchanging. The aromatic region integrated 4:36 with the aromatic butyl substituents but the imine integrated as 0.5. The peak for the proton on the carbon α to the *N*-atom was shifted downfield in the complex, from 3.32 to 4.99 ppm, and was significantly broadened. The IR spectrum of the ligand showed a broad OH stretch at 3431 cm<sup>-1</sup>, aromatic and aliphatic stretches at 2954 and 2868 cm<sup>-1</sup> and an imine stretch at 1623 cm<sup>-1</sup>. The OH stretch was not observed in the complex, the aromatic and aliphatic stretches were similar at 2961 and 2876 cm<sup>-1</sup> but the imine stretch was moved to significantly higher frequency at 1659 cm<sup>-1</sup>. There were also large stretches at 910 and 733 cm<sup>-1</sup> in the complex. However, electrospray mass spectrometry revealed the structure to have the following formula C<sub>36</sub>H<sub>52</sub>N<sub>2</sub>O<sub>2</sub>NbO. The CHN data were in agreement giving a structure which corresponds to (342).

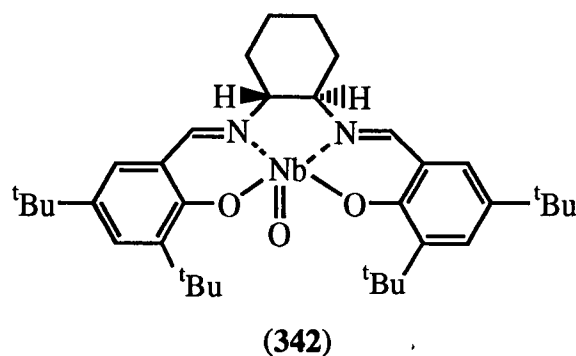


Figure 88

It is likely that the attempted recrystallisation of the complexes allowed water to react with the expulsion of HCl leading to the oxo complex above. In the case of reactions, no such exposure to the atmosphere was allowed and consequently it is believed that the original chloro species were the catalysts in the test Diels–Alder reaction.

### 4.2.3 Results

Tables XVII and XVIII show the results for the Diels–Alder reaction of cyclopentadiene with crotonaldehyde and methacrolein respectively, catalysed by niobium

**Table XVII: Diels–Alder reaction catalysed by niobium with crotonaldehyde as dienophile**

Ligand	Yield (%)	<i>Endo:Exo</i>	EE (%)
(335)	7.0	92:8	N/O
(336)	27.0	85:15	N/O
(337)	25.1	89:11	N/O
(338)	22.2	88:12	N/O
(339)	38.9	89:11	25 ( <i>R</i> )
(340)	28.0	85:15	27 ( <i>S</i> )

N/O = Not Observed

**Table XVIII: Diels–Alder reaction catalysed by niobium with methacrolein as dienophile**

Ligand	Yield (%)	<i>Endo:Exo</i>	EE (%)
(335)	12.1	7:93	N/O
(336)	40.0	10:90	N/O
(337)	67.8	11:89	11 ( <i>R</i> )
(338)	99.0 <sup>a</sup>	8:92	N/O
(339)	67.2 <sup>a</sup>	9:91	40 ( <i>R</i> )
(340)	49.1	10:90	38 ( <i>S</i> )

<sup>a</sup> Reaction carried on for 48 h instead of 24 h

Tables XIX and XX show the results for the Diels–Alder reaction using tantalum as Lewis acid and with crotonaldehyde and methacrolein as dienophiles, respectively.

**Table XIX: Diels–Alder reaction catalysed by tantalum with crotonaldehyde as dienophile**

Ligand	Yield (%)	<i>Endo:Exo</i>	EE (%)
(335)	N/R	–	–
(336)	N/R	–	–
(337)	15.0	82:18	10 (R)
(338)	18.7	84:16	N/O
(339)	N/R	–	–
(340)	N/R	–	–

N/R = No Reaction

**Table XX: Diels–Alder reaction catalysed by tantalum with methacrolein as dienophile**

Ligand	Yield (%)	<i>Endo:Exo</i>	EE (%)
(335)	N/R	–	–
(336)	N/R	–	–
(337)	33 <sup>a</sup>	9:91	25 (R)
(338)	25.3	14:86	N/O
(339)	N/R	–	–
(340)	N/R	–	–

Tables XXI–XXIV describe the Diels–Alder reactions, as above, with NH<sub>4</sub>PF<sub>6</sub> added as co-catalyst

**Table XXI: Diels–Alder reaction catalysed by niobium, in the presence of NH<sub>4</sub>PF<sub>6</sub>, with crotonaldehyde as dienophile**

Ligand	Yield (%)	<i>Endo:Exo</i>	EE (%)
(335)	18.1	85:15	N/O
(336)	39.2	87.13	N/O
(337)	70.8	88.12	N/O
(338)	35.3	87.13	N/O
(339)	58.1	76:24	19 ( <i>R</i> )
(340)	60.9	79.21	25 ( <i>S</i> )

**Table XXII: Diels–Alder reaction catalysed by niobium, in the presence of NH<sub>4</sub>PF<sub>6</sub>, with methacrolein as dienophile**

Ligand	Yield (%)	<i>Endo:Exo</i>	EE (%)
(335)	35.9	15.85	10 ( <i>S</i> )
(336)	87.1	8:92	10 ( <i>S</i> )
(337)	70.2	9.91	23 ( <i>R</i> )
(338)	55.9	10:90	N/O
(339)	86.0	7.93	40 ( <i>R</i> )
(340)	74.1	6:94	42 ( <i>S</i> )

**Table XXIII: Diels–Alder reaction catalysed by tantalum, in the presence of NH<sub>4</sub>PF<sub>6</sub> with crotonaldehyde as dienophile**

Ligand	Yield (%)	<i>Endo:Exo</i>	EE (%)
(335)	7.0	83.17	N/O
(336)	8.2	89.11	N/O
(337)	18.1	87:13	14 ( <i>R</i> )
(338)	44.9	80.20	N/O



(339)	45.1 <sup>a</sup>	81 19	11( <i>R</i> )
(340)	18 9	80 20	10 ( <i>S</i> )

**Table XXIV: Diels–Alder reaction catalysed by tantalum, in the presence of NH<sub>4</sub>PF<sub>6</sub> with methacrolein as dienophile**

Ligand	Yield (%)	<i>Endo:Exo</i>	EE (%)
(335)	11.0	25.75	N/O
(336)	10.1	16 84	N/O
(337)	84.1 <sup>a</sup>	12.88	25 ( <i>R</i> )
(338)	83.9	14.86	N/O
(339)	72.1 <sup>a</sup>	4.96	29 ( <i>R</i> )
(340)	53 8	2.98	31( <i>S</i> )

Tables XXV and XXVI show the use of niobium and tantalum as Lewis acid, methacrolein as dienophile and the addition of activated and unactivated 4Å molecular sieves, respectively, to the reaction mixture.

**Table XXV: Diels–Alder reaction using methacrolein as dienophile in the presence of activated 4Å molecular sieves**

Metal	Ligand	Yield (%)	<i>Endo:Exo</i>	EE (%)
Nb	(335)	43.1	2.98	52 ( <i>S</i> )
	(336)	35.2	6 94	20 ( <i>S</i> )
	(337)	40.8	2 98	35 ( <i>R</i> )
	(338)	32 6	3.97	17 ( <i>S</i> )
	(339)	60.4	7.93	55 ( <i>R</i> )
	(340)	46.0	8:92	48 ( <i>S</i> )
Ta	(339)	34 1	7.93	18 ( <i>R</i> )
	(340)	43.2	8 92	15( <i>S</i> )

**Table XXVI: Diels–Alder reaction using methacrolein as dienophile in the presence of unactivated 4Å molecular sieves**

Metal	Ligand	Yield (%)	<i>Endo:Exo</i>	EE (%)
Nb	(335)	67.7	7.93	31 ( <i>S</i> )
	(336)	54.1	6.94	N/O
	(337)	44.2	1.99	23 ( <i>R</i> )
	(338)	41.0	9.91	N/O
	(339)	65.9	7.93	35 ( <i>R</i> )
	(340)	34.1	8.92	28 ( <i>S</i> )
Ta	(339)	32.3	7.93	8 ( <i>R</i> )
	(340)	39.3	7.93	8 ( <i>S</i> )

A number of parameters were examined in the execution of the Diels–Alder reaction. According to Evans, in his Cu-catalysed Diels–Alder reaction, rate enhancement and dramatic improvements in ee were achieved when counterions were used, including OTf<sup>-</sup>, PF<sub>6</sub><sup>-</sup> and SbF<sub>6</sub><sup>-</sup>.<sup>120</sup> In addition, as discussed in Chapter 2, the use of molecular sieves has given varied results, with some groups claiming improved enantioselectivity with activated sieves,<sup>110</sup> while another found that unactivated sieves gave the best results.<sup>122</sup> Thus the use of NH<sub>4</sub>PF<sub>6</sub> as co-catalyst and that of activated and unactivated 4Å molecular sieves was examined. Other solvents, such as MeCN and THF were also investigated.

The enantiomeric excesses achieved using these ligands were significantly better than those seen in Chapter 3. In the standard reaction involving niobium it can be seen that ee was achieved using the Jacobsen ligand for crotonaldehyde and methacrolein as dienophiles and also using phenyl pybox (337) using methacrolein. The results were, however, quite low. Significantly (337) was the only ligand to give an ee with Ta in the absence of any additives to the reaction. This result is also the only tantalum-based reaction to give a better result than the niobium version.

The addition of NH<sub>4</sub>PF<sub>6</sub> (five equivalents) to the reaction caused an improvement in ee for the Nb-catalysed reactions of methacrolein with both (335) and (336) giving 10% (*S*). Interestingly (338), the benzyl pybox and largest of the substituents showed no

stereoenhancement. In terms of the crotonaldehyde reaction, little difference was seen. In the Ta-catalysed reactions, (337) gave good results and the Jacobsen ligands showed stereoselectivity, though not as high as that seen for Nb.

The use of activated molecular sieves caused a dramatic improvement in the ee's achieved using the pybox ligand, with (335), that with the smallest substituent, giving 52% (*S*). This is the first time an ee was observed using benzyl pybox (338). Again the *R,R*-Jacobsen ligand showed the highest result at 55% (*R*). The use of unactivated sieves gave lower enantiomeric excess but in the same order and orientation as with the activated. Butyl and benzyl pybox gave racemic products

Masamune *et al* reported that the order of enantioselective induction was dependent on the ligand substituent in the order *t*-Bu > phenyl > *i*-Pr > benzyl, where *bis*-oxazolines of the type (286) or (287) were used.<sup>140</sup> In this case, where pybox ligand was used and a comparison could be made, the order was phenyl > *i*-Pr = *t*-Bu > benzyl. However, the addition of molecular sieves changed that order to *i*-Pr > phenyl > *t*-Bu > benzyl. The difference between the *bis*-oxazoline and the pybox ligands might be attributed to different "bite angles".<sup>150</sup>



Figure 89

The relative position of the metal to the substituent is quite different and thus the manner in which it influences the co-ordination of the metal by substrate will also be different. In addition, Nb and Ta are significantly larger atoms than Cu, which Masamune used, and again the relative position of the substituent and the metal will be affected by this factor. The addition of counterion did not affect the ee as much as the addition of activated molecular sieves. The activated sieves improved the ee in the case of the pybox ligands considerably and this may be due to the removal of adventitious water. Great pains were taken to maintain an inert atmosphere for the reactions, but it is possible that some moisture was present. This might have the effect of altering the co-ordinative structure of the complex, by addition of one or more molecules of water, as described by Desimoni *et al*<sup>157</sup>

The Jacobsen ligand gave better ee than any of the pybox ligands except for the example mentioned above. This can reasonably be attributed to the fact that the metal centre of its complex is more enclosed and backed by a cyclohexyl ring which is non-planar as opposed to the planar pybox ligand.

The *endo:exo* ratios in the standard reaction were generally observed to be lower for crotonaldehyde. This is in contrast to the results observed in Chapters 2 and 3. The ratio actually disimproves for crotonaldehyde on addition of  $\text{NH}_4\text{PF}_6$ , in the cases of both Nb and Ta. In the case of methacrolein as dienophile, a slight drop is observed for Nb-catalysed reactions whereas results using Ta were variable. The pybox ligands in this case showed 25:75–12:88 as the range of selectivities whereas *R, R*- and *S, S*-Jacobsen ligand showed *endo:exo* ratios of 4:96 and 2:98, respectively (Table XXIV).

The yields of the reactions were influenced by a number of factors. In the case of Ta, no reaction occurred for four out of six complexes where no additions were made to the reaction mixture. This is in contrast to Nb where 99% yield was achieved when the reaction was allowed to proceed for 48 h (Table XVIII, entry 4). The addition of  $\text{NH}_4\text{PF}_6$  caused a dramatic difference to the Ta-catalysed reactions and also an overall increase in yield in the Nb-catalysed adduct formation. This is consistent with the findings of Evans.<sup>120</sup> It was most obvious where crotonaldehyde was used as dienophile and catalytic turnover was achieved in five out of six of the Nb-catalysed reactions (Table XXI) and in two out of six of the Ta-catalysed reactions (Table XXIII). The larger  $\text{PF}_6^-$ -counterion associating with the metal centre may cause product–catalyst binding to be weakened, leading to turnover. (For a discussion on the influence of product binding on turnover, see Chapter 2).

The addition of molecular sieves showed marginally higher yields for the unactivated variety when pybox ligand was involved. In terms of the Jacobsen ligands, the reaction involving Ta, which did not proceed in their absence, gave yields in the region 32–43%.

The use of THF and MeCN as alternative solvents was examined. It was found that in either case, whether additives such as  $\text{NH}_4\text{PF}_6$  or molecular sieves were involved or not, that the yield was never above 2–3%. In the presence of co-ordinating solvents, it would appear that Nb and Ta were unable to act effectively as Lewis acids.

Thus in the group V metal-catalysed Diels–Alder reaction, the choice of ligand, addition of counterion or molecular sieves and the choice of solvent greatly affected the yield, enantioselectivity and *endo:exo* ratio.

### 4.3 CONCLUSION

Semicorrins, bidentate and tridentate *bis*-oxazoline ligands are a relatively recent group of related chiral ligands which have been applied to numerous enantioselective reactions, particularly copper-catalysed cyclopropanations. The synthesis of pybox ligands was attempted according to a method proposed by Nishiyama *et al.*<sup>144</sup> In their synthesis they describe the formation of the HCl salt of the desired oxazoline which was then hydrolysed by stirring in methanolic NaOH. However it would appear that this is not in fact the mechanism and that the material described as a salt, though not characterised, was the intermediate chloro-amido material. This is supported by the work of Denmark *et al.* who isolated an analogue<sup>159</sup> and by the isolation of the material during the course of the work described in this chapter. The most productive method of forming the pybox ligands was found to be ring closure of the intermediate amido alcohol by addition of MsCl and base. The use of base in the chromatographic mobile phase, during purification, was important for recovery.

The use of pybox ligands as well as the *R, R*- and *S, S*-Jacobsen ligands in the Lewis-acid catalysed Diels–Alder reaction of cyclopentadiene with crotonaldehyde or methacrolein was examined. Niobium and tantalum were used as the Lewis acids. Complexes of niobium and one pybox ligand and *R, R*-Jacobsen ligand were isolated and examined. The complex with the Jacobsen ligand displayed a monomeric structure with one oxygen atom present on the metal. This was most likely the result of reaction between the chloro complex, initially formed, and atmospheric water.

In the Diels–Alder reaction, the Jacobsen ligand proved to be the most effective ligand at inducing chiral induction under almost all conditions. Of the pybox ligands, the phenyl was consistently most effective, except in the case of addition of activated molecular sieves where isopropyl pybox prevailed. The addition of  $\text{NH}_4\text{PF}_6$  caused a dramatic improvement in yield and, in some cases, ee also. The use of activated molecular sieves gave the highest results for chiral induction and the sense of induction was consistent with the orientation of the ligands throughout.

The results achieved using pybox and Jacobsen ligands, in terms of chiral induction are the most impressive of the ligand systems used. However, these results are not as high as those achieved with other metals, notably copper in the presence of  $\text{SbF}_6^-$ . Achieving substantial enantiomeric excess in the Diels–Alder reaction, using niobium and tantalum catalysts, has remained elusive

## 4.4 EXPERIMENTAL

The purification of solvents and the equipment used were described in Chapters 2 and 3

### 4.4.1 Ligand Synthesis

#### Formation of pyridine 2, 6-dicarboxyl chloride (A)

Pyridine 2,6-carboxylic acid (8.40 g, 0.050 mol) and  $\text{SOCl}_2$  (8.65 ml, 14.30 g, 0.120 mol) were placed in a 100-ml round-bottom flask with 50 ml of  $\text{CHCl}_3$  and stirred for 18 h. No reaction was observed so the mixture was heated under reflux for 18 h. No reaction was observed. Solvent was removed under reduced pressure and 60 ml of  $\text{SOCl}_2$  added. The reaction was stirred for 24 h. Starting material was recovered. The material was again stirred in thionyl chloride, this time with heating under reflux. After 6 h the solution had turned black. The  $\text{SOCl}_2$  was removed by distillation and an intractable black tar remained.

#### Formation of 2,6-pyridine dicarboxyl chloride (B)

Pyridine 2, 6-dicarboxylic acid (8.40 g, 0.050 mol) was mixed with  $\text{PCl}_5$  (23.00 g, 0.110 mol) in a 50-ml round-bottom flask and stirred with heating. When the mixture had become liquid it was boiled under reflux for 25 min. The resulting  $\text{POCl}_3$  was removed by distillation under reduced pressure. The semi-solid material was left under

vacuum overnight and recrystallised from benzene PE (2.3). A white crystalline powder resulted. Yield = 5.00 g (49.1%) m.p. 54–56°C (Lit 56–59°C) IR  $\nu_{\max}$  3011, 1672, 1214  $\text{cm}^{-1}$ .  $\delta_{\text{H}}[\text{CDCl}_3]$  showed the following signals:- 8.20 (1 H, t,  $J=7.9$  Hz), 8.37 (2 H, d,  $J=7.9$  Hz)  $\delta_{\text{C}}[\text{CDCl}_3]$  showed the following signals - 128.64, 139.06, 148.70

#### **Formation of 2,6-bis[4'-(*S*)-isopropylloxazolin-2'-yl]pyridine (335) (A)**

*S*-Valinol (4.50 g, 0.0436 mol) was dissolved in 100 ml  $\text{CHCl}_3$  in a 250-ml round-bottom flask and 20 ml of TEA (0.125 mol) added. The solution was cooled to 0°C and a solution of 2,6-pyridine dicarboxyl chloride (4.45 g, 0.022 mol) in 30 ml of  $\text{CHCl}_3$  added dropwise with continuous stirring under a stream of argon. This was stirred for 24 h. at room temperature. The solution was again cooled to 0°C and  $\text{SOCl}_2$  (25 ml, 41.34 g 0.338 mol) added. The mixture was heated under reflux for 3.5 h at which time the solution was black in colour. The contents were collected and then poured into ice-water. The organic layer was washed twice with brine and sat  $\text{Na}_2\text{CO}_3$ . It was dried over  $\text{MgSO}_4$  and the solvent removed under vacuum. Yield = 6.52 g.  $R_f$  of the main spot was at 0.80. The material was chromatographed using DCM:DEE (3:2). The most pure fractions were combined and the material dissolved in methanolic NaOH (12 g of NaOH in MeOH:water (3:2)). This was stirred for 72 h. The mixture was extracted with 3 x 30 ml of DCM. The organic fractions were combined and washed with brine. The solvent was dried over  $\text{MgSO}_4$  and the solvent removed under vacuum. Yield = 1.33 g and showed four spots on TLC. One of these spots matched the literature value of  $R_f=0.60$ . This spot was recovered. Yield = 0.34 g (5.42%) m.p. = 131–134°C (Lit. 152–153°C). IR  $\nu_{\max}$  1634  $\text{cm}^{-1}$ .  $\delta_{\text{H}}[\text{CDCl}_3]$  showed the following signals:- 0.92 (6 H, dd,  $J=6.9$  Hz), 1.02 (6 H, dd,  $J=6.8$  Hz), 1.84 (2 H, sept,  $J=6.9$  Hz), 4.13 (2 H, m), 4.19 (2 H, dd,  $J=7.9$  Hz), 4.50 (2 H, dd,  $J=7.9$  Hz), 7.81 (1 H, t,  $J=7.9$  Hz), 8.24 (2 H, d,  $J=7.9$  Hz). Impurities also present.  $\delta_{\text{C}}[\text{CDCl}_3]$  showed the following signals:- 18.9, 19.4, 33.1, 71.11, 75.13, 124.8, 137.00, 146.50, 163.21. These data matched the literature values closely<sup>144</sup>

#### **Formation of 2,6-bis[4'-(*S*)-isopropylloxazolin-2'-yl]pyridine (335) (B)**

*S*-Valinol (4.90 g, 0.048 mol) and pyridine 2,6-dicarboxyl chloride (4.41 g, 0.022 mol) were treated as described above. After addition of  $\text{SOCl}_2$ , reflux and aqueous work-up, the yield was 7.69 g. The material was chromatographed on silica gel using the mobile phase DCM:DEE (3:2). Recovery following column was 4.69 g. Methanolic NaOH

reaction carried out as before. 3.40 g of material recovered This material showed only aromatic peaks in  $^1\text{H}$  NMR

#### **Formation of 2,6-bis[4'-(R)-phenyloxazolin-2'-yl]pyridine (337) (A)**

R-Phenyglycinol (6.44 g, 0.047 mol) and pyridine 2, 6-dicarboxyl chloride (4.80 g, 0.024 mol) were treated as described above. The initial material (10 g) was purified by column chromatography using DEE:DCM (80:20) as mobile phase. The material collected was stirred in methanolic NaOH, as above, for 5 days. The product was extracted as above and the DCM layer was treated with decolourising charcoal twice. The recovered material was purified by column chromatography (DEE:DCM (80:20)) the purest fractions were combined. Crude yield = 1.30 g. Foam. IR  $\nu_{\text{max}}$  3313, 1687, 1535, 909, 733  $\text{cm}^{-1}$ .  $\delta_{\text{H}}[\text{CDCl}_3]$  showed the following signals:- 4.01 (4 H, d,  $J=9.9$  Hz), 5.57 (2 H, t,  $J=9.9$  Hz), 7.34–7.41 (10 H, m), 8.07, (1 H, t,  $J=7.9$  Hz), 8.37 (2 H, d,  $J=7.9$  Hz), 8.54 (2 H, d,  $J=7.9$ ).  $\delta_{\text{C}}[\text{CDCl}_3]$  showed the following signals - 68.05, 72.59, 125.79, 126.61, 128.61, 129.20, 137.41, 137.66, 146.72, 162.72. Halogen test positive. These data are consistent with structure phenyl-(330).

#### **Formation of 2,6-bis[4'-(S)-benzyloxazolin-2'-yl]pyridine (338) (A)**

S-phenylalaninol (7.41 g, 0.049 mol) and pyridine 2, 6-dicarboxyl chloride (5.00 g, 0.025 mol) were reacted as described above. No  $\text{SOCl}_2$  was added. Solvent was removed under vacuum. The resulting material was dissolved in  $\text{CHCl}_3$  and washed with water. The solution was dried over  $\text{MgSO}_4$  and the solvent removed under vacuum. Phosphorous pentachloride (10.72 g, 0.510 mol) was added and the mixture heated. When liquefied it was heated under reflux for 10 min. Dissolved in DCM and washed with water and base. Material was purified by column chromatography (DCM:DEE (20:80)) The purest fractions were combined and stirred in methanolic NaOH as above. Material worked up aqueously and chromatographed as above. Major product had  $R_f=0.80$ . Foam, yield = 2.62 g. IR  $\nu_{\text{max}}$  3416, 3337, 2933, 1679, 1520, 915, 727  $\text{cm}^{-1}$ .  $\delta_{\text{H}}[\text{CDCl}_3]$  showed the following signals:- 3.09 (4 H, t,  $J=8.9$  Hz), 3.68 (2 H, dd,  $J=3.0, 11.2$  Hz), 3.78 (2 H, dd,  $J=3.0, 11.2$  Hz), 4.65–4.72 (2 H, m,  $J=3.0, 8.8$  Hz), 7.26–7.35 (10 H, m), 8.05 (1 H, t,  $J=7.9$  Hz), 8.09 (2 H, d,  $J=7.9$  Hz), 8.34 (2 H, d,  $J=7.9$  Hz).  $\delta_{\text{C}}[\text{CDCl}_3]$  showed the following signals.- 37.57, 46.76, 50.72, 125.17, 126.97, 128.76, 129.22, 136.67, 129.18, 148.31, 162.66. Halogen test positive. These data are consistent with structure benzyl-(330)



### Formation of 2,6-bis[4'-(*S*)-benzyloxazolin-2'-yl]pyridine (338) (B)

Benzyl-(330) (0.50 g, 1.095 mmol) was placed in a 50-ml round-bottom flask and 20 ml of dry acetone was added. Sodium iodide (1.50 g, 10.00 mmol) were added and the solution heated under reflux for 4 h. Dry TEA, (10 ml, 63.0 mmol) were added and heated under reflux for 2 days. TLC (DCM:DEE (60:40)) showed the disappearance of starting material and a major spot at  $R_f=0.80$ . Column chromatography gave yield = 0.14 g (33.5%). White powder. m.p =150–152°C (Lit=156°C).  $\nu_{\max}$  3435, 2917, 1641, 700  $\text{cm}^{-1}$ .  $\delta_{\text{H}}[\text{CDCl}_3]$  showed the following signals.- 2.72–2.78 (2 H, dd,  $J=8.9, 4.9$  Hz), 3.25–3.29 (2 H, dd,  $J=8.9, 4.9$  Hz), 4.26 (2 H, dd,  $J=7.9$  Hz), 4.46 (2 H, dd,  $J=8.9$  Hz), 4.65 (2 H, m,  $J=5.9$  Hz), 7.24–7.33 (10 H, m), 7.90 (1 H, t,  $J=7.9$  Hz), 8.20 (2 H, d,  $J=7.9$ ).  $\delta_{\text{C}}[\text{CDCl}_3]$  showed the following signals -41.49, 53.45, 125.44, 126.56, 128.31, 128.90, 138.15, 139.39, 148.35, 162.75. Matches lit values<sup>158</sup>

### Formation of pyridine 2,6-dicarboxylic acid, diethyl ester.

Pyridine 2,6-dicarboxylic acid (11.53 g, 0.070 mol) was placed in a 250-ml round-bottom flask and 40 ml of EtOH added. A further 100 ml of toluene were added with 11.20 g of TsOH (1.1 equivalents). The mixture was boiled under reflux using Dean and Stark apparatus for 48 h. The solvent was removed and the remaining oil treated with sat. aq.  $\text{Na}_2\text{CO}_3$ . This solution was extracted with 4 x 50 ml of brine. Dried over  $\text{MgSO}_4$  and the solvent removed. Crude yield of oil 10.60 g (67.8%). Crystals then formed and these were collected and washed with PE. Yield = 5.58 g (25%).  $R_f=0.50$  (Mobile phase = DEE:DCM (80:20)). m.p =40–42°C. IR  $\nu_{\max}$  1710  $\text{cm}^{-1}$ .  $\delta_{\text{H}}[\text{CDCl}_3]$  showed the following signals,- 1.42 (6 H, t,  $J=14.8$  Hz), 4.46 (4 H, q,  $J=14.8$  Hz), 7.98 (1 H, t,  $J=7.9$  Hz), 8.25 (2 H, t,  $J=7.9$  Hz).  $\delta_{\text{C}}[\text{CDCl}_3]$  showed the following signals.- 14.17, 62.32, 127.81, 138.21, 148.54, 164.58

### Formation of 2,6-bis[4'-(*R*)-phenyloxazolin-2'-yl]pyridine (337) (B)

A 50-ml round-bottom flask was charged with  $\text{LaCl}_3$  (49.1 mg, 0.20 mmol), *R*-phenylglycinol (0.69 g, 5.00 mmol) and 20 ml of toluene as solvent. The solution was cooled to 0°C and  $\text{BuLi}$  (2 ml, 4.40 mmol) was added slowly. The mixture was allowed to stir for 15 min. The solution was warmed and then heated under reflux and a solution of pyridine 2,6-dicarboxylic acid, diethyl ester (0.22 g, 1.00 mmol) in 2 ml of toluene added. Reaction was carried out for 12 h. No pure products were isolated and no products matching the amido alcohol or pybox ligand were recovered.

### Formation of 2,6-bis[4'-(*S*)-isopropylloxazolin-2'-yl]pyridine (335) (C)

*S*-Valinol (2.00 g, 0.019 mol) and TEA (15 ml, 0.200 mol) were placed in a three-neck, 250-ml round-bottom flask with 80 ml of clean dry CHCl<sub>3</sub>. This was cooled to 0°C and stirred for 1 h. A solution of pyridine 2,6-dicarboxyl chloride (1.84 g, 0.009 mol) in 20 ml of CHCl<sub>3</sub> was added dropwise with stirring under a stream of argon. The solution was stirred overnight. The solvent was removed and the remaining solid was dissolved in ethyl acetate. Organic phase was washed with 3 x 10 ml of water, dried over MgSO<sub>4</sub> and solvent removed under vacuum. The solid was dissolved in 25 ml of dry DCM and 4 ml of TEA added. The solution was cooled to 0°C and MsCl (1.2 ml, 1.75 g, 0.015 mol) added slowly. The solution was stirred on ice for 2 h. The organic layer was washed with 2 x 10 ml water and dried over MgSO<sub>4</sub>. Solvent was removed and the solid reconstituted in 40 ml of methanolic NaOH (0.256 g in MeOH:H<sub>2</sub>O (1:5)). The solution was stirred for 2 days. The solvent was removed and the remaining material taken up in 20 ml DCM. This was washed with water (2 x 10 ml) and dried as before. Yield = 1.94 g (71%) crude material. This material was columned using DCM:MeOH:TEA (95:5:3) and the yield was 0.94 g (35%). This was not entirely pure so the material was purified again using DCM:DEE:TEA (60:40:3). Yield = 516.5 mg (20%). Procedure was repeated and 1.88 g (26%) of material recovered. White powder, m.p. 148–150°C (lit 152–153°C). IR  $\nu_{\max}$  3439, 1642, 1102, 1074 cm<sup>-1</sup>.  $\delta_{\text{H}}[\text{CDCl}_3]$  showed the following signals 0.93 (6 H, d,  $J=6.9$  Hz), 1.04 (6 H, d,  $J=6.9$  Hz), 1.85 (2 H, sept,  $J=6.9$  Hz), 4.15 (2 H, dd,  $J=9.9, 6.9$  Hz), 4.21 (2 H, dd,  $J=7.9, 9.9$ ), 4.52 (2 H, dd,  $J=7.9, 9.9$ ), 7.83 (1 H, t,  $J=7.9$  Hz), 8.17 (2 H, t,  $J=7.9$  Hz).  $\delta_{\text{C}}[\text{CDCl}_3]$  showed the following signals:-18.29, 18.99, 32.81, 70.97, 72.83, 125.61, 137.22, 146.74, 162.14. These data match the lit. values.<sup>144</sup>

### Formation of 2,6-bis[4'-(*S*)-isobutyloxazolin-2'-yl]pyridine (336) (A)

*S*-Isoleucinol (4.13 g, 0.035 mol) and pyridine 2,6-dicarboxyl chloride (3.42 g, 0.017 mol) were treated as described above. Yield = 2.86 g (52%). Off-white solid, m.p.=139–141°C (Lit=143–144°C). IR  $\nu_{\max}$  3428, 2967, 1639, 1468 cm<sup>-1</sup>.  $\delta_{\text{H}}[\text{CDCl}_3]$  showed the following signals 0.93 (6 H, t,  $J=5.9$  Hz), 0.95 (6 H, d,  $J=6.9$  Hz), 1.32–1.39, (2 H, m,  $J=7.9, 6.9, 5.9$  Hz), 1.66–1.73 (2 H, m,  $J=6.9, 5.9$  Hz), 1.79–1.85 (2 H, m,  $J=6.9, 5.9$  Hz), 4.06 (2 H, dd,  $J=8.9, 7.9$  Hz), 4.32–4.40 (2 H, m,  $J=7.9, 8.9$  Hz), 4.58 (2 H, dd,  $J=8.9$  Hz), 7.83 (1 H, t,  $J=7.9$  Hz), 8.12 (2 H, d,  $J=7.9$  Hz)  $\delta_{\text{C}}[\text{CDCl}_3]$  showed the following signals:- 11.49, 22.66, 25.35, 45.39, 65.25, 73.74, 73.86, 125.50, 137.23, 146.79, 162.02. These data match lit values.<sup>144</sup>

### Formation of 2,6-bis[4'-(*R*)-phenyloxazolin-2'-yl]pyridine (337) (B)

*R*-Phenyl glycinol (5.25 g, 0.038 mol) and pyridine 2,6-dicarboxyl chloride (3.77 g, 0.038 mol) were treated as described above. Yield = 2.40 g (47%) White powder, m.p = 166–168°C (Lit=170–172°C). IR  $\nu_{\max}$  3435, 3034, 2893, 1652, 1570, 980, 731, 700  $\text{cm}^{-1}$ .  $\delta_{\text{H}}[\text{CDCl}_3]$  showed the following signals.- 4.41 (2 H, dd,  $J=8.9$  Hz), 4.92 (2 H, dd,  $J=8.9, 7.9$  Hz), 5.45 (2 H, dd,  $J=7.9$  Hz), 7.26–7.38 (10 H, m), 7.91 (1 H, t,  $J=7.9$  Hz), 8.33 (2 H, d,  $J=7.9$  Hz).  $\delta_{\text{C}}[\text{CDCl}_3]$  showed the following signals.- 70.25, 75.45, 126.26, 126.76, 127.74, 128.76, 137.42, 141.59, 146.64, 163.38. These data match the lit values<sup>144</sup>

### Formation of 2,6-bis[4'-(*S*)-benzyloxazolin-2'-yl]pyridine (338) (D)

*S*-phenylalaninol (2.60 g, 0.017 mol) and pyridine 2,6-dicarboxyl chloride (1.67 g, 0.008 mol) were treated as described above. Yield = 0.86 g (26%) White powder, m.p = 152–154°C (Lit=156°C). IR  $\nu_{\max}$  3428, 3034, 2932, 1637, 1459, 1385, 731  $\text{cm}^{-1}$ .  $\delta_{\text{H}}[\text{CDCl}_3]$  showed the following signals 2.74 (2 H, dd,  $J=8.9, 4.9$  Hz), 3.26 (2 H, dd,  $J=7.9, 4.9$  Hz), 4.25 (2 H, dd,  $J=7.9$  Hz), 4.45 (2 H, dd,  $J=8.9, 9.9$  Hz), 4.65 (2 H, dd,  $J=6.9, 4.9$  Hz), 7.21–7.32 (10 H, m), 7.89 (1 H, t,  $J=7.9$  Hz), 8.20 (2 H, d,  $J=7.9$  Hz).  $\delta_{\text{C}}[\text{CDCl}_3]$  showed the following signals.-41.62, 68.04, 72.54, 125.76, 126.56, 128.56, 129.17, 137.34, 146.72, 162.67. These data match the lit values.<sup>158</sup>

## 4.4.2 Synthesis of the Complexes

### Niobium pentachloride and ligand (336) to give complex (341)

A suspension of  $\text{NbCl}_5$  (299.0 mg, 1.107 mmol) in DCM was formed and the mixture purged with argon. Isobutyl pybox (336) (335.5 mg, 1.00 mmol) was added slowly under argon with stirring at room temperature. The suspension clarified and the resulting pale yellow solution was stirred for 18 h. At this stage it was green in colour and was filtered through a plug of silica to remove excess  $\text{NbCl}_5$ . The resulting solution was dried under vacuum and reconstituted in DCM. This solution was allowed to stand in a narrow tube for several weeks, at which time the resulting powder was analysed. IR  $\nu_{\max}$  1655  $\text{cm}^{-1}$ .  $\delta_{\text{H}}[\text{CDCl}_3]$  showed the following signals - 0.87–0.94 (11 H, m), 1.21–1.35 (11 H, m), 1.57–1.65 (11 H, m), 2.15 (2 H, s), 3.74 (1 H, dd,  $J=5.9, 4.9$  Hz), 3.94 (1 H, dd,  $J=7.9, 3.0$  Hz), 4.60 (1 H, br s), 4.75 (1 H, br s), 4.96 (1

H, br s), 5.65 (1 H, br s), 8.09–8.17 (2 H, m,  $J=7.4, 7.9, 9.9$  Hz), 8.62 (1 H, d,  $J=7.4$  Hz), 9.61 (1 H, d,  $J=7.4$  Hz) Electrospray mass spectrometry was attempted, however, no discernible peaks were observed

#### Niobium pentachloride and *R, R*-Jacobsen ligand (339) to give (342)

Niobium pentachloride (299.0 mg, 1.107 mmol) and (339) (547.0 mg, 1.000 mmol) were treated as described above. After recrystallisation yellow needles were recovered  $[\alpha]_D^{25} = -82.3^\circ$  IR  $\nu_{\max}$  2961, 2876, 2234, 1659, 1602, 1474, 1239, 919, 733  $\text{cm}^{-1}$ .  $\delta_{\text{H}}[\text{CDCl}_3]$  showed the following signals - 0.84–0.89 (1 H, m,  $J=3.9, 2.0$  Hz), 1.13 (2 H, d,  $J=5.9$  Hz), 1.27–1.33 (36 H, d,  $J=20.7$  Hz), 1.66 (1 H, br s), 1.96 (1 H, br s), 2.09 (1 H, br s), 2.31 (2 H, br s), 4.99 (1 H, br s), 7.16–7.26 (1 H, dd,  $J=21.7, 6.9, 7.9$  Hz), 7.67 (2 H, s), 8.05 (1 H, br s), 9.67 (1 H, br s)  $m/z = 653.304$  (ES+). Analysis. calculated for  $\text{C}_{36}\text{H}_{52}\text{N}_2\text{O}_2\text{NbO}$ . C (66.81%), H (8.04%), N (4.29%), found: C (67.69%), H (8.45%), N (4.14%)

### 4.4.3 Diels–Alder Reactions

#### Niobium pentachloride and ligand (335)

A suspension of  $\text{NbCl}_5$  (270.0 mg, 1.000 mmol) in dry DCM was prepared. One equivalent of ligand (335) (305.0 mg, 1.012 mmol) was added over 20 min under a stream of argon and the solution allowed to stir overnight whereupon it developed a green colour. It was then divided into two round-bottom flasks by syringing from the original vessel under a stream of argon. The DCM was removed under vacuum and each of the vessels charged with dry DCM and cooled to  $-40^\circ\text{C}$  on a cold plate. Cyclopentadiene was added to each vessel, 880.0 mg (13.33 mmol) to vessel 1 and 880.0 mg (13.33 mmol) to vessel 2. Crotonaldehyde (175.0 mg, 2.497 mmol) was added to vessel 1 and methacrolein (225.0 mg, 3.210 mmol) to vessel 2. Reaction was allowed to proceed for 18 h and products were separated using column chromatography (PE:DCM (50:50)). Adduct A:- yield = 17.9 mg (7.0 %) Adduct B - yield = 41.4 mg, (12.0%) The adducts were derivatised as described in Chapter 2 in order to determine ee. None observed

#### Niobium pentachloride and ligand (336)

Niobium pentachloride (271.7 mg, 1.006 mmol) and ligand (336) (340.5 mg, 1.034 mmol) were treated as described above. Vessel 1 cyclopentadiene (800 mg, 12.12

mmol), crotonaldehyde (175.0 mg, 2.497 mmol); Vessel 2: cyclopentadiene (775 mg, 11.74 mmol), methacrolein (190 mg, 2.711 mmol). Results: Adduct A: Yield = 89.7 mg (26.5%), No ee, Adduct B: Yield = 137.0 mg (40.3%), no ee.

#### **Niobium pentachloride and ligand (337)**

Niobium pentachloride (278.2 mg, 1.030 mmol) and ligand (337) (387.66 mg, 1.050 mmol) were treated as described above. Vessel 1: cyclopentadiene (750 mg, 11.34 mmol), crotonaldehyde (165.0 mg, 2.354 mmol), Vessel 2: cyclopentadiene (825 mg, 12.50 mmol), methacrolein (205 mg, 2.925 mmol). Results: Adduct A: Yield = 80.0 mg (25.0%), No ee, Adduct B: Yield = 270.9 mg (68.1%), no ee.

#### **Niobium pentachloride and ligand (338)**

Niobium pentachloride (270.8 mg, 1.003 mmol) and ligand (338) (410.4 mg, 1.033 mmol) were treated as described above. Vessel 1: cyclopentadiene (775 mg, 11.74 mmol), crotonaldehyde (210.0 mg, 2.568 mmol), Vessel 2: left for 48 h, cyclopentadiene (795 mg, 12.04 mmol), methacrolein (180 mg, 2.711 mmol). Results: Adduct A: Yield = 76.8 mg (22.0%), No ee; Adduct B: Yield = 365.0 mg (99.0%), no ee.

#### **Niobium pentachloride and ligand (339)**

Niobium pentachloride (270.1 mg, 1.000 mmol) and ligand (339) (549.0 mg, 1.004 mmol) were treated as described above. Vessel 1: cyclopentadiene (600 mg, 9.090 mmol), crotonaldehyde (140.0 mg, 1.997 mmol), Vessel 2: cyclopentadiene (650 mg, 9.848 mmol), methacrolein (170 mg, 2.425 mmol). Results: left for 48 h, Adduct A: Yield = 104.6 mg (38.5%), ee = 25% (*R*), Adduct B: Yield = 221.3 mg (67.1%), ee = 40% (*R*)

#### **Niobium pentachloride and ligand (340)**

Niobium pentachloride (270.5 mg, 1.000 mmol) and ligand (340) (549.2 mg, 1.004 mmol) were treated as described above. Vessel 1: cyclopentadiene (800 mg, 12.12 mmol), crotonaldehyde (175 mg, 2.497 mmol), Vessel 2: cyclopentadiene (840 mg, 12.72 mmol), methacrolein (180 mg, 2.568 mmol). Results: Adduct A: Yield = 95.1 mg (28.0%), ee=27% (*S*), Adduct B: Yield = 169.4 mg (48.5%), ee=38% (*S*)

#### **Tantalum pentachloride and ligand (335)**

Tantalum pentachloride (359.0 mg, 1.002 mmol) and ligand (335) (310.0 mg, 1.029 mmol) were treated as described above. Vessel 1: cyclopentadiene (800 mg, 12.12 mmol), crotonaldehyde (175.0 mg, 2.497 mmol), Vessel 2: cyclopentadiene (800 mg, 12.12 mmol), methacrolein (175 mg, 2.497 mmol). Results: Adduct A: Yield = none; Adduct B: Yield = none

#### **Tantalum pentachloride and ligand (336)**

Tantalum pentachloride (361.0 mg, 1.010 mmol) and ligand (336) (340.0 mg, 1.032 mmol) were treated as described above. Vessel 1: cyclopentadiene (800 mg, 12.12 mmol), crotonaldehyde (175.0 mg, 2.497 mmol), Vessel 2: cyclopentadiene (800 mg, 12.12 mmol), methacrolein (175 mg, 2.497 mmol). Results: Adduct A: Yield = none, Adduct B: Yield = none.

#### **Tantalum pentachloride and ligand (337)**

Tantalum pentachloride (371.0 mg, 1.039 mmol) and ligand (337) (380.4 mg, 1.030 mmol) were treated as described above. Vessel 1: cyclopentadiene (800 mg, 12.12 mmol), crotonaldehyde (175 mg, 2.497 mmol), Vessel 2: cyclopentadiene (800 mg, 12.12 mmol), methacrolein (175 mg, 2.497 mmol). Results: Adduct A: left for 48 h, Yield = 51.7 mg (15.2%), ee=10% (R), Adduct B: left for 48 h, Yield = 113 mg (33.2%), ee=25% (R)

#### **Tantalum pentachloride and ligand (338)**

Tantalum pentachloride (360.1 mg, 1.007 mmol) and ligand (338) (410.5 mg, 1.033 mmol) were treated as described above. Vessel 1: cyclopentadiene (800 mg, 12.12 mmol), crotonaldehyde (175 mg, 2.497 mmol); Vessel 2: cyclopentadiene (800 mg, 12.12 mmol), methacrolein (175 mg, 2.497 mmol). Results: Adduct A: Yield = 63.5 mg (18.7%), no ee, Adduct B: Yield = 85.91 mg (25.3%), no ee.

#### **Tantalum pentachloride and ligand (339)**

Tantalum pentachloride (349.0 mg, 0.976 mmol) and ligand (339) (552.0 mg, 1.011 mmol) were treated as described above. Vessel 1: cyclopentadiene (800 mg, 12.12 mmol), crotonaldehyde (175.0 mg, 2.497 mmol); Vessel 2: cyclopentadiene (800 mg,

12.12 mmol), methacrolein (175 mg, 2.497 mmol). Results Adduct A Yield =none, Adduct B: Yield = none.

#### **Tantalum pentachloride and ligand (340)**

Tantalum pentachloride (354.0 mg, 0.999 mmol) and ligand (340) (550.0 mg, 1.007 mmol) were treated as described above. Vessel 1: cyclopentadiene (800 mg, 12.12 mmol), crotonaldehyde (175.0 mg, 2.497 mmol); Vessel 2: cyclopentadiene (800 mg, 12.12 mmol), methacrolein (175 mg, 2.497 mmol). Results Adduct A Yield =none; Adduct B: Yield = none.

#### **Niobium pentachloride and ligand (335) with addition of NH<sub>4</sub>PF<sub>6</sub>**

Niobium pentachloride (271.7 mg, 1.006 mmol) and ligand (335) (305.0 mg, 1.003 mmol) were treated as described above with addition of NH<sub>4</sub>PF<sub>6</sub> (820.0 mg, 5.031 mmol). Vessel 1: cyclopentadiene (800 mg, 12.12 mmol), crotonaldehyde (175.0 mg, 2.497 mmol), Vessel 2: cyclopentadiene (800 mg, 12.12 mmol), methacrolein (175 mg, 2.497 mmol). Results Adduct A: Yield = 59.0 mg (18.0%), No ee; Adduct B: Yield = 125.1 mg (36.0%), ee=10% (*S*).

#### **Niobium pentachloride and ligand (336) with addition of NH<sub>4</sub>PF<sub>6</sub>**

Niobium pentachloride (270.5 mg, 1.001 mmol) and ligand (336) (344.1 mg, 1.044 mmol) were treated as described above with addition of NH<sub>4</sub>PF<sub>6</sub> (835.0 mg, 5.123 mmol). Vessel 1: cyclopentadiene (800 mg, 12.12 mmol), crotonaldehyde (175.0 mg, 2.497 mmol); Vessel 2: cyclopentadiene (800 mg, 12.12 mmol), methacrolein (175 mg, 2.497 mmol). Results: Adduct A: Yield = 131.9 mg (38.8%), No ee; Adduct B: Yield = 296.2 mg (87.1 %), ee=10% (*S*).

#### **Niobium pentachloride and ligand (337) with addition of NH<sub>4</sub>PF<sub>6</sub>**

Niobium pentachloride (270.4 mg, 0.998 mmol) and ligand (337) (380.4 mg, 1.031 mmol) were treated as described above with addition of NH<sub>4</sub>PF<sub>6</sub> (835.0 mg, 5.123 mmol). Vessel 1: cyclopentadiene (800 mg, 12.12 mmol), crotonaldehyde (175.0 mg, 2.497 mmol); Vessel 2: cyclopentadiene (800 mg, 12.12 mmol), methacrolein (175 mg, 2.497 mmol). Results Adduct A: Yield = 247.5 mg (71.0%), No ee, Adduct B: Yield = 233.8 mg (70.0%), ee=23% (*R*).

**Niobium pentachloride and ligand (338) with addition of NH<sub>4</sub>PF<sub>6</sub>**

Niobium pentachloride (269.4 mg, 0.997 mmol) and ligand (338) (408.5 mg, 1.028 mmol) were treated as described above with addition of NH<sub>4</sub>PF<sub>6</sub> (835.5 mg, 5.126 mmol). Vessel 1: cyclopentadiene (800 mg, 12.12 mmol), crotonaldehyde (175.0 mg, 2.497 mmol), Vessel 2: cyclopentadiene (800 mg, 12.12 mmol), methacrolein (175 mg, 2.497 mmol) Results: Adduct A: Yield = 119.5 mg (35.1%), No ee, Adduct B: Yield = 188.8 mg (55.5%), no ee.

**Niobium pentachloride and ligand (339) with addition of NH<sub>4</sub>PF<sub>6</sub>**

Niobium pentachloride (270.4 mg, 1.001 mmol) and ligand (339) (550.1 mg, 1.007 mmol) were treated as described above with addition of NH<sub>4</sub>PF<sub>6</sub> (489.4 mg, 3.002 mmol). Vessel 1: cyclopentadiene (800 mg, 12.12 mmol), crotonaldehyde (175.0 mg, 2.497 mmol); Vessel 2: cyclopentadiene (800 mg, 12.12 mmol), methacrolein (175 mg, 2.497 mmol). Results: Adduct A: Yield = 198.5 mg (58.0%), ee=19% (*R*), Adduct B: Yield = 292.7 mg (86.1%), ee=40% (*R*)

**Niobium pentachloride and ligand (340) with addition of NH<sub>4</sub>PF<sub>6</sub>**

Niobium pentachloride (270.8 mg, 1.000 mmol) and ligand (340) (551.1 mg, 1.008 mmol) were treated as described above with addition of NH<sub>4</sub>PF<sub>6</sub> (492.5 mg, 3.021 mmol). Vessel 1: cyclopentadiene (800 mg, 12.12 mmol), crotonaldehyde (175.0 mg, 2.497 mmol), Vessel 2: cyclopentadiene (800 mg, 12.12 mmol), methacrolein (175 mg, 2.497 mmol) Results: Adduct A: Yield = 210.9 mg (62.0%), ee=25% (*S*), Adduct B: Yield = 252.7 mg (74.0%), ee=42% (*S*)

**Tantalum pentachloride and ligand (335) with addition of NH<sub>4</sub>PF<sub>6</sub>**

Tantalum pentachloride (359.0 mg, 1.000 mmol) and ligand (335) (311.1 mg, 1.023 mmol) were treated as described above with addition of NH<sub>4</sub>PF<sub>6</sub> (835.0 mg, 5.123 mmol). Vessel 1: cyclopentadiene (800 mg, 12.12 mmol), crotonaldehyde (175.0 mg, 2.497 mmol), Vessel 2: cyclopentadiene (800 mg, 12.12 mmol), methacrolein (175 mg, 2.497 mmol). Results: Adduct A: Yield = 24.5 mg (7.2%), No ee; Adduct B: Yield = 36.8 mg (10.8%), no ee.



**Tantalum pentachloride and ligand (336) with addition of NH<sub>4</sub>PF<sub>6</sub>**

Tantalum pentachloride (361.0 mg, 1.007 mmol) and ligand (336) (335.4 mg, 1.018 mmol) were treated as described above with addition of NH<sub>4</sub>PF<sub>6</sub> (849.0 mg, 5.209 mmol). Vessel 1: cyclopentadiene (800 mg, 12.12 mmol), crotonaldehyde (175.0 mg, 2.497 mmol); Vessel 2: cyclopentadiene (800 mg, 12.12 mmol), methacrolein (175 mg, 2.497 mmol). Results: Adduct A: Yield = 27.1 mg (8.0%), No ee; Adduct B: Yield = 34.0 mg (10.0%), no ee.

**Tantalum pentachloride and ligand (337) with addition of NH<sub>4</sub>PF<sub>6</sub>**

Tantalum pentachloride (372.1 mg, 1.038 mmol) and ligand (337) (385.1 mg, 1.042 mmol) were treated as described above with addition of NH<sub>4</sub>PF<sub>6</sub> (851.0 mg, 5.221 mmol). Vessel 1: cyclopentadiene (800 mg, 12.12 mmol), crotonaldehyde (175.0 mg, 2.497 mmol); Vessel 2: cyclopentadiene (800 mg, 12.12 mmol), methacrolein (175 mg, 2.497 mmol). Results: Adduct A: Yield = 60.3 mg (17.7%), ee=14% (*R*); Adduct B: reaction left on for 48 h, Yield = 250.2 mg (84%), ee=31% (*R*).

**Tantalum pentachloride and ligand (338) with addition of NH<sub>4</sub>PF<sub>6</sub>**

Tantalum pentachloride (355.0 mg, 0.992 mmol) and ligand (338) (400.9 mg, 1.009 mmol) were treated as described above with addition of NH<sub>4</sub>PF<sub>6</sub> (823.0 mg, 5.049 mmol). Vessel 1: cyclopentadiene (800 mg, 12.12 mmol), crotonaldehyde (175.0 mg, 2.497 mmol); Vessel 2: cyclopentadiene (800 mg, 12.12 mmol), methacrolein (175 mg, 2.497 mmol). Results: Adduct A: Yield = 152.8 mg (45%), no ee; Adduct B: Yield = 284.1 mg (83.5%), no ee.

**Tantalum pentachloride and ligand (339) with addition of NH<sub>4</sub>PF<sub>6</sub>**

Tantalum pentachloride (350.4 mg, 0.977 mmol) and ligand (339) (550.4 mg, 1.007 mmol) were treated as described above with addition of NH<sub>4</sub>PF<sub>6</sub> (489.5.0 mg, 3.003 mmol). Vessel 1: cyclopentadiene (800 mg, 12.12 mmol), crotonaldehyde (175.0 mg, 2.497 mmol); Vessel 2: cyclopentadiene (800 mg, 12.12 mmol), methacrolein (175 mg, 2.497 mmol). Results: Adduct A: Yield = 152.2 mg (45%), ee=11% (*R*); Adduct B: reaction left for 48 h, Yield = 243.5 mg (10.8%), ee=14% (*R*).

#### **Tantalum pentachloride and ligand (340) with addition of NH<sub>4</sub>PF<sub>6</sub>**

Tantalum pentachloride (359.7 mg, 1.003 mmol) and ligand (340) (551.2 mg, 1.010 mmol) were treated as described above with addition of NH<sub>4</sub>PF<sub>6</sub> (493.4 mg, 3.027 mmol). Vessel 1: cyclopentadiene (800 mg, 12.12 mmol), crotonaldehyde (175.0 mg, 2.497 mmol); Vessel 2: cyclopentadiene (800 mg, 12.12 mmol), methacrolein (175 mg, 2.497 mmol). Results: Adduct A: Yield = 63.9 mg (19%), ee=10% (*S*); Adduct B: Yield = 184.8 mg (54.0%), ee=16% (*S*).

#### **Niobium pentachloride and ligand (335) with addition of molecular sieves**

Niobium pentachloride (270.7 mg, 1.000 mmol) and ligand (335) (320.0 mg, 1.053 mmol) were treated as described above. Vessel 1: Activated molecular sieves, cyclopentadiene (800 mg, 12.12 mmol), methacrolein (175 mg, 2.497 mmol); Vessel 2: Unactivated molecular sieves, cyclopentadiene (800 mg, 12.12 mmol), methacrolein (175 mg, 2.497 mmol). Results: Adduct 1: Yield = 163.5 mg (43.2%), ee=52% (*S*); Adduct 2: Yield = 256.5 mg (68.0%), ee=31% (*S*).

#### **Niobium pentachloride and ligand (336) with addition of molecular sieves**

Niobium pentachloride (270.1 mg, 1.000 mmol) and ligand (336) (330.0 mg, 1.002 mmol) were treated as described above. Vessel 1: Activated molecular sieves, cyclopentadiene (800 mg, 12.12 mmol), methacrolein (175 mg, 2.497 mmol); Vessel 2: Unactivated molecular sieves, cyclopentadiene (800 mg, 12.12 mmol), methacrolein (175 mg, 2.497 mmol). Results: Adduct 1: Yield = 134.5 mg (34.5%), ee=22% (*S*). Adduct 2: Yield = 236.5 mg (55.3%), no ee.

#### **Niobium pentachloride and ligand (337) with addition of molecular sieves**

Niobium pentachloride (271.2 mg, 1.004 mmol) and ligand (337) (380.0 mg, 1.028 mmol) were treated as described above. Vessel 1: Activated molecular sieves, cyclopentadiene (800 mg, 12.12 mmol), methacrolein (175 mg, 2.497 mmol); Vessel 2: Unactivated molecular sieves, cyclopentadiene (800 mg, 12.12 mmol), methacrolein (175 mg, 2.497 mmol). Results: Adduct 1: Yield = 158.3 mg (41.0%), ee=35% (*R*); Adduct 2: Yield = 236.5 mg (55.3%), ee=23% (*R*).

**Niobium pentachloride and ligand (338) with addition of molecular sieves**

Niobium pentachloride (271.0 mg, 1.003 mmol) and ligand (338) (400.0 mg, 1.008 mmol) were treated as described above. Vessel 1: Activated molecular sieves, cyclopentadiene (800 mg, 12.12 mmol), methacrolein (175 mg, 2.497 mmol); Vessel 2: Unactivated molecular sieves, cyclopentadiene (800 mg, 12.12 mmol), methacrolein (175 mg, 2.497 mmol). Results: Adduct 1: Yield = 122.4 mg (33.0%), ee=17% (*S*); Adduct 2: Yield = 158.9 mg (41.0%), no ee.

**Niobium pentachloride and ligand (339) with addition of molecular sieves**

Niobium pentachloride (270.6 mg, 1.002 mmol) and ligand (339) (547.7 mg, 1.003 mmol) were treated as described above. Vessel 1: Activated molecular sieves, cyclopentadiene (800 mg, 12.12 mmol), methacrolein (175 mg, 2.497 mmol); Vessel 2: Unactivated molecular sieves, cyclopentadiene (800 mg, 12.12 mmol), methacrolein (175 mg, 2.497 mmol). Results: Adduct 1: Yield = 216.7 mg (60.0%), ee=55% (*R*); Adduct 2: Yield = 237.7 mg (66.0%), ee=35% (*R*).

**Niobium pentachloride and ligand (340) with addition of molecular sieves**

Niobium pentachloride (269.3 mg, 0.997 mmol) and ligand (340) (352.0 mg, 1.017 mmol) were treated as described above. Vessel 1: Activated molecular sieves, cyclopentadiene (800 mg, 12.12 mmol), methacrolein (175 mg, 2.497 mmol); Vessel 2: Unactivated molecular sieves, cyclopentadiene (800 mg, 12.12 mmol), methacrolein (175 mg, 2.497 mmol). Results: Adduct 1: Yield = 158.5 mg (46.4%), ee=48% (*S*); Adduct 2: Yield = 132.6 mg (34.1%), ee=28% (*S*).

**Tantalum pentachloride and ligand (339) with addition of molecular sieves**

Tantalum pentachloride (360 mg, 1.006 mmol) and ligand (339) (554.7 mg, 1.015 mmol) were treated as described above. Vessel 1: Activated molecular sieves, cyclopentadiene (800 mg, 12.12 mmol), methacrolein (175 mg, 2.497 mmol); Vessel 2: Unactivated molecular sieves, cyclopentadiene (800 mg, 12.12 mmol), methacrolein (175 mg, 2.497 mmol). Results: Adduct 1: Yield = 127.8 mg (34.0%), ee=18% (*R*); Adduct 2: Yield = 123.2 mg (32.0%), ee=8% (*R*).

**Tantalum pentachloride and ligand (340) with addition of molecular sieves**

Tantalum pentachloride (358 mg, 0.999 mmol) and ligand (340) (562.8 mg, 1.031 mmol) were treated as described above. Vessel 1: Activated molecular sieves, cyclopentadiene (800 mg, 12.12 mmol), methacrolein (175 mg, 2.497 mmol), Vessel 2: Unactivated molecular sieves, cyclopentadiene (800 mg, 12.12 mmol), methacrolein (175 mg, 2.497 mmol). Results: Adduct 1: Yield = 174.3 mg (43.0%), ee=15% (*S*), Adduct 2: Yield = 132.4 mg (39%), ee=8% (*S*)

## **CHAPTER 5**

### **COMPARING MODES OF CHIRALITY USING NIOBIUM AND TANTALUM COMPLEXES**

## 5.1 INTRODUCTION

In this chapter the attempted synthesis of some chiral organometallic group V species and their potential application to enantioselective synthesis will be discussed

### 5.1.1 Modes of Chirality

Chirality in molecules is normally thought of in terms of central chirality such as that seen around carbon atoms (343) or the sulphur of a sulfoxide group (344).



Figure 90

However, the importance of other types of chirality, such as planar or helical chirality, has been little investigated. Structure (345) possesses a plane of chirality through its centre and thus the two forms are non-superimposable. In fact, each enantiomer will rotate the plane of polarised light in opposite directions.

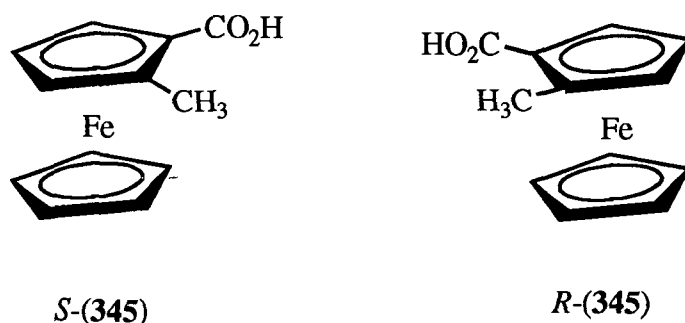
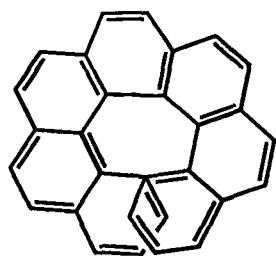
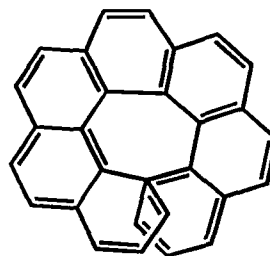


Figure 91

Similarly, the helicenes (346) are non-superimposable. Neither can they interconvert as the top ring cannot “pass over” the bottom ring.



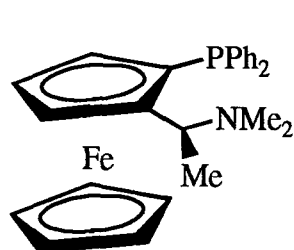
*M*-(346)



*P*-(346)

**Figure 92**

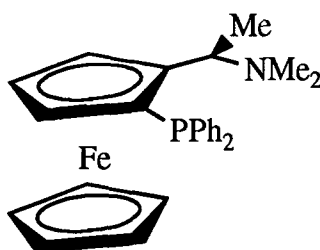
A paper which described the use of a compound bearing both central and helical chirality as a catalyst in a Grignard reaction prompted interest in comparing these two modes of induction.<sup>163</sup> Molecules (347–349) were coupled to NiCl<sub>2</sub> and the complex used to catalyse the asymmetric cross-coupling of phenylethylmagnesium chloride and vinyl bromide



*S*-*R*-PPFA

(347)

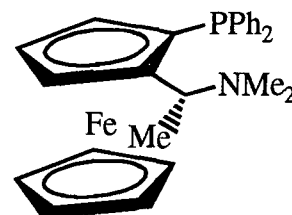
Product 66% ee (*R*)



*R*-*S*-PPFA

(348)

Product 68% ee (*S*)



*R*-*R*-PPFA

(349)

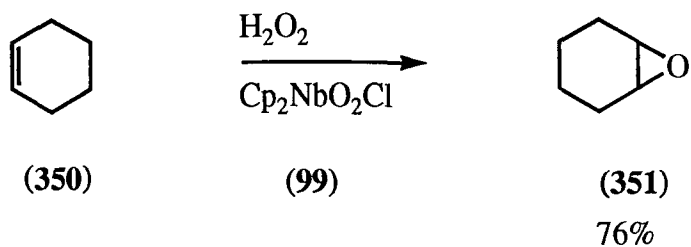
Product 54% ee (*R*)

**Figure 93**

Compounds (347) and (349) bear the same element of planar chirality and opposite elements of central chirality. Compounds (348) and (349) bear the same elements of central chirality but opposite elements of planar chirality. It can be seen from the orientation of the products that changing the rotation of the chiral centre has a minimal effect whereas reversing the chiral plane leads to a substantial difference. We wished, therefore, to compare elements of central, planar and helical chirality, to investigate whether these modes would produce substantially different results

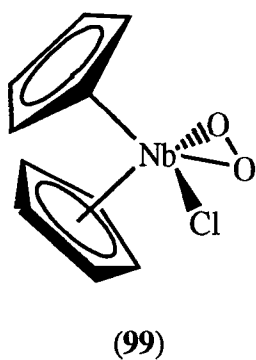
### 5.1.2 Group V metal-based catalysts

A niobium peroxo complex has been used to catalyse the epoxidation of cyclohexene in the presence of H<sub>2</sub>O<sub>2</sub>.<sup>65</sup>



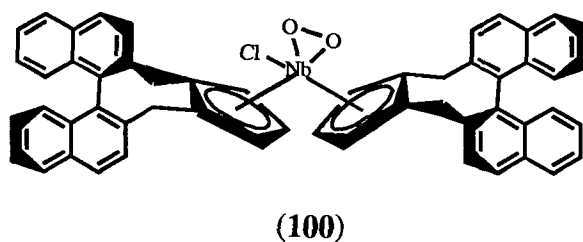
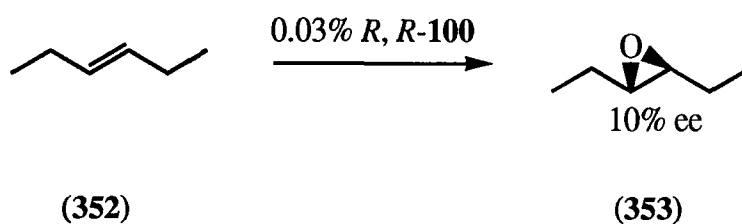
**Scheme 107**

The structure of the catalyst was later determined by X-ray crystallography<sup>164</sup>. The chlorine and oxygen atoms were found to be in a plane with the cyclopentadiene rings at an angle



**Figure 94**

A chiral molecule, based on this system, was used by Coletti and Halterman to catalyse the epoxidation of *trans* 3-hexene<sup>66</sup>



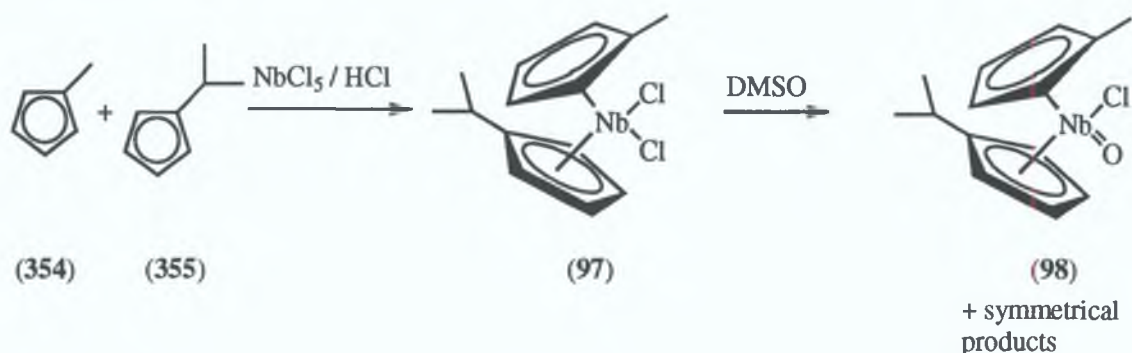
**Scheme 108**



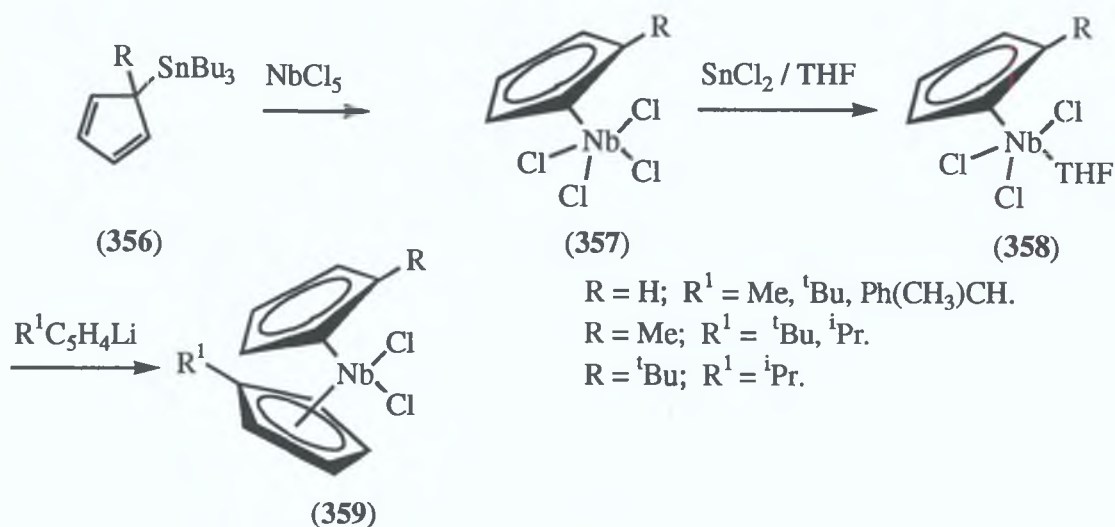
This appeared to be an appropriate test reaction for any catalysts which might be synthesised.

### 5.1.3 Chiral niobium and tantalum compounds

As discussed in Chapter 1, chiral Nb-centred compounds were synthesised by Broussier *et al.* in the 1970's (Scheme 109)<sup>62b</sup> and later in a sequential fashion to give one racemic product (Scheme 110).<sup>64</sup>



Scheme 109



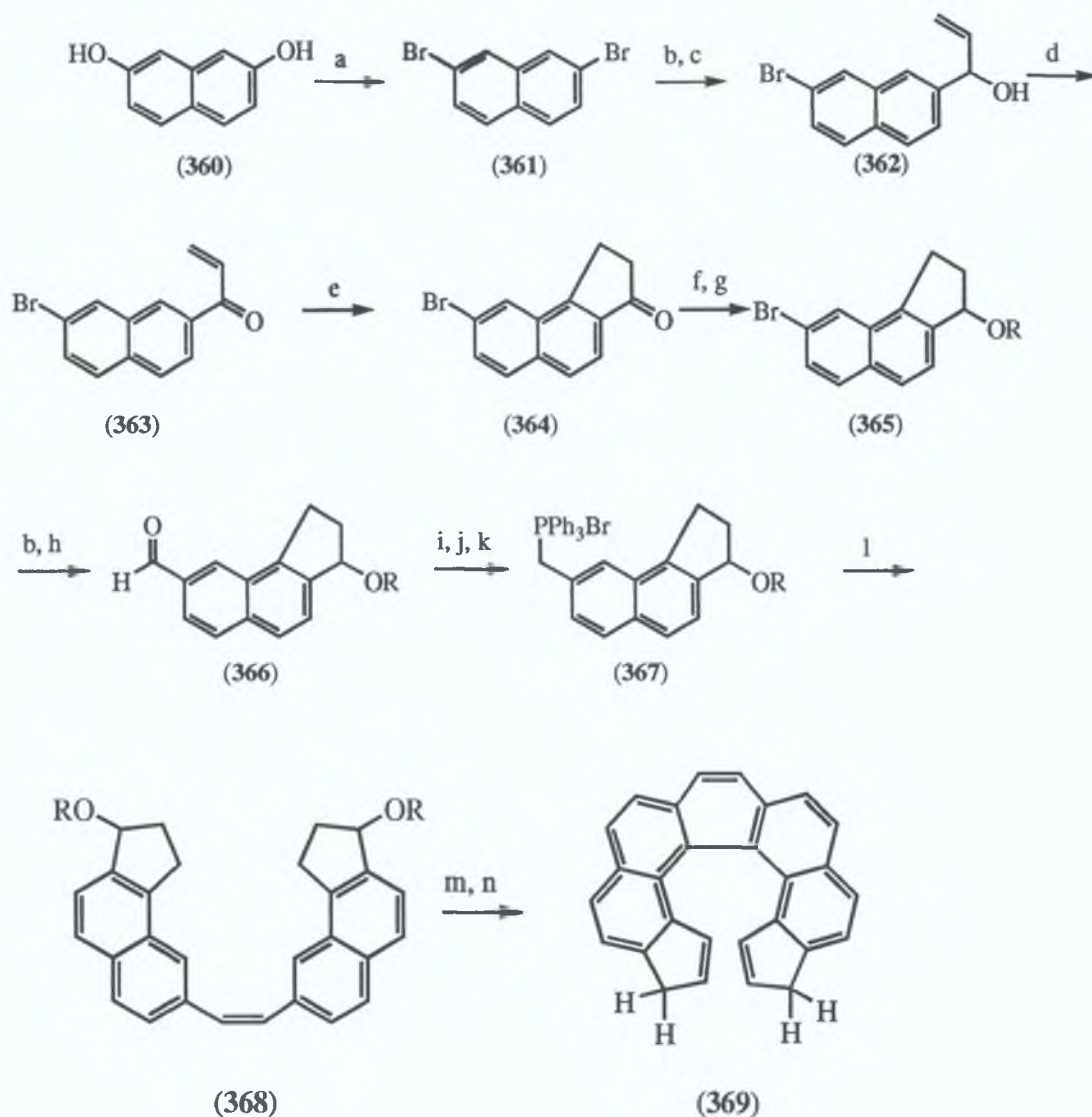
Scheme 110

By analogous reactions it was believed that the synthesis of chiral peroxo niobium and tantalum compounds could be effected.

### 5.1.4 Helicenes

Heptahelicenes with terminal five-membered rings have been synthesised by the Katz group.<sup>165</sup> This particular molecule is appealing in that the five-membered rings are

suitable for  $\eta^5$ -co-ordination to niobium and also because the terminal rings are almost overlapping. The route is shown below.

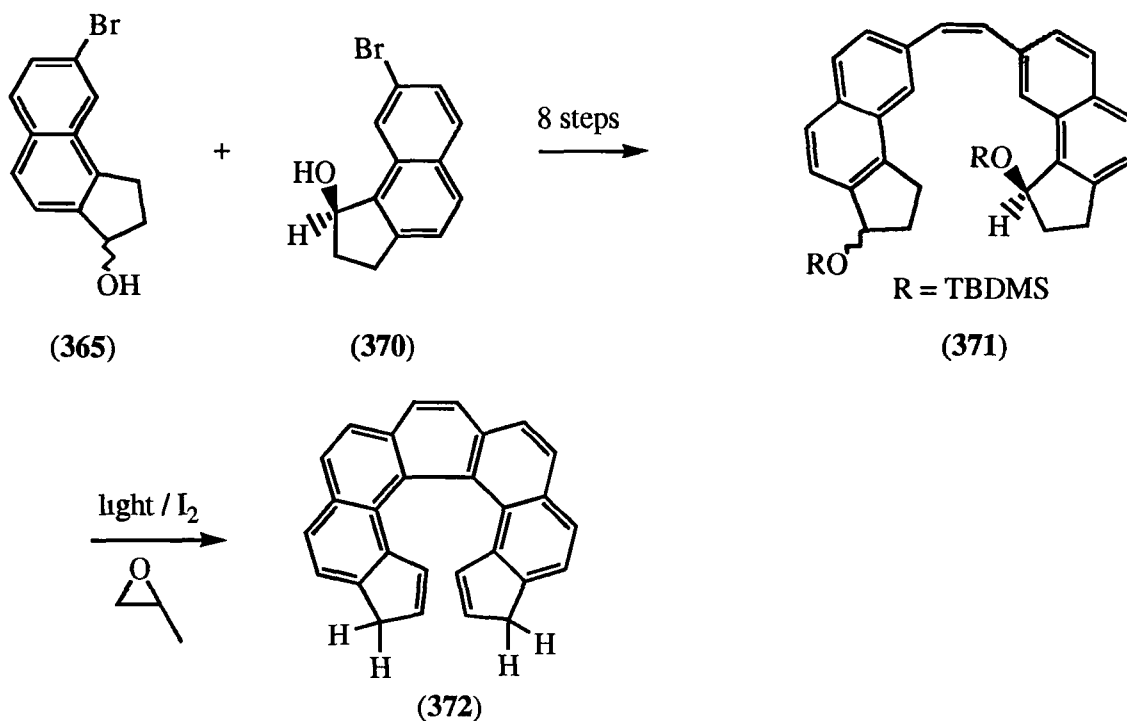


a)  $\text{Ph}_3\text{PBr}_2$ ,  $320^\circ\text{C}$ ; b)  $\text{BuLi}$  / THF,  $-55^\circ\text{C}$ ; c) acrolein, THF; d)  $\text{MnO}_2$  /  $\text{CH}_2\text{Cl}_2$ ; e) conc.  $\text{H}_2\text{SO}_4$ ; f)  $\text{LiEt}_3\text{BH}$  / THF; g)  $t\text{-BuMe}_2\text{SiCl}$  / imidazole / DMF; h) DMF / THF,  $-70^\circ\text{C}$ ; i)  $\text{DiBAL-H}$  / Hexane; j)  $(n\text{-C}_8\text{H}_{17})_3\text{P}$ ,  $\text{CBr}_4$  / ether; k)  $\text{Ph}_3\text{P}$  / benzene,  $80^\circ\text{C}$ ; l)  $\text{LiOEt}$  /  $\text{EtOH}$ ; m) light /  $\text{I}_2$ ; n)  $p\text{-TsOH}$ ,  $\text{H}_2\text{O}$  / benzene,  $60^\circ\text{C}$ .

Scheme 111

The major features of the synthesis are the initial use of 2, 7-dihydroxynaphthalene (360) and its nucleophilic substitution to form (361), the acid-catalysed ring-closure of (363) to form (364) and the photochemical/ $\text{I}_2$  oxidation to close the helicene structure. Both the *cis* and *trans* form of (368) will give the helicene. This was used to form a helical ferrocene structure.

Katz and Sudhaker later developed a synthesis which allowed the formation of the helicene enantioselectively.<sup>166</sup>



**Scheme 112**

It was found that either enantiomer of (365) could be used, but as long as a single enantiomer of (370) was used, the reaction would give a large excess of one enantiomer of product. However, if enantiopure (365) and racemic (370) were used, the product was largely racemic. The authors found that it was important to prevent the elimination of ROH from (371) which they did by adding propylene oxide to the reaction mixture. Thus the position of the large OTBDMS group (OR) was such that the half of the molecule with structure (370) would cause the helicene to wind such that this group was placed “upward” or outside the helicene.

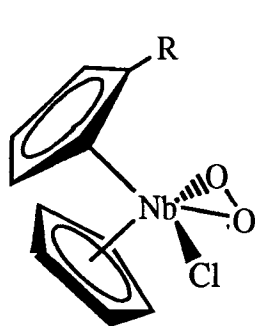
Thus the synthesis of compounds bearing central, planar and helical chirality was attempted.

## 5.2 RESULTS AND DISCUSSION

### 5.2.1 Planar Chirality

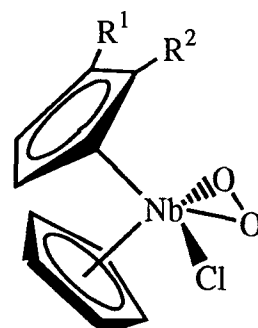
#### 5.2.1.1 Strategy

In order to include planar chirality in a niobium or tantalum complex, one of the cyclopentadienyl (Cp) rings must be 1,2-disubstituted in an unsymmetrical manner while the other Cp ring remains mono- or unsubstituted.



(372)

Central Chirality

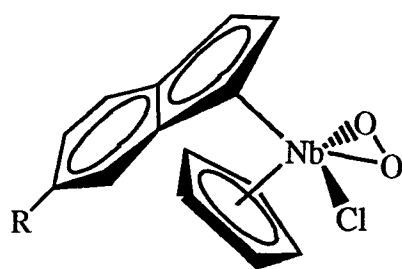


(373)

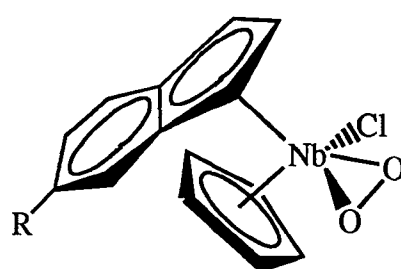
Central and Planar Chirality

Figure 95

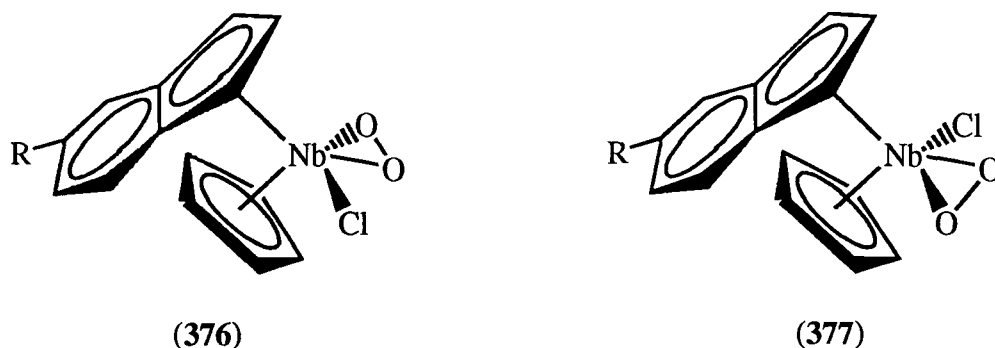
Formation of such species *via* the method of Broussier *et al.* appeared to be possible. A suitable candidate for a second ligand was a substituted indene and compounds bearing central and planar chirality might provide separable diastereomers.



(374)

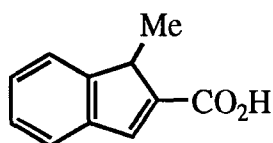


(375)



**Figure 96**

The acid (378) has the added advantage of being derivatisable with a chiral alcohol such that, in the complex, it would have two centres of chirality and a plane of chirality. This might allow enantiomers, analogous to (375) and (376), to be separated from each other, followed by removal of the chiral alcohol.



(378)

**Figure 97**

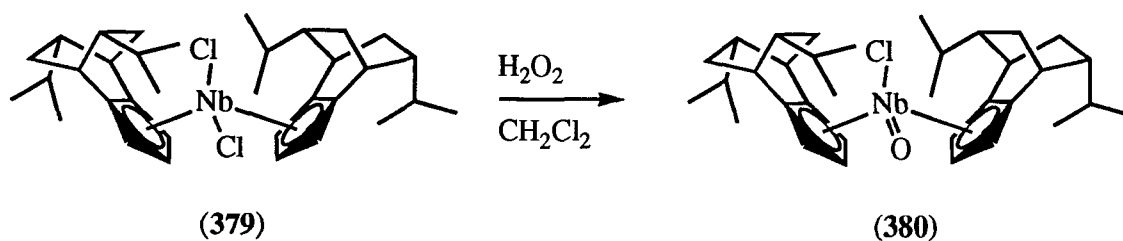
The compound is, however, expensive and it was decided to perform a number of test reactions prior to its use.

### 5.2.1.2 Test Reactions using H<sub>2</sub>O<sub>2</sub>

Literature reactions of metallocene-type compounds had variously given the oxo complex<sup>167,168</sup> or the peroxo complex<sup>65</sup>. Of the oxo complexes, Treichel and Werber formed theirs unexpectedly as a by-product of the reaction



Presumably, atmospheric oxygen played a part in this. Halterman *et al.* used H<sub>2</sub>O<sub>2</sub> as their oxidant. Despite this also being used to form the peroxo compound, their mass spectral data confirmed the presence of a single oxygen and IR showed an Nb=O stretch at 820 cm<sup>-1</sup> but lacked the O–O stretch at 870 cm<sup>-1</sup>.

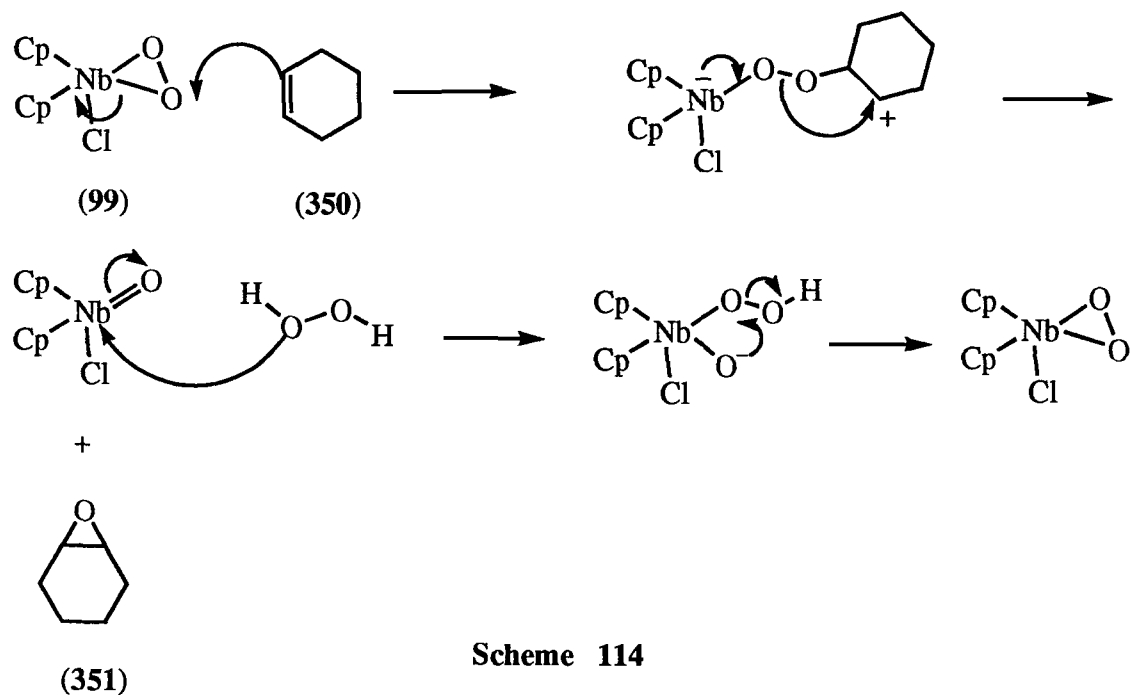


**Scheme 113**

The fact that the oxo compound was achieved, as opposed to the peroxy compound might be due to the fact that the product was recrystallised from ethanol.

Reactions between niobocene dichloride and  $\text{H}_2\text{O}_2$  were carried out. A suspension of niobocene was made up in dry oxygen-free DCM and 30 %  $\text{H}_2\text{O}_2$  added slowly. After stirring for 1 h, the resulting solution had turned from brown to yellow. Following work-up and removal of solvent the yellow solid was recrystallised from ethanol. Proton NMR gave a singlet at 6.27 ppm and  $^{13}\text{C}$  NMR a single peak at 114.94 ppm. IR gave a peak at  $825\text{ cm}^{-1}$ .

Then the reaction was performed according to Sala-Pala *et al.*,<sup>65</sup> *i.e.* without recrystallisation from ethanol. The DCM solution was allowed to evaporate and from there crystals were recovered. The  $^1\text{H}$  NMR showed a single peak at 6.21 ppm and  $^{13}\text{C}$  NMR showed a peak at 114.92 ppm. The IR spectrum showed a stretch at  $868\text{ cm}^{-1}$ . The fact that these compounds could be made *via* such a similar route suggested a possible mechanism for the epoxidation described by Sala-Pala.

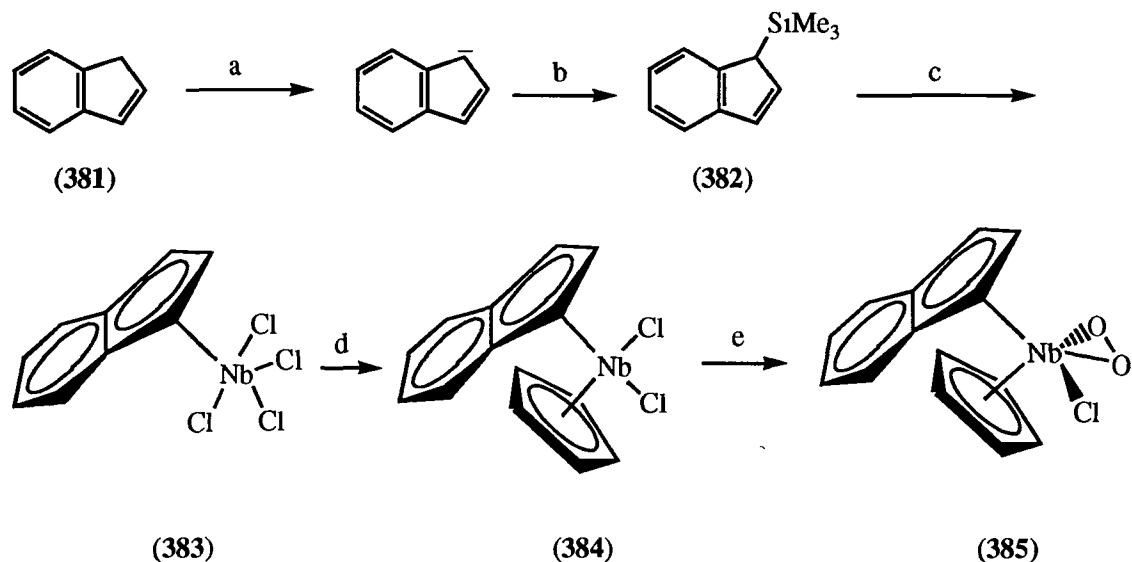


**Scheme 114**

The niobium peroxide catalyses the epoxidation while  $\text{H}_2\text{O}_2$  reacts with the resulting oxoniobium compound to reform the peroxy species. There was, however, no direct evidence for this mechanism.

## 5.2.2 Unsymmetrical Niobium Compounds

As an initial test reaction it was decided to synthesise an unsymmetrical niobium peroxy species (**385**) in order to determine whether the more complex reaction with indene acid (**378**) was possible. The chosen route is shown below



a) K / THF, reflux, b) TMSCl / THF, reflux, c) NbCl<sub>5</sub> / DCM, r t, d) NaCp / DCM, r t, e) H<sub>2</sub>O<sub>2</sub> / DCM, r t

Scheme 115

Although there was literature precedent for all of these reactions, (**385**) had not been previously synthesised. It was necessary to transmetallate from TMS-indene to NbCl<sub>5</sub> because addition of the indene anion directly would have yielded half an equivalent of the *bis* sandwich complex.

High surface area sodium was made by cleaning the metal in toluene and transferring to THF. This was then boiled and shaken vigorously, when melted, to produce a large number of small balls of metal. Once cooled it was ready for use in the reduction of indene. Indene is susceptible to photochemical reactions and thus it was freshly distilled before each use. It was added to THF containing the sodium and boiled under reflux. Caution is required as, on several occasions, the metal dried and caused the solvent to ignite. The reaction was allowed to continue for 24 h at which time the solution was worked up and the resulting oil distilled. The yield of TMS-indene was generally less than 50%.

The second step of the reaction involved the addition of TMS-indene to NbCl<sub>5</sub> in dry DCM under argon at room temperature. A suspension of NbCl<sub>5</sub> was formed followed by dropwise addition of the reagent. A deep red colour developed immediately. This was allowed to stir in the absence of light and an equivalent of NaCp was added. The resulting material was a brown suspension.

It was believed that compound (384) should have resulted at this stage. However (384) is paramagnetic, being a 17-electron species, like niobocene dichloride. It was thus decided to react this directly with H<sub>2</sub>O<sub>2</sub> in order to produce the 18-electron peroxy species (385). Thus the solvent was removed, in order to eliminate any HCl which might have been present, and the solid reconstituted in DCM. Hydrogen peroxide was then added and an orange biphasic solution resulted. However, on work-up, only a brown tar was recovered. As a yellow solid might reasonably have been expected, this was obviously a failed reaction.

In the first instance, all the stages of the experiment were performed without recourse to purification, except in the case of TMS-indene. Even with distillation, it was found that a small amount of indene could be found in the product. An added difficulty was, that on TLC, TMS-indene and indene had the same R<sub>f</sub> in 100% PE. This meant that analysis of the product could only be effected by NMR and that purification by silica-gel flash chromatography was not possible. It was decided, therefore, to attempt purification and analysis at each stage of the reaction.

Because of the poor yield of TMS-indene using sodium metal to form the indenyl anion, butyl lithium was used instead. Using the alternative method a yield of distilled indene of up to 69% was achieved.

Again the TMS-indene was reacted with NbCl<sub>5</sub> resulting in the formation of a solution containing a red powder which was partially dissolved. This was boiled under reflux for 10 min which was according to the procedure of Clark *et al* for the formation of CpNbCl<sub>4</sub><sup>63c</sup>. Filtration gave a small yield of powder but this was increased on removal of excess solvent and further filtration, giving a yield of approximately 84.3% based on (383). The compound was purified by sublimation at 120°C under vacuum. However, elemental analysis of the compound showed that it was not the desired material. It is



unclear whether there were difficulties in sublimation or whether the compound had not originally been made.

The material from the above reaction had also been reacted with LiCp (formed from the reaction of cyclopentadiene and BuLi). The materials were mixed in DCM and boiled under reflux for 2 h. A brown solid resulted. This was sublimed under vacuum. However, there was evidence of decomposition and only a small amount of sublimate (25 mg) was recovered. Elemental analysis showed that, again, this was not the desired compound (384).

Synthesis of the target compound *via* addition of Cp ligand to NbCl<sub>5</sub> *first* was then attempted. By following the method of Clark *et al.*<sup>63c</sup> whereby the mixture of NbCl<sub>5</sub> and TMS-Cp were mixed in DCM and boiled under reflux a brown mixture, which was difficult to filter, resulted. To avoid this, the heating step was removed and the mixture stirred for 1 h. The expected red solution thus resulted. Prior to addition of the anion of indene (formed from the reaction of indene with BuLi) the CpNbCl<sub>4</sub> was analysed by NMR. Proton NMR was consistent with the structure and the melting point of (173–175°C) was close to the literature value of 180°C. The CpNbCl<sub>4</sub> was then reduced by addition of Al powder to a solution in MeCN, leaving overnight. This reduction step was an alternative method described by Broussier *et al.*<sup>64</sup> The MeCN was removed and THF added followed by addition of a solution of the indenyl anion. The solution turned brown and a powder was recovered. As before, however, sublimation afforded very little product and showed further evidence of decomposition.

The reason for the failure to synthesise this test compound remains unclear. However Halterman *et al.* described difficulties in the synthesis of *bis*-indenyl chloroniobium peroxide (386)

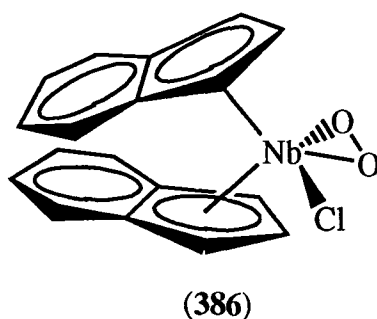
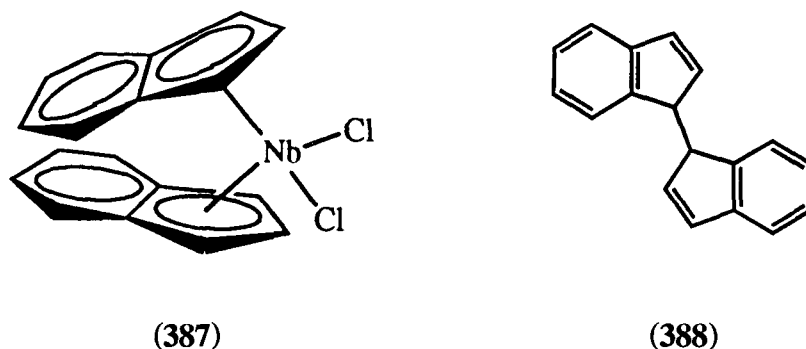


Figure 98

They reacted indenyllithium with  $\text{NbCl}_4(\text{THF})$  and had a yield of **(387)** around 30%. They subsequently discovered that the major product of the reaction was 1,1-bi-indene **(388)**.



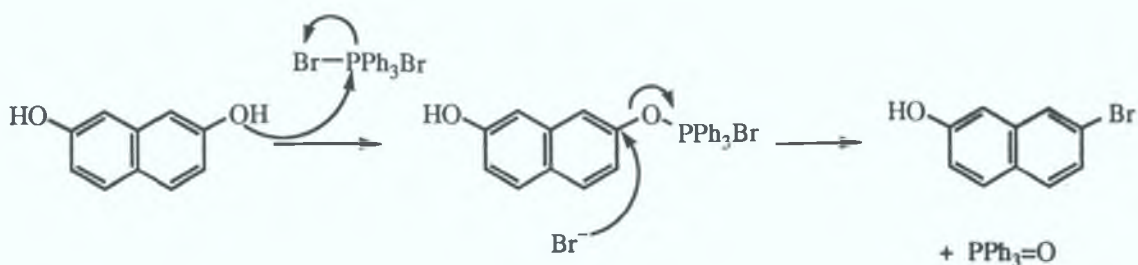
**Figure 99**

It appears that higher valent niobium species have a tendency to reductively eliminate **(388)**. They solved this problem by the use of  $\text{NbCl}_3(\text{DME})$  and forgoing the isolation of **(387)** prior to reaction with  $\text{H}_2\text{O}_2$ . The strategy used here to overcome this difficulty was to preform  $\text{CpNbCl}_4$ , as the analogous side-reaction with cyclopentadiene does not occur. However, yet again, no useful products were obtained. In the absence of success in making a compound such as **(385)**, it seemed unlikely that a more complex molecule, such as the menthyl ester of **(378)** would permit facile synthesis and attempts were discontinued.

### 5.2.3 Helicene Synthesis

#### 5.2.3.1 Katz Synthesis

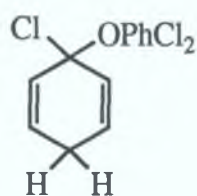
The synthesis of a helical ligand, with the potential for inclusion in a niobium species was undertaken. Initially, the method described by Katz and Pestu was followed (Scheme 95).<sup>165</sup> The first step in this route involved the reaction of 2,7-dihydroxynaphthalene with  $\text{Ph}_3\text{PBr}_2$ . This was based on a reaction developed by Wilby *et al.*<sup>168</sup> which is general for both alkyl and aryl halides. The authors did not describe the mechanism for the reaction but found that, in the case of *p*-chlorophenol, they formed *p*-chlorobromobenzene without any positional isomerism. As triphenylphosphine oxide is formed, it would appear that a nucleophilic substitution occurs with the driving force being the formation of the  $\text{P}=\text{O}$  bond in triphenylphosphine oxide.



Scheme 116

The brominating reagent was formed by addition of bromine to an acetonitrile solution of  $\text{PPh}_3$ , while maintaining the temperature below  $55^\circ\text{C}$ . The solvent was then removed and the hydroxynaphthalene added to give a solventless reaction with heating to  $200^\circ\text{C}$  for 5 days. However, only a small amount of impure material was recovered, the major problem being that  $\text{PPh}_3=\text{O}$  was very difficult to remove from the desired material.

A procedure involving the use of  $\text{PhPCl}_2$ , which involves the production of  $\text{PhP(O)Cl}_2$  as a by-product, was investigated. The stated advantage of this method is that phenylphosphonic dichloride can be removed from the reaction mixture by aqueous work-up.<sup>170</sup> This procedure has been used for both aryl and alkyl alcohols. In the case of a chiral alkyl alcohol, the product chloride was recovered in 94% ee inversion, suggesting an  $\text{S}_{\text{N}}2$  mechanism. However, in the case of aryl alcohols, the mechanism is less clear, possibly having a quinone intermediate such as (389).



(389)

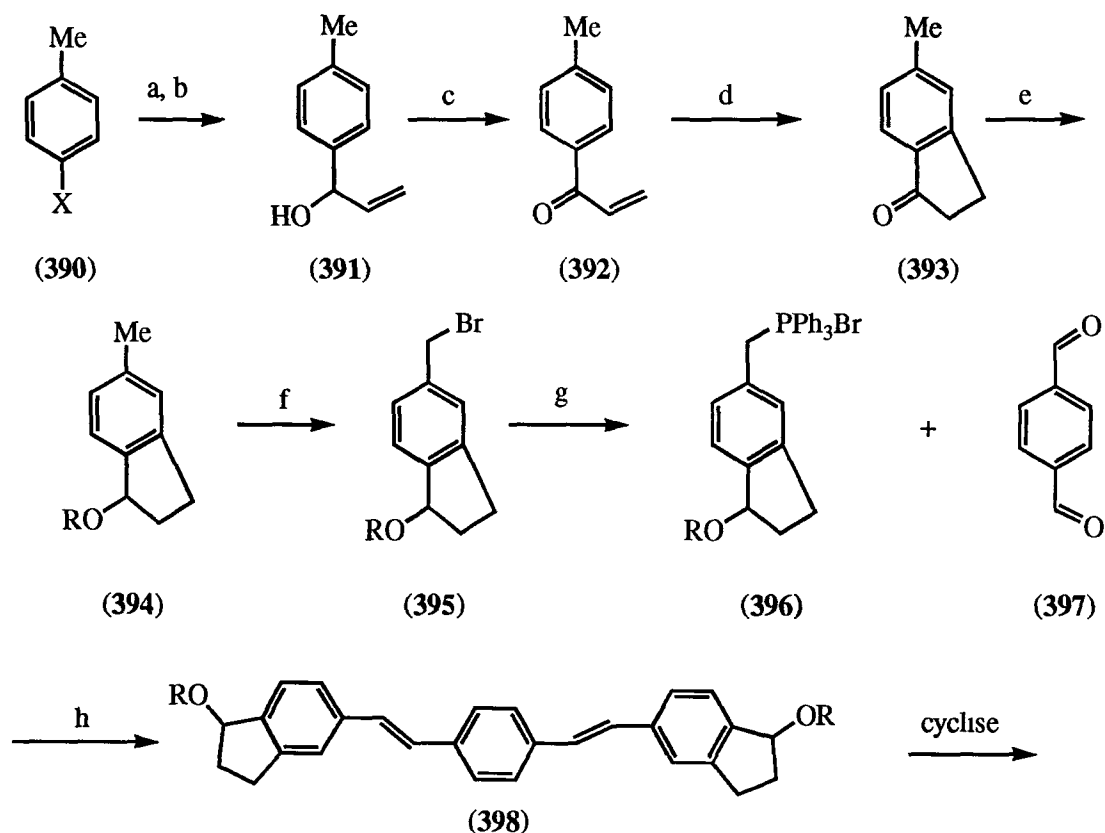
Figure 100

The reaction was performed *via* addition of  $\text{Cl}_2$  gas to  $\text{PhPCl}_2$ , maintaining the temperature below  $80^\circ\text{C}$ . A clear yellow liquid, which solidified on cooling, was formed. The 2,7-dihydroxynaphthalene was then added and the reaction heated to  $100^\circ\text{C}$  in the absence of solvent. The product was worked up and found to contain two major products. These were isolated using column chromatography with PE (100%) as the mobile phase. However, it was evident from  $^1\text{H}$  NMR that, although the material could not be further purified using chromatography, there was a mixture of several

isomers present. The expected symmetrical spectrum for 2,7-dichloronaphthalene was not present. Thus the method was discontinued.

### 5.2.3.2 Second Method

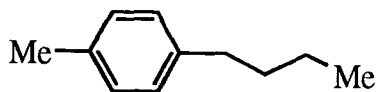
A new reaction scheme, based in part on the Katz synthesis, was then devised, which did not depend on the use of 2,7-dihydroxynaphthalene.



a) BuLi / THF, b) acrolein, c) chromic acid / acetone, d) conc H<sub>2</sub>SO<sub>4</sub>, e) Base, RCl / THF, f) NBS / CCl<sub>4</sub>, g) PPh<sub>3</sub> / MeOH, h) Base / DCM,

Scheme 117

A number of variants of this route were attempted. The initial reaction between halotoluene and acrolein was performed using either a Grignard reaction or BuLi. It was found that reaction with chlorotoluene did not proceed. There was an initial difficulty with the bromo compound in that a large amount of an impurity was found to be present if BuLi was used. NMR revealed this to be 4-*n*-butyl toluene (399).



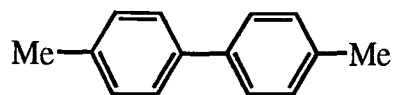
(399)

Figure 101

This was caused by allowing the reaction mixture of bromotoluene and BuLi to warm to 0°C from -78°C, prior to the addition of acrolein. This allowed the toluyl anion to attack BuBr. Maintaining low temperature prior to addition of acrolein was found to eliminate the problem. Following reaction the recovered material was worked up and distilled under vacuum at 150°C. NMR and IR were consistent with the proposed structure. Of particular note was the symmetrical aromatic structure and the vinylic peaks in NMR between 5.14 and 5.36 ppm and 6.01 and 6.09 ppm. In IR the OH stretch at 3413 cm<sup>-1</sup> was the most prominent feature.

The material was oxidised using chromic acid, prepared by a literature method<sup>171</sup>. The alcohol was dissolved in acetone and then cooled to 0°C followed by dropwise addition of oxidant. The orange solution turned blue/green as the dichromate was reduced. Recovery of the ketone proved difficult, requiring extended extraction of the aqueous/acetone solution with ethyl acetate, followed by several column clean-ups and finally distillation at 125°C. The resulting liquid gave IR and NMR spectra which were consistent with the structure of (392). The IR spectrum displayed an absence of the OH peak seen in the starting material and the presence of a carbonyl stretch at 1651 cm<sup>-1</sup>.

Because the ketone was formed in relatively low yield, a number of alternative syntheses were attempted. Firstly, it was considered whether the formation of the alcohol could be avoided by reaction of the toluyl anion or toluyl Grignard reagent with acryloyl chloride. This kind of procedure has literature precedent.<sup>172</sup> It was necessary to prepare the Grignard and then add this dropwise to two equivalents of acryloyl chloride in order to prevent the desired ketone from being reduced to an alcohol by another molecule of toMgBr. A number of compounds were recovered from the Grignard reaction but analysis showed that none was the desired ketone. For the major product, IR revealed the absence of a C=O or an OH functionality. NMR showed that there were no vinyl protons and thus structure (400) was postulated.

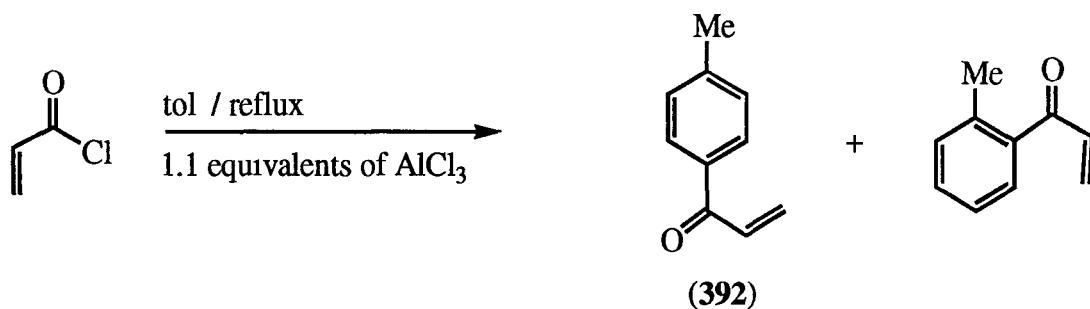


(400)

Figure 102

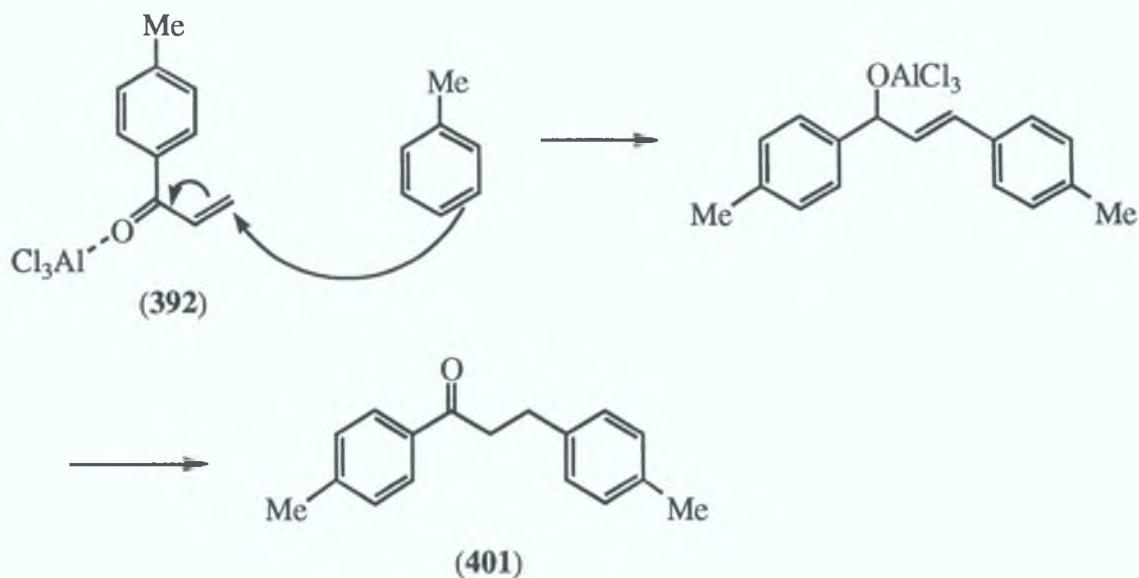
The formation of the ketone, using BuLi to generate the toluyl anion was slightly more successful. A compound, whose NMR spectrum matched that of ketone previously synthesised was recovered from the reaction. Again anion in THF was added to a solution containing two equivalents of acryloyl chloride. Unfortunately the yield of ketone *via* this method was extremely low and thus this route was discontinued.

A Friedel-Crafts acylation of toluene was then attempted. The benzene ring of toluene is activated and the presence of a methyl group in the 1-position causes *ortho* substitution to be unfavoured. Even if there was *ortho* substitution the ease of the reaction and the low cost of the reagents made it an attractive alternative.



Scheme 118

The reaction was carried out by addition of clean dry toluene to AlCl<sub>3</sub> followed by addition of acryloyl chloride in a dropwise manner. The material was worked up in the usual manner. However TLC analysis and a nominal yield of 150%<sup>1</sup> revealed that the ketone had not been formed. The liquid product was distilled at 180°C (ketone 125°C) and analysed by NMR and IR. IR revealed the presence of a carbonyl group with a peak at 1675 cm<sup>-1</sup>. This was confirmed in <sup>13</sup>C NMR with a peak at 198.96 ppm. However there were no vinylic peaks visible in proton NMR whereas alkyl peaks were in evidence. There was also a lack of symmetry in the aromatic region and two methyl peaks were present. The likely product was (401) formed by conjugate addition of toluene to compound (392).



**Scheme 119**

Ketones are more susceptible to Michael-type addition than acyl halides and the presence of the Lewis acid probably contributed to the formation. Attempts to perform this reaction in other solvents failed to produce any products.

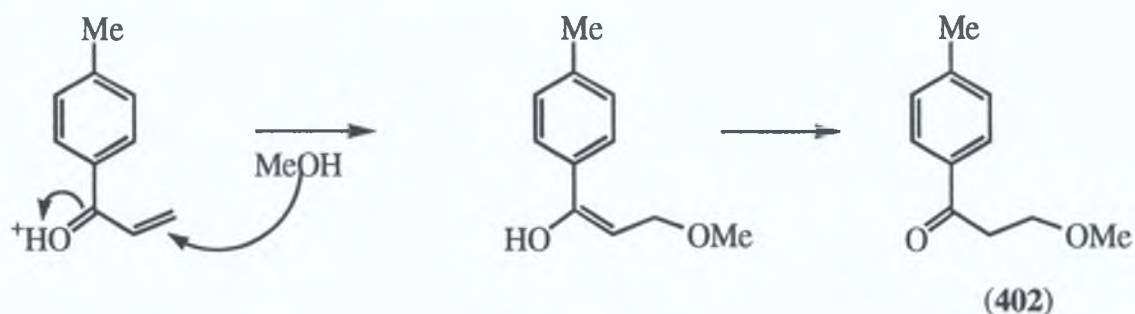
Two of the procedures in the overall mechanism were likely to be problematic, namely, the bromination of the toluyl vinyl ketone and the closure of the ketone to form an indanone-type molecule. It was decided to investigate these reactions.

The bromination reaction was attempted on a small scale by adding the ketone to NBS and benzoyl peroxide in either benzene or carbon tetrachloride. The reaction proceeded overnight at 50°C in each case. However, only starting material was recovered. This was evidenced by NMR where the integration of the methyl group was the same as before and had not been shifted downfield as might be expected in the case of a benzyl bromide.

The ring-closure of the vinyl ketone to the indanone was attempted in two ways. Firstly, the method of Katz and Pesti was examined.<sup>165</sup> The ketone was added to cold concentrated H<sub>2</sub>SO<sub>4</sub> whereby a deep red colour evolved. This was most likely due to the formation of an aromatic radical. The reaction was allowed to stir overnight. The acid was carefully neutralised using KOH solution and the product recovered by extraction with DEE. However, NMR of the products revealed that mostly starting material was present. An alternative procedure using polyphosphoric acid (PPA) was also attempted.<sup>173</sup> Ketone and PPA were added together and heated at 130°C for 30 min. The acid was cooled and then extracted with ether followed by neutralisation and

washing of the solvent. A large number of products were formed, making this method unsuitable.

It was decided to attempt to close the ring using a protic solvent and an acid catalyst to see if nucleophilic attack by the benzene ring on the vinyl group could be effected in an intramolecular fashion. Again the solvent proved to be the best nucleophile and the reaction actually observed was that shown below.

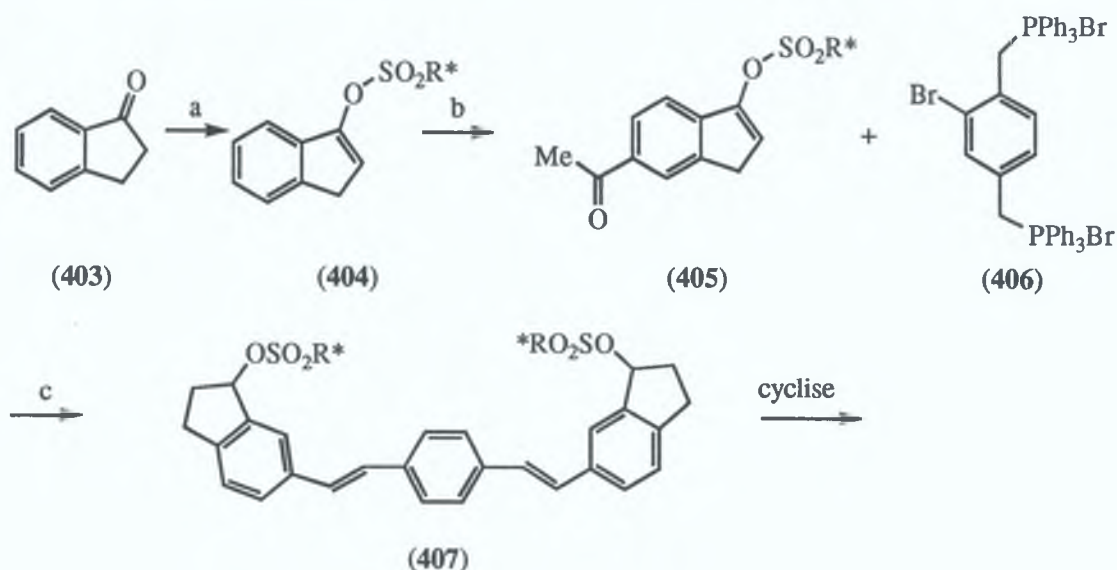


Scheme 120

NMR analysis showed two methyl groups, two triplets for the alkyl chain and a symmetrical aromatic region. IR gave a C=O stretch at  $1677\text{ cm}^{-1}$ . At this stage the unsuitability of the proposed route to the helicene was obvious.

### 5.2.3.3 Possible Alternative

A further route based on the use of indanone as a starting material might be possible.



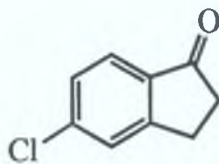
a) LDA / THF,  $\text{R}^*\text{SO}_2\text{Cl}$ ; b)  $\text{AlCl}_3$ ,  $\text{CH}_3\text{COCl}$  / nitrobenzene; c) base / DCM.

Scheme 121

This method has the advantage of possessing a five-membered terminal ring in place. The second step could produce a number of isomers, which is a weakness, but the use



of a compound such as (408) with the formation of the anion (after protection of the ketone) might overcome this problem.



(408)

**Figure 103**

The bromine atom on the aromatic ring of (406) forces the compound to cyclise internally giving helicene as opposed to an S-shaped compound.<sup>174</sup>

It was ultimately not feasible to synthesise the helicene structure due to lack of resources. Thus the goal of comparing forms of chirality was not fulfilled.

### 5.3 CONCLUSION

In enantioselective reactions, the ligands used generally bear elements of central chirality. A comparison with the inductive powers of other forms of chirality such as planar and helical chirality have not been made. The potential to form compounds of niobium and tantalum, bearing these various elements of chirality, was seen as a useful point of departure to investigate this area.

There was literature precedent for the formation of chiral *bis*-sandwich niobium complexes, either by direct route or by the initial formation of half-sandwich complexes. The latter route was seen as being more efficient and was chosen for this work. A niobocene peroxo compound was used in the catalytic epoxidation of cyclohexene and this was seen as a possible test reaction on which to compare the inductive powers of each mode of chirality.

The target molecule, in terms of planar chirality was one bearing an indene ligand with 1, 2-substitution. As part of the investigation, test reactions involving unsubstituted indene were attempted. However, despite repeated attempts to form the unsymmetrical  $CpInNbO_2Cl$ , it was found that this was not possible. The fact that Nb compounds catalyse the formation of 1, 1-bi-H-indene may have been responsible.

The synthesis of a terminal five-membered ring heptahelicene was attempted. Initially a literature procedure was attempted. However, a significant number of the reactions used in the formation of helicene by this method failed to produce the expected results in our hands. Alternative synthetic routes were examined. Attempting to synthesise toluyl vinyl ketone, directly, by the use of a Friedel-Crafts reaction or the addition of toluyl anion to acryloyl chloride failed to provide the required product. Thus the initial formation of alcohol and subsequent oxidation to the ketone was the most efficient method. The failure of some key reactions, significantly the closure of the vinyl ketone to the indanone structure and the formation of the bromo compound, made this particular reaction route unfavourable. A route starting from an indanone-type compound might yield better results.

Overall the organometallic chemistry of niobium proved to be complex and challenging. The performance of reactions which were superficially analogous to literature reactions bore little fruit as the actual differences appear to have been substantial. The investigation of different modes of chirality still appears to be a worthwhile venture, though perhaps niobium chemistry does not provide the accessibility required.

## 5.4 EXPERIMENTAL

Equipment used and purifications performed were as described in previous chapters.

### 5.4.1 Reactions with Peroxide

#### Niobocene dichloride and hydrogen peroxide (1)

Niobocene dichloride (59.2 mg, 0.201 mmol) was placed in a dry 50-ml round-bottom flask with dry DCM (20 ml). The suspension was purged with argon for 5 min to remove oxygen. It was then stirred and H<sub>2</sub>O<sub>2</sub> (30% aq soln, 0.6 ml) was added dropwise. The resulting solution was left stirring for 1 h, whereupon it had turned from brown to pale yellow. The aqueous layer was extracted with DCM (3 x 4 ml) and the organic fractions were combined. The solvent was evaporated and the resulting crude solid (50.4 mg, 91%) was recrystallised from EtOH. Yield = 35.2 mg (63.6%) m.p

185–187°C (Lit 195°C). IR  $\nu_{\max}$  3035, 1247, 825  $\text{cm}^{-1}$ .  $\delta_{\text{H}}[\text{CDCl}_3]$  showed the following signal:- 6.27 (s).  $\delta_{\text{C}}[\text{CDCl}_3]$  showed the following signal - 114.94

#### Niobocene dichloride and hydrogen peroxide (2)

Niobocene dichloride (310.4 mg, 1.056 mmol) was placed in dry DCM and treated with  $\text{H}_2\text{O}_2$  (30% aq. soln, 2.50 ml) as described above. However the recovered solid was recrystallised from DCM rather than EtOH. Yield = 168.3 mg (55.0%) m.p. 175–177°C (Lit. 180°C). IR  $\nu_{\max}$  3057, 1100, 868  $\text{cm}^{-1}$ .  $\delta_{\text{H}}[\text{CDCl}_3]$  showed the following signals - 6.21 (s).  $\delta_{\text{C}}[\text{CDCl}_3]$  showed the following signals - 114.92

### 5.4.2 Unsymmetrical Niobium Compounds

#### Cyclopentadienyl indenyl chloroniobium peroxide (385) (A)

High surface area sodium (900 mg) was made by first freeing the metal of oil in toluene with heating to remove the surface oxide layer. The clean metal was placed in dry toluene and the mixture boiled. The solvent, containing the melted metal, was then shaken vigorously at which point the sodium formed small pellets. These were transferred to the reaction vessel. Freshly distilled indene (2.36 g, 0.020 mol) was added and the solution boiled under reflux for 24 h. Trimethylsilyl chloride (2.36 g, 0.022 mol) was then added and boiling continued for a further 24 h. The solution was filtered and the solvent removed under vacuum. The resulting oil was distilled under vacuum with the desired TMS-indene distilling at 90°C (indene 40°C). Yield = 1.82 g (28.7%).  $\nu_{\max}$  3011  $\text{cm}^{-1}$ .  $\delta_{\text{H}}[\text{CDCl}_3]$  showed the following signals - 0.04 (9 H, s), 3.55 (1 H, s), 6.68 (1 H, d,  $J=3.7$  Hz), 7.00 (1 H, d,  $J=5.6$  Hz), 7.26 (1 H, t,  $J=7.4$  Hz), 7.32 (1 H, t,  $J=7.4$  Hz), 7.49 (2 H, t,  $J=7.4$ ).  $\delta_{\text{C}}[\text{CDCl}_3]$  showed the following signals - -0.26, 46.47, 122.63, 123.54, 124.69, 128.80, 135.74. (382). Several batches were made and the highest yield was 40%.

Compound (382) (1.08 g, 5.700 mmol) were dissolved in DCM (20 ml) and added to a suspension of  $\text{NbCl}_5$  (1.43 g, 5.258 mmol) in dry DCM (10 ml) in a 50-ml round-bottom flask. A deep red colour developed immediately. Solvent was removed and the solid (383) protected from light. Sodium cyclopentadienide (0.48 g, 5.500 mmol) was added to a suspension of (383) in DCM. The mixture was stirred for 24 h in an inert atmosphere. Solvent was removed to reveal a brown solid. Fresh DCM was added along with  $\text{H}_2\text{O}_2$  (30% aq. soln, 1.5 ml). The mixture was allowed to stir for 1 h. The

aqueous layer was extracted with DCM and the organic layers combined and dried over  $\text{MgSO}_4$ . Solvent was filtered and removed under vacuum. A brown tar, which showed an extremely large number of broad peaks in  $^1\text{H}$  NMR (indicating paramagnetic impurities) was recovered. Attempts to purify this failed.

#### **Indenyl niobium tetrachloride**

Indene (4.27 g, 0.037 mol) was placed in dry DCM in a 100-ml round bottom flask. The solution was purged with argon and cooled to  $-78^\circ\text{C}$ . Butyl lithium (2.5 M, 15 ml) was added slowly and allowed to react for 1 h. Freshly distilled  $\text{TMSCl}$  (4.40 g, 0.041 mol) was added slowly and the solution allowed to warm to room temperature. The mixture was stirred for 12 h. The mixture was poured into ice-water and stirred for 30 min. The organic layer was recovered and the aqueous layer was washed with PE (3 x 10 ml). The organic fractions were combined and washed with water, dried over  $\text{MgSO}_4$ , filtered and the solvent removed under vacuum. The resulting oil was distilled at  $90^\circ\text{C}$  under vacuum. Yield = 4.79 g, (69.0%). NMR matched the details described above.

Niobium pentachloride (6.56 g, 0.024 mol) was placed in dry DCM and stirred under argon. TMS-indene (4.79 g, 0.025 mol) was dissolved in DCM and added slowly to the suspension of  $\text{NbCl}_5$ . A deep red colour resulted. The material was boiled under reflux for 10 min. Solvent was removed and a red powder was recovered. Yield = 7.50 g (84.3%). A portion of this was sublimed at  $120^\circ\text{C}$  under vacuum and a small amount of material was recovered. Analysis: Calculated for  $\text{C}_9\text{H}_7\text{NbCl}_4$ ; % C (30.91) H (2.02); Found; % C (42.84) H (3.82). Elemental analysis revealed that the desired compound was not present.

#### **Cyclopentadienyl indenyl niobium dichloride (384)**

The compound synthesised above (2.12 g, 6.00 mmol) was placed in dry DCM under argon and stirred. A solution of  $\text{LiCp}$  (0.47 g, 6.50 mmol) in 5 ml DCM was added slowly and the mixture allowed to stir for 18 h. The resulting brown solid was filtered and washed with PE (4 x 5 ml). It was dried under vacuum for 24 h and elemental analysis performed. Analysis: Calculated for  $\text{C}_{14}\text{H}_{12}\text{NbCl}_2$ ; % C (48.73) H (3.51); Found; % C (60.21) H (4.43). This revealed it not to be the desired compound.

### Cyclopentadienyl indenyl chloroniobium peroxide (385) (B)

Cyclopentadiene (3.22 g, 0.047 mol) was dissolved in THF at  $-80^{\circ}\text{C}$ . Butyl lithium (2.5 M, 19 ml) was added slowly. The solution was allowed to stir for 1 h. Trimethylsilyl chloride (5.30 g, 0.049 mol) was added slowly and the solution allowed to warm to room temperature. It was stirred for 18 h. The mixture was poured into ice-water and stirred for 30 min. The material was then worked up as described for TMS-indene. The oil resulting was distilled at  $80^{\circ}\text{C}$  at normal atmosphere.  $\delta_{\text{H}}[\text{CDCl}_3]$  showed the following signals: -0.03 (9 H, s), 3.43 (1 H, s), 6.51 (2 H dd,  $J=5.7, 3.5$  Hz), 6.61 (2 H, dd,  $J=5.7, 3.5$  Hz)

Niobium pentachloride (3.27 g, 0.012 mol) was placed in a 100-ml round-bottom flask with dry DCM. Trimethylsilyl cyclopentadiene (2.00 g, 0.013 mol) were added as a solution in DCM. A red colour immediately appeared. The material was stirred for 1 h before being filtered and washed with 4 x 5 ml PE. The solid was dried under vacuum overnight. Yield = 1.14 g (27.5%).  $\delta_{\text{H}}[\text{DMSO}]$  showed the following signals - 5.86 (15 H, br s), 6.25 (5 H, s). The peak at 6.25 ppm matches the literature value and the peak at 5.86 is probably due to water from DMSO co-ordinating to the metal.

Cyclopentadienyl niobium tetrachloride (1.14 g, 3.300 mmol) was placed in MeCN under argon and Al powder (42.5 mg, 1.574 mmol) added. The solution was stirred for 18 h. The solvent was removed and dry THF added. Indenyl lithium (459.0 mg, 3.297 mmol) was added. The reaction was stirred for 2 h at which time a brown solid was filtered out. This was washed with PE (2 x 5 ml). It was redissolved in DCM and  $\text{H}_2\text{O}_2$  added. No solid products could be recovered from this reaction.

### 5.4.3 Helicene Synthesis

#### Formation of 2,7-dibromonaphthalene

Triphenyl phosphine (15.98 g, 0.061 mol) was placed in dry MeCN and partially dissolved. Bromine (26.30 g, 5.12 ml, 0.329 mol) was added over 2.5 h, keeping the temperature below  $50^{\circ}\text{C}$ . The solvent and excess bromine were removed under vacuum and 2,7-dihydroxynaphthalene (7.99 g, 0.050 mol) added. DMF was also added and the mixture boiled under reflux for 5 days. The material was worked up by placing the solution in ice-water and stirring. The aqueous layer was extracted with DEE. A

minute amount of material was recovered, but was found to be contaminated with  $\text{Ph}_3\text{P}=\text{O}$

#### **Formation of 2,7-dichloronaphthalene**

Chlorine gas was formed by the action of 30 ml of conc HCl on 3.52 g of  $\text{KMnO}_4$ . Phenylphosphorous dichloride (8.95 g, 0.050 mol) were placed in a 250-ml three-neck round-bottom flask and  $\text{Cl}_2$  was passed through. The temperature was maintained below  $80^\circ\text{C}$ . 2,7-Dihydroxynaphthalene (4.00 g, 0.025 mol) was added in one portion. The material was heated to  $150^\circ\text{C}$  with stirring and allowed to react for 18 h. The resulting black mixture was poured into ice-water and stirred. It was neutralised with KOH. The aqueous phase was extracted with 5 x 40 ml DEE. Analysis by TLC (mobile phase = 100% PE) revealed two spots. The largest of these was purified out and analysed by  $^1\text{H}$  NMR  $\delta_{\text{H}}[\text{CDCl}_3]$  showed the following signals:- 7.31 (dd), 7.47 (d), 7.49 (s), 7.52 (s), 7.67 (s), 7.69 (s), 7.74 (s), 7.76 (t), 8.26 (d). This did not match the NMR expected for 2,7-dichloronaphthalene and probably was a mixture of inseparable isomers

#### **Formation of (391) (A)**

4-Bromotoluene (8.55 g, 0.050 mol) was dissolved in dry THF. The solution was purged with argon and cooled to  $-78^\circ\text{C}$ . Butyl lithium (2.5 M, 20 ml) was added slowly and the solution allowed to warm to room temperature. The solution was cooled again and freshly distilled acrolein (3.08 g, 3.65 ml, 0.055 mol) was added dropwise. The reaction was allowed to warm to room temperature and stirred for 18 h. The THF was poured into ice-water and stirred for 30 min. The mixture was extracted with 3 x 20 ml DEE. The solvent was removed and an oil recovered. Yield = 8.62 g. IR  $\nu_{\text{max}}$  2995, 2887, 1553, 1390, 705  $\text{cm}^{-1}$ .  $\delta_{\text{H}}[\text{CDCl}_3]$  showed the following signals - 1.11 (3 H, q,  $J=6.9$  Hz), 1.54 (2 H, br m,  $J=7.9$  Hz), 1.76 (2 H, br m,  $J=2.9$  Hz), 2.48 (3 H, s), 2.75 (br m,  $J=7.88, 4.5$  Hz), 7.24 (2 H, d,  $J=7.9$ ), 7.25 (2 H, d,  $J=7.9$ ).  $\delta_{\text{C}}[\text{CDCl}_3]$  showed the following signals:- 21.02, 25.50, 67.85, 75.04, 114.70, 126.20, 129.12, 140.32. These data are consistent with 4-*n*-butyl toluene

#### **Formation of (391) (B)**

4-Bromotoluene (17.10 g, 0.100 mol),  $\text{BuLi}$  (2.5 M, 40 ml) and acrolein (6.85 g, 7.3 ml, 0.110 mol) were treated as described above, except that the solution was not allowed to warm following addition of  $\text{BuLi}$ . The resulting oil was distilled on Kugelrohre at  $150^\circ\text{C}$ . Yield = 10.05 g (40.0%) IR  $\nu_{\text{max}}$  3412, 3010, 2919, 1507, 810

cm<sup>-1</sup>  $\delta_{\text{H}}$ [CDCl<sub>3</sub>] showed the following signals - 2.38 (3 H, s), 2.55 (1 H, br s), 5.15 (1 H, d,  $J=5.9$  Hz), 5.19 (1 H, d,  $J=10.8$  Hz), 5.22 (1 H, d,  $J=16.74$  Hz), 6.01–6.09 (1 H, m,  $J=5.9, 6.9, 4.9$  Hz), 7.19 (2 H, d,  $J=7.9$  Hz), 7.28 (2 H, d,  $J=7.9$  Hz).  $\delta_{\text{C}}$ [CDCl<sub>3</sub>] showed the following signals.- 21.07, 75.09, 14.78, 126.26, 129.17, 139.68, 149.33

#### Formation of (392) (A)

Alcohol (391) (10.00 g, 0.067 mol) was dissolved in 25 ml of acetone and cooled on ice. An excess of chromic acid was added dropwise and the orange colour turned to green/blue. The reaction was observed to be complete when the orange colour returned. Isopropyl alcohol was then added to quench. This solution was extracted with ethyl acetate. The solvent was dried, filtered and removed under vacuum. The resulting yellow oil was distilled at 125°C. Yield = 2.65 g (27.1%). IR  $\nu_{\text{max}}$  2909, 1651, 1398, 1234, 770 cm<sup>-1</sup>.  $\delta_{\text{H}}$ [CDCl<sub>3</sub>] showed the following signals.- 2.43 (3 H, s), 5.90 (1 H, dd,  $J=10.3, 2.0$  Hz), 6.43 (1 H, dd,  $J=1.5, 16.9$  Hz), 7.17 (1 H, dd,  $J=10.3, 6.9$  Hz), 7.28 (2 H, d,  $J=7.9$  Hz), 7.87 (2 H, d,  $J=7.9$  Hz).  $\delta_{\text{C}}$ [CDCl<sub>3</sub>] showed the following signals.- 21.61, 128.79, 129.28, 129.67, 129.81, 132.29, 134.68, 198.95

#### Formation of (392) (B)

Magnesium metal (2.00 g, 0.080 mol) was placed in dry THF and one crystal of I<sub>2</sub> added. 4-Bromotoluene (6.84 g, 0.040 mol) was added dropwise in THF. Reaction proceeded vigorously. In a separate vessel acryloyl chloride (7.35 g, 0.081 mol) was dissolved in THF. This was cooled to -78°C and the Grignard reagent added over 30 min. The reaction was left for 18 h. 5.49 g of an oil was recovered after work-up. TLC was inconsistent with the ketone.  $\delta_{\text{H}}$ [CDCl<sub>3</sub>] showed the following signals - 2.41 (3 H, s), 7.25 (2 H, d,  $J=7.9$  Hz), 7.49 (2 H, d,  $J=7.9$  Hz).  $\delta_{\text{C}}$ [CDCl<sub>3</sub>] showed the following signals - 21.07, 126.79, 129.42, 138.27. This is consistent with structure (400).

#### Formation of (392) (C)

4-Bromotoluene (17.10 g, 0.100 mol) was dissolved in dry THF and cooled to -78°C. BuLi (2.5 M, 40 ml) was added slowly. After 30 min acryloyl chloride (19.00 g, 17.00 ml, 0.2 mol) was added slowly. The reaction was allowed to warm to room temperature and it proceeded for 18 h. After work-up a small amount of oil was recovered and distilled. Yield = 1.21 g (8.3%). NMR data matched that of (392) above

### Formation of (392) (D)

Aluminum trichloride (16.02 g, 0.120 mol) was added to freshly distilled toluene (50 ml). Acryloyl chloride (9.05 g, 8.1 ml, 0.100 mol) was added slowly over 15 min. The solution changed from yellow to red and on boiling under reflux for 1 h, to brown. The mixture was poured onto ice and KOH added. The aqueous layer was extracted with 2 x 20 ml DEE. This was washed, dried over MgSO<sub>4</sub>, filtered and solvent removed. The resulting oil was distilled and 21.56 g of material collected. (Nominal yield = 150%). IR  $\nu_{\max}$  2968, 1675, 751 cm<sup>-1</sup>.  $\delta_{\text{H}}[\text{CDCl}_3]$  showed the following signals: 2.34 (3 H, s), 2.43 (3 H, s), 3.04 (2 H, dd,  $J=9.8, 8.9$  Hz), 3.27 (2 H, dd,  $J=9.8, 8.9$  Hz), 7.14–7.18 (4 H, m), 7.26 (2 H, d,  $J=7.9$  Hz), 7.89 (2 H, d,  $J=7.9$  Hz).  $\delta_{\text{C}}[\text{CDCl}_3]$  showed the following signals: 19.29, 21.57, 29.73, 40.44, 126.09, 126.21, 128.09, 128.23, 128.65, 129.12, 135.49, 143.79, 198.98. These data are consistent with structure (401).

### Formation of bromo-(392)

Compound (392) (292.0 mg, 2.00 mmol) was placed in a 50-ml round-bottom flask and 20 ml of CCl<sub>4</sub> added. *N*-bromosuccinimide (NBS) (360.0 mg, 2.00 mmol). Benzoyl peroxide (20 mg) was added as initiator. The reaction was heated to 50°C for 3 h. After filtration and work-up, starting material was recovered.

### Formation of indanone (A)

Compound (392) (1.00 g, 6.850 mmol) was added dropwise at 0°C to conc. H<sub>2</sub>SO<sub>4</sub>. The reaction was allowed to proceed for 24 h. The acid was carefully neutralised and the resulting solution extracted with DEE. Starting material was recovered.

### Formation of indanone (B)

Compound (392) (1.00 g, 6.850 mmol) was added dropwise to polyphosphoric acid in a 25-ml round-bottom flask. The reaction was heated to 130°C for 30 min. The mixture was added to water and extracted with DEE. This was then neutralised and washed and dried as before. The solution was treated with decolourising charcoal. TLC analysis revealed eight products.

### Formation of indanone (C)

Compound (392) (1.00 g, 6.850 mmol) was stirred in MeOH and TsOH (50 mg) was added. The mixture was heated under reflux for 72 h. The mixture was worked up and the product purified by column chromatography (PE:EA (90:10)). Yield = 161.0 mg.



IR  $\nu_{\max}$  2986, 2931, 1677, 1606, 1330, 1115, 978, 794  $\text{cm}^{-1}$ .  $\delta_{\text{H}}[\text{CDCl}_3]$  showed the following signals 2.37 (3 H, s), 3.18 (2 H, dd,  $J=6.9, 9.8$  Hz), 3.39 (3 H, s), 3.79 (2 H, dd,  $J=6.9, 9.8$  Hz), 7.22 (2 H, d,  $J=7.9$ ), 7.84 (2 H, d,  $J=7.9$ ) These data are consistent with structure **(402)**

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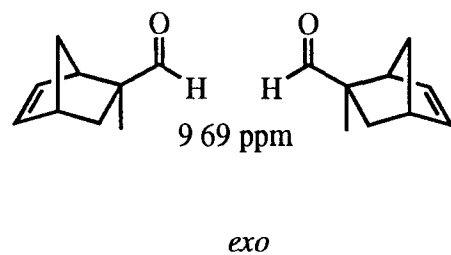
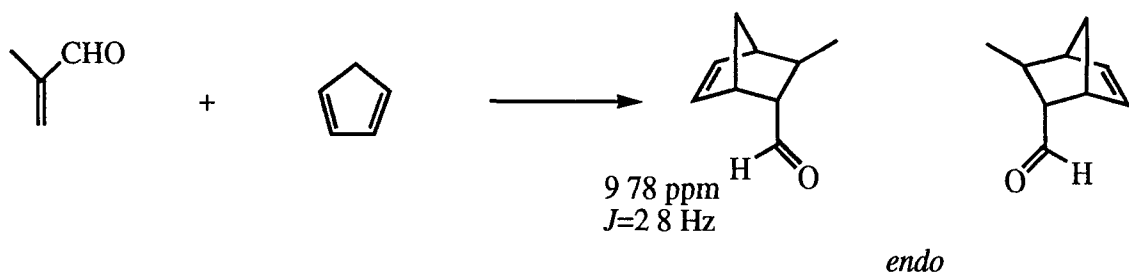
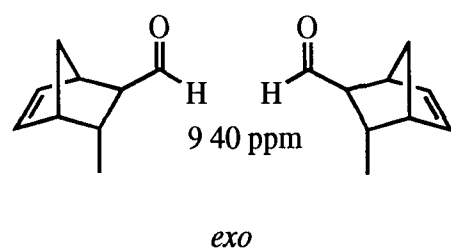
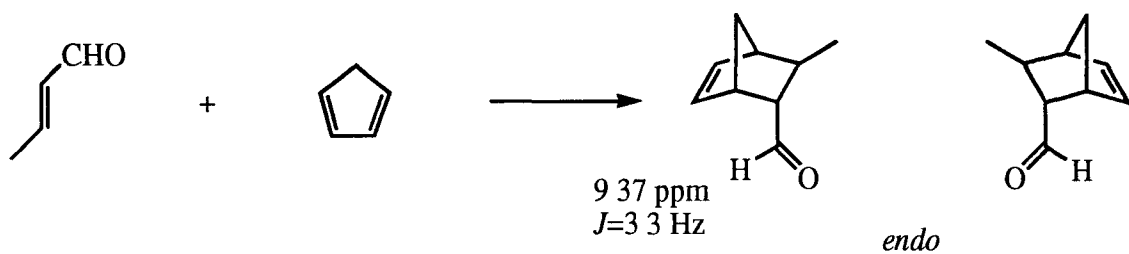


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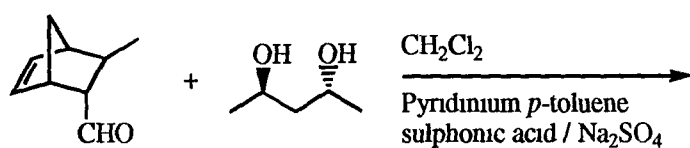
## APPENDIX A

### Structure of the products from the Diels–Alder Reaction and the shifts for the Aldehydic Protons

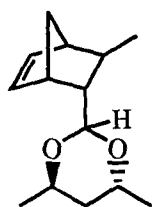


## APPENDIX B

### Determination of Enantiomeric Excess for the Crotonaldehyde Adduct using 2*R*,4*R*-Pentanediol

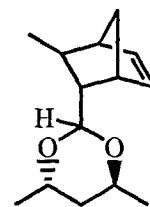


All isomers



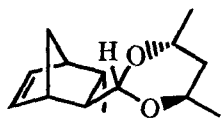
4.11 ppm, doublet,  $J=2.1$  Hz

*Endo S* Product



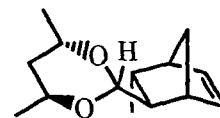
4.13 ppm, doublet,  $J=2.1$  Hz

*Endo R* Product



4.64 ppm, doublet,  $J=1.9$  Hz

*exo S* Product

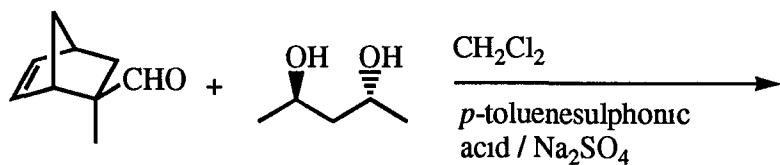


4.64 ppm, doublet,  $J=1.9$  Hz

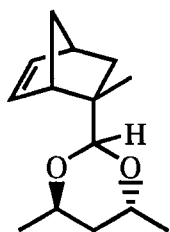
*exo R* Product

## APPENDIX C

### Determination of Enantiomeric Excess for the Methacrolein Adduct using 2*R*,4*R*-Pentanediol

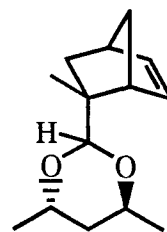


All isomers



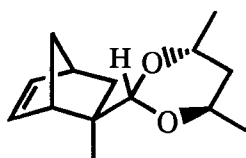
4 20 ppm, singlet

*Endo R* Product



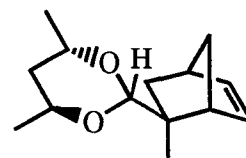
4 22 ppm, singlet

*Endo S* Product



4 66 ppm, singlet

*exo R* Product



4 68 ppm, singlet

*exo S* Product