Asymmetric Catalysis of Cyanide Addition Reactions Using Metal(Salen) Complexes

A thesis submitted for the Degree of Doctor of Philosophy

by

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Contents.

Declaration

The work presented in this thesis was carried out at the University of Newcastle Upon Tyne chemistry department between September 2006 and September 2009. The work contains no material which has been accepted for the award of any other degree or diploma in any other university or other institution, and, to the best of my knowledge and belief, contains no material previously published or written by any other person, except where due reference has been made in the text.

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Acknowledgements

Firstly I would like to thank my supervisor Professor Michael North for his guidance throughout the past three years and, also to the EPSRC and the University of Newcastle Upon Tyne for the financial support throughout my studies. Without this, this work would not have been possible. I would also like to thank all the technical and clerical staff in the department, past and present, for their help with various issues throughout my time at Newcastle University.

I have so many people I want to thank, first my family for all their support especially towards the end of my PhD. Next I would like to warmly thank all the great friends I made over the past three years. Unfortunately some of these people have now left Newcastle and moved onto other things. I would like to thank; Carl, Marta, Pedro, Eisuke, Jamie, Riccardo, Jaisiel, Ruth, Sophie, Victoria, Jenny, Kris and Luke. I hope I have not missed anyone!

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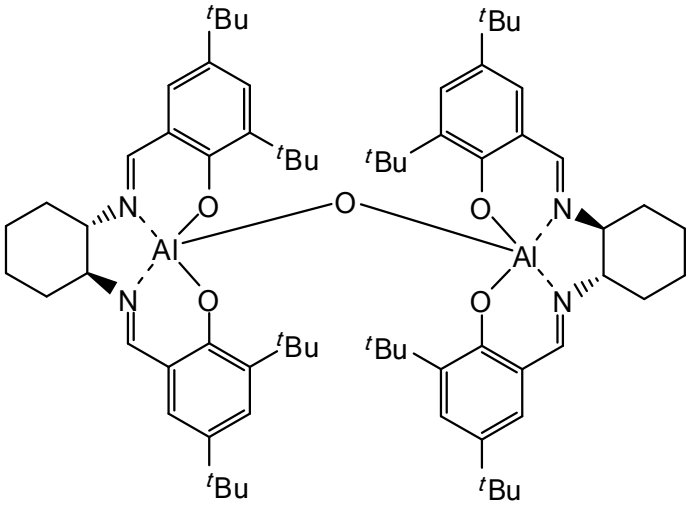
Thank you to you all. I am grateful for the support you have all given me.

Abbreviations

$[\alpha]_D$	optical rotation at the sodium-D-line
ee	enantiomeric excess
GC	gas chromatography
IR	infrared
Lit.	literature
MS	mass spectrometry
NMR	nuclear magnetic resonance
UV	ultraviolet

Abstract.

Chiral cyanohydrins and α-aminonitriles are versatile intermediates and are of great importance to the pharmaceutical industry due to the ability to convert them into useful chemicals via simple chemical transformations. Chiral cyanohydrins and α-aminonitriles can be obtained from asymmetric cyanohydrin synthesis and asymmetric Strecker reactions respectively. In this project, bimetallic aluminium(salen) complex **1** was studied extensively and was shown to be very active in cyanohydrin synthesis using trimethylsilylcyanide (TMSCN), giving the cyanohydrin trimethylsilyl ether derived from benzaldehyde with 89% (*S*) enantioselectivity and 80% conversion after 18 hours at -40 ^{o}C. A variety of substituted benzaldehydes were screened giving moderate to excellent enantioselectivities. Ketones were also shown to be substrates when used in this catalytic system. Extensive kinetic studies of complex **1** gave the rate equation; rate = k[TMSCN][Ph_3PO][**1**] which is zero order with respect to benzaldehyde. A Hammett study using complex **1** showed that this catalytic system was dominated by Lewis basic catalysis, resulting from the activation of trimethylsilylcyanide by triphenylphosphine oxide. The catalyst was then responsible for the chirality of the product rather than the activation of the aldehyde.



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A variety of other titanium and vanadium(salen) complexes, containing various substituents on the aromatic ring of the salen ligand were synthesised and screened in the Strecker reaction and cyanohydrin synthesis under different reaction conditions. Enantiomeric excesses of 10-95% (*R* and *S*) were achieved with conversions of 10-100% for both reactions.

1.1 Introduction

1.1.1 Salen Ligands in Asymmetric Catalysis.

Salen ligands are commonly used throughout asymmetric synthesis as chiral ligands. The ligand can act as a tetradentate dianionic species, with the ability to co-ordinate to almost any element in the Periodic Table. This opens up the possibility to synthesise a large number of metal salen complexes, displaying catalytic activities in a wide range of useful organic transformations. These transformations include; alkene epoxidation,[1] Darzen's condensations,[2] CO_2 fixation to form cyclic carbonates[3] and many others.[4,5] The structure of the salen ligand can vary depending on the aromatic substituents and the nature of the diamine used in the synthesis. The basic salen structure is shown in Figure 1. The structure of these ligands can vary enormously as the possible number of substituents for both the aromatic rings and diamine moieties are vast and can be prepared using simple chemical techniques.[6,7] Having the ability to modify the ligand structure allows any salen metal complex to be finely tuned, both sterically and electronically, to meet the requirements of the reaction for which it will be used. Since many of these complexes have been shown to display high levels of stereocontrol, this is a huge advantage in a forever expanding, vital area of synthetic and asymmetric catalytic chemistry.

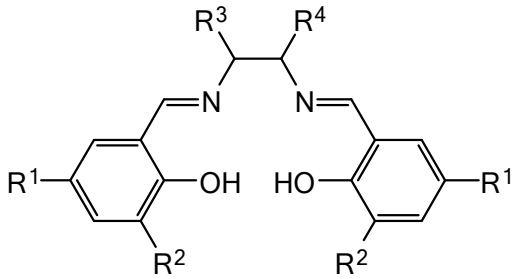


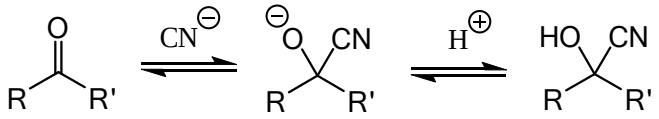
Figure 1: basic structure of the salen ligand

Due to the diverse applications of salen ligands in asymmetric reactions, metal(salen) complexes were chosen as the focus of this research concentrating on two fundamental reactions in asymmetric catalysis; the Strecker reaction and cyanohydrin synthesis.

1.1.2 Introduction to Cyanohydrin Synthesis.

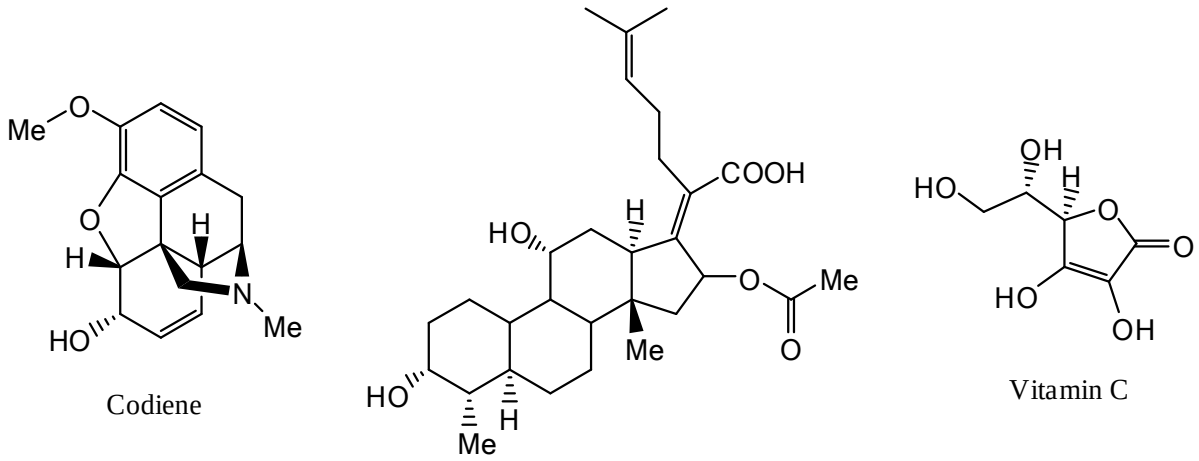
Cyanohydrin synthesis (Scheme 1) is the nucleophilic addition of cyanide to a carbonyl bond, forming the cyanohydrin functional group. Cyanohydrin synthesis is one of the most fundamental reactions in organic synthesis as a new carbon-carbon bond is formed. The first reported cyanohydrin synthesis was in 1832[8] and this involved the use of hydrogen cyanide. Due to the toxicity of this reagent, a lot of work has followed, exploring the use of alternative cyanide sources. A variety of reagents have been found to be effective at

delivering cyanide to the carbonyl bond, including; cyanoformates,[9] cyanophosponates[10] and acyl cyanides.[11]



Scheme 1: cyanohydrin synthesis.

Trimethylsilylcyanide is the most common cyanide source used in cyanohydrin chemistry. The advantage of using trimethylsilylcyanide is that it is a liquid, so handling is easier and also the product obtained is the silyl protected cyanohydrin. Protected cyanohydrins are less susceptible to hydrolysis back to the starting materials and are less prone to racemisation. From this species a variety of different products can be obtained via simple chemical transformations. Addition of cyanide to a carbonyl transforms the carbon from sp^2 to sp^3 hybridisation and may cause the product to be chiral. Asymmetric synthesis is an increasingly important area of chemical synthesis and is widely used in the production of many commonly used drug molecules. Figure 2 shows some common molecules used in the pharmaceutical and drugs industry which all possess multiple chiral centres.



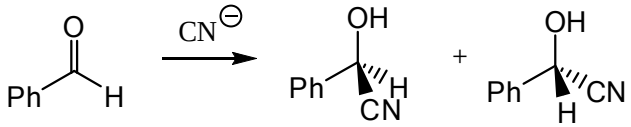
Codiene

Fusidic Acid

Vitamin C

Figure 2: common drug molecules containing stereocentres.

The introduction of chirality into target molecules is the foundation of asymmetric synthesis. The cyanohydrin forming reaction shown in Scheme 2 shows the formation of a racemic product. The cyanide can add to the *re* or *si* face of the carbonyl with equal ease to form a racemic mixture.



Scheme 2: asymmetric cyanohydrin synthesis.

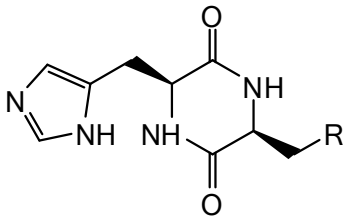
The enantiomers are denoted *R* and *S* in accordance with the Cahn-Ingold-Prelog (CIP) rules.[12] Biologically active molecules may demonstrate different activity depending on which enantiomer is being administered. One enantiomer may display positive biological activity, whilst the other maybe inactive; or the presence of one enantiomer in the racemic mixture may render the other enantiomer inactive. Also, an enantiomer may be toxic, causing a variety of side effects in the patient. Therefore, it is common for drugs to be administered as single enantiomers.

1.1.3 Asymmetric Cyanohydrin Synthesis.

The first example of asymmetric cyanohydrin synthesis was reported in 1908 by Rosenthaler[13] who successfully added hydrogen cyanide to benzaldehyde using the enzyme oxynitrilase. This enzyme was known to catalyse the hydrolysis of cyanohydrins back to hydrogen cyanide and aldehyde. As this reaction is reversible, the enzyme also catalyses the synthesis of cyanohydrins. Oxynitrilases are also capable of asymmetrically catalysing the one pot conversion of alcohols to cyanohydrins using 2,2,6,6-tetramethylpiperdine-1-oxyl (TEMPO), PhI(OAc) and hydrogen cyanide.[14] The majority of cyanohydrin forming reactions catalysed by oxynitrilases utilise hydrogen cyanide as the cyanide source. Due to the high toxicity of this species an alternative would be advantageous. Oxynitrilases have been shown to catalyse the transcyanantion between aldehydes and acetone cyanohydrin or racemic ketone derived cyanohydrins.[15] Ethyl cyanoformate can also be used as the cyanide source. The reaction takes place under organic-aqueous biphasic reaction conditions to give the (*R*)-cyanohydrin.[16]

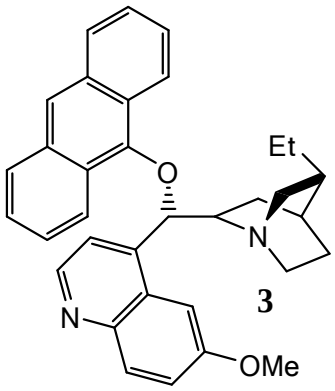
Enzymes are highly specialised biological catalysts, they work under specific conditions and with specific substrates. Due to this highly specialised nature, their effectiveness as catalysts can be limited. Changes in reaction conditions such as pH, temperature, and solvent can significantly reduce the reactivity. Enzyme structures cannot easily be optimised to improve the reaction outcome. The substrate has to be compatible with the enzyme and it may not be possible to find an enzyme to suit every reaction. If the product with the opposite stereochemistry is required, an appropriate enzyme may not be available. To overcome the limitations of enzyme based systems, various methods have been developed for asymmetric synthesis. These methods are more cost effective and give chiral products with high selectivities. For cyanohydrin synthesis, many different chiral catalysts have been developed. Based on research using enzymes, a variety of organocatalysts have been developed that can catalyse cyanohydrin forming reactions very effectively. In 1912, Bredig and Fiske demonstrated the first use of alkaloids to catalyse the addition of hydrogen cyanide

to aldehydes.[17] Chiral polyamines[18] and linear peptides[19] are also catalysts for cyanohydrin synthesis, however enantioselectivites were much lower (>20%). This was also accompanied by lower conversions.



1) R= Ph
2) R= ^{i}Pr

Inoue *et al* demonstrated the use of a cyclic dipeptide (diketopiperazine) **1** derived from phenylalanine and histidine, in the addition of hydrogen cyanide to benzaldehyde giving cyanohydrin product with 97% (*R*) enantioselectivity.[20] Catalyst **1** was compatible with aromatic aldehydes, but gave lower enantioselectivites with aliphatic substrates. Modified diketopiperazine **2** gave higher selectivity for aliphatic substrates than aromatic substrates, a result which is uncommon in cyanohydrin synthesis. Catalysts **1** and **2** gave comparable results to oxynitrilases and could utilise acetone cyanohydrin as the cyanide source, though reaction rates were lowered compared to the use of hydrogen cyanide.[21] The mechanisms of reactions catalysed by catalysts **1** and **2** are not fully understood, though kinetics studies have shown that two catalyst molecules are involved in the catalytic cycle. The reaction displays enantioselective autocatalysis and is also heterogeneous in nature with the reaction occurring in the gel phase. No further attempts have been made to improve on these findings or to optimise the catalyst structure.[22]



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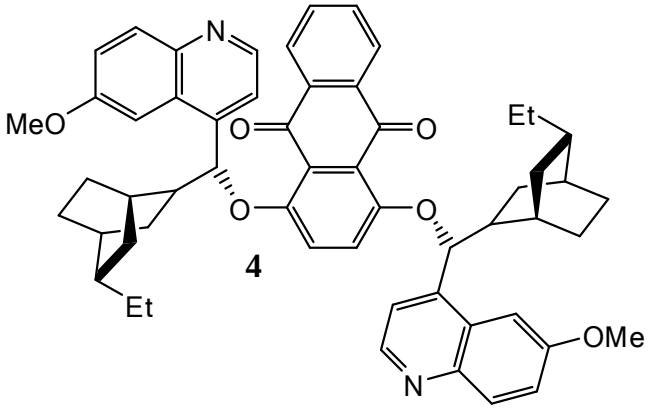

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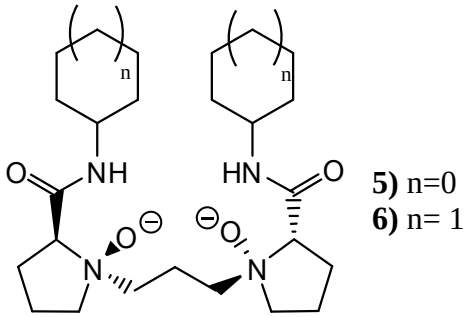
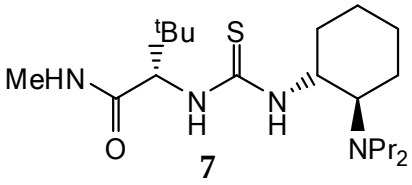
In 2001, Deng *et al* showed that monomeric **3** and dimeric **4** *O*-arylated cinchona alkaloids were excellent catalysts for cyanohydrin synthesis.[23] The group reported the addition of cyanide to aliphatic ketones using ethyl cyanoformate to give cyanohydrin ethyl carbonates with 97% enantioselectivty. Extensive analysis of the reaction mechanism revealed that this high selectivity was the result of a dynamic kinetic resolution rather than

highly selective cyanide addition. Trimethylsilylcyanide was also an efficient cyanide source and was found to be more compatible with monoacetal and 1,2-diketone substrates. Enantioselectivities of >90% were achievable using these substrates.

Nájera showed that dimeric cinchona alkaloid derived ammonium salts were effective catalysts when used in the same reaction along with the addition of triethylamine.[24] Feng used monomeric cinchona alkaloid ammonium salts in the cyanoformylation of aromatic aldehydes with enantioselectivities of 61-72%.[25] Feng also illustrated the use of chiral *N*-oxides as catalysts for racemic and asymmetric cyanohydrin synthesis,[26] thus compounds **5** and **6** will catalyse the addition of trimethylsilylcyanide to aromatic aldehydes. Interestingly, compound **5** gave better results with ketones than aldehydes giving 85-93% enantioselectivity. Compound **6** gave enantioselectivites of 53-73% with aldehyde substrates.



5) n=0
6) n= 1



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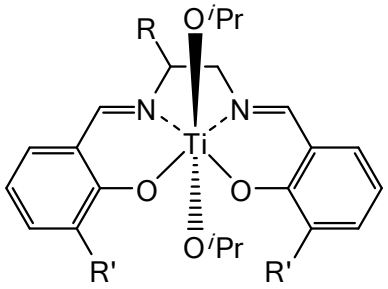
Jacobsen demonstrated the use of thioureas as asymmetric catalysts in cyanohydrin synthesis. Compound **7** was found to catalyse the addition of trimethylsilylcyanide to ketones with 86-97% enantioselectivity. Trifluoroethanol was a required additive suggesting that the true cyanating agent in this case is hydrogen cyanide. The structure of compound **7** was further optimised to allow catalysis with aliphatic ketones. This was achieved by modifying the structure of the secondary amine within the catalyst.[27]

All of the above systems have been shown to give cyanohydrin product with good to excellent enantioselectivities, however more recent advancements in ligand and catalyst design have led to much improved systems. The limitations of enzymes and organocatalysts are that the structures of the catalysts can be complex and difficult to synthesise. Also the C_1-symmetry shown by these systems makes it more difficult to study the reaction and to understand the details of the reaction mechanisms. An understanding of a reaction mechanism can be a great advantage to this research area, as improvements in both the reactivity and enantioselectivity can be achieved. Although a lot of research has been carried out with regard to enzymes and organocatalysts in the synthesis of cyanohydrin derivatives, there is still much speculation as to how these catalysts function when employed in asymmetric synthesis.

1.2 Titanium Based Salen Complexes as Catalysts for Asymmetric Cyanohydrin Synthesis.

1.2.1 Asymmetric Cyanation of Aldehydes Using Titanium Salen Complexes.

A vast area of research over the past ten years has focused on the use of C_2-symmetric ligands, a large part of which was carried out in the North group focusing on the use of metal(salen) complexes. Due to the high Lewis acidity of titanium, and the ability of the metal to coordinate to the oxygen atom of carbonyl groups, early research focused on the use of C_1-symmetric titanium catalysts. The first of these complexes to be synthesised for testing in cyanohydrin synthesis were complexes **8-11** using titanium tetraisopropoxide as the titanium source and trimethylsilylcyanide as the cyanide source.[28] The optimum reaction conditions allowed the synthesis of cyanohydrin products to be achieved with enantioselectivities of 25-76% using 20 mol% of catalyst at reaction temperatures of -78 ^{o}C. The most enantioselective catalyst was found to be complex **9** with benzaldehyde being cyanated with an enantioselectivity of 65%. Although these results were encouraging, stereoinduction was shown not to be as high as when using organocatalysts as the diketopiperazine and cinchona alkaloid systems were capable of giving cyanohydrin products with enantiomeric excesses as high as 97%.

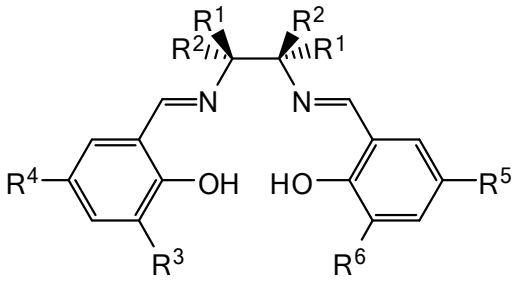


8) R = $MeS(CH_2)_2$; R' = H
9) R = $MeS(CH_2)_2$; R' = ^{t}Bu
10) R = ^{n}Pr; R' = ^{t}Bu
11) R = Me_2CHCH_2; R' = ^{t}Bu

Kim developed a range of C_1-symmetric titanium(salen) complexes that were shown to be more enantioselective than the North system discussed previously.[29] Complexes **12-16** were prepared using titanium tetraisopropoxide as the titanium source. Benzaldehyde was again chosen as the test substrate and the highest enantiomeric excesses were obtained using complex **12**. Using 10 mol% of complex **12** in dichloromethane at -80 ^{o}C, cyanohydrin product was obtained with 90% (*R*) enantiomeric excess in a chemical yield of 65% after a reaction time of 24 hours. Supporting complex **12** on MCM-41 improved on this result even further, giving an enantioselectivity of 94%. Using complex **16** under these reaction conditions gave product with an enantiomeric excess of 72%. Lowering the reaction temperature to -5 ^{o}C or -25 ^{o}C did not improve on the results as enantioselectivities of 30% and 51% (*R*) respectively were obtained. Electron-rich and electron-deficient aldehydes were

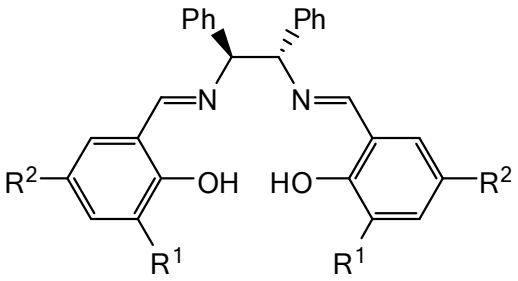
also screened using complex **12** under the optimum reaction conditions, thus 4-methoxybenzaldehyde and 4-chlorobenzaldehyde gave the corresponding cyanohydrin products with 73% and 87% (*R*) enantiomeric excess.

The advantages of this system over previous titanium(salen) systems was the lower catalyst loading (10 mol% as opposed to 20 mol%) required to give a higher enantioselectivity than that reported by North *et al;* however, a lower reaction temperature of -80 ^{o}C was required to achieve these high enantioselectivities. In addition, high activity was also observed when supporting the catalyst on MCM-41 which is very attractive for the commercial application of these catalysts as catalyst recyclability can be greatly improved when immobilising catalysts.



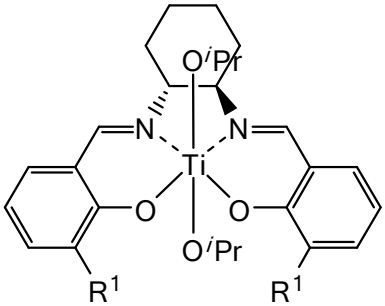
12) $R^1=(CH_2)_4$; $R^2=R^3=R^4=H$; $R^5=R^6={}^t$Bu
13) R^1 = Ph; R^2 = H; $R^3=R^4$ = H; $R^5=R^6={}^t$Bu
14) R^1 = $(CH_2)_4$; R^2= H; R^3= OMe;R^4= H; R^5=; R^6= ^{t}Bu.
15) R^1 =$(CH_2)_4$; $R^2=R^3=R^4=R^5$= H;R^6=OMe
16) R^1 = Ph; $R^2=R^3=R^4=R^5$= H; R^6= OMe

The development of C_2-symmetric salen based catalysts for cyanohydrin synthesis was developed in 1996 by Jiang *et al*.[30] The use of C_2-symmetric catalysts reduces the possible number of transition states by a factor of two, due to the symmetry axis. A common consequence of this is greater enantioselectivity. A wide variety of C_2-symmetric salen ligands have been developed for the cyanation of carbonyl compounds, for example ligands **17-24** were prepared from 1,2-diphenylethylenediamine and salicyaldehydes. Using titanium tetraisopropoxide as the metal source, the addition of trimethylsilylcyanide to benzaldehyde was then studied. Catalyst **20** was the most stereoselective, giving the corresponding cyanohydrin product with 84% (*R*) enantiomeric excess in 82% yield using 20 mol% of the catalyst at -78 ^{o}C after a 24 hour reaction time in dichloromethane.[31] Ligand **18** gave a poor result of only 5% (*R*) enantioinduction and a chemical yield of 30% under the same reaction conditions. Ligands **17** and **19** gave cyanohydrin product with moderate enantioselectivity (39% and 24% (*R*) respectively) under the same reaction conditions. These ligands instantly improved the enantioselectivity when using metal(salen) complexes in cyanohydrin synthesis, however low reaction temperatures were still required, accompanied by long reaction times.



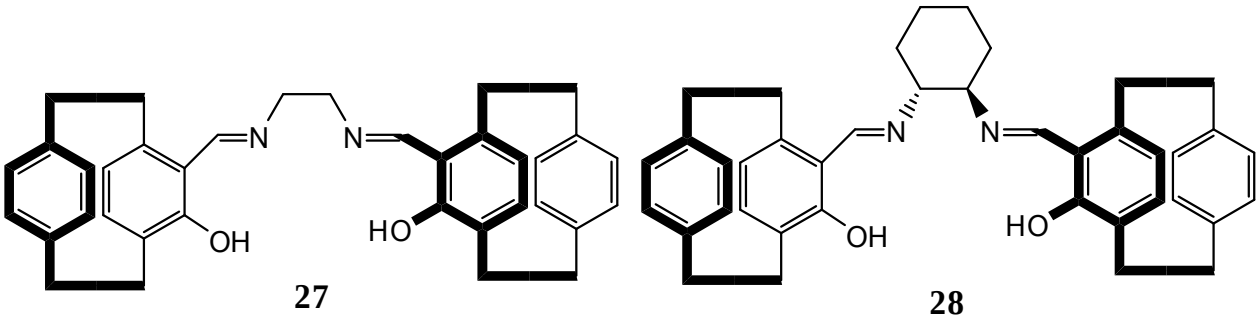
17) $R^1=R^2= {}^t$Bu
18) $R^1= CHPh_2$; $R^2=$ Me
19) $R^1=$ OMe; $R^2=$ H
20) $R^1=R^2=$ H
21) $R^1=$ H; $R^2= NO_2$
22) $R^1=$ H; $R^2=$ Br
23) $R^1=$ H; $R^2=$ Cl
24) $R^1=$ H; $R^2=$ OMe

Belokon and North *et al* extended their previous studies of C_1-symmetric salen ligands in cyanohydrin synthesis by studying complexes **25** and **26**, though with no real improvement to the previous findings by Jiang, discussed previously.[32] A catalyst loading of 20 mol% was still required and low reaction temperatures of -78 ^oC gave cyanohydrin product with enantiomeric excesses of 60-77%. The most stereoselective complex was shown to be complex **26**.



25) $R^1=$ H
26) $R^1= {}^t$Bu

Catalysts **27-29**, based on planar-chiral 5-formyl-4-hydroxy-[2.2]paracyclophane (FHPC) and different amines were also investigated by the North group, again with no improvement in enantioselectivity.[33] Table 1 summarises these results and it is clear that, although these catalysts did show some stereoinduction, enantioselectivities of no greater than 50 % were observed.



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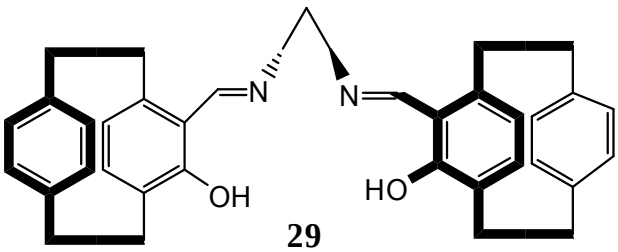

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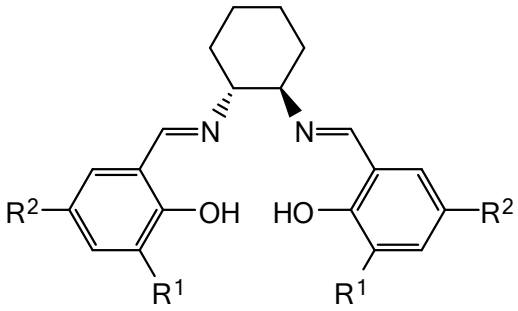
Table 1; results achieved using chiral ligand (*R*) and (*S*)-FHPC-**28**.

Entry [a]	Catalyst	Temperature ^{o}C	Time, h	Yield %	ee %
1	((*S*)-FHPC)-**28**	-78	24	0	0
2	((*S*)-FHPC)-**28**	-78	120	50	17
3	((*S*)-FHPC)-**28**	-78	168	70	23
4	((*S*)-FHPC)-**28**	+25	3	90	0
5	((*R*)-FHPC)-**28**	-78	24	90	35
6	((*R*)-FHPC)-**28**	-78	120	90	48
7	((*R*)-FHPC)-**28**	+25	1	90	44

[a] reactions were conducted with 10 mol% of complex **28** and always with the (*R,R*)-cyclohexane diamine unit and dichloromethane as the reaction solvent.

In a further study, a variety of substituted salen ligands were synthesised in an attempt to optimise the structure of complex **26**. Ligands **30-33** were synthesised and screened in the cyanation of benzaldehyde using trimethylsilylcyanide as the cyanide source and titanium tetraisopropoxide as the metal source. Compound **30** displayed the greatest stereocontrol, giving product with an enantiomeric excess of 72% (*S*) at -80 ^{o}C. Compounds **31, 32** and **33** gave cyanohydrin product with enantiomeric excesses of 60%, 76% and 69% (*S*) respectively at -80 ^{o}C. Table 2 summarises the results obtained when using compound **30** with a range of aldehydes and ketones.



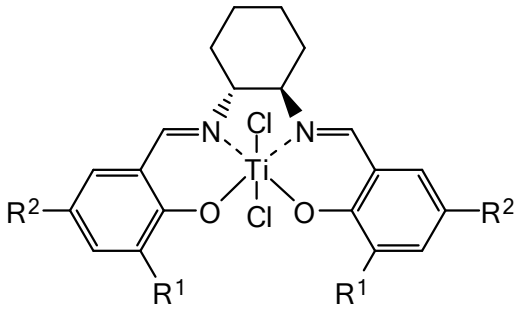
30) $R^1 = R^2 = {}^t$Bu
31) $R^1 = {}^t$Bu; R^2= Me
32) $R^1 = {}^t$Bu; R^2= OMe
33) $R^1 = R^2$= Cl

Complexes **34-39** gave enantioselectivities of 18-86% (*S*) in the cyanosilylation of benzaldehyde at room temperature using trimethylsilylcyanide as the cyanide source. Only 0.1 mol% of the complexes was required to achieve these results, as opposed to previous catalysts, **25-33** that required catalytic loadings of 10-22 mol% and much lower reaction temperatures to achieve similar enantiomeric excesses. Catalyst **37** gave the highest enantioselectivity of the catalysts screened; 86% (*S*) after 24 hours with complete conversion to the silylated mandelonitrile at room temperature. The results obtained using complexes **34-39** are presented in Table 3.

Table 2; results obtained when using compound **30** with a range of aldehydes and ketones.

Entry [a]	Aldehyde	Yield %	ee%
1	3-MeC_6H_4CHO	81	92
2	2-MeC_6H_4CHO	90	80
3	4-$F_3CC_6H_4CHO$	58	3
4	4-$O_2NC_6H_4CHO$	60	10
5	CH_3CH_2CHO	100	58
6	Me_3CCHO	100	36
7	PhCOMe	0	-
8	$MeCOCH_2CH_2CH_3$	0	-
9	$CH_3(CH_2)_4COMe$	0	-

[a] reactions carried out in dichloromethane at -80 ^oC with reaction times of 24-100 hours.



34) $R^1=R^2=$ H
35) $R^1=$ ^{t}Bu; $R^2=$ H
36) $R^1=$ ^{t}Bu; $R^2=$ OMe
37) $R^1=R^2=$ ^{t}Bu
38) $R^1=$ ^{t}Bu; $R^2=$ CPh_3
39) $R^1=$ ^{t}Bu; $R^2=$ NO_2

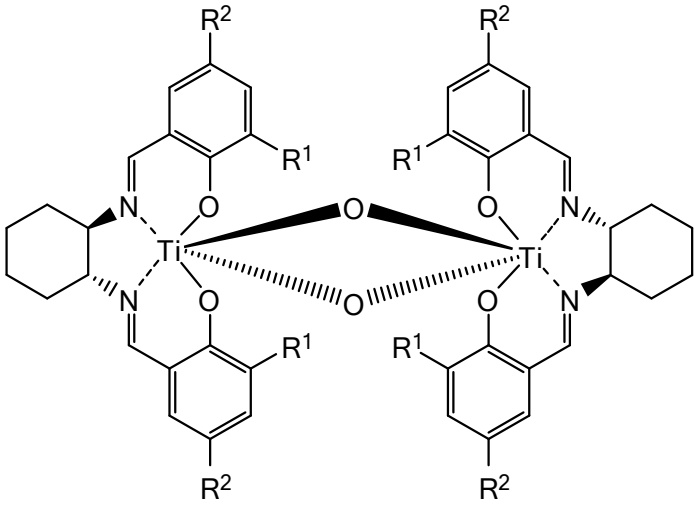
Table 3; results obtained using complexes **34-39** with benzaldehyde as the reaction substrate.

Entry	Complex	Yield %	ee% [a]
1	**34**	100	18
2	**35**	100	63
3	**36**	100	67
4	**37**	100	86
5	**38**	100	58
6	**39**	100	21

[a] the absolute configuration was determined as *S*.

A major break through was achieved when the role of water in the these systems was investigated. Reactions carried out under strictly anhydrous conditions, using the ligand **30**-$Ti(O^iPr)_4$ complex *or* complex **37**, gave depressed catalytic activity. Complexes **34** and **37** were re-tested using benzaldehyde was the reaction substrate, this time deliberately adding

water and triethylamine to the anhydrous reaction mixture. Using one equivalent of water and two equivalents of triethylamine restored the enantioselectivity to 86% (*S*). It was hypothesised that complex **37** and the titanium tetraisopropoxide complex of ligand **30** were precatalysts to an identical catalytically active species formed by a hydrolysis reaction involving residual water from the reagents and solvents. Complexes **34, 37** and **39** were reacted with one equivalent of water and the bimetallic titanium species **40-42** were isolated with the structure of complex **40** being confirmed by X-ray crystallography.[35]



40) $R^1=R^2=$ H
41) $R^1=R^2=$ ^{t}Bu
42) $R^1=$ ^{t}Bu; $R^2=$ NO_2

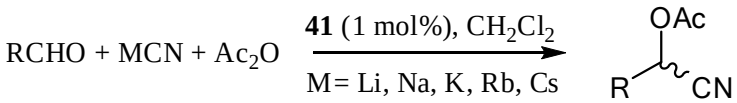
Complex **41** was shown to be by far the most active catalyst for cyanohydrin synthesis when using benzaldehyde as reaction substrate. Full conversion to silylated mandelonitrile was achieved with only 0.1 mol% of the bimetallic complex after a five minute reaction time at room temperature. This enhanced activity led to the conclusion that complex **41** was the true catalyst in the previous systems studied. A range of aromatic and aliphatic aldehydes were screened using complex **41**, the results being summarised in Table 4. Benzaldehyde was shown to be a good substrate with complex **41**, however, when studying Table 4 it is clear that this activity is not demonstrated with other substrates. Enantioselectivities as low as 76% (Entry 1) were observed with some aromatic substrates and aliphatic substrates all gave much lower enantioselectivities when used with complex **41**. The unique feature of complex **41** is the fast reaction rate of the cyanosilylation achieved using a low catalyst loading and a high reaction temperature, which was not achievable with the other complexes leading up to the development of complex **41**. However, without the development of the earlier complexes, the successful synthesis of complex **41** would not have been possible and althought complexes **25-29** were shown to be inferior catalysts to complex **41** they have played a very valuable role in the development and understanding of this catalytic system.

Table 4; results obtained from a substrate screen using complex **41**.

Entry	Aldehyde	ee% (*S*)
1	2-MeC_6H_4CHO	76
2	3-MeC_6H_4CHO	90
3	4-MeC_6H_4CHO	87
4	2-$MeOC_6H_4CHO$	88
5	3-$MeOC_6H_4CHO$	92
6	4-$MeOC_6H_4CHO$	84
7	4-$F_3CC_6H_4CHO$	86
8	4-$O_2NC_6H_4CHO$	50
9	Me_3CCHO	66
10	Me_2CHCHO	64
11	CH_3CH_2CHO	52

[a] all reactions were performed using 0.1 mol% of complex **41** with a one hour reaction time at ambient temperature. All reactions gave 100% conversion.

With the success of complex **41** in the cyanosilylation of benzaldehyde using trimethylsilylcyanide as the cyanide source, Belokon and North *et al* next looked at the possibility of using alternative cyanide sources with catalyst **41** which would also improve the applicability of this complex in industry.[34, 35] The combined use of metal cyanides and acetic anhydride, to form cyanohydrin acetates, was therefore investigated as an alternative to using trimethylsilylcyanide (Scheme 3). Alkali metal cyanides used in conjunction with acetic anhydride were shown to produce chiral cyanohydrin acetates with the level of stereoinduction depending strongly on the cyanide counterion.



Scheme 3: cyanohydrin synthesis using complex **41** and potassium cyanide.

Lithium cyanide gave cyanohydrin acetate with the lowest enantioselectivity of only 4% (*R*) after a reaction time of eight hours at -40 ^{o}C when using dihydrocinnamaldehyde as the substrate and the (*S,S*)-**41** complex. Using sodium cyanide led to an improvement in the enantioselectivity of the system, giving cyanohydrin acetate with 56% (*R*) enantiomeric excess. The highest enantioselectivity was obtained with potassium cyanide which gave an

enantioselectivty of 82% (*R*). Rubidium and caesium cyanides gave lower enantioselectivities of 76% and 54% (*R*) respectively. enantioselectivity of 90% (*S*) when using the (*R*,*R*)-**41** complex using potassium cyanide. To improve the solubility of the potassium cyanide, water (10 mol%) and *tert*-butanol (1 equivalent) were added to the reaction system. Using complex (*S*,*S*)-**41** a variety of aldehydes were then screened under these optimum reaction conditions. Table 5 summarises these results.

Table 5; results from a substrate screen using complex **41** with potassium cyanide**.**

Entry [a]	Aldehyde	Yield %	ee%
1	4-$MeOC_6H_4CHO$	74	93
2	3-$MeOC_6H_4CHO$	99	93
3	3-$PhOC_6H_4CHO$	99	89
4	4-FC_6H_4CHO	99	93
5	3-FC_6H_4CHO	99	89
6	2-FC_6H_4CHO	86	82
7	2-ClC_6H_4CHO	89	88
8	Me_2CHCHO	62	72
9	Me_3CCHO	40	60

[a] reactions stirred for 10 hours using aldehyde, KCN and acetic anhydride in a ratio of 1:1:4 with 1 mol% of complex **41** at -40 ^{o}C in dichloromethane, ^{t}BuOH and water were used in a ratio of 2500:10:1.

Alternative carboxylic acid anhydrides were studied showing that the nature of the acid anhydride has little effect on the steroinduction of catalyst **41** with the exception of benzoic anhydride.[36] Benzoic anhydride gave a lower enantioselectivity of 56% (*R*) after a reaction time of 72 hours. To further test the effect of altering the anhydride in the reaction, a variety of aldehydes were screened using the acid anhydrides tested, with the exception of benzoic anhydride as shown in Table 6.

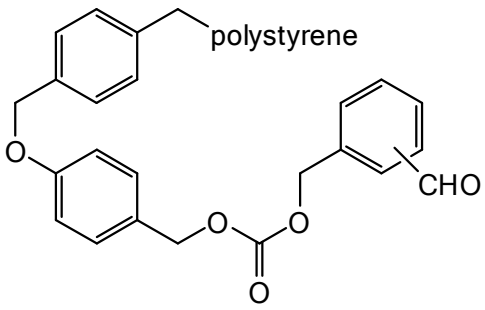
Potassium cyanide was shown to be a compatible cyanide source when using complex **41**, however the addition of further additives was required to achieve these enantioselectivities along with much lower reaction temperatures. Complex **41** in the presence of trimethylsilylcyanide requires the addition of no other additives and reaction temperatures of +25 ^{o}C to give the same results. Potassium cyanide is however a more attractive cyanide source as it is a solid at room temperature and an easier cyanide source to handle especially in these small scale reactions.

Table 6; results obtained when screening alternative anhydride sources in conjunction with potassium cyanide and complex **41**.

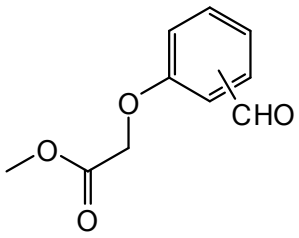
Aldehyde	Anhydride	Time, h	Conversion %	ee % (*S*)
PhCH=CHCHO	propanoic	48	73	95
	pivalic	72	50	75
4-$CF_3C_6H_4CHO$	propanoic	50	100	94
	pivalic	50	100	62
3-$MeOC_6H_4CHO$	acetic	10	99	93
	propanoic	48	100	9
4-$MeOC_6H_4CHO$	acetic	10	74	93
	propanoic	48	100	91
Me_3CCHO	acetic	10	62	72
	propanoic	48	100	78
2-MeC_6H_4CHO	propanoic	28	100	81
3-MeC_6H_4CHO	propanoic	36	98	95
4-MeC_6H_4CHO	propanoic	36	98	89
4-ClC_6H_4CHO	propanoic	16	100	90
CyCHO	propanoic	72	95	41

[a] all reactions carried out at -40 ^oC in dichloromethane using 1 mol% of complex **41**.

Polymer supported aldehydes **43** were also investigated and were shown to be cyanated with a high level of stereocontrol using complex **41**.[37] Using potassium cyanide/propanoic anhydride system, Using 2 mol% of complex **41**, *para*-substituted aldehydes were converted into cyanohydrin esters with up to 91% enantiomeric excess. Non-polymer supported analogues **44** were converted into cyanohydrin esters with enantiomeric excesses of up to 81%.

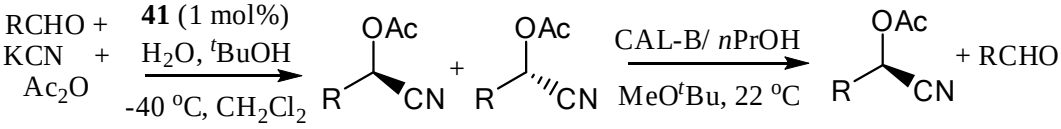


43) polymer supported aldehyde.



44) analogous non-polymer supported aldehyde.

North *et al* also developed the use of enzymes in the cyanation of aldehydes using potassium cyanide/acetic anhydride in combination with complex **41**.[38,39] The synthesis of the cyanohydrin acetate was carried out under the normal optimised conditions after which the product was treated with a lipase enzyme. This enzyme was specifically chosen as it targets the minor enantiomer of the cyanohydrin ester and hydrolyses it so giving a highly enantioenriched product (Scheme 4). The studied enzymes were *Candida antarctica* lipase-B (CAL-B), *Alcaligenes sp.* lipase (ASL), *Pseudomonoa stutzeri* lipase (PSL), *Pseudomonas cepacia* lipase (PCL) and *Candida rugosa* esterase (CRE), starting from a non-racemic sample of *O*-acetylmandelonitrile with 77% enantiomeric excess. CAL-B was shown to be the optimum enzyme for this application as the enantiomeric excess of the sample was shown to increase to >99% in five hours.



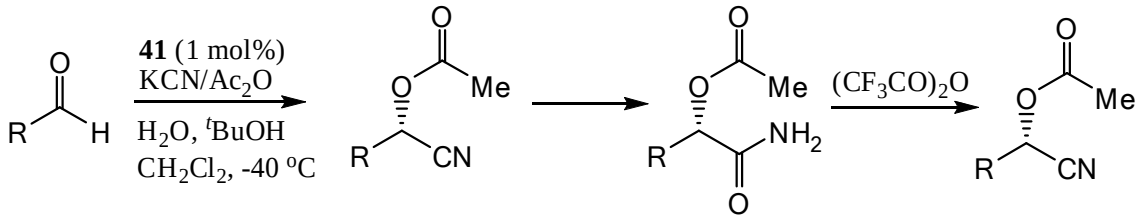
Scheme 4: cyanohydrin synthesis utilising enzymatic kinetic resolution.

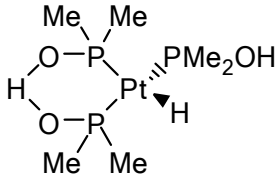
Testing a range of aldehydes showed that the CAL-B treatment improved the enantiomeric excess of the *O*-acetyl cyanohydrins in all cases except for pivaldehyde cyanohydrin acetate where no change was observed. The greatest improvement was seen with aliphatic substrates, in some cases the enantiomeric excesses were improved by as much as 27% as observed with *iso*-butanal cyanohydrin acetate. After the cyanohydrin acetate forming step of the synthesis, the enantiomeric excess was determined to be 47%. Following treatment with CAL-B for 24 hours, the enantiomeric excess was shown to have increased to 74%. Cyclohexanecarboxaldehyde was found to undergo an increase in enantiomeric purity of only 8% from 60% after treatment with complex **41**, to 68% after treatment with CAL-B. The results of this study are summarised in Table 7 and it is apparent that this system improved the enantioselectivity for the majority of the aldehyde substrates tested.

The utility of cyanohydrins was demonstrated by North *et al* by selectively hydrolysing the nitrile group within cyanohydrin esters to the amide using the platinum catalyst **45** Synthesis back to the cyanohydrin resulted in no loss in enantioselectivity (Scheme 5).[40]

Table 7; comparative data obtained from cyanohydrin synthesis carried out using complex **41** and enzymatic catalysis.

Aldehyde	ee % with **41**	ee % with CAL-B	Time, h
PhCHO	76	97	26
4-ClC_6H_4CHO	89	99	7
2-ClC_6H_4CHO	75	89	22
3-$MeOC_6H_4CHO$	93	97	23
2-MeC_6H_4CHO	64	80	22
furan-2-carboxaldehyde	76	99	23
$Me(CH_2)_7CHO$	69	92	22





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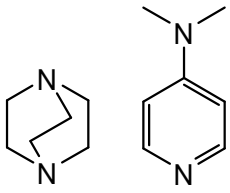
Scheme 5: demonstration of the chemoselectivity of complex **41.**

Moberg *et al* developed a synthesis of *O*-acetyl cyanohydrins using acetyl cyanide in the presence of Lewis bases. A variety of Lewis bases were investigated including; triethylamine, 1,4-diazabicyclo[2.2.2]octane (DABCO) **46**, 4-dimethylaminopyridine (DMAP) **47** and various cinchona alkaloids. The highest enantioselectivities (96% (*S*)) were achieved using the cinchona alkaloid, cinchonidine **48**, with benzaldehyde as the substrate at a reaction temperature of -40 ^oC using 10 mol% of (*R*,*R*)-**41**. DABCO **46**, triethylamine, DMAP **47** and quinine **49** gave enantiomeric excesses of 92%, 94%, 94%, 92% (*S*) respectively.[41] Using cinchonidine **48** in the absence of (*R*,*R*)-**41** resulted in some selectivity as cyanohydrin product was obtained with 40% enantiomeric excess. A variety of aromatic and aliphatic aldehydes were screened, using triethylamine as the Lewis base (10 mol%) at a reaction temperature of -40 ^oC in dichloromethane. The acetylated cyanohydrins were obtained in 64-95% yields with enantiomeric excesses of 20-96% after typical reaction times of 6-12 hours. Other acyl cyanides were studied, and gave similar results to those obtained using acetyl cyanide.

From these results it is clear to see that complex **41** is one of the most active complexes for use in the asymmetric synthesis of cyanohydrins. Moberg studied the use of complex **41** in the presence of a variety of chiral and achiral Lewis bases. The results were shown to be very promising with enantioselectivies of greater than 90 % (*S*) being achieved, however the reaction times required to achieve these results were longer than when using complex **41** in the absence of any additives. Also, a reaction temperature of -40 ^{o}C was required. Although this is a valuable piece of work and contributes greatly to the understanding of the role of additives in these systems it can be concluded that the addition of additives to the reaction system is of no benefit in this case**.**



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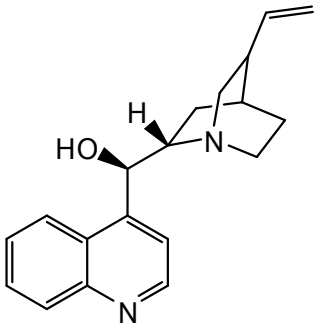

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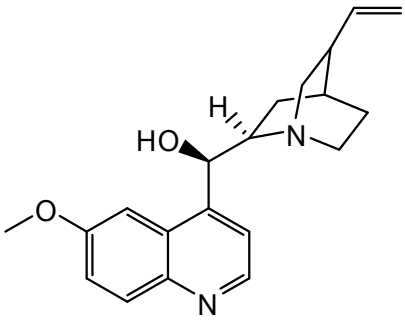

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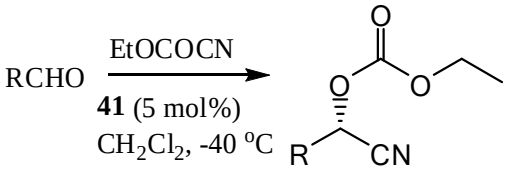
Belokon and North *et al* also investigated the use of cyanoformates as alternative cyanide sources.[42] Using benzaldehyde with ethyl cyanoformate and complex **41** at -40 ^{o}C in dichloromethane gave mandelonitrile ethyl carbonate with 95% (*S*) enantioselectivity in 100% yield. Complex **41** was required at a catalyst loading of 5 mol% and a reaction time of 18 hours was needed. Adding potassium cyanide in a 1 mol% catalyst loading was shown to increase both the rate and the enantioselectivity of the system. Using these optimized reaction conditions (Scheme 6), a variety of aliphatic and aromatic aldehydes were screened, Table 8.



Scheme 6: cyanohydrin synthesis utilising ethyl cyanoformate as the cyanide source.

In an attempt to improve the solubility of the potassium cyanide co-catalyst in dichloromethane, a potassium cyanide/18-crown-6 complex was added to the reaction. This led to consistently high enantioselectivities for a range of aldehydes (71-100%). A 1 mol% loading of the potassium cyanide/18-crown-6 complex along with 1.5 mol% of complex **41** gave the best results. No significant improvement in enantioselectivity was achieved

compared to those obtained in the absence of 18-crown-6, however, the catalyst and co-catalyst loadings were further reduced. These results are presented in Table 9. [43]

Table 8; results obtained from cyanohydrin synthesis using complex **41** and ethyl cyanoforamate as the cyanide source.

Entry	Aldehyde	EtOCOCN (eq)	Yield %	ee%
1	PhCHO	2	90	95
2	4-$MeOC_6H_4CHO$	2	92	95
3	3-$MeOC_6H_4CHO$	2	94	99
4	2-$MeOC_6H_4CHO$	1.2	95	98
5	4-MeC_6H_4CHO	1.2	95	94
6	4-$F_3CC_6H_4CHO$	2	84	76
7	4-ClC_6H_4CHO	1.2	96	94
8	$CH_3(CH_2)_7CHO$	2	54	84
9	CyCHO	1.2	82	79
10	Me_3CCHO	1.2	69	76
11	PhCH=CHCHO	1.2	99	94

Table 9; results obtained when using potassium cyanide as a co-catalyst with **41** and ethyl cyanoformate as the cyanide source.

Entry[a]	**41** mol%	KCN mol%	Temperature ^oC	Time h	Conversion %	ee [b] %
1	1	0	25	90	5	89
2	1	1	25	48	100	51
3	1	10	25	48	98	68
4	1	10	-40	19	87	81
5	2	10	-40	26	100	95
6	1	10	-70	24	0	-

[a] Reactions carried out at -40 ^oC in dichloromethane using benzaldehyde as the reaction substrate. [b] The absolute configuration of the product was shown to be *S*.

As seen with potassium cyanide when used in conjunction with complex **41**, extremely high enantioselectivities were observed when using ethyl cyanoformate as the cyanide source, however, again lower reaction temperatures of -40 ^oC were required along with a catalyst loading of 5 mol%. Adding potassium cyanide to the reaction resulted in the lowering of the catalyst loading of complex **41** to 2 mol%, however, this system now

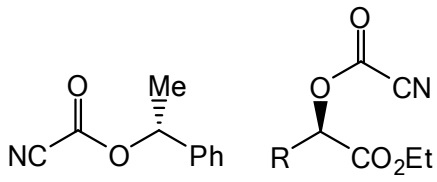
required the use of two cyanide sources to achieve an enantioselectivity of over 90%. Also, a reaction temperature of -40 ^{o}C was required to give this result. Increasing the reaction temperature led to a decrease in enantioselectivity.

Ethyl cyanoformate has also been investigated by a number of other groups with similar or inferior results being obtained when compared to the North/Belokon system. Feng *et al* screened a variety of C_2-symmetric cyclohexanediamine derived salen units with titanium tetraisopropoxide for the *in situ* formation of titanium salen complexes. Ethyl cyanoformate was used as the cyanide source for the cyanation of aldehydes. Ligand **30** was found to the most effective and gave the highest enantioselectivities. Under the optimum conditions adopted for complex **41** (Scheme 6), benzaldehyde was cyanated with 91% (*S*) enantiomeric excess and with a yield of 99% after a 16 hour reaction time. The solvent system for these reactions was *iso*-propanol and dichloromethane and therefore it was hypothesised that the **30**-titanium complex is being formed *in situ* and that ethyl cyanoformate was reacting with the *iso*-propanol to generate cyanide. This cyanide could then behave as a co-catalyst, much like potassium cyanide in Belokon and North's system discussed previously.[44] Moberg *et al* also investigated the use of ethyl cyanoformate in the cyanation of benzaldehyde in a similar study to the one discussed previously using acetyl cyanide and triethylamine as a reaction additive and complex **41** as catalyst.[42] Benzaldehyde was cyanated to give the corresponding cyanohydrin with 95% yield and 92% (*S*) enantioselectivity after a reaction time of four hours at -40 ^{o}C. Following on from this work, Moberg investigated the effect that the addition of a Lewis base had on the reaction rate of the cyanation of benzaldehyde using ethyl cyanoformate. The Lewis base had a beneficial effect on the reaction rate with the best results being obtained with DMAP **47** (10 mol%) and triethylamine. Reaction times were significantly reduced from 18 hours to four hours in some cases. Consistently high enantioselectivities were obtained for a range of aldehydes when using triethylamine as the Lewis base, Table 10.

Table 10; substrate screen using complex **41** with triethylamine as a Lewis base additive.

Aldehyde	Time h	Yield %	ee%
PhCHO	4	95	92
4-MeC_6H_4CHO	6	88	94
4-$MeOC_6H_4CHO$	6	79	94
4-ClC_6H_4CHO	4	90	93
PhCH=CHCHO	7	97	93
Me_3CCHO	5	81	73
$CH_3(CH_2)_4CHO$	5	83	89

Chiral cyanoformates **50-54** have also been used in the asymmetric addition of cyanide to aldehydes using complex **41** and potassium cyanide as catalysts. Matched/mis-matched studies showed that cyanoformate (*R*)-**50** and catalyst (*R,R*)-**41** form a matched pair, whilst (*S*)-**50** used in combination with (*R,R*)-**41** gave a lower diastereoselectivity, confirming this combination to be the mis-matched pair. This was the case with both benzaldehyde and pivaldehyde. Using cyanoformate **51**, similar results were obtained using both enantiomers of complex **41**. The product obtained using (*R,R*)-**41** was diastereomeric to the product obtained using (*S,S*)-**41**. Cyanoformates **52-54** gave no product with either benzaldehyde or pivaldehyde.



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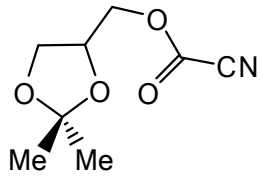
51) R= Me
52) R= Ph



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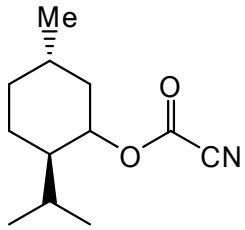

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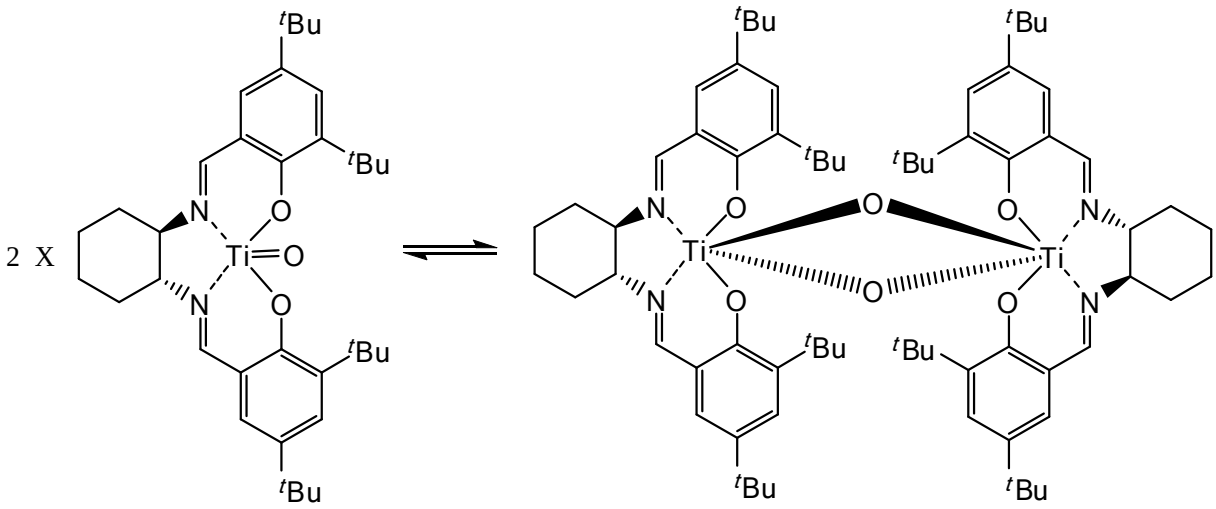
1.2.2 Mechanistic Studies on Titanium Salen Complexes.

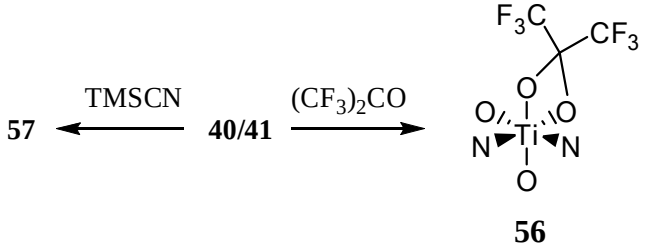
Due to the high activity of complex **41** in cyanohydrin synthesis using trimethylsilylcyanide, potassium cyanide and ethyl cyanoformate as cyanide sources, detailed mechanistic studies have been carried out on this catalyst to determine a possible reaction mechanism. Mechanistic studies not only provide an insight into the mechanism of a catalytic cycle, but the information gained from such a study can lead to further improvements of a system. ^{1}H NMR studies showed that in deuterated dichloromethane and chloroform, both the monomeric **55** and dimeric form of catalyst **41** were present in solution (Scheme 7). In deuterated benzene, this equilibrium did not appear to exist, with no evidence for the formation of complex **55**.



Scheme 7: equilibrium showing the formation of the momomeric and dimeric forms of the titanium(salen) catalysts.

Kinetic studies showed that asymmetric cyanohydrin synthesis was first order with respect to trimethylsilylcyanide and zero order with respect to benzaldehyde.[44] Varying the catalyst concentration allowed the order with respect to catalyst to be determined. The kinetics were carried out on complexes **40**-**42**; **40** showed a catalyst order of 1.6; **41** showed a catalyst order of 1.3 and **42** showed a catalyst order of 1.8. These results indicated that more than one metal centre was involved in the catalytic cycle.

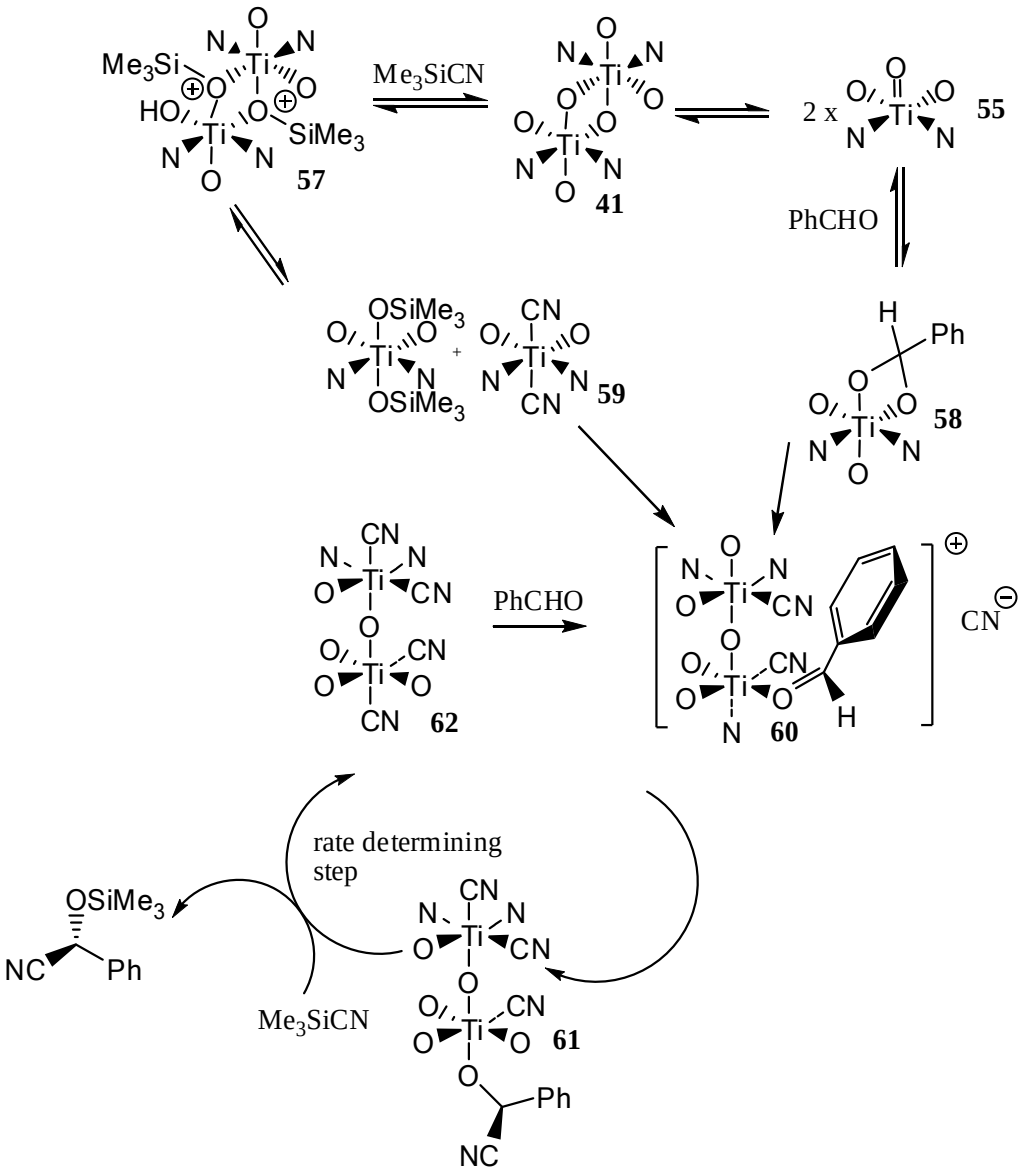
Experiments were carried out in order to determine how complexes **40**/**41** behave in the presence of trimethylsilylcyanide and hexafluoroacetone. Mixing catalysts **40**/**41** with hexafluoroacetone resulted in the formation of metalloacetals **56** (Scheme 8) giving an insight into how carbonyls interact with the catalyst.



Scheme 8: formation of metalloacetals from complexes **40**/**41** and hexafluoroacetone.

Treatment of complex **41** with trimethylsilylcyanide resulted in silylation of the bridging oxygen atoms to give complex **57**. From these results, a mechanism was proposed as shown in Scheme 9. Complex **41** reacts with benzaldehyde and trimethylsilylcyanide in separate reactions to form the mononuclear species **58** and **59**. The active bimetallic species **60** is then formed from monomers **58** and **59**. Both titanium atoms are involved in the catalytic cycle in a dual activation where one titanium atom activates the aldehyde and the

other titanium atom activates the cyanide. Intramolecular transfer of the cyanide to the aldehyde occurs preferentially to the *re*-face of the carbonyl, determined by the arrangement of the transition state, assuming the catalyst possess the (*R*,*R*)-stereochemistry. The rate determining step of the reaction is the silylation of complex **61** to give the silylated cyanohydrin and the C_2-symmetrical-bis-cyanide complex **62**. Complex **62** can then react with the aldehyde to reform complex **60** and the catalytic cycle can continue. Figure 3 shows the arrangement of complex **60**. Further evidence for bimetallic catalyst formation was obtained by mixing complexes **41** and **42**. ^{1}H NMR spectroscopy showed the formation of a bimetallic complex **63** formed by the metathesis of complexes **41** and **42**. Kinetics carried out using complex **63** gave an order with respect to the catalyst of 1.9. The rate of the reaction was shown to be between the rate established for complex **41** and the rate established for complex **42.** This gave further evidence for dimeric species being responsible for the catalysis, because if the monomeric forms were catalysing the reaction, then the rate of the reaction using complex **63** would be similar to the rate that was obtained using complex **41** alone as monomeric complex **55** would be present in solution in both cases. This transition state explains why ketones are less reactive than aldehydes and also why aliphatic substrates are less selective than aromatic substrates. The aldehyde has to orientate in a way that reduces steric interactions between the phenyl of the aldehyde and the cyclohexanediamine. There is sufficient space to accommodate the aldehyde hydrogen, but if the size of this group is increased, it can no longer be accommodated within the transition state so activity decreases. Aliphatic substrates may have more flexibility when bound to the titanium atom. Addition to both the *re*- and *si*-face may then take place, lowering the enantiomeric excess of the cyanohydrin product.



Scheme 9: proposed mechanistic cycle using complex **41**.

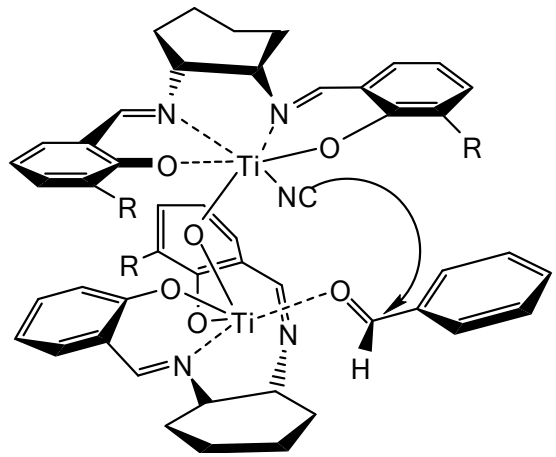
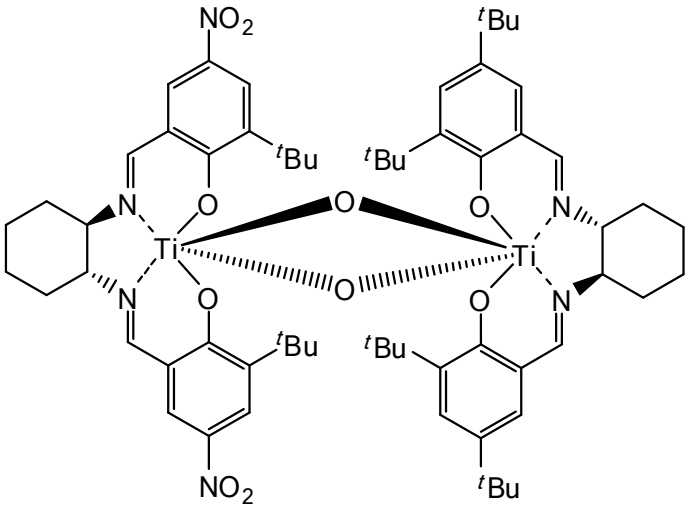
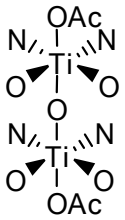


Figure 3: proposed transition state in cyanohydrin synthesis using complex **41**.



63



64

The mechanism shown in Scheme 9 can also be used to explain the ability to use other cyanide sources with catalyst **41**. For the potassium cyanide/acetic anhydride system; complex **41** is known to form a bimetallic bis-acetate complex **64** on treatment with acetic anhydride. The acetate groups are then displaced by cyanide and the aldehyde to generate complex **60,** only in this instance with an acetate counterion. After formation of the titanium bound cyanohydrin, acetic anhydride would acetylate the cyanohydrin to reform complex **64**, and the catalytic cycle could then continue. This mechanism would also be valid for other cyanoformates and other anhydrides. For reactions involving the use of Lewis bases and co-catalysts with acyl cyanides or cyanoformates, the role of the Lewis base can be explained by its reaction with the acyl cyanide to give cyanide ions and/or a more reactive acylating agent. Cyanide ions are needed to form species like **60** and the acylating agent is required for the acylation of the cyanohydrin to release the cyanohydrin from the catalyst in the rate determining step to form species such as **62** or **64**.[42]

1.2.3 Other Titanium(Salen) Complexes used in Cyanohydrin Synthesis.

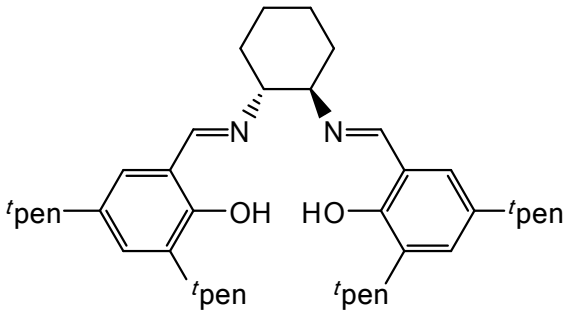
North *et al* have made a huge contribution to the study of cyanohydrin synthesis over the last fifteen years, with the development of complex **41**. The catalyst is so effective at catalysing the enantioselective addition of cyanide to the carbonyl bond that it was used on an industrial scale under the trade name of Cachy®. This work is a good example of how asymmetric catalysts are synthesised and developed with early work, using C_1-symmetric complexes **8-11**, demonstrating the potential of these titanium(salen) complexes to catalyse asymmetric cyanohydrin synthesis. From these initial studies and the early understanding of the reaction mechanism, the development of C_2-symmetric complexes was studied and the development of complex **41** was achieved. As a result of this work, many other research

groups have also developed their own salen ligands, albeit none have thus far been shown to be as active as complex **41**. The following paragraphs present a selection of work from a number of research groups showing the diverse range of research that has been carried out in this field, including further research from the North group.

Bu and Liang *et al* modified the structure of ligand **30**, exchanging the *tert*-butyl groups for *tert*-pentyl groups on the aromatic rings to form ligand **65**.[45] Using 5 mol% of titanium tetraisopropoxide with ligand **65** gave cyanohydrin product with 97% (*S*) enantiomeric excess in 92% yield after a 12 hour reaction time at -78 ^{o}C when using benzaldehyde as the substrate and trimethylsilylcyanide as the cyanide source. Increasing the reaction temperature to -10 ^{o}C resulted in a small decrease in enantioselectivity to 90% (*S*). A variety of aromatic aldehydes were screened using the **65**-titanium tetraisopropoxide complex, all giving excellent enantioselectivities and yields as shown in Table 11. These results were comparable with those obtained using complex **41,** however a higher catalyst loading was required along with lower reaction temperatures and longer reaction times.

Table 11; substrate screen using ligand **65** in cyanohydrin synthesis.

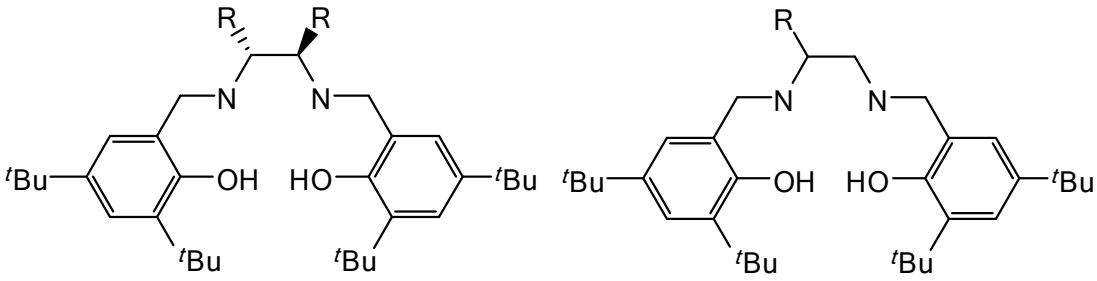
Entry	Aldehyde	Yield %	ee %
1	3-MeC_6H_4CHO	92	97
2	4-MeC_6H_4CHO	85	92
3	4-EtC_6H_4CHO	84	94
4	4-^{i}PrC_6H_4CHO	93	93
5	4-^{t}BuC_6H_4CHO	94	95
6	4-ClC_6H_4CHO	89	97
7	3-ClC_6H_4CHO	87	97
8	4-FC_6H_4CHO	92	96



65

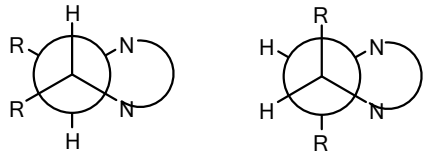
North *et al* investigated the use of various chiral diamines in the synthesis of C_1- and C_2-symmetric salen ligands. Titanium and vanadium complexes were then synthesised from these ligands.[46] The titanium complexes synthesised via treatment of ligands **66-70** with

titanium tetrachloride, gave much lower enantioselectivities than those obtained using complex **37** (75%). A possible explanation for this lowered enantioselectivity was the different conformations that salen complexes can adopt depending on the structure of the salen ligand. Cyclic diamines have a rigid structure that locks the salen ligand into a single conformer, so that asymmetric reactions take place in a defined chiral environment. This is reflected in the enantioselectivities obtained using salen ligands derived from cyclic diamines. Acyclic diamines have more conformational freedom, so the chiral environment is not as well defined. Salen complexes derived from acyclic diamines adopt an anti-conformation to minimize steric interactions within the complex whilst cyclic diamines must adopt a gauche-conformation, as shown in Figure 4.



66) R= Ph
67)R= Me
68) R= propyl
69) ^{i}Pr
70) ^{t}Bu

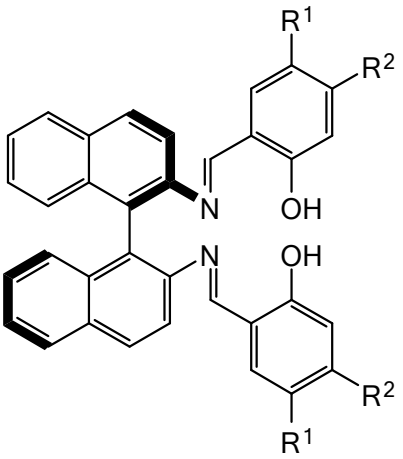
71) R= Me (*S*)
72) R= CH_2Ph (*S*)
73) R= Ph (*R*)
74) R= $CHMe_2$ (*S*)

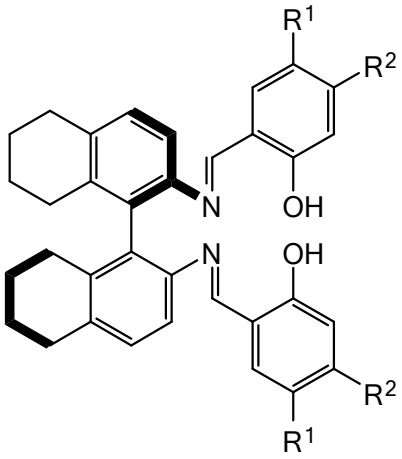


Gauche Anti

Figure 4; Newman Projections of the *gauche* and *anti* configurations for salen complexes

Che *et al* also studied a wide range of salen ligands synthesised from BINAM derived diamines. Using titanium tetraisopropoxide in combination with ligands **75-86**, benzaldehyde was cyanated using trimethylsilylcyanide at -78 ^{o}C in dichloromethane. The best results were achieved using 20 mol% of ligand **78**, which gave mandelonitrile with 93% enantioselectivity after a reaction time of 120 hours using 20 mol% of ligand **78**. Table 12 shows the results obtained with the other ligands.[47]





75) $R_1=R_2=$ H; **80)** $R_1=$ ^{t}Bu; $R_2=$ H **84)** R= H
76) $R_1=R_2=$ Cl; **81)** $R_1=$ ^{t}Bu; $R_2=$Cl **85)** R= Cl
77) $R_1=R_2=$ Br; **82)** $R_1=$ Cl; $R_2=$ ^{t}Bu **86)** R= ^{t}Bu
78) $R_1=R_2=$ ^{t}Bu; **83)** $R_1=$ Et; $R_2=$ H
79) $R_1=R_2=$ NO_2

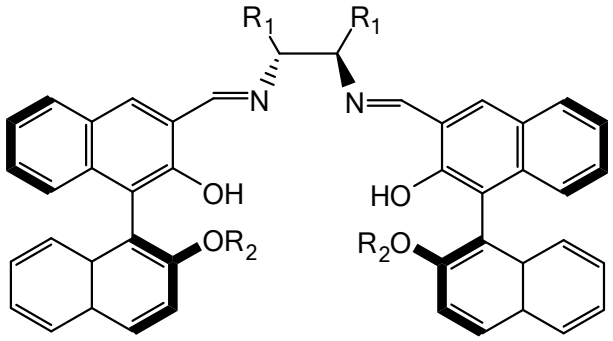
Table 12; results obtained using complexes **75-86** in asymmetric cyanohydrin synthesis.

Entry[a]	Ligand	(*R/S*)	Yield %	ee %	*R/S*
1	**75**	*R*	76	38	*S*
2	**76**	*R*	53	47	*S*
3	**77**	*R*	60	81	*S*
4	**78**	*R*	92	93	*S*
5	**79**	*R*	0	-	-
6	**80**	*R*	53	35	*S*
7	**81**	*R*	82	86	*S*
8	**82**	*R*	73	75	*S*
9	**83**	*R*	85	75	*S*
10	**84**	*R*	54	24	*S*
11	**85**	*S*	75	38	*S*
12	**86**	*S*	68	29	*S*

[a] all reactions were carried out at -78 ^{o}C in dichloromethane for 120 hours.

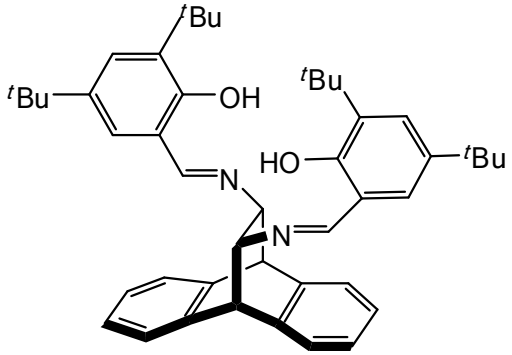
Pu *et al* carried out a similar study using ligands **87-91** for the cyanation of aldehydes.[48] Titanium tetraisopropoxide and titanium tetrachloride were used for *in situ* formation of the metal complex. Using 10 mol% of ligand **90** with titanium tetraisopropoxide using benzaldehyde as the reaction substrate, gave product with a 52% (*S*) enantioselectivity. The optimum conditions were found to be a 12 mol% loading of ligand **90** along with 10 mol% of

titanium tetraisopropoxide in dichloromethane at -20 ^{o}C with silylated cyanohydrin beinng obtained with an 89% asymmetric induction after a reaction time of four hours. Ligands **87-89** and **91** gave inferior results to thoses obtained using ligand **90.**



87) R^1= $(CH_2)_4$; R^2= H
88) R^1= $(CH_2)_4$; R^2= Me
89) R^1= $(CH_2)_4$; R^2= ^{i}Pr
90) R^1= $(CH_2)_4$; R^2= $^{n}C_6H_{13}$
91) R^1= Ph; R^2= $^{n}C_6H_{13}$

Zhou *et al* used an anthracene derived C_2-symmetric ligand **92** in asymmetric cyanohydrin synthesis. At -20 ^{o}C in dichloromethane, benzaldehyde was cyanated giving product with 68% (*R*) enantiomeric excess in 89% chemical yield. A 20 mol% ligand loading was required along with titanium tetraisopropoxide as the titanium source.[49]



92

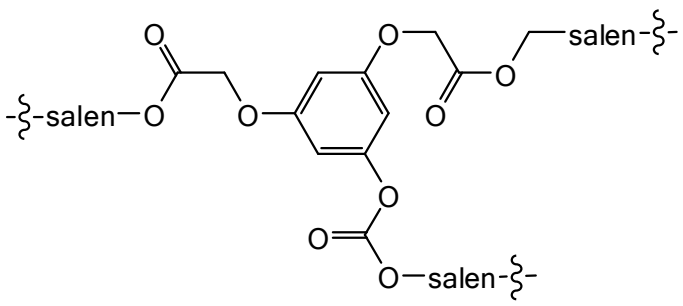
This short review demonstrates the diversity of salen ligands and how their structures can be manipulated to produce a wide variety of catalytic systems. All of the above systems have been shown to catalyse the addition of cyanide to aldehydes giving moderate to excellent enantioselectivities. However, in the majority of cases, high catalyst loadings, low reaction temperatures and long reaction times were required.

1.2.4 Immobilized C_2-symmetric Salen Derived Ligands

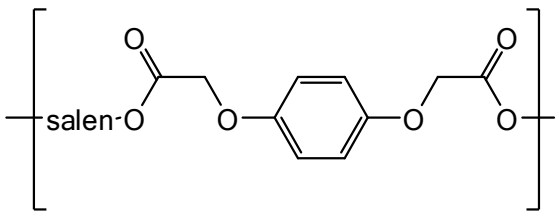
Titanium(salen) catalysts have been shown to be very active in cyanohydrin synthesis. Research following on from the previously discussed homogeneous systems led to the immobilisation of these titanium catalysts in an attempt to increase their activity further and

increase their recyclability which is always an attractive option if these catalysts are to be used on an industrial scale. The immobilisation of catalysts for this purpose is an ongoing and important area of research, however, the immobilisation of catalysts can lead to very different and unexpected results compared to those obtained with the unimmobilisied equivalent catalyst. Below is presented is a short review of some of this work.

Zheng covalently immobilised salen complex **30** onto cross-linked polymers for use in the addition of potassium cyanide and acetic anhydride to aldehydes.[50,51] The polymers were obtained in linear and branched forms **93-95.** Benzaldehyde was cyanated using 1 mol% of catalysts **93-95**, with results comparable to those obtained using complex **41**. The highest enantioselectivity was achieved with a linear to branched ratio of 100 to 0 with an enantioselectivity of 89% (*S*) after four hours. Increasing the amount of branched polymer **94** had a relatively small effect on the enantiomeric excess of the product but a linear:branced ratio of 0:100 **95** gave cyanohydrin product with a lower enantiomeric excess of 55% (*R*).



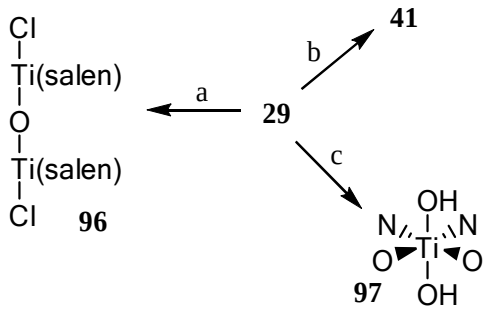
Branched polymer



Linear polymer

93) Linear:branched 100:0
94) Linear:branched 100:0.5 to 100:50
95) linear:branched 0:10

Kim *et al* also attempted to immobilise variations of catalyst **41** using mesoporous silica MCM-41 and silica gel as the solid supports.[52] Homogeneous systems were first investigated using complex **37** which was treated with different amounts of water and triethylamine to give complexes **41**, **96** and **97**, (Scheme 10). Complexes **37, 41**, **96** and **97** all gave cyanohydrin product with 100% conversion when using benzaldehyde as the substrate after a reaction time of 24 hours. The modified catalysts **96** and **97** gave slightly lowered enantioselectivities of 72% and 78% (*S*) respectively when using a 10 mol% catalyst loading at room temperature in dichloromethane. Catalyst **37** gave cyanohydrin product with an enantiomeric excess of 75% (*S*) with complete conversion under the same reaction conditions.



a) H_2O (0.5 eq), Et_3N
b) H_2O (1 eq), Et_3N
c) H_2O (2 eq)

Scheme 10: formation of the first homogeneous catalysts in cyanohydrin synthesis.

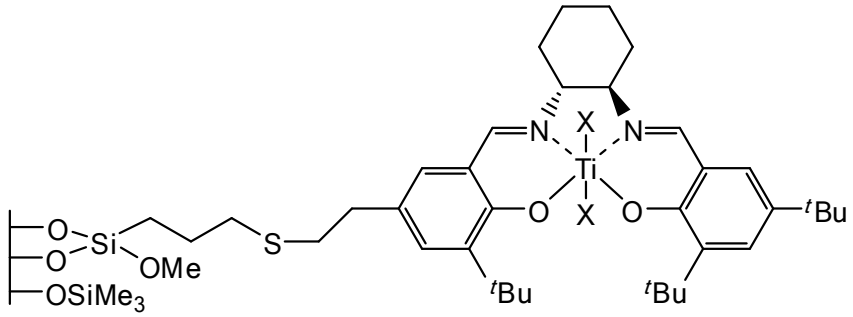
Immobilisation of these complexes onto MCM-41 was carried out using two methods. The first method involved covalently bonding the catalyst at the five-position of the aromatic ring of the salen unit, replacing a *tert*-butyl group to give complexes **98** and **99**. The second method anchored the complexes to the solid support using the oxygen atoms bonded to the titanium atoms and the bridging oxygens of the dimeric structure to give complexes **100-103.** Complexes **98-103** were used in the cyanosilylation of benzaldehyde giving cyanohydrin product with varying conversions and enantioselectivities. Table 13 shows the results obtained for complexes **98-103**.

Table 13; results obtained when using complexes **98-103** in cyanohydrin synthesis with benzaldyde as the reaction substate.

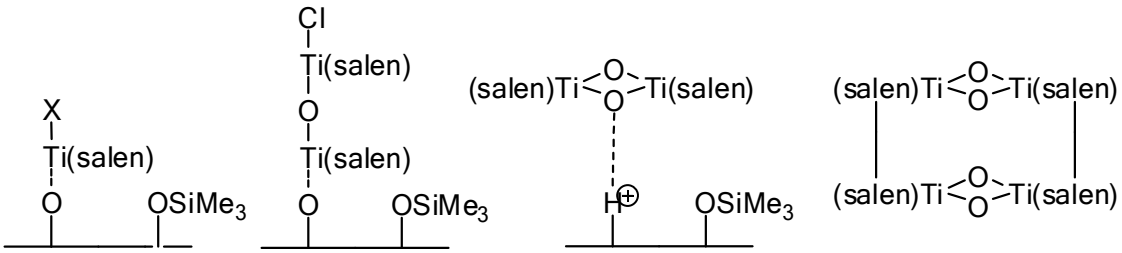
Catalyst [a]	Conversion %	ee % (*S*)
98	23	87
99	28	89
100	36	60
101	40	64
102	39	59
103	38	43

[a] all reactions were carried out for 24 hours at ambient temperature in dichloromethane.

Khan *et al* modified ligand **30** to give ligand **105** which was then used to prepare the *bis*-dimeric titanium complex **104** which was tested as an asymmetric catalyst in the cyanation of benzaldehyde using potassium cyanide/acetic anhydride as the cyanide source.[53] When using benzaldehyde as the reaction substrate; potassium cyanide gave the cyanohydrin acetate with 92% (*S*) enantiomeric excess whilst sodium cyanide gave cyanohydrin acetate with 89% (*S*) enantiomeric excess.

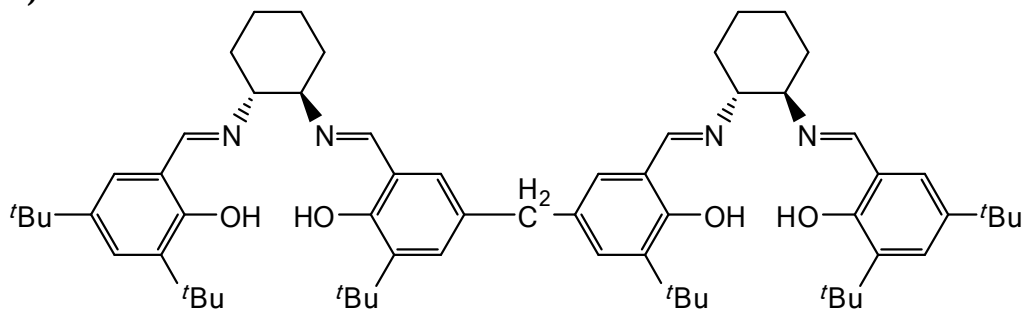


98) X = C**l**
99) X = OH



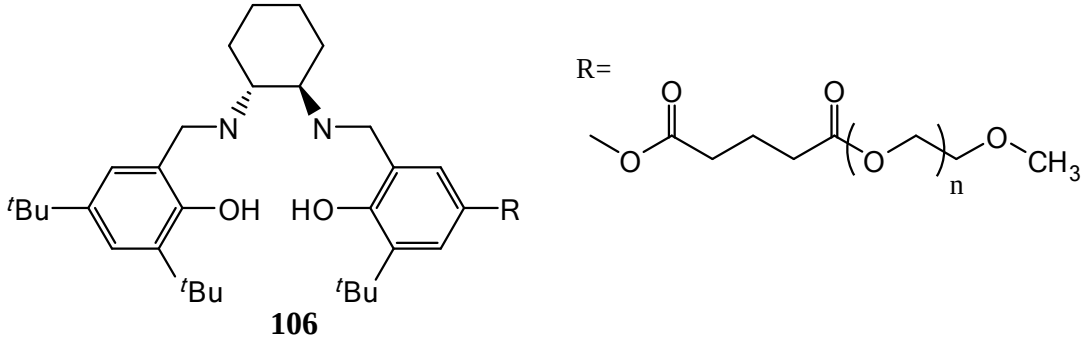
100) X = Cl
101) X = OH

102 **103** **104**



105

Venkataraman *et al* also modified complex **30** by changing the *tert*-butyl groups in the *para*-positions of the aromatic rings of the salen ligand units to polymeric fragments of low molecular weight to give ligand **106**.[54] Using titanium tetrachloride with ligand **106** gave a soluble titanium complex that could be separated from the cyanohydrin product using Soxhlet dialysis techniques. The titanium complex was able to catalyse the addition of trimethylsilylcyanide to benzaldehyde a total of five times before a decrease in activity was observed with enantioselectivities of 86% being achieved at room temperature after 24 hours



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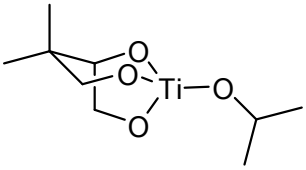
1.2.5 Asymmetric Cyanation of Ketones Using Titanium Salen Complexes.

Ketones are less reactive than aldehydes due to the increase in the size of the substituents on the carbonyl. The alkyl substituent can prevent the cyanide ion from attacking the carbonyl carbon if steric interactions are large enough. Also, the change from a proton to an alkyl substituent decreases the electrophilicity of the carbonyl carbon due to the electron donating nature of the alkyl substituent. The increase in electron density around the carbonyl group reduces the attractive electrostatic interaction with any incoming nucleophile such as a cyanide ion. Asymmetric cyanohydrin synthesis involving ketones as substratres illustrates these problems as ketones are found to be less reactive even with the most active catalysts.

The first example of the catalysed asymmetric cyanation of ketones was reported in 1997 by Choi.[55] These reactions required high temperatures and pressure to obtained any cyanated product. Thus, acetophenone was cyanated using trimethylsilylcyanide at a pressure of 0.8 GPa using 1 mol% of complex **107**. Even under these harsh reaction conditions, cyanohydrin product was obtained with just 60% enantiomeric excess. Carrying out the same reaction at atmospheric pressure gave cyanohydrin product with only 7% enantioselectivity.



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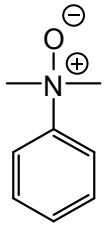


108

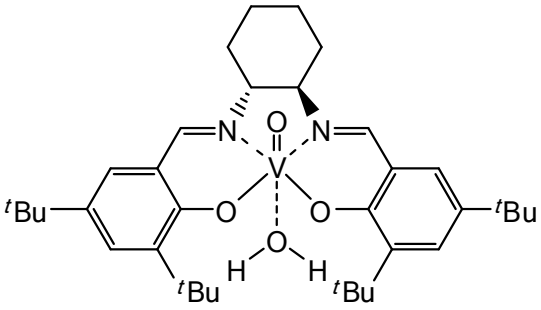
Despite these problems, a number of titanium(salen) systems have been developed for the asymmetric cyanation of ketones. Belokon and North *et al* used complex **41** in the cyanation of ketones giving the corresponding cyanohydrin products in yields of 64-100% and enantiomeric excesses of 32-72%. These results were achieved at atmospheric pressure and ambient temperature.[56] Acetophenone and 2-methoxyacetophenone gave the best results whilst *iso*-propyl and *tert*-butyl-phenylketones gave no cyanohydrin product when used under these conditions. Longer reaction times (1-5 days) were required for all these substrates.

Feng *et al* investigated the use of Lewis basic additives in combination with Lewis acidic complexes in the cyanation of ketones. As with previous studies using titanium salen complexes in the asymmetric cyanation of aldehydes,[26] a number of ligands were screened using titanium tetraisopropoxide as the titanium source and trimethylsilylcyanide as the cyanide source.[57] Ligand **17** was found to be the most stereoselective when used with *N*-oxide **108**. Ligand **17** was used at a loading of 2 mol% and with an additive loading of 1

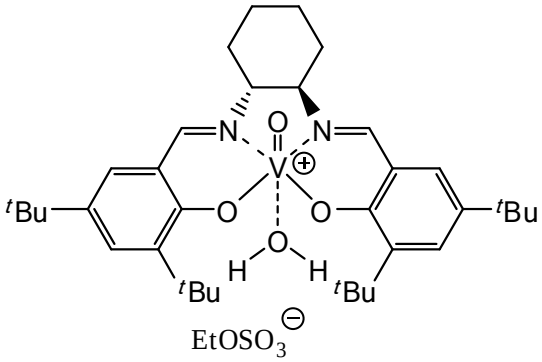
mol%. Enantiomeric excesses of 83-84% were obtained for the corresponding cyanohydrin products when screening a wide variety of ketones. A range of *N*-oxides were also screened all giving similar results to those obtained when using *N*-oxide **108**.

1.3. Vanadium(Salen) Based Catalytic Systems for Cyanohydrin Synthesis.

Cyanohydrin synthesis using titanium complexes is a well established line of research dating back to 1991[58] and has been extensively reviewed.[31f] However, it was not until 2000 that vanadium was investigated as a possible metal source for catalysts for asymmetric cyanohydrin synthesis when Belokon and North *et al* [59] demonstrated the use of vanadium(salen) complexes in asymmetric cyanohydrin synthesis. Complexes **109** and **110** were prepared from ligand **30** using vanadyl sulphate hydrate as the vanadium source and their structure was determined by X-ray crystallography.



109



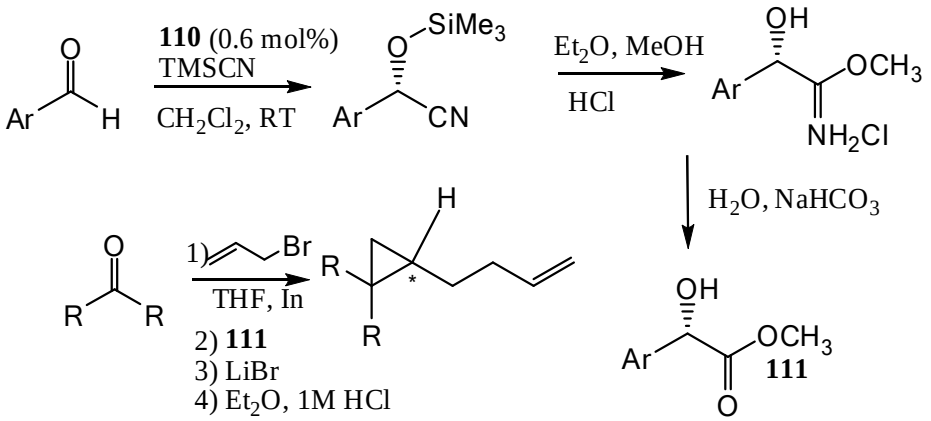
110

Complex **109** was initially thought to be an active catalyst for cyanohydrin synthesis. Thus, a catalyst loading of 0.1 mol% catalysed the addition of trimethylsilylcyanide to aromatic aldehydes in dichloromethane, giving cyanohydrin silyl ethers with 90-95% enantiomeric excess (Table 14). All aldehydes were completely transformed into the cyanohydrin product in 24 hours at ambient temperature. The rate of reaction observed with complex **109** was lower than that obtained using titanium based complexes, however the enantioselectivities were higher. Further investigation of this system revealed that the true catalyst was the vanadium(V) complex **110** obtained via oxidation of complex **109** by air. The high enantioselectivities obtained using complex **110** has prompted its use by other other research groups. Thus, the group of Lloyd-Jones[60] were investigating the asymmetric homoallyl cyclopropanation of dibenzylideneacetone using indium halide reagents (Scheme 11). They found that the enantioselectivity of the cyclopropanation could be enhanced by using a modifier, in particular β-amino alcohols or methyl mandelate analogues **111** which were prepared by asymmetric cyanohydrin synthesis using complex **110.**

Table 14; comparative data obtained from a substrate screen using complex **110** with trimethylsilylcyanide and potassium cyanide as the cyanide sources.

Aldehyde	TMSCN [a] ee%	KCN/Ac_2O [b] ee%
PhCHO	90	90
3-$MeOC_6H_4CHO$	85	85
4-$MeOC_6H_4CHO$	90	-
3-MeC_6H_4CHO	95	-
4-MeC_6H_4CHO	94	-
2-ClC_6H_4CHO	-	78
Me_3CCHO	68	-
PhCOMe	22	-

[a] all aldehydes gave *O*-silyl protected cyanohydrins with complete conversion in 24 hours at ambient temperature.
[b] all aldehydes gave *O*-acetyl protected cyanohydrins with reaction conditions of; -40 ^oC, *tert*-butanol-water (10:1), 10 hours, 1mol% of **110.**

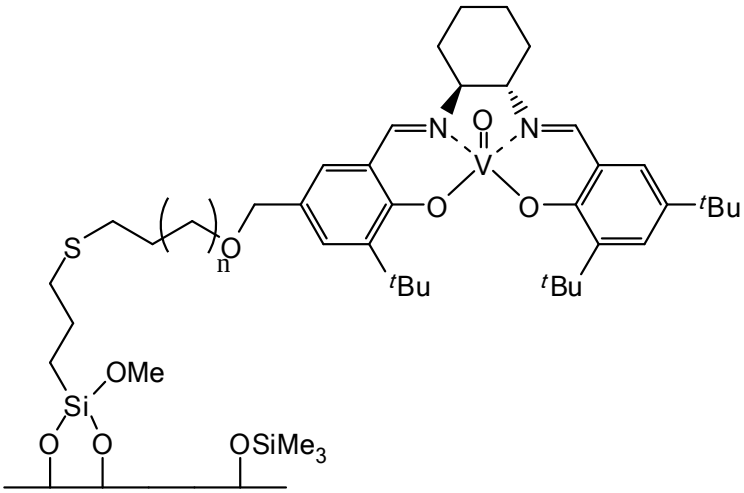


Scheme 11: example of the application of complex **110**.

The high activity displayed by complex **110** prompted its immobilisation in an attempt to increase the catalytic turnover of the system. The first work carried out in this field was by Gigante and Corma in 2003 and utilised silica and zeolites as solid supports.[61] Using silica supported catalyst **112**, tethered at the *para*-position of one of the aromatic rings, the length of the alkyl chain tether was varied with longer tether lengths being shown to be more enantioselective (n = 11 gave an enantioselectivity of 63% when using benzaldehyde as the reaction substrate).

In 2004, Gigante and Corma also explored the use of a mesoporous organosilica zeolite as a possible solid support.[62] This was loaded with complex **113,** and employed in the addition of cyanide to benzaldehyde. Using the mesoporous organosilica zeolite as the solid support did not improve on the previous findings as mandelonitrile trimethylsilyl ether was

obtained with only 30% enantiomeric excess. Immobilisation of complex **110** onto single walled carbon nanotubes to give **114** gave modest results of 66% enantioselectivity after 72 hours at 0 ^{o}C using a catalyst loading of 0.3 mol%.[63]



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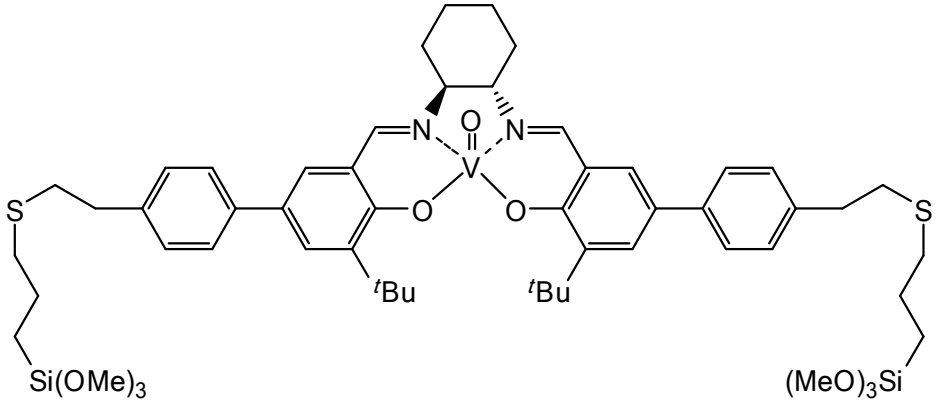
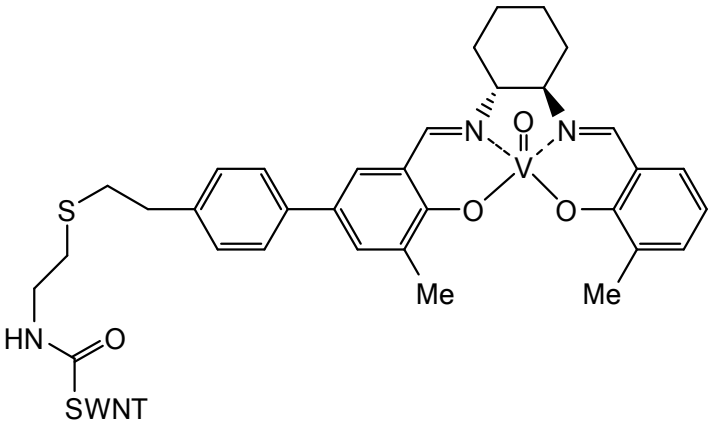


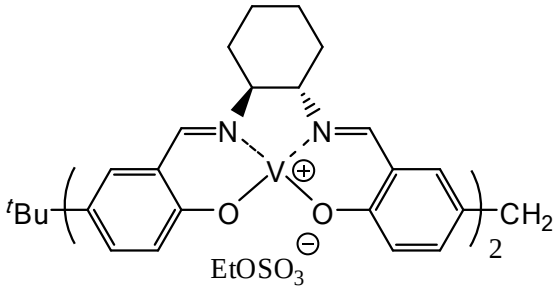
113



114) SWNT = single walled carbon nanotube.

Work by the same group investigated the use of ionic liquids as a medium for asymmetric cyanohydrin synthesis using complex **110**.[64] Screening of a variety of different ionic liquids showed that 1-ethyl-3-methyl imidazolium hexafluorophosphate gave the best results. Cyanation of benzaldehyde using trimethylsilylcyanide was achieved in 24 hours at room temperature giving the silyl protected cyanohydrin product with 89% enantiomeric

excess. Khan *et al*[65] synthesised dimeric **(115)** and polymeric (**116)** versions of complex **110**. Using complex **115** and potassium cyanide as the cyanide source, a variety of aldehydes were cyanated with enantioselectivities varying from 88 to 95% and with 90-99% chemical yields. To achieve these results, a reaction temperature of -20 ^{o}C was required with dichloromethane as the solvent. Complex **116** did not improve on these results, or on those obtained using complex **110**. Enantioselectivities of 82-96% were attained for aromatic substrates, though aliphatic aldehydes gave products with lower enantiomeric excesses of 82-96%.



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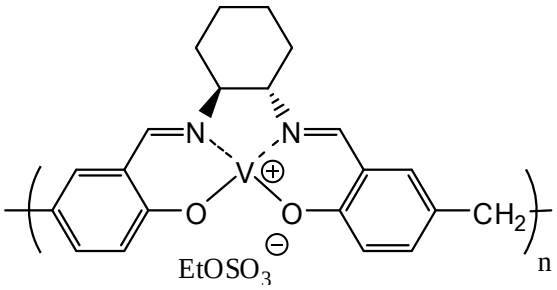
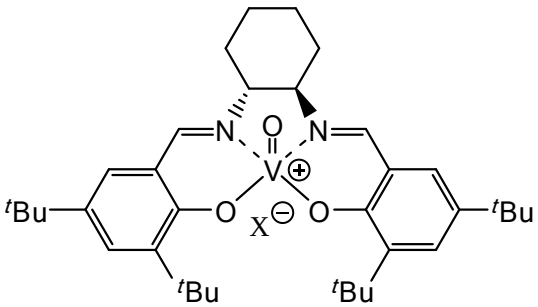


116

Although vanadium(V)(salen) complexes were found to be more enantioselective than titanium(salen) complexes, the rates of these reactions were slower than those observed when using titanium(salen) complexes. In a further study of vanadium(V)(salen) complexes, Belokon and North[66] prepared a range of vanadium(V) complexes (**117-122**) possessing different counterions. All these complexes were tested in cyanohydrin synthesis using trimethylsilylcyanide as the cyanide source under the following conditions; **117-122** (0.2 mol%), in dichloromethane at 0 ^{o}C. Table 15 summarises the results obtained. The activity is represented by the length of time required to convert 50% of the benzaldehyde into cyanohydrin.



117) X= BF_4
118) X= Cl
119) X= Br
120) X= CF_3SO_3
121) X= F
122) X=CN

Table 15; catalyst screen using benzaldehyde as the reaction substrate and trimethylsilylcyanide as the cyanide source.

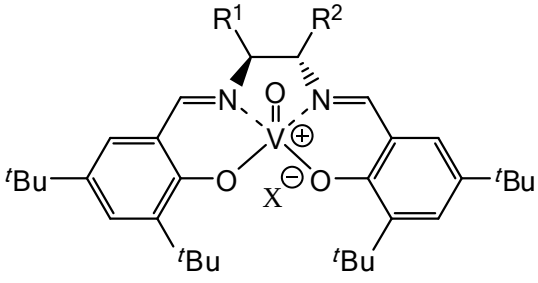
Catalyst	t_{50} (mins)	ee %
117	78.2	90
118	8.6	93
119	50.3	94
120	-	-
121	7.6	91
122	201.9	91
110	370.0	91

Literature precedent[67] suggested that in the case of complex **119**, the bromide counterion would remain uncoordinated to the vanadium centre with the sixth coordination position occupied by a water molecule. The same was true for complex **120.**[68] ^{19}F NMR spectra showed that for complex **117**, the tetrafluoroborate counterion is present in an equilibrium between the coordinating and the dissociated form. In the uncoordinated form, the sixth site is occupied by a solvent molecule.[69] Complex **118** was expected to contain a vanadium-chloride covalent bond.[70] An initial hypothesis predicted that complexes possessing non-coordinating counterions would be the most Lewis acidic and so give the highest rates of reaction. Screening the catalysts in the addition of trimethylsilylcyanide to benzaldehyde however, gave results that were inconsistent with the above hypothesis. Complex **120** with a triflate counterion was totally inactive and the next least active of the active catalysts was complex **110**, which converted 50% of the benzaldehyde to cyanohydrin in 370 minutes. The most active complex screened in this study was complex **121** bearing a fluoride anion ($t_{50\%}$= 7.6 minutes) followed by complex **118** containing a chloride anion ($t_{50\%}$= 8.6 minutes). Complex **118** was the most catalytically active isolatable catalyst. The catalytic activity thus increased with the basicity of the counterion. Complexes **118** and **121** were fifty times more active than **110**, though the counterion had little effect on the enantioselectivity of the reaction as all of the complexes gave enantioselectivities of 90-94% in favour of the *S*-enantiomer, confirming that the anion is not involved in the stereodetermining step of the reaction.

Kinetic studies revealed that at 273K, all the complexes displayed second order overall kinetics, resulting from the reaction being first order in benzaldehyde concentration and first order in trimethylsilylcyanide concentration. This distinguished these complexes from the titanium(salen) dimer **41** which had been shown to catalyse the addition of

trimethylsilylcyanide to benzaldehyde with first order overall kinetics; the rate depending on the trimethylsilylcyanide concentration, but not the benzaldehyde concentration. The difference in rate equations suggests that the two catalytic systems have different catalytic cycles. The rate equation was also shown to change with temperature for complexes **117** and **119.** Decreasing the reaction temperature from 273K to 263K changed the overall reaction order from second order to zero order. The reaction atmosphere was also shown to have a significant affect on the rate of reaction as changing it from air to argon either totally deactivated the catalyst or caused the catalyst to deactivate before the reaction was complete. Previous studies had shown that the vanadium(IV)(salen) complex **109** was catalytically inactive and oxidation to the corresponding vanadium(V)(salen) complex by air was required to generate the catalytically active species *in situ*. Throughout the course of an asymmetric cyanohydrin synthesis, the vanadium appears to be reduced to the inactive vanadium(IV)(salen) complex. The vanadium(IV) complex has to then undergo a re-oxidation back to a vanadium(V) species if the catalytic cycle is to continue. Under an argon atmosphere, this re-oxidation cannot take place, resulting in catalyst deactivation. This observation can also explain the switch from second to zero order kinetics as the reaction temperature decreases. At lower temperatures, re-oxidation becomes the rate determining step of the reaction and therefore the rate becomes independent of both benzaldehyde and trimethylsilylcyanide concentrations.

North *et al* also conducted an investigation into the influence of the chiral diamine of the salen unit on the catalytic activity.[48] A range of vanadium(V)(salen) chloride and ethylsulphonate complexes **123-131** were prepared and tested in cyanohydrin synthesis. The best enantioselectivities were obtained using complexes **123** and **131** (80% and 81% respectively). The diphenyldiamine derived complex **123** required 1 mol% of the complex to achieve this result whilst only 0.1mol% of valine derived complex **131** was required. Catalysts **123-127** were found to be less active than complexes **128-131** which is probably due to the different counterions within the complexes as previously discussed. All of complexes **123-131** were shown to be less active than the corresponding complexes **110** and **118** derived from cyclohexanediamine.



123) R^1=R^2= Ph; X= $EtOSO_3$
124) R^1=R^2= Me; X= $EtOSO_3$
125) R^1=R^2= ^{n}Pr; X= $EtOSO_3$
126) R^1=R^2= ^{i}Pr; X= $EtOSO_3$
127) R^1=R^2= ^{t}Bu; X= $EtOSO_3$
128) R^1= H, R^2= Me; X= Cl
129) R^1= H, R^2= CH_2Ph; X= Cl
130) R^1= H, R^2= Ph; X= Cl
131) R^1= H, R^2= $CHMe_2$; X= Cl

Further to this study, a more detailed analysis was carried out on complexes **117-119** and **121.**[71] The reaction order with respect to each catalyst was determined by monitoring the kinetics of reactions carried out with different catalyst concentrations. The results are summarised in Table 16. Complexes **117-119** all displayed orders with respect to catalyst of 0.7-0.9 suggesting that the predominant active species is the monomeric form of the complex. This exists in solution in equilibrium with the dinuclear species which may also exhibit some catalytic activity. In contrast, for complex **121,** the order with respect to catalyst was found to be 2.45, suggesting that the predominant catalytically active species is a dinuclear complex. The high value of the order with respect to catalyst obtained for this complex may even suggest that larger oligomers exist in solution for complex **121** which may be responsible for the higher catalytic activity observed with this catalyst. Vanadium(salen) fluoride complexes have been shown to exist as oligomers.[72]

Table 16; kinetic data obtained from kinetic analysis of complexes **117-121**.

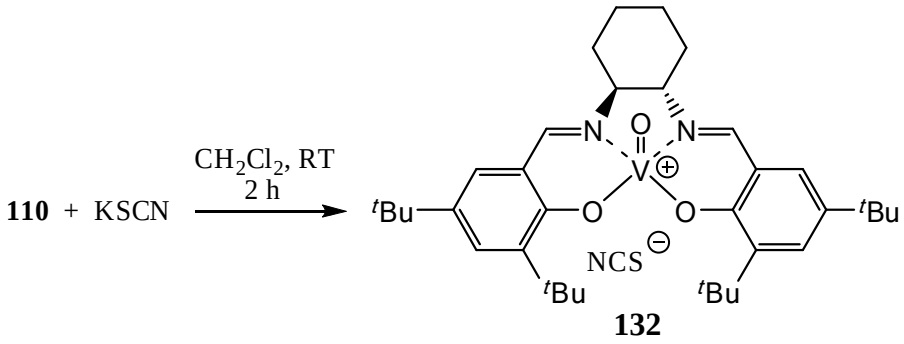
Complex	Order of Reaction with Respect to Catalyst
117	0.84
118	0.88
119	0.74
121	2.45

It was hypothesised that the counterion influences the equilibrium between the monomeric and the dimeric forms of the complex. The less active catalysts exist predominantly as monomers and the more active catalysts exist predominantly as dimers in solution. Mass spectrometry experiments carried out on all the complexes confirmed the existence of dimeric as well as monomeric species in solution. Thus, these vanadium(V)(salen) complexes appeared to be catalysing cyanohydrin synthesis via two different reaction mechanisms depending on the counterion present in the complex. For the less active complexes, the predominant active species was shown to be the monomer, therefore only activation of the benzaldehyde was possible. The more active species (**121**) was shown to exist predominantly as a dimeric species, therefore activation of both the benzaldehyde and the trimethylsilylcyanide was possible resulting in a more active catalyst.

Based on the criteria discussed above for formation of the most active vanadium(V)(salen) complexes, complex **132** was prepared by stirring complex **110** with potassium thiocyanate in dichloromethane (Scheme 12). Thus, benzaldehyde was converted into the corresponding cyanohydrin using trimethylsilylcyanide as the cyanide source, using

0.1 mol% of complex **132**, in dichloromethane under an air atmosphere, in two hours at room temperature. The cyanohydrin trimethylsilyl ether was obtained with 91% (*S*) enantiomeric excess in 99% chemical yield. Kinetics experiments confirmed that reactions catalysed by complex **132** displayed overall second order kinetics at 273K. The reaction atmosphere had no influence on the activity of the catalyst in this case, as performing the reaction under an argon atmosphere had no detrimental affect on the activity of the system. It was hypothesised that the high activity of complex **132** ensured that the reaction was complete before any redox processes could lead to catalyst deactivation.

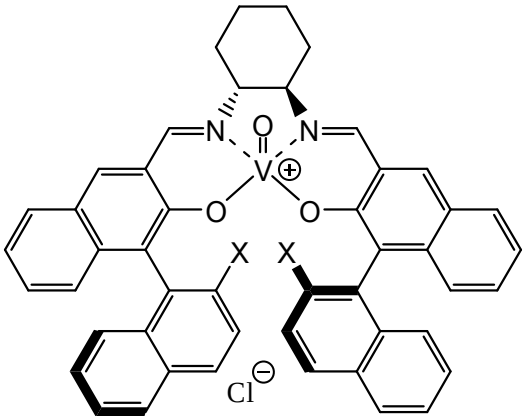
The work carried out using complexes **117-132** clealry demonstrates that these vanadium complexes are much more enantioselective than the titanium(salen) dimer **41**. Complex **132** is by far the most active salen complex developed by the North group with a great deal of attention being paid to the study and understanding of the reaction kinetics. Without a through understanding of a reaction mechanism, it can be very difficult to gain a through insight into the catalytic system. This study, along with the kinetic analysis carried out with regard to complex **441**, displays the vast amount of information that can be gained from such a study and the importance of developing and optimising a system that can also be studied mechanistically.



132

Scheme 12: formation of complex **132** from complex **110** using potassium thiocyanate.

All the vanadium(salen) systems discussed thus far have utilised trimethylsilylcyanide or potassium cyanide as the cyanide source in cyanohydrin synthesis. However, in 2004, Katsuki demonstrated the use of an oxovanandium(salen) complex **133** as a catalyst for the addition of acetone cyanohydrin to aldehydes in the presence of a base.[73] 3-Phenylpropanal was cyananted, giving cyanohydrin product with 90% enantiomeric excess from a reaction carried out at 0 ^{o}C for 24 hours. Complex **133** was tested with a range of aromatic and aliphatic aldehydes and moderate to good enantioselectivity was observed with aliphatic substrates. Interestingly however, benzaldehyde gave a lower enantioselectivity of 45%.



133) X= Ph

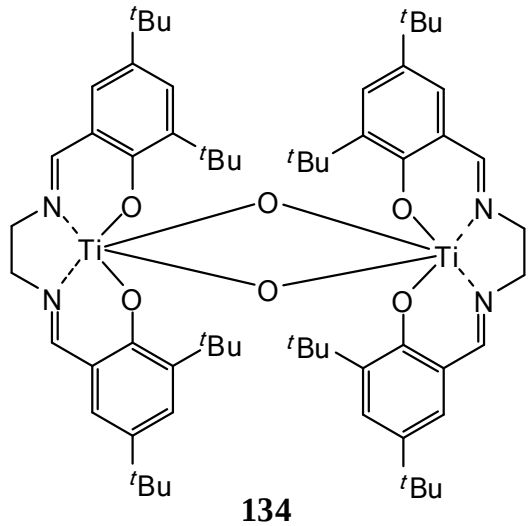
1.3.1 Asymmetric Cyanation of Aldehydes Using Heterobimetallic Catalyst Systems of Vanadium and Titanium.

Complex **41** has been shown to be a very active catalyst in the asymmetric cyanation of aldehydes. Catalysts **110** and **118** have been shown to be highly enantioselective, giving cyanohydrin product with enantiomeric excesses of >90%. Due to the dissociative behaviour of complex **41** in solution, North *et al* prepared heterobimetallic complexes in an attempt to obtain both the high activity displayed by the titanium catalysts and the high enantioselectivity displayed by the vanadium catalysts. Belokon and North *et al* carried out a series of experiments involving the mixing of complex **110** with complex **41** where complexes **110** and **41** contained the opposite stereochemistry within the cyclohexanediamine unit.[74] In the absence of heterobimetallic complex formation, predictions were that catalysis would be carried out solely by the titanium complex as this is by far the most active of the two systems. The stereochemistry of the cyanohydrin product would however reveal which species had actually been responsible for the catalysis.

Thus a mixture of monomeric (*S*,*S*)-**110** and bimetallic (*R*,*R*)-**41** in a 2:1 ratio was prepared and used in the cyanation of benzaldehyde using trimethylsilylcyanide as the cyanating agent. Cyanohydrin product was obtained with an enantiomeric excess of 84% (*R*). This indicated that the species responsible for the asymmetric induction was (*S*,*S*)-**110**. Varying the ratio of complex **110** to complex **41** showed that only 10% of the vanadium complex was required for it to have total influence over the stereochemistry of the product. Kinetic studies of this system revealed that the rate of the reaction was intermediate between the rates found for complexes **110** and **41** individually. These results strongly suggested that the formation of a heterobimetallic complex was occurring *in situ*. The complex was hypothesised to contain both a titanium and vanadium atom as shown in Figure 5. During the stereodetermining step within the transition state, the aldehyde appeared to be coordinating to

the more Lewis acidic, positively charged vanadium atom with an intramolecular transfer of cyanide from the titanium atom to benzaldehyde.

Further work focused on the combination of both chiral and achiral metal salen complexes.[75] Achiral complexes **134** and **135** were synthesised and used in combination with chiral complexes **40-42** and **136-138** in the cyanation of benzaldehyde using trimethylsilylcyanide. As with previous studies, the asymmetric induction was shown to be controlled by the vanadium atom. Chiral complex (*R,R*)-**41** in combination with achiral complex **135** (1:2 ratio) gave cyanohydrin product with a very low enantiomeric excess of 18% (*S*) with complete conversion after a reaction time of 24 hours. Using the opposite combination of achiral complex **134** in combination with (*R,R*)-**136** gave (*S*)-mandelonitrile with an enantiomeric excess of 92%. Similar complex combinations gave the same results, always indicating that the species responsible for the asymmetric induction was the vanadium component of the catalyst. To investigate the structure of these heterobimetallic complexes, ^{1}H NMR spectroscopy and high resolution electrospray mass spectrometry were used and gave structural evidence to support the structure presented in Figure 5. Mass spectroscopy showed the characteristic isotope pattern for one titanium atom and one vanadium atom.



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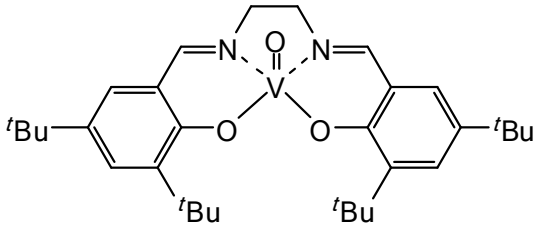

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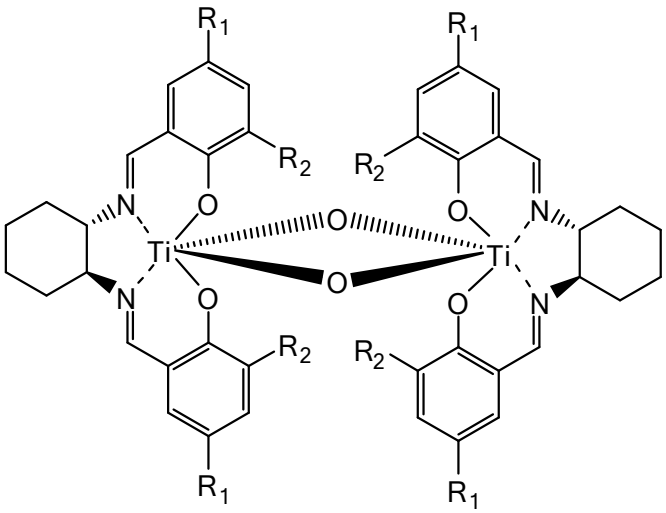


136) R_1= OMe; R_2= ^{t}Bu
137) R_1=R_2=H
138) R_1=MeO; R_2= ^{t}Bu

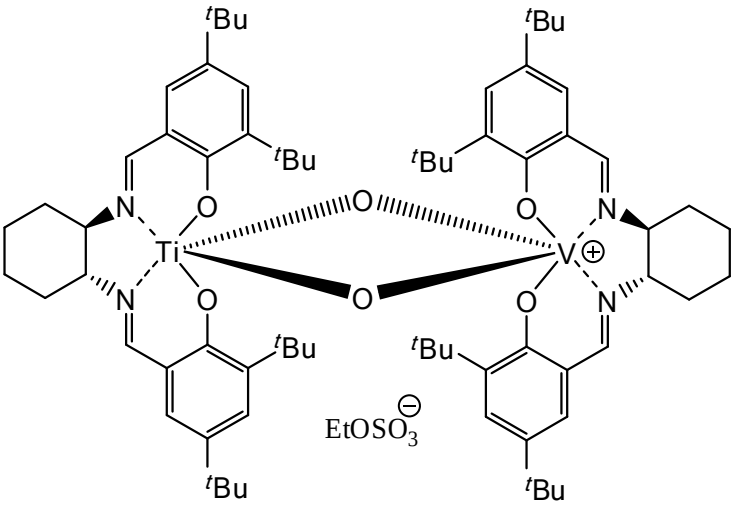
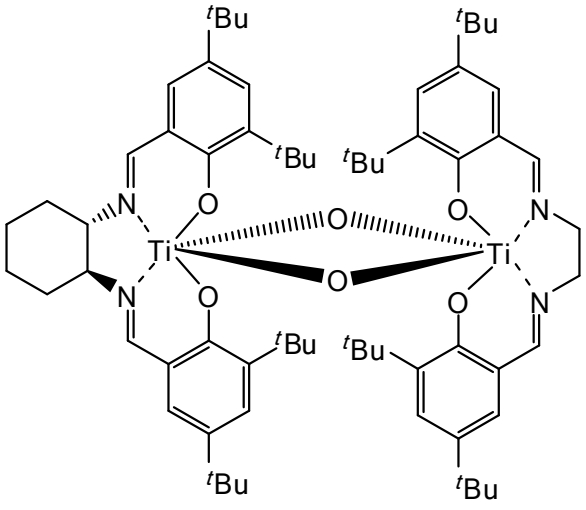


Figure 5: proposed heterobimetallic complex formed by mixing complexes **110** and **41**.

Mixtures of two titanium complexes were also investigated. Chiral complex **41** and achiral complex **134** were mixed and used in a cyanohydrin reaction. An enantiomeric excess of half the enantiomeric excess obtained when using complex **41** alone was obtained and the yield was lower than that obtained using complex **41**. Mass spectrometry again confirmed the formation of a mixed bimetallic complex **139**. The metal atoms in complex **139** have equal Lewis acidity and therefore there is an equal probability that the benzaldehyde will coordinate to the either of the titanium atoms in the bimetallic complex, one of which has an achiral salen ligand attached to it, thus resulting in a halving of the asymmetric induction. Electron-rich and electron-deficient complexes were also investigated. A reasonable enantioselectivity (58%) was obtained when using the methoxy-substituted complex **138** alone. Using the nitro-substituted complex **42** gave a much lower enantioselectivity of only 19%. Combining the two complexes again gave an enantioselectivity mid-way between the two individual complexes.

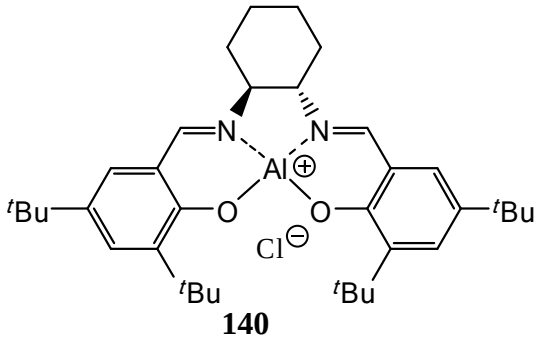


139

The purpose of this study was not to develop a more active catalyst than titanium complex **41** or vanandium complexes **110** and **118**, but to gain an insight into the role of these two metals when used in conjunction with each other. Interesting and important results were gained from this study that are crucial in understanding the high activity of these catalysts.

1.4 Aluminium Based Catalytic Systems for the Cyanation of Aldehydes.

The literature on the use of aluminium(salen) complexes as catalysts for asymmetric cyanohydrin synthesis is not as extensive as for titanium or vanadium(salen) complexes, however, there are some examples of aluminium based systems used in the cyanation of both aldehydes and ketones. Kim *et al* [76,77] first demonstrated the use of an aluminium(salen) complex in asymmetric cyanohydrin synthesis. Complex **140** was shown to catalyse the addition of trimethylsilylcyanide to benzaldehyde with 86% enantioselectivity and in 94% chemical yield after a reaction time of 18 hours at -50 ^{o}C in dichloromethane. The presence of a Lewis basic additive was necessary to achieve these results and triphenylphosphine oxide was found to give the best results when added to the reaction in a 10 mol% loading along with 1 mol% of complex **140**. Enantioselectivities of 72-86% in favour of the (*R*)-enantiomer of the product were obtained with the best results being observed for aromatic substrates. The aluminium metal behaves as a Lewis acid, coordinating to the aldehyde and bringing it into a chiral environment, thus this system displays dual activation in which both the trimethylsilylcyanide and aldehyde are activated. This is a common theme throughout aluminium(salen) catalysis in asymmetric cyanohydrin synthesis.



140

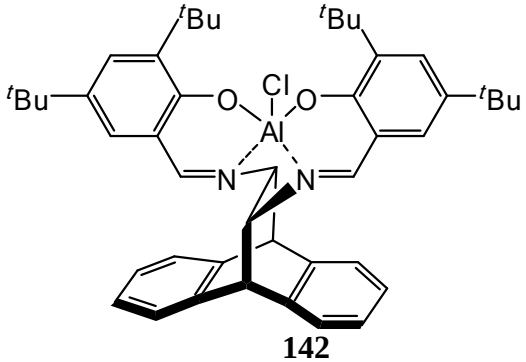
Corey suggested that trimethylsilylcyanide would react with triphenylphosphine oxide to produce species **141** (Scheme 13).[78] Species **141** is believed to be the true cyanating agent in this cyanohydrin synthesis reaction. Evidence to support the generation of species **141** was presented by Corey using ^{1}H and ^{13}C NMR experiments. Mixing triphenylphosphine oxide and trimethylsilylcyanide (1:1) in deuterated chloroform at 23 ^{o}C led to the formation of a new trimethylsilyl peak at 0.05 ppm compared to trimethylsilylcyanide which gives a

trimethylsilyl peak at 0.36 ppm. ^{13}C NMR experiments also showed the formation of a new trimethylsilyl peak at 1.84 and a peak at 110.1 for the cyanide carbon. Infra-red spectroscopy also showed the appearance of a new C=N stretch at 2072 cm^{-1} which was different to trimethylsilylcyanide which shows an IR C=N stretch at 2095 cm^{-1}. ^{31}P NMR experiments also indicated the formation of a new phosphorus containing species as a new peak was observed to form at 28.77 ppm whilst tiphenylphosphine oxide gives a ^{31}P NMR signal at 28.24 ppm. Although Corey acknowledges that the formation of species **141** needs confirmation, there is strong evidence indicate that trimethylsilylcyanide does interact with triphenylphosphine oxide to give a species such as **141**which can then react with the carbonyl substrate directly to give a racemic mixture of product or via a Lewis acidic catalyst to give the enantiomerically enriched product.

$$Ph_3P{=}O \;+\; TMSCN \rightleftharpoons \underset{\textbf{141}}{Ph_3P(OTMS)(N{=}C^{\bullet})}$$

Scheme 13: proposed reaction of triphenylphosphine oxide with trimethylsilylcyanide to give complex **141**.

Zeng *et al* [79] utilised complex **142** containing a modified bridging diamine moiety. As with complex **140**, the addition of a phosphine oxide additive was necessary to achieve catalytic activity so trioctylphosphine oxide was added in a 10 mol% loading along with 1 mol% of complex **142** in dichloromethane at 10 ^{o}C to give (*S*)-mandelonitrile with 86% enantiomeric excess. Use of triphenylphosphine oxide as the Lewis basic additive gave the cyanohydrin with a slightly lowered enantioselectivity of 80% under these reaction conditions. The catalyst was also compatible with both aromatic and aliphatic substrates, all giving respectable enantioselectivities of 78-92%.



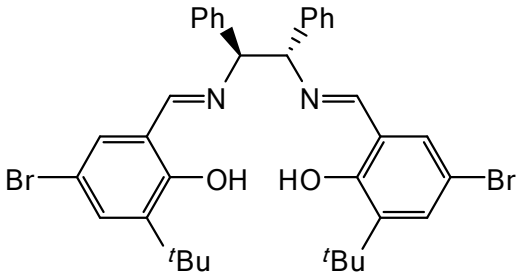
142

Kim and Zeng have both demonstrated the use of aluminium(salen) complexes in the asymmetric cyanosilylation of aldehydes. However, there is a lack of mechanistic studies to provide a more thorough insight into the mode of action of these complexes. The role of the triphenylphosphine oxide is speculative although Corey does provide strong evidence for the

formation of a complex **141**. The dual activation of both the carbonyl substrate and cyanide source by separate catalysts is a concept not seen with the analogous titanium and vanadium(salen) complexes, and a further understanding of the reaction mechanism would be beneficial in these cases.

1.4.1 Aluminium Salen Based Catalytic Systems for the Cyanation of Ketones.

In 2004 Feng *et al*[80] utilised an aluminium(salen) complex prepared *in situ* from salen ligand **143** and triethylaluminium. It was found that in the presence of 1 mol% of pyridine *N*-oxide, this complex would catalyse the addition of trimethylsilylcyanide to a wide selection of ketones, with enantioselectivities of 79-94% at -20 ^{o}C in tetrahydrofuran. A 1:1 ratio of ligand **143** to triethylaluminium was found to produce the optimal results. Ligands **144, 145** and **146** were also screened as potential ligands, but gave inferior results to ligand **143**.



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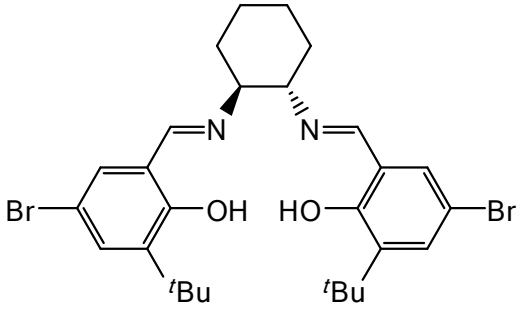

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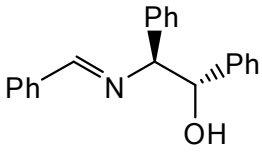

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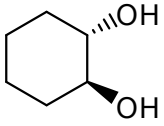

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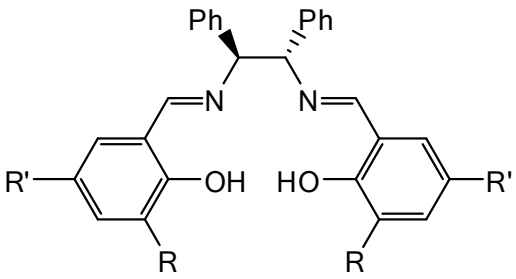


147) R= ^{t}Bu, R'= Me
148) R=R'= Cl
149) R= adamantly, R'= ^{t}Bu

Many other variables were investigated in this study. Altering the structure of ligand **143** had various affects on the enantioselectivity. Ligand **147** gave lower enantioselectivity (70% *R*) but a chemical yield of 99%. **147-148**. Electron-deficient ligand **148** gave lowered enantioselectivities (53% *R*) and (73% *R*) respectively. Steric effects were investigated by increasing the substituent size to an adamantly group in ligand **149**, however, in this case no cyanohydrin product was formed. Lowering the reaction temperature had an unfavourable effect on the enantioselectivity as well as on the yield as the rate of the reaction decreased.

Temperatures of -40 and -78 ^{o}C gave cyanohydrin product with just 57 and 66% (*R*) enantioselectivity respectively.

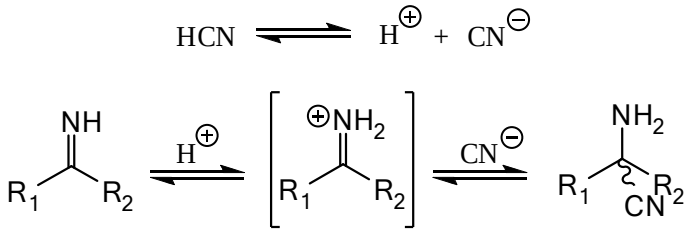
Kim also used complex **140** in the trimethylsilylcyanation of ketones.[81] Triphenylphosphine oxide was again required as a Lewis basic additive in a 10 mol% loading. was used as the test substrate and trimethylsilylcyanide as the cyanide source. Using 1 mol% of complex **140** at room temperature in dichloromethane, *p*-chlorophenylacetophenone was cyanated to obtain cyanohydrin product with 68% (*R*) enantioselectivity after a reaction time of 12 hours. Lowering the reaction temperature to -40 ^{o}C improved the enantioselectivity to 81% (*R*), however, the reaction time was extended to 200 hours. Screening a range of ketones showed that this catalyst was capable of accommodating a variety of ketone substrates with results comparable to those obtained using aldehyde substrates (60-75%). Acetophenone gave cyanohydrin product with 78% (*R)* enantiomeric excess in 93% chemical yield.

1.5 Asymmetric Strecker Reaction using Chiral Catalysts.

1.5.1 Introduction to the Strecker Reaction.

The Strecker reaction was discovered in 1850[82] and is one of the most direct and efficient methods for the synthesis of α-aminonitriles, which are useful precursors to α-amino acids. The Strecker reaction involves the nucleophilic addition of cyanide anion to an imine bond to form an α-aminonitrile. Hydrolysis then affords the amino acid product (Scheme 14). The Strecker reaction is sensitive to pH with the optimum reaction occuring at pH = 7. For efficient cyanation of the imine bond, the cyanide anion must be available in solution, resulting from the dissociation of hydrogen cyanide into the corresponding proton and cyanide anion. In acidic conditions, the cyanide anion will remain fully protonated however, protonation of the imine nitrogen will also occur increasing the electrophilicity of the imine bond. If the nucleophilicity of the cyanide anion is compromised this will lead to a slower addition to the imine bond, regardless of the increased this electrophilicity of the imine bond.

In basic conditions the cyanide anion will be deprotonated so increasing the nucleophilicity of the anion. However at this increased pH, the protonation of the imine nitrogen (shown in the first step of the reaction in Scheme 14) will not be as effective and so the electrophilicity of the carbon will be greatly reduced in basic conditions. For an optimum Strecker reaction, a compromise must be met between the nucleophilicity of the cyanide and the electrophilicity of the imine bond. This occurs at a pH of 7.

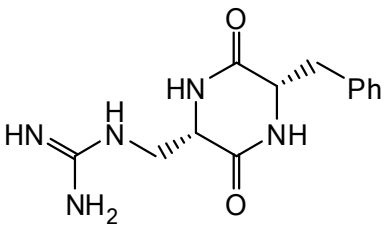


Scheme 14: Strecker reaction.

The corresponding aldehyde can also be used as starting material and by adding the appropriate amine, the imine is synthesised *in situ* and is then subjected to nucleophilic attack by the cyanide ion. The Strecker reaction is analogous to cyanohydrin synthesis, however, the lower electrophilicity of the carbon atom within the imine bond means that Strecker reactions have lower rates of reaction than cyanohydrin synthesis. This is reflected in the literature with higher catalyst loadings and longer reaction times being required.[83]

1.5.2 Asymmetric Strecker Reactions Catalysed by Non-Metal Catalysts.

Non-metallic catalysts have been employed in the asymmetric Strecker reaction, giving enantioselectivities as high as their metal containing counterparts. Below is a review of some of the most important research carried out in this area. Work carried out in 1996 by Lipton *et al.* investigated the use of diketopiperazine **150** as a chiral catalyst in the Strecker reaction.[84] The group investigated the addition of cyanide to a variety of *N*-benzhydryl imines with a catalyst loading of 2 mol% at -25 ^{o}C in methanol using hydrogen cyanide as the cyanide source. *N*-Benzylidene benzylamine **151** (Scheme 15) was found to give aminonitrile product **152** with the most promising enantioselectivity of >99% and with a chemical yield of 95%. A variety of benzhydrylimines were screened and the results are summarised in Table 17. The Lipton system is particulary attractive as a catalyst loading of only 2 mol% was found to give enantioselectivities as high as 99% depending on the substrate. The Strecker reaction usually requires a higher catalyst loading due to the lower reactivity of the imine bond and so to develop a system which requires a relatively low catalyst loading is a very valuable contribution to this area of research.



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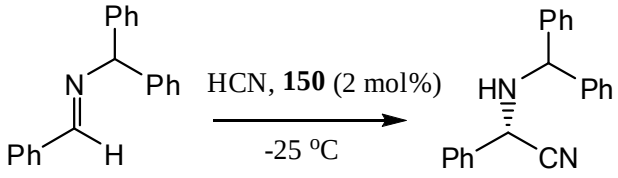


151 **152**

Scheme 15; reaction scheme for Strecker reaction using complex **150**.

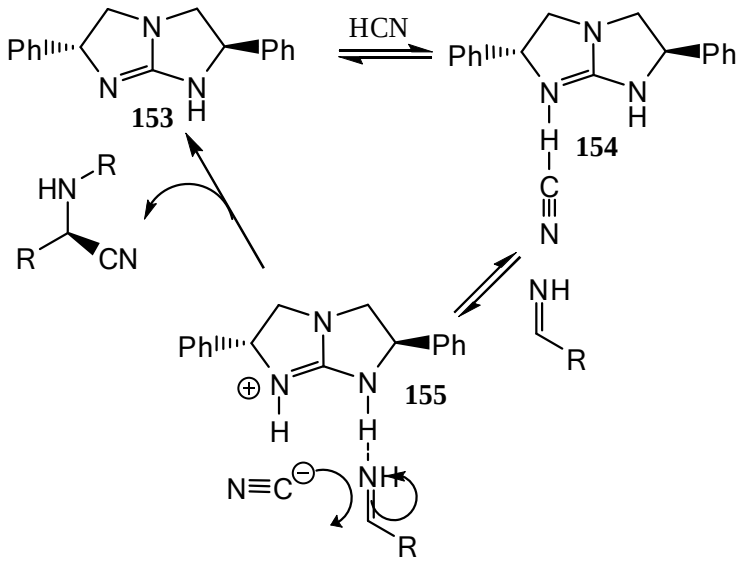
Table 17; results obtained from a substrate screen using complex **150.**

Entry	$RCH=NCHPh_2$	Temperature ^oC	Yield %	ee %
1	C_6H_4	-25	97	>99
2	$4\text{-}ClC_6H_4$	-25	97	83
3	$4\text{-}OMeC_6H_4$	-25	96	63
4	$3\text{-}OMeC_6H_4$	-75	82	80
5	$3\text{-}ClC_6H_4$	-75	80	>99
6	$3\text{-}NO_2C_6H_4$	-75	71	>10
7	^iPr	-75	81	<10
8	^tBu	-75	80	17

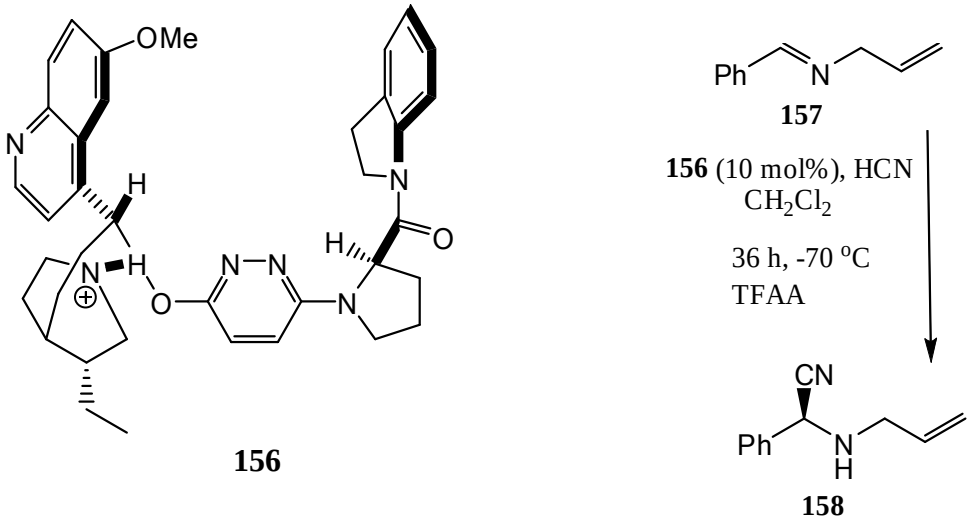
Corey showed that a chiral bicyclic guanidine **153** could also be used as a chiral catalyst in the Strecker reaction.[85] With similar reaction conditions to Lipton's work, aminonitrile **152** was synthesised in 96% yield and with 86% enantioselectivity. Screening a wide range of *N*-benzhydryl imines once again showed that electron-donating and electron-withdrawing substituents on the aromatic ring still produced aminonitriles with respectable enantioselectivities of 50-88%. A mechanistic cycle was proposed as shown in Scheme 16 in which the hydrogen cyanide hydrogen bonds to catalyst **153** forming a guanidine cyanide complex **154.** The imine can hydrogen bond to complex **154** to form complex **155**, then attack of cyanide on the coordinated imine affords the desired product with the catalyst regenerated at the end of the reaction sequence. When considering the three dimensional arrangement of this transition state, the enantioselectivity becomes apparent. The cyanide is positioned to attack the *re*-face of the imine and one of the phenyl groups of the catalyst can undergo π-stacking with one of the benzhydryl phenyls of the imine. The *si*-face of the imine bond is blocked by the other benzhydryl phenyl ring. Van der Waals interactions between the guanidine core and the phenyl edge of the catalyst prevent the imine from rotating through 180^o which would lead to formation of the opposite enantiomer of the aminonitrile.

Corey also demonstrated that chiral ammonium salt **156** is an effective catalyst for asymmetric Strecker reactions.[86] Compound **156** had previously been shown to be very effective for the enantioselective dihydroxylation of alkenes using osmium tetroxide.[87] The hypothesis for the use of this catalyst in the enantioselective Strecker reaction was the presence of a U-shaped cavity which, in theory, could act as a binding pocket to hold imine **157**. Due to the configuration of the proposed transition state, compound **157** should be aligned for attack of cyanide on its *re*-face, producing the (*S*)-α-aminonitrile. An interesting finding from this work was that these reactions tended to be most effective with

dichloromethane as the solvent. This is in contrast to previous studies as the majority of research into the Strecker reaction is performed in toluene as this solvent has been shown to give the highest enantioselectivities. Cyanation of *N*-allyl benzaldimine **157** proceeded efficiently using two equivalents of hydrogen cyanide and 10 mol% of compound **156** in dichloromethane at -70 ^{o}C to give the aminonitrile product **158** with 92% (*S*) enantiomeric excess (Scheme 17). The major drawback with this system is the very low reaction temperatures that are required to gain the high enantioselectivities claimed by Corey. As a result of this low temperature, a reaction time of 36 hours is also necessary along with a 10 mol% catalyst loading.



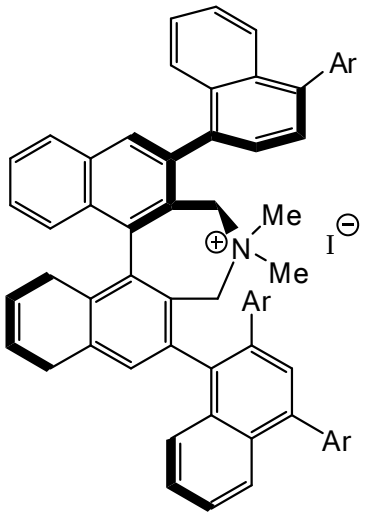
Scheme 16: proposed mechanistic cycle for complex **153** in the Strecker reaction.



Scheme 17; use of complex **158** in the asymmetric Strecker reaction.

Recent work by Ooi *et al* also investigated the use of a chiral quaternary ammonium iodide salt **159** using *N*-arylsulfonyl imines (Scheme 18) as reaction substrates.[88] These were

prepared *in situ* from α-amido sulfones, using phase transfer catalysis. The cyclohexanecarboxaldehyde derived α-amido sulfone was treated with a mixture of one and a half equivalents of potassium cyanide and 1 mol% of **159** in toluene-water (1:3), at 0 ^{o}C. Complete conversion was achieved after one and a half hours, producing the aminonitrile product with 97% enantioselectivity. A selection of these results are presented in Table 18, with Scheme 18 showing the model system used in this study. When comparing this work to the previously discussed work by Corey, it can be seen that this system is far more appealing in the asymmetric catalysis of the Strecker reaction. A catalyst loading of only 1 mol% is required at a much higher reaction temperature of 0 ^{o}C to give an enantiomeric excess of 97%. A direct comparison is difficult due to the nature of the reaction substrates being different, however on the basis of reaction conditions, this system is far superior to Corey's system and gives comparable results to Corey's previous system using complex **150**.



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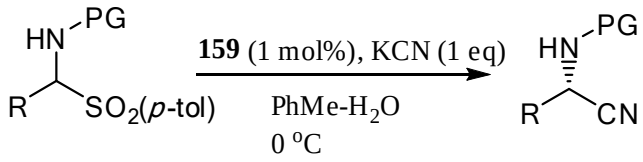


160

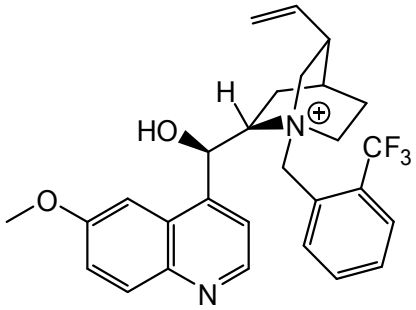
Scheme 18; Strecker reaction using complex **159.**

Table 18; substrate screen using complex **159** with various *N*-protected α-amido sulfones.

R	PG	Yield %	ee %
c-Hex	Mts	99	97
c-Oct	Mts	99	98
$Ph(CH_2)_2$	Mts	99	94
$(CH_3)_2CHCH_2$	Mts	96	91
$Ph(CH_2)_2$	Mtr	98	96

Phase transfer catalysis has also been explored by Herrera *et al* as a possible method for inducing stereoselectivity in the addition of cyanide to imines.[89] The authors investigated the

possibility of using cyanohydrins as a cyanide source, with *N*-Boc protected α-amido sulfones as imine precursors. Acetone cyanohydrin was selected because of its commercial availability and low cost. The study began with the α-aminosulfone of 3-phenylpropionaldehyde as a model substrate to search for appropriate reaction conditions using biphasic conditions of potassium carbonate and an organic solvent (Scheme 19). Several chiral quaternary ammonium salts were screened as potential organocatalysts for the system and the quinine derived catalyst **160** was found to be the most effective, giving enantioselectivities of 60% with excellent yields. Electron withdrawing groups, such as trifluoromethyl, in the *ortho*-position of the *N*-benzyl substituent were found to be important for high catalytic activity as *para*-substituted catalysts were less effective, giving a very low enantiomeric excess of 16%.



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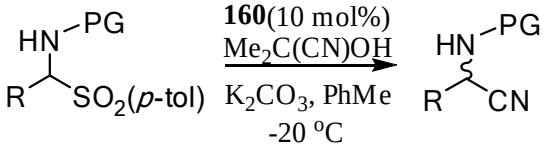
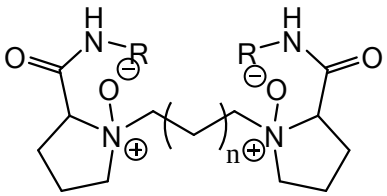


Scheme 19; Strecker reaction using ligand **160**.

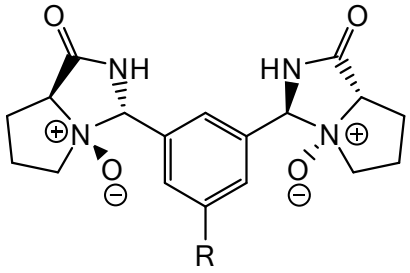
The (*S*)-α-aminonitrile products were synthesized with moderate to excellent enantiomeric excesses. The size of the aliphatic substituents appeared to have no bearing on the reaction outcome, thus when R = Me and R = ^{t}Bu, enantioselectivities of 78% and 88% (*S*) were obtained respectively. *N*-Boc protected α-amino sulfones were the best substrates in this reaction since use of other protecting groups had a detrimental effect on the enantioselectivity. This system was shown to be catalytically active, however not as active previous systems as enantioselectivities above 90% were not seen with the substrates tested. The use of cyanohydrins as a cyanide source is a novel idea and opens up the possibility of autocatalysis in the Strecker reaction, a method of catalysis that has not been explored in this area of research.

N,N'-Dioxides have also proved to be useful as chiral catalysts in this application. Huang *et al* explored the applicability of these compounds using *N*-tosyl ketimines, (Scheme 20) as substrates.[90] Early work showed that in the absence of any catalyst, *N*-tosyl ketimines remain unchanged after treatment with trimethylsilylcyanide whilst addition of a catalytic amount of *N*-oxide encourages the production of α-aminonitrile in quantative yield. A wide variety of catalysts derived from prolinamide were screened, all of which contained an alkyl

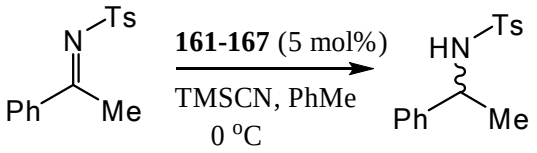
linkage (**161** and **162)**. These catalysts exhibited low enantioselectivities, therefore more rigid catalyst structures (**163-167**) were synthesized which proved beneficial for the enantioselectivity.



161) n= 0
162) n= 1

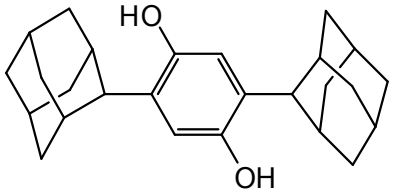


163) R=H
164) R=Me
165) R= ^{t}Bu
166) R= OMe
167) R= NO_2



Scheme 20: Strecker reaction using complexes **161-167**.

Catalyst **163** proved to be far superior to the other catalysts screened giving an enantiomeric excess of 70% and a chemical yield of 99% after a reaction time of 36 hours in toluene at 0 ^{o}C. Catalysts **164** and **165** gave reasonable enantioselectivities of 44% and 33%, whilst catalysts **166** and **167** gave low enantioselectivities of 11% and 15% respectively though all the catalysts gave product in 82-99% yield after reaction times of 36 hours. As with previous studies, attention then turned to the use of additives as a way of increasing the reaction rate. A range of alcohols was selected and all were found to increase the rate of the reaction. The majority of the additives chosen for study reduced the reaction time to 20 hours under the optimum reaction conditions. 2,5-Di-(1-adamantyl)hydroquinone (DAHQ) **168** was found to be the most effective additive, increasing the enantioselectivity to 85%. 2,5-Di-*tert*-butylhydroquinone (DBHQ) **169** gave product with 78% enantioselectivity and in 99% chemical yield. All reactions were carried out using catalyst **163** at a 5 mol% loading, 20 mol% loading of additive with 1.5 equivalents of trimethylsilylcyanide at 0 ^{o}C. This system gave similar results to Herrera's system, with enantioselectivities averaging 70%. The lower catalyst loading and higher reaction temperature are beneficial, however when comparing this system to Lipton's system using catalyst **150** and Corey's system's using catalysts **153** and **156**, there is a great deal of room for improvement.



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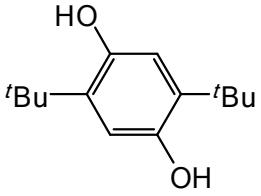

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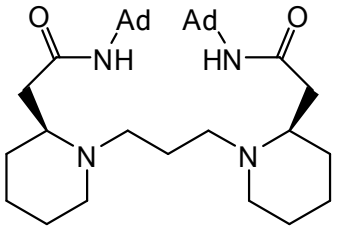
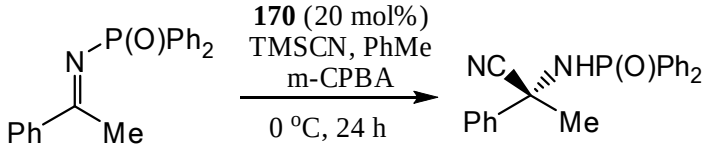


170

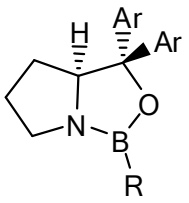
Huang *et al* [91] extended this work to investigate the cyanation of phoshinoyl ketoimine derived substrates (Scheme 21) using catalysts prepared *in situ* from chiral bisamides. Bifunctional *N,N'*-dioxides were again found to induce high enantioselectivity, with precatalyst **170** giving the best results of 80% enantiomeric excess at a 20 mol% loading. *m*-Chloroperoxybenzoic acid (*m*-CPBA) (40 mol%) was used to form the bis-*N*-oxide *in situ*. Altering the length of the carbon chain tether of catalyst **170** lowered the enantioselectivity of the reaction.[92]



Scheme 21: Strecker reaction using complex **170**.

Increasing the catalyst loading reduced the enantioselectivity to 64% although complete conversion was obtained, whilst reducing the loading to 5 mol% resulted in no loss in enantioselectivity. The loading of *m*-chloroperoxybenzoic acid and trimethylsilylcyanide were also investigated. Increasing and decreasing these loadings had detrimental effects on the reaction outcome with optimal quantities found to be 10 mol% of *m*-chloroperoxybenzoic acid and 1.5 equivalents of trimethylsilylcyanide. The temperature of the reaction was found to be a key factor in determining the reaction outcome as reducing the temperature to -20 °C gave an enantioselectivity of 90%.

Recent work has investigated the use of chiral oxazoborolidine **171** and oxazaborolidinium cation **172** in the asymmetric Strecker reaction.[93] Compound **171** was shown to convert *N*-benzyl-benzylidene imine to the Strecker product with 94% conversion with an enantiomeric excess of 71% (*S*) when used at a catalyst loading of 20 mol% at -20 °C in toluene (Scheme 22).



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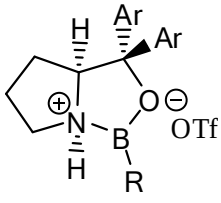

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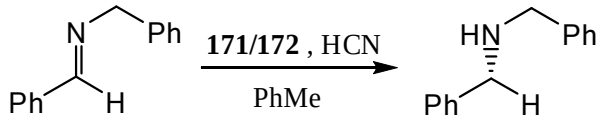
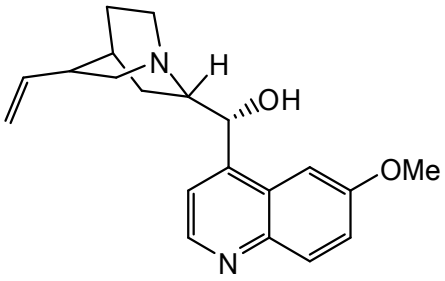
R = Me; **Ar** = Ph



Scheme 22: Strecker reaction using complexes **171-172**.

Work carried out using protonated oxazoborolidene **172** found that the rate of the reaction was greatly increased and complete conversion to aminonitrile occurred in two hours. Using catalyst **172,** the enantioselectivity was lowered, but surprisingly, the stereoinduction was found to be reversed giving the *R* enantiomer of the product with an enantiomeric excess of 38%. Lowering the catalyst loading to 10 mol% had little effect on the reaction outcome. Using both neutral **171** and cationic catalyst **172**, a variety of substrates were investigated. In all cases the stereoinduction was found to be reversed when the protonated oxazoborolidene was used as the catalyst.



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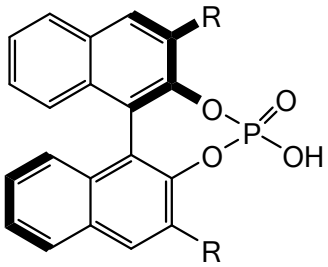
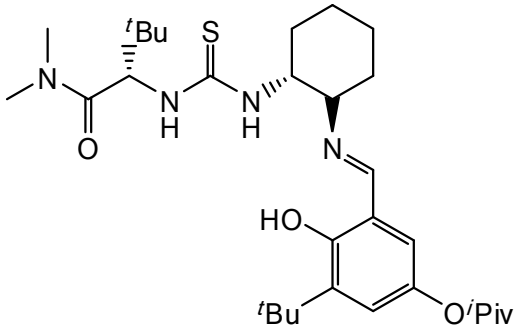


174) R =Ph
175) R = $SiPh_3$
176) R= 2,6-$Me_2C_6H_3$

Pan *et al* studied the use of chiral amines in the acylcyanation of imines using acetyl cyanide as the cyanide source.[94,95] Thus compound **173** catalyed the racemic addition of cyanide to the imine bond, giving aminonitrile in 88% yield at 0 ^{o}C. Bronsted acids were found to accelerate the rate of reaction. The cinchona alkaloid, quinine **173**, also catalysed the addition of acetyl cyanide to *N*-benzyl benzylimine at 0 ^{o}C, however racemic product was again obtained. This prompted research into the use of chiral phosphoric acids **174-176** which all gave moderate enantioselectivities, however, the temperature had to be decreased to -40 ^{o}C to achieve this. A reaction time of 48 hours was then required to give enantiomeric ratios of 61:39, 52:48 and 76:24 respectively. Further study revealed that thiourea based catalysts gave good to excellent enantiomeric ratios, in particular catalyst **177** (10 mol%) gave an enantiomeric ratio of >99:1 at -40 ^{o}C in toluene after a 24 hour reaction time (Scheme 23). Screening of a variety of imines using the optimum reaction conditions, using thiourea **177** demonstrated the compatibility of this catalyst with a range of substrates with the results being summarised in Table 19.



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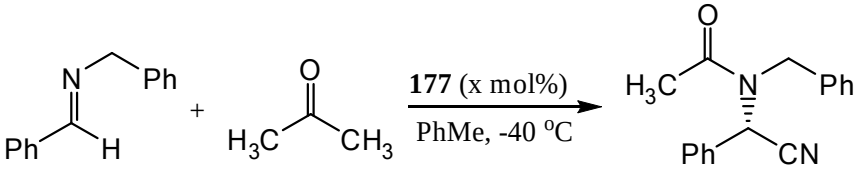


Scheme 23: Strecker reaction using complex **177** and acetyl cyanide as the cyanide source.

Table 19; data obtained from a substrate screen using ligand **177.**

Entry	R	Yield %	dr
1	Ph	94	98:2
2	4-$MeOC_6H_4$	95	98:2
3	4-ClC_6H_4	87	99:1
4	2-ClC_6H_4	86	99:1
5	2-napthyl	92	98:2
6	2-furyl	94	95:5
7[a]	*i*Pr	87	98:2
8	*c*-hexyl	88	96:4
9	*t*-Bu	62	98:2
10	*t*$BuCH_2$	87	98:2

[a] 5 mol% of **177**.

This system is one of the most active non-metal based catalytic systems for the asymmetric Strecker reaction. Under relatively mild reaction conditions, a series of aldehydes were cyanated with excellent enantioselectivities and good yield for aromatic, heteroaromatic and aliphatic substrates. A catalyst loading of 5 mol% is an obvious benefit; however a lower catalyst loading would be more beneficial. Also the choice of cyanide source is also advantageous as it avoids the use of more toxic cyanide sources such as trimethylsilylcyanide and potassium cyanide.

Catalyst **177** was also studied in a three component acyl-Strecker reaction, again employing acetyl cyanide as the cyanide source. Benzaldehyde, benzylamine, acetyl cyanide, magnesium sulphate and 5 mol% of compound **177** were mixed together in toluene at 0 ^{o}C and allowed to stir for 24 hours. Lowering the reaction temperature to -40 ^{o}C improved this result, giving product in an enantiomeric ratio of 94:6. Changing the drying agent to 5Å molecular sieves and changing the solvent to dichloromethane improved this result even further to an enantiomeric ratio of 97:3. Table 20 shows the results obtained when using different aldehydes with benzylamine and acetyl cyanide. The three component Strecker reaction was shown not to be as active as the direct cyanation of the imine but good enantioselectivity was still achieved.

Table 20; substrate screen when using the three component Strecker reaction with ligand **177.**

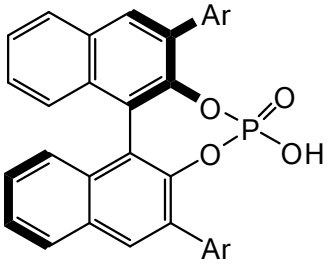
Entry	R	Yield %	e.r
1	Ph	94	97:3
2	4-$MeOC_6H_4$	88	96:4
3	4-ClC_6H_4	78	96:4
4	2-naphthyl	92	97:3
5	CH_2=CHPh	82	96:4
6	^{i}Pr	92	96:4
7	^{t}Bu	46	97:3
8[a]	$^{t}BuCH_2$	97	96:4

[a] 10 mol% of complex **177.**

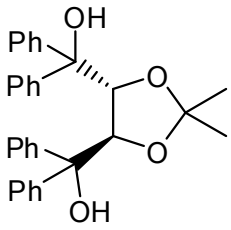
Chiral BINOL and TADDOL derivatives have been used as catalysts in the asymmetric Strecker reaction. In 2007, work carried out using BINOL phosphates demonstrated the use of these catalysts in the cyanation of imines using hydrogen cyanide as the cyanide source.[96] After screening a variety of BINOL phosphates, complex **178** was shown to be the most active, giving aminonitrile product with 70% enantiomeric excess. Hydrogen cyanide was added in excess (1.5 equivalents) along with 5 mol% of complex **178**, Scheme 24. A substrate screen showed that this catalytic system was compatible with aromatic substrates, though no aliphatic substrates were screened. Both electron-rich and electron-deficient substrates gave enantioselectivities of 60-80%. 4-Bromo substituted benzylimine gave the best result of 80% enantioselectivity and 69% yield.

The same reaction was performed using TADDOL **179** as a chiral catalyst at a 10 mol% loading along with hydrogen cyanide in toluene at -40 ^{o}C. This catalyst gave much

lower selectivity than BINOL phosphate **178** as the *para*-bromobenzyl protected imine gave only 14% enantioselectivity in this case. This system was shown to be less active than any of the other systems studied and also requires the use of hydrogen cyanide as the cyanide source which is extremely toxic and difficult to handle. The commercial availability of the BINOL and TADDOL ligands also make these systems of commercial interest, however optimisation studies were unsuccessgul in trying to increase the selectivity of the system.



178) Ar= 9-phenanthryl



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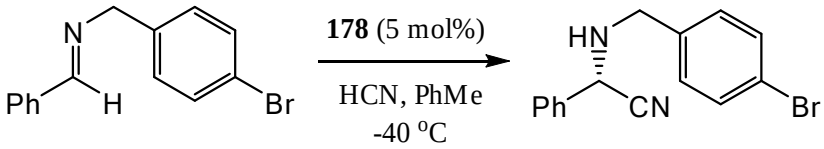


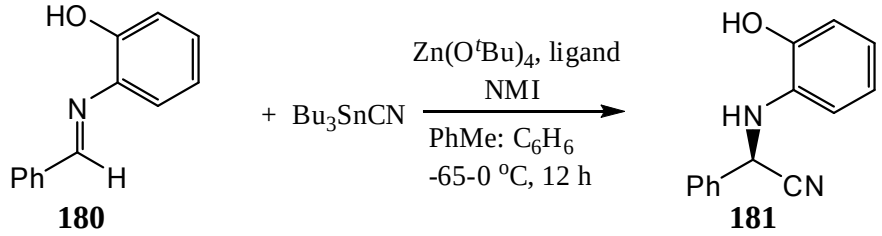
Scheme 24: Strecker reaction using complex **178**.

Non-metals are efficient catalysts when used in the Strecker reaction, as some of these systems have demonstrated. Corey and Lipton have made some very valuable contributions to this area of research with catalysts **150**, **156** and **159** showing high activity. A variety of different imines were cyanated in good to excellent enantioselectivities under relatively mild reaction conditions. By far the most active of these systems was Pan's system utilising thiourea **177**. Consistantly high enantioselectivities were achieved across a wide range of substrates using a 5 mol% catalyst loading and a reaction temperature of -40 °C. A higher reaction temperature would improve this system further however, to achieve the enantiomeric excesses reported, this reaction temperature was shown to be optimum. The main drawback with these systems is the complexity of the catalyst structures. These catalysts can be difficult to synthesise, and so the cost and time to develop them may outweigh the catalytic activity of the complexes. Due to these factors, these catalysts may not be practicable from a commercial perspective, however from an academic point of view, these systems are certainly worth investigating.

1.5.3 Metal Catalysts Used in the Asymmetric Strecker Reaction.

1.5.3.1 Enantioselective Strecker Reactions using Metal BINOL Complexes.

Over the last ten years attention has turned to the use of metal-based catalysts for asymmetric Strecker reactions and much of this work has focused on the use metal complexes of BINOL particularly zirconium and aluminium. In 1998, Kobayashi *et al* showed that cyanation of aldimines can be achieved using tributyltin cyanide as the cyanide source (Scheme 25).[97] The zirconium catalyst was prepared *in situ* by mixing $Zr(O^tBu)_4$, (*R*)-dibromo-1,1'-bi-2-naphthols ((*R*)-6-Br—BINOL and (*R*)-3-Br—BINOL) and *N*-methylimidazole (NMI) in dichloromethane at -45 ^oC. The zirconium catalyst was found to convert aldimine **180** into the corresponding aminonitrile **181** in 70% yield and with an enantiomeric excess of 55%. Further research showed that a mixture of toluene and benzene (1:1) used as the reaction solvent, gave a vastly improved result of 90% yield and 91% enantioselectivity.



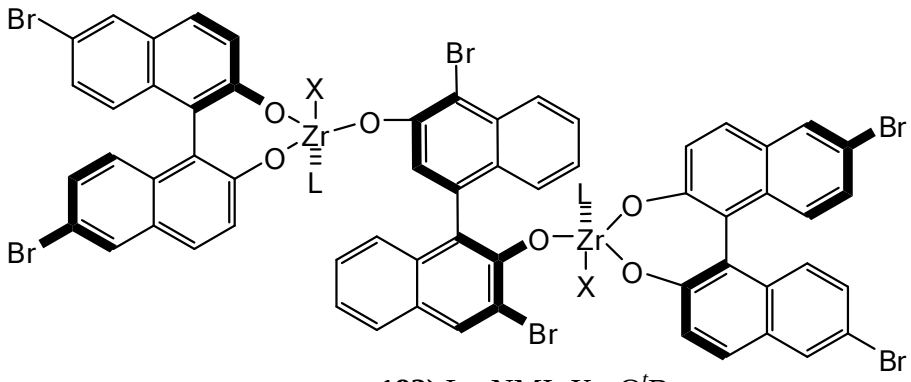
180 **181**

Scheme 25: Strecker reaction using complexes **182/183**.

Extensive study of the catalyst structure using ^1H NMR spectroscopy showed that complex **182** which contained two zirconium centres; two (*R*)-6-Br-BINOL ligands, one (*R*)-3-Br-BINOL ligand and two *N*-methylimidazole units was responsible for this elevated activity. Complex **182** was also shown to form when using different molar ratios of the BINOL ligand units and its structure was confirmed using ^1H and ^{13}C NMR spectroscopy. A variety of aldimines were screened using the optimum reactions conditions and the results are summarised in Table 21.

This work was extended in 2000 with ligand combinations being tested in a three component Strecker reaction using isobutylaldehyde, 2-amino-3-methylphenol and hydrogen cyanide as the cyanide source. [98, 99] Combining these components in dichloromethane at -45 ^oC with catalyst **182**, the corresponding α-aminonitrile was produced in 99% yield and with 94% enantiomeric excess. To clarify the effect of the two BINOL ligands in the reaction, a variety of BINOL derivatives were examined. Substituting (*R*)-3-Br-BINOL for (*R*)-3-Cl-BINOL resulted in no change to the enantioselectivity. ^1H NMR studies confirmed that bimetallic complexes such as **182** were not observed when opposite ligand configurations were used. Biphenols were also shown to be compatible ligands with (*R*)-6 or (*R*)-3-Br-

BINOL units. Further ^{1}H NMR studies showed that the catalytically active species was complex **183** where the *tert*-butoxy groups had been exchanged for cyanide ligands.

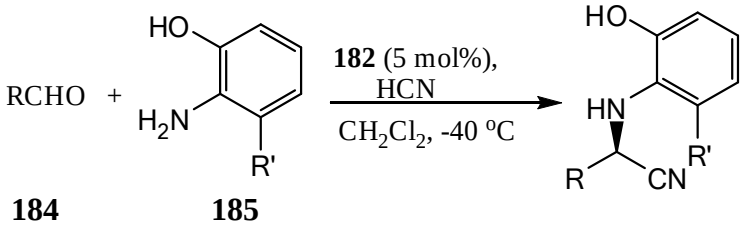


182) L= NMI; X= O^{t}Bu
183) L = NMI; X= CN

Table 21; substrate screen using complex **182** in the asymmetric Strecker reaction.

Entry	R	Yield %	ee %
1	Ph	92	91
2	p-Cl	90	88
3	p-Me	97	76
4	o-Me	96	89
5	$Ph(CH_2)_2$	55	83
6	^{i}Bu	79	83
7	C_8H_{17}	72	74

Screening a variety of imine substrates showed that this system was more active than the one component system when using complex **182** as catalyst. Varying the substituent on both the aldehyde **184** and amine **185** was investigated (Scheme 26), with all the combinations studied giving consistently good results as shown in Table 22.

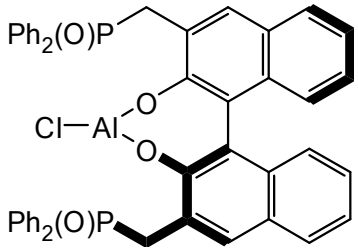


184 **185**

Scheme 26: Strecker reaction using complex **182.**

Table 22; results obtained from the three component Strecker reaction using complex **182.**

Entry	R	R'	Yield %	ee %	*R/S*
1	Ph	H	80	86	*S*
2	^{i}Bu	H	83	85	*S*
3	C_8H_{17}	Me	83	90	*S*
4	$Ph(CH_2)_2$	Me	85	94	*S*
5	^{i}Pr	Me	94	90	*S*
6	Bu	Me	100	86	*S*



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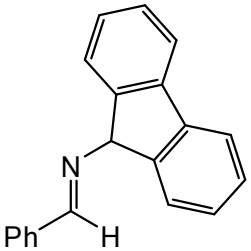

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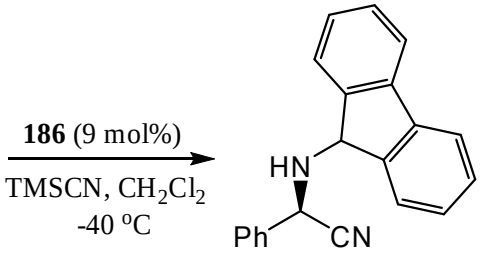


188

Scheme 27: Strecker reaction utilising complex **186.**

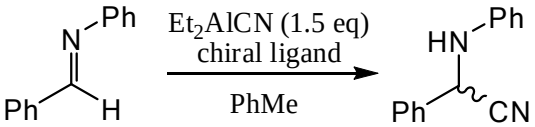
Aluminium BINOL complexes have also been extensively utilised as catalysts for the asymmetric Strecker reaction. Takamura *et al* highlighted that the Strecker reaction was still not satisfactory in giving α-aminonitriles derived from aliphatic imines, especially *n*-aldimines and α,β-unsaturated imines.[94] The group developed a catalyst, in the form of an aluminium BINOL complex. Studies showed that reacting trimethylsilycyanide with *N*-allyl benzaldehyde imine, in the presence of complex **186,** at a 9 mol% catalyst loading in dichloromethane for 67 hours at -40 ^{o}C gave aminonitrile product with only 4% (*R*) enantiomeric excess in 67% yield. *N*-Fluoroenylimine **187** gave aminonitrile product **188** with a much higher enantioselectivity of 95% with a yield of 97% after 111 hours when using 9 mol% of complex **186** (Scheme 27). Protic additives (110 mol%) were shown to decrease the reaction time from 192 hours to just 22 hours. Optimisation studies later decreased this loading to 20 mol%. The high activity of complex **186** when using substrate **187** is explained by the dual activation exhibited in this system. Simultaneous activation of the imine by the Lewis acidic aluminium and activation of the trimethylsilylcyanide via the oxygen atom of the phosphine oxide leads to a very active catalytic system, commonly seen in the analogous cyanohydrin synthesis reaction when using aluminium based catalysts.[80, 81, 82, 83] A variety of *N*-fluorenylaldimines were then investigated using the optimum reaction conditions and the

results are summarised in Table 23. Uniformly high enantioselectivities were seen with all substrates screened with enantiomeric excesses as high as 96% being observed with some substrates.

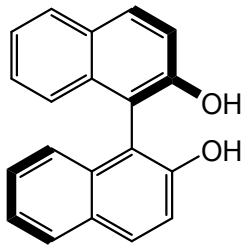
Table 23; tabulated data from a substrate screen using complex **186.**

Entry	RCH=NFl	Time h	Yield %	ee %
1	Ph	44	92	95
2	4-ClC_6H_4	44	92	95
3	4-$MeOC_6H_4$	44	93	93
4	*trans*-PhCH=CH	41	80	96
5	*trans*- $CH_3(CH_2)_3CH$=CH	24	66	86
6	*i*-Pr	44	89	72
7	*t*-Bu	44	97	78
8	CH_3CH_2	44	84	70

Nakamura *et al* demonstrated the use of (*R*)-BINOL **189** as a chiral ligand along with (+)-TADDOL **179**, diacetone $_D$-glucose (DAG) **190** and ligands **191, 192** and **193.**[100] Diethylaluminium cyanide was employed as the cyanating agent and also as the aluminium source (Scheme 28). In the absence of any chiral ligand, no reaction was observed at -78 ^oC. On the addition of a chiral additive, ligands **189**, **179** and **190**, the reaction was shown to go to completion within 30 minutes at -78 ^oC in toluene. Ligands **191, 192** or **193** were found to give no sterochemical induction at -78 ^oC, however, ligand **193** was observed to accelerate the rate of reaction giving aminonitrile product in 60 minutes as opposed to 24-48 hours required when using ligands **191** and **192**. Using 1.5 equivalents of ligands **189** and **179**, aminonitrile product was formed with complete conversion and with 48 and 35% (*S*) enantiomeric excess respectively. Three equivalents of ligand **190** were required to achieve an enantioselectivity of 22% (*S*) at -78 ^oC. Increasing the loading of (*R*)-BINOL to 4.5 equivalents was found to reverse the stereochemistry of the product and gave 52% (*R*) enantioselectivity.



Scheme 28: Strecker reaction using diethylaluminium cyanide as the cyanide source and ligands **179** and **189-193**.



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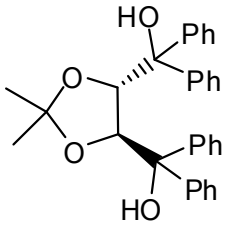

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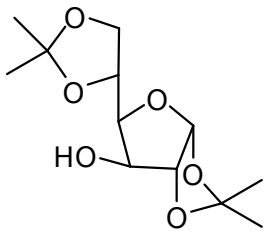

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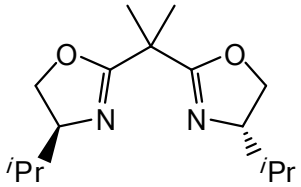

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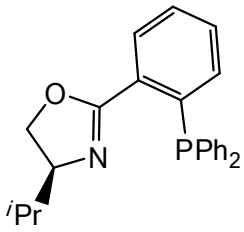

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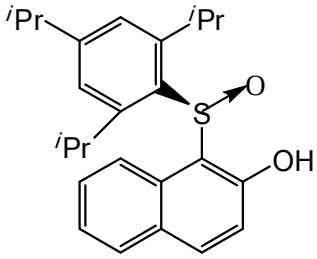


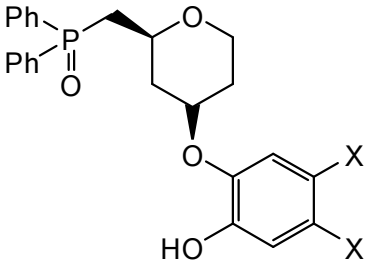
193

This system was shown to be far inferior when compared to other metal containing catalytic systems used in the asymmetric Strecker reaction, though the commercial availability of the BINOL and TADDOL make this system worth exploring further. Additional optimisation studies would be valuable in this case. The above systems were shown to be relatively active in the Strecker reaction; however it is apparent that these systems are not as active as the non-metal systems discussed previously. Catalysts **182** and **183** gave enantioselectivities of 74-91% with a catalyst loading of 5 mol%. Hydrogen cyanide was used as the cyanide source and a reaction temperature of -40 ^{o}C was required to achieve these enantiomeric excesses. Aluminium BINOL complex **186** required the use of 9 mol% of catalyst also at -40 ^{o}C. Slightly higher enantiomeric excesses were achieved especially with aromatic substrates, however this selectivity decreased when aliphatic substrates were tested. Nakamura utilised a variety of different chiral ligands in combination with aluminium and as was previously shown in the corresponding non-metal based systems, these ligands display lower selectivity.

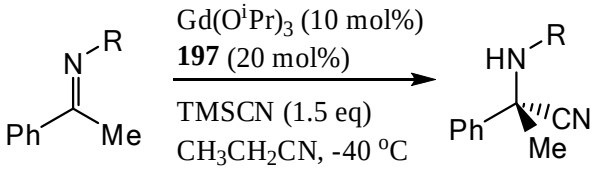
1.5.3.2. Enantioselective Strecker Reactions using Lanthanide Metal Complexes

Lanthanide metal complexes have also been of interest in the Strecker reaction. Extensive work has been carried out on the use of gadolinium based complexes and also, but to a lesser extent, europium. In 2003, Masumoto *et al* studied gadolinium as the metal source with acetophenone derived imines as reaction substrates.[101] It was found that reacting the *N*-benzyl protected imine **194** with gadolinium *iso*-propoxide at a 10 mol% loading, along with ligand **196** and 1.5 equivalents of trimethylsilylcyanide in CH_3CH_2CN at -40 ^{o}C, gave the

corresponding aminonitrile product with 72% enantiomeric excess (Scheme 29). Using chiral ligand **197** containing a difluorocatechol, increased the enantioselectivity of the system further to 96% when using substrate **195**. Substrate generality was investigated and the optimised reaction conditions were found to be effective for a wide variety of ketoimines (Table 24).



194) R=Bn
195) R= $P(O)Ph_2$
196) X=H
197) X= F



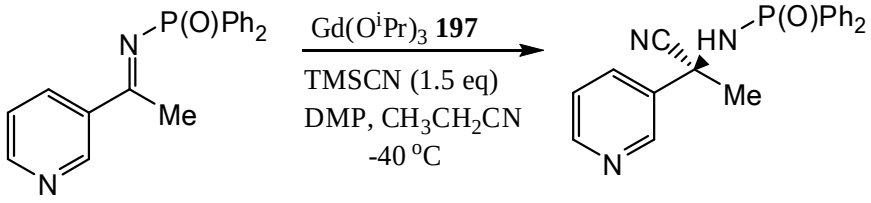
Scheme 29: Strecker reaction using complex **197**.

Table 24; results obtained from a subsrate screen using complex **197** as a catalyst.

Entry	RC(Me)=NP(O)Ph_2	Catalyst mol%	Time h	Yield %	ee%
1	CH_2CH_2Ph	10	5	87	89
2	C_5H_{11}	8	65	73	72
3	$C_5H_{11}CH=CH_2$	5	68	79	83
4	cyclohexene	5	67	58	90
5	^{i}Pr	5	48	74	51
6	naphthalene	2.5	72	67	94
7	Ph	2.5	24	94	95
8	Ar *o*-Cl	2.5	67	84	89
9	Ar *o*-Me	2.5	52	93	98

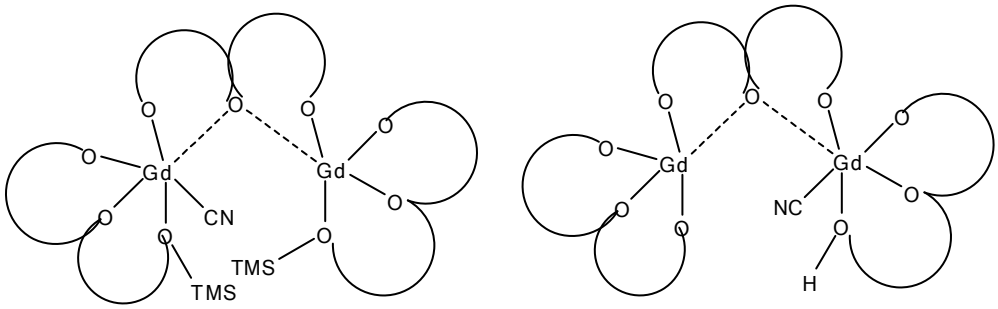
This work was extended in 2004 to investigate the use of additives and so improve on the Strecker reaction for heteroaromatic and cyclic ketoimines.[102,103] 3-Pyridylketoimine **198** was chosen as the test substrate and ligand **197** was used in a 10 mol% loading (Scheme 30) giving aminonitrile product **199** with 33% enantiomeric excess. Increasing the catalyst loading to 20 or 30 mol% led to an improvement in the reaction rate, accompanied by a dramatic improvement in enantioselectivity to 78% and 88% respectively at -40 ^{o}C. Due to the increased amount of ligand used in this improved system, it was hypothesised that the excess ligand may be acting as a proton source, therefore the effect of protic additives was investigated. Phenol and 2,6-dimethylphenol were found to be the most effective additives when added in a 100 mol% loading along with 5 mol% of ligand **197.** The enantioselectivity

was also greatly improved; adding phenol or 2,6-dimethylphenol gave the corresponding aminonitrile with 99% enantiomeric excess with a 20 minute reaction time. Due to the great improvement in reactivity brought about by the addition of an additive, it was proposed that the additive may be changing the active catalyst structure therefore the constitution of the catalyst was investigated using ESI-MS studies. The catalyst was prepared using gadolinium isopropoxide and ligand **197** in a 1:2 ratio followed by addition of trimethylsilylcyanide (15 equivalents) in acetonitrile at room temperature. A peak corresponding to a molecular weight of 1862 was observed in the ESI-MS spectrum which was consistent with previous findings for the O-silylated 2:3 complex **200**. Addition of 2,6-dimethylphenol (10 equivalents) resulted in the disappearance of the peak at 1862 and the appearance of a new peak corresponding to *m/z*= 1691 thus the additive appeared to be changing the catalyst structure from the *O*-silylated form **200** to the *O*-protonated form **201**. Catalyst **201** would appear to be the more active catalyst due to the greater enantioselectivity and catalytic activity observed on the addition of 2,6-dimethylphenol.



198 **199**

Scheme 30: Strecker reaction using ligand **197** with gadolinium isopropoxide.

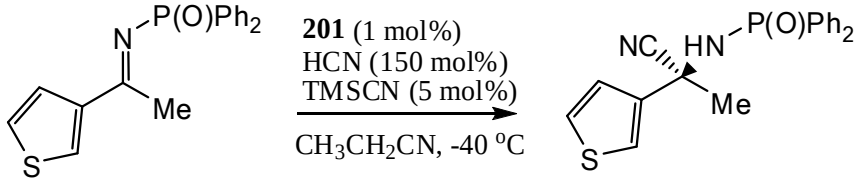


200 **201**

The Strecker product is obtained via cyanide transfer from complex **201** to the activated imine, therefore, only a catalytic amount of trimethylsilylcyanide is required to obtain the high enantioselectivities. Ketoimine **202** was converted into aminonitrile **203** with 99% enantioselectivity using 2.5 mol% of catalyst, 10 mol% of trimethylsilylcyanide and 150 mol% of hydrogen cyanide in CH_3CH_2CN at -40 ^oC (Scheme 31). Reducing the catalyst loading to 1 mol% resulted in a lowered enantioselectivity of 97%, however, reducing the catalytic loading of trimethylsilylcyanide to 5 mol% restored the high enantioselectivity. Loss of enantioselectivity using higher ratios of trimethylsilylcyanide suggests the existence

of an equilibrium between complex **200** and complex **201**. Increasing the amount of trimethylsilylcyanide in the reaction mixture encourages the formation of complex **200** which is less enantioselective than complex **201**. Decreasing the loading of trimethylsilylcyanide enhances the formation of the more active complex **201** and so the enantioselectivity increases.

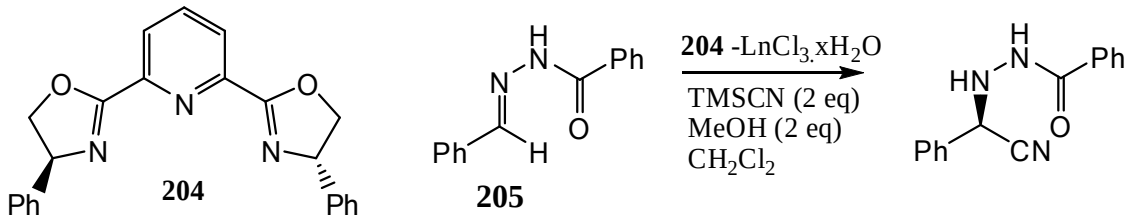
This system showed an extremely high selectivity using a low catalyst loading of 1 mol%. A major disadvantage with this system however, is the use of two cyanide sources, hydrogen cyanide and trimethylsilylcyanide. The use of lanthanide metals will also raise the issue of cost when developing these catalyst systems as lanthanide metals are not as accessible as metals such as titanium and vanadium, two common metals of choice when studying the analogous cyanohydrin synthesis. However, the system gave comparable results to those obtained when using complexes **150**, **153** and **156,** which were shown to be the most active systems when using non-metal catalysts. ^{1}H NMR studies also gave an insight into a possible mechanism for this system.



202 **203**

Scheme 31: Strecker reaction utilising the gadolium cyanide complex, **201**

Jacobsen *et al* demonstrated the use of lanathanide complexes of (*S*)-*i*-PrPYBOX **204** in the asymmetric hydrocyanation of hydrazones.[104] Using a variety of lanthanide chlorides in combination with ligand **204**, an *N*-benzoyl-protected substrate **205** was converted into the corresponding aminonitrile using trimethylsilylcyanide and methanol in dichloromethane, Scheme 32. The enantioselectivity increased with increasing atomic number of the lanthanide metal, reaching a peak with erbium, then falling sharply if the atomic number of the lanthanide metal was increased further. Using erbium trichloride with ligand **204** gave aminonitrile product with 40% enantiomeric excess in 89% chemical yield. Optimisation experiments showed that the best reaction temperature was 0 ^{o}C in freshly distilled chloroform, giving aminonitrile products with high enantioselectivity and high chemical yields after reaction times of two to three days. A variety of hydrazones were found to be compatible with the catalytic system as shown in Table 25.



Scheme 32: reaction scheme for the Strecker reaction using ligand **204**

Table 25; results obtained from a substrate screen using complex **204** in the asymmetric Strecker reaction.

Entry	RCH=NNHBz	Time, days	Yield %	ee %
1	4-$Me_2NC_6H_4$	3	85	97
2	4-$BnOC_6H_4$	3	92	93
3	3,4$(MeO)_2C_6H_3$	3	90	85
4	2,3,4,$(MeO)_3C_6H_2$	3	87	80
5	4-MeC_6H_4	3	89	76
6	4-ClC_6H_4	3	94	84
7	Ph_2CH	2	98	69
8	*t*-Bu	2	98	66
9	$PhCH_2$	2	99	31

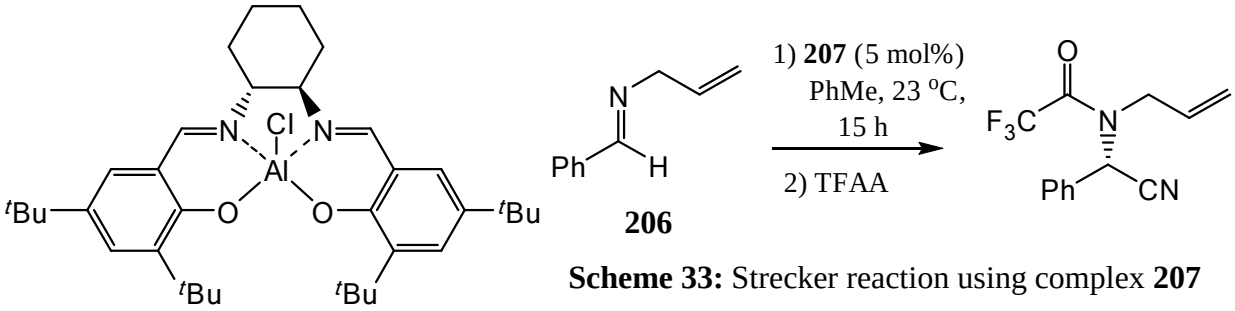
Comparable results to Masumoto's system were obtained using the Jacobsen system however the issue of cost is once again raised as the use of lanthanide metals is explored. Another disadvantage of using lanthanide metals in these catalysts is the issue of stereocontrol in the transition states of these systems. Lanthanide metals have co-ordination numbers of nine to ten and so the ability of the metal centre to co-ordinate the reacting substrate and the chiral ligand of choice maybe dramatically compromised. A large proportion of space around the metal centre maybe occupied by solvent molecules so making the chiral reaction less efficient. A more through understanding of the transition states in these systems would be of interest, along with the role of the metal centre.

1.5.3.3 Enantioselective Strecker Reactions catalysed by Metal(Salen) Complexes

Metal(salen) complexes have been used in a wide range of organic transformations.[105] Research into their applicability to Strecker reactions began in 1998 when Jacobsen's group introduced the first case of metal(salen) complexes catalysing the addition of cyanide to imines.[106] A range of metal(salen) complexes were screened for the addition of cyanide to *N*-allyl benzaldimine **206**. The first metal to be investigated in conjunction with salen ligands

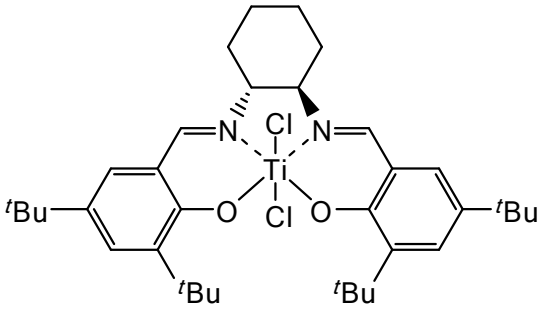
was aluminium with the aluminium(salen) complex **207** being shown to be the most effective catalyst when cyanating the imine substrate **206** (Scheme 33).

Complex **207** was found to give an enantioselectivity of 45% with complete conversion after a reaction time of 15 hours, at 23 ^{o}C in toluene when using 5 mol% catalyst with 1.2 equivalents of trimethylsilylcyanide. No reaction was observed under strictly anhydrous reaction conditions, suggesting that the true cyanide source is hydrogen cyanide produced by reaction of trimethylsilylcyanide with residual moisture. Under catalysed conditions, lower reaction temperatures were found to be very beneficial to the enantioselectivity of the reaction, increasing it to 95% with 91% yield after 15 hours. A survey of *N*-allyl imines showed that substituted aromatic substrates all gave the corresponding aminonitrile in moderate to excellent enantioselectivity and with high yields. Electron-rich substrates gave the highest enantioselectivities; *p*-OMe and *p*-Me benzaldehye derived imines gave products with enantiomeric excesses of 91 and 94% respectively. Electron-deficient substrates gave lower enantiomeric excesses; 79-81% and aliphatic substrates gave still lower enantioselectivity. Thus, the imine obtained from cyclohexane carboxaldehyde gave aminonitrile product with 57% enantiomeric excess in 77% chemical yield and the pivaldehyde derived substrate gave extremely poor results with only 33% enantioselectivity and 69% yield.



Scheme 33: Strecker reaction using complex **207**

North *et al* extended this study to investigate the use of titanium and vanadium(salen) complexes in asymmetric Strecker reactions.[107] Jacobsen *et al* had reported that the titanium(salen) dichloride species **37** was ineffective at inducing enantioselectivity, giving an α-aminonitrile with only 24% enantiomeric excess. Attempts to use complex **37** in the cyanation of *N*-benzyl benzylimine were also unsuccessful using trimethylsilylcyanide as the cyanide source and 5 mol% of complex **37** at room temperature. Reducing the reaction temperature to -40 ^{o}C and again employing the use of trimethylsilylcyanide as the cyanide source resulted in complete conversion, but to racemic product.



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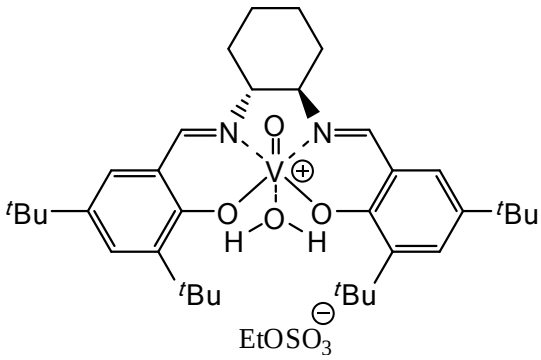


110

Attempts to improve the enantioselectivity were undertaken using an *in situ* prepared complex. Mixing titanium tetraisopropoxide with the salen ligand **30** resulted in a slight improvement in enantioselectivity. In dichloromethane, using trimethylsilylcyanide as the cyanide source, even at -78 ^{o}C, only a 7% enantiomeric excess was obtained in 52% yield after 46 hours. Changing the solvent to toluene gave a slightly improved enantioselectivity of 15% at -78 ^{o}C. Increasing the reaction temperature to -40 ^{o}C improved both the enantioselectivity and the yield; 30% (*S*) and 100% respectively. Attention then turned to the analogous vanadium(salen) complex **110** containing a positively charged vanadium 5+ metal centre. Using 5 mol% of complex **110** in toluene gave aminonitrile product with 30% enantiomeric excess at -40 ^{o}C after 20 hours. Increasing the catalyst loading to 10 mol% increased the enantioselectivity to 77% (*R*) after a reaction time of 23 hours. As with previous studies, investigation into the true cyanating agent was carried out by adding additives to the system. Adding water to the reaction improved the enantioselectivity, though it was still lower than previously obtained. Addition of methanol (1.2 equivalents) to the reaction gave aminonitrile product with complete conversion and 79% enantiomeric excess after 19 hours at -40 ^{o}C. The increase in activity on addition of methanol suggests that the true cyanating agent is hydrogen cyanide rather than trimethylsilylcyanide. The generation of hydrogen cyanide could also explain why the *in situ* prepared titanium catalyst showed some catalytic activity. Isopropanol would be generated in this system which would have the same effect as methanol, reacting with the trimethylsilylcyanide to liberate hydrogen cyanide. These optimised reaction conditions were used to screen a variety of *N*-benzyl imines. The effect of substituents on the aldehyde derived aromatic ring of *N*-benzyl benzylimine was investigated and the results are summarised in Table 26.

Table 26; results obtained from a variety of substituted aromatic imine substrates using complex **110** in the Strecker reaction.

Entry	RCH=NBn	Yield %	ee %
1	Ph	88	75
2	3-ClC_6H_4	76	57
3	4-ClC_6H_4	48	57
4	4-$F_3CC_6H_4$	65	31
5	4-$MeOC_6H_4$	50	51
6	3-$MeOC_6H_4$	70	59
7	Me_3C	80	16

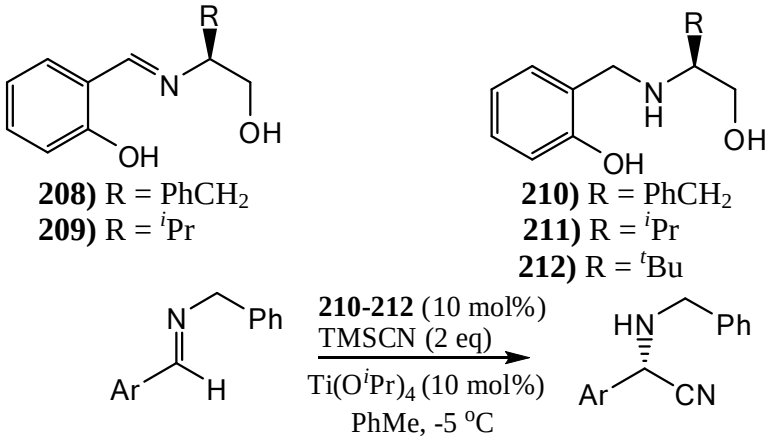
Jacobsen's and North's results are very valuable to research into the asymmetric Strecker reaction, and can be considered as an extension of the work performed in cyanohydrim synthesis. With regard to North's work, a higher catalyst loading of 10 mol% was found to be optimum, but this is not surprising as exchanging the carbonyl oxygen for a nitrogen reduces the reactivity of the imine bond and so higher catalyst loadings are to be expected. Complex **207** only required a catalyst loading of 5 mol% suggesting that complex **207** is the more active of the three systems. Also complexes **37** and **110** require the addition of reaction additives in the form of alcoholic species and all these metal(salen) systems are inactive in anhydrous reaction conditions. This raises the question of the role of these additives, and their possible interaction with the trimethylsilylcyanide to generate hydrogen cyanide, a more reactive cyanide source. Complex **207**, containing an aluminium centre, has been shown to be more active than the corresponding titanium and vanadium complexes, **37** and **110** respectively. This is the opposite to the trend observed in cyanohydrin synthesis, with titanium/vanadium(salen) complexes being more active in the analogous aluminium systems. What is somewhat lacking in these studies is a more detailed understanding of the reaction mechanism and so a kinetic study would benefit these studies a great deal and may help in answering some of these questions.

1.5.3.4 Enantioselective Strecker Reaction Using other Metal Ligand Complexes.

Mansawat *et al* investigated the use of *N*-salicyl-β-amino alcohol ligands **208** and **209** as chiral ligands for asymmetric Strecker reactions using titanium tetraisopropoxide as the metal source.[108] These C_1-symmetric Schiff bases were synthesised using benzaldehyde and the appropriate amino alcohol, (*S*)-phenylalaninol and (*S*)-valinol respectively. Ligand **208** or **209** (10 mol%) was mixed with titanium tetraisopropoxide (10 mol%) in toluene at -5 ^oC

along with trimethylsilylcyanide (two equivalents) and used to catalyse the cyanation of *N*-benzyl benzylimine giving aminonitrile product with low enantioselectivity. A catalytically active species was being formed *in situ,* however, mainly racemic product was being formed. In order to investigate the effect of the ligand structure in this Strecker reaction, compounds **210** and **211** were synthesised by a sodium borohydride reduction of the imine precursor. Compound **210** was shown to give aminonitrile product with an enantioselectivity of 79% in toluene at 0 ^{o}C after a reaction time of six hours.

Under optimum conditions, compounds **210-212** were screened using *N*-benzylidenebenzylamine as substrate and trimethylsilylcyanide as the cyanide source. Compounds **211** and **212** showed the highest enantioselectivities of 82 and 86% (*S*) respectively whilst ligand **210** gave a product with a 76% enantiomeric excess, but in just 9% chemical yield. These results showed the importance of the steric bulk of the ligand on the enantioselectivity of the reaction. Further increasing the size of the substituents on the ligand decreased the enantioselectivity of the reaction. Using ligands **210** and **212,** a range of aromatic substrates were screened using the optimised reaction conditions shown in Scheme 34 and the results are outlined in Table 27.



208) R = $PhCH_2$
209) R = ^{i}Pr

210) R = $PhCH_2$
211) R = ^{i}Pr
212) R = ^{t}Bu

Scheme 34: Strecker reaction using complexes **210-212**.

Further work demonstrated that the use of protic additives enhanced the rate of the reaction. Additives such as water and propanol were added to the reaction under the optimum reaction conditions and were shown to bring about the conversion of *N*-benzylidenebenzylamine to aminonitrile product in two hours at 0 ^{o}C. The optimal loading of protic additive was established to be one equivalent. This system was shown to be one of the leaset active of the systems discussed.

Table 27; substrate screen using complexes **210**-**212** in the Strecker reaction.

Entry	Ligand	Ar	Yield %	ee %
1	**210**	4-ClC_6H_4	84	72
2	**210**	3-ClC_6H_4	98	80
3	**210**	3-$O_2NC_6H_4$	>99	64
4	**210**	4-MeC_6H_4	>99	67
5	**210**	3-$PhOC_6H_4$	90	75
6	**210**	4-$MeOC_6H_4$	98	44
7	**212**	4-$MeOC_6H_4$	92	48
8	**212**	2-$MeOC_6H_4$	>99	39

1.6 Aims

Due to the diverse applications of salen ligands in asymmetric reactions, metal(salen) complexes were chosen as the focus of this research concentrating on two fundamental reactions in asymmetric catalysis; the Strecker reaction and cyanohydrin synthesis. Figure 6 shows the many variations of salen ligand that are possible by changing the substituents on the diamine moiety and the aromatic rings.

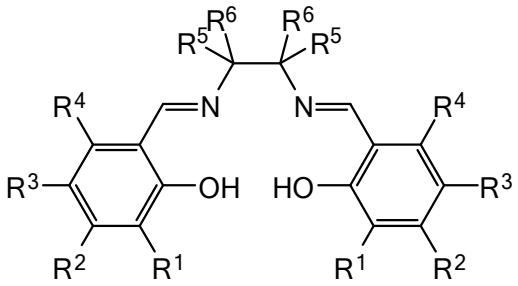


Figure 6: basic structure of the salen ligand.

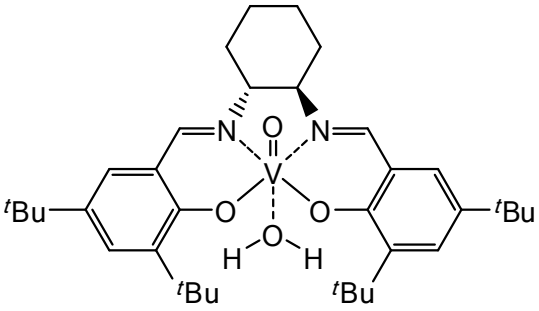
Two reactions are going to be the focus of this work; asymmetric cyanohydrin synthesis and the asymmetric Strecker reaction. Firstly, attempts will be made to improve on the current enantioselectivities being obtained in the Strecker reaction using complex **118**.[112] A range of different variables will be investigated including the addition of additives and if other additives can be used in the Strecker reaction to increase the enantioselectivity of complex **118** and other variables such as reaction temperature and reaction solvent will also be investigated. As was demonstrated in the introduction in *Section 1.5.3.3* there are no thorough kinetic studies that have been performed with regard to the Strecker reaction. This is seen throughout the literature and so it would be a major breakthough in the understanding of this reaction. A variety of different techniques will be employed to try and address this issue such as stop-flow kinetics, UV spectroscopy and ^{1}H NMR spectroscopy. Ligand **30** containing *tert*-butyl substituents has long been thought to be the most selective ligand for use in the Strecker reaction and cyanohydrin synthesis, Ligands bearing even larger substituents are yet to be investigated and so the development of new ligands will be synthesised containing large aromatic substituents, for testing in the Strecker reaction and cyanohydrin synthesis. The metal sources used will be limited to titanium and vanadium so a direct comparison of the results obtained using the newly synthesised catalysts against current literature precedent can be carried out. Other metal sources may be explored with zirconium and hafnium being of particular interest due to the larger size of their atomic radii and the effect this could have on the salen ligand arrangement and the subsequent effect on enantioselective reactions.

Aluminium has been shown to be active in the asymmetric addition of cyanide to both aldehydes and ketones when using complex **140**, and so a more extensive study will be attempted using aluminium(salen) complexes. The obvious lack of kinetic data with regards to complex **140** will be addressed and the role of additives will be investigated when using aluminium(salen) complexes in cyanohydrin synthesis. If possible, Hammett and Arrhenius studies will be performed and the results analysed accordingly to hopefully give a thorough understanding of aluminium(salen) complexes in cyanohydrin synthesis as has been shown with complexes **41** and **132**.

2.1 Results and Discussion.

2.1.1 Ligand and Catalyst Synthesis.

The catalyst which has been shown to exhibit the highest activity in the Strecker reaction is the (*R,R)*-vanadium(V)(salen) chloride complex **118**.[112] Synthesis of catalyst **118** is accomplished by a two step procedure, the first being the synthesis of the salen ligand **30** and the second being the complexation of vanadium to ligand **30**.



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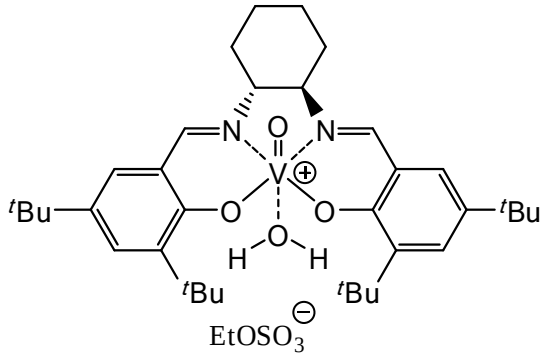

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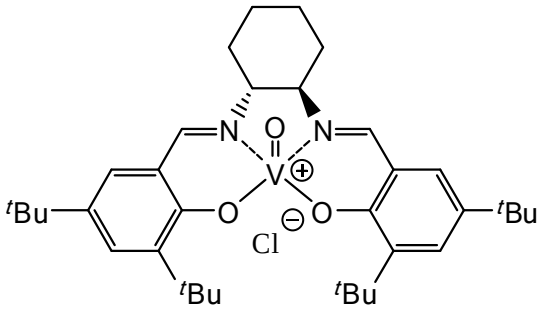
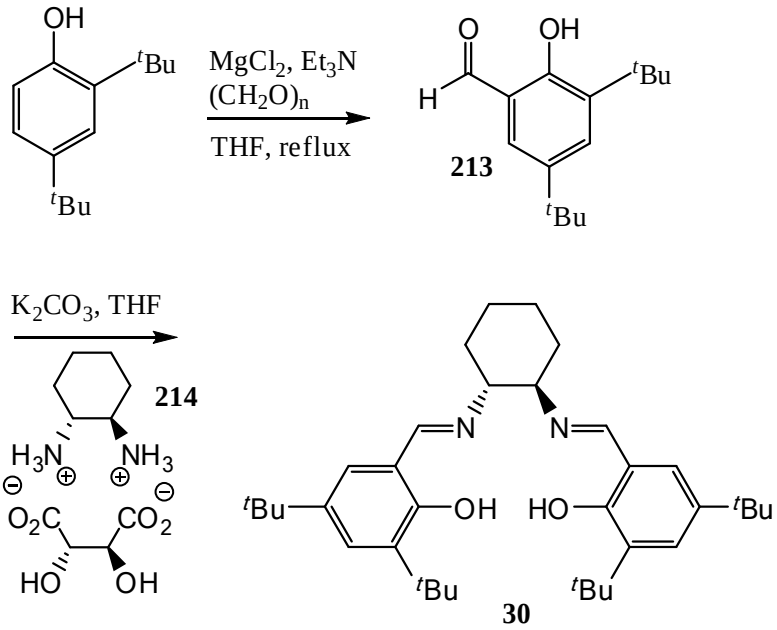


118

The chosen procedure for the synthesis of salen ligand **30** was Hansen's route.[7] This was used in favour of the Jacobsen procedure as it is an easier protocol to follow and only requires a one step synthesis.[7] Aldehyde **213** was prepared *in situ* from 2,4-di-*tert*-butylphenol, triethylamine, magnesium chloride and paraformaldehyde, in tetrahydrofuran, by refluxing for three hours (Scheme 35). The formation of the aldehyde was apparent from the colour change of the solution to an intense yellow. Aldehyde **213** was not isolated, rather; to the solution, potassium carbonate and (*R,R*)-1,2-diaminocyclohexane tartrate salt **214** were added and the solution was then refluxed for a further three hours. Removal of the solvent and extraction into dichloromethane, followed by washing with water, gave salen ligand **30** as a yellow solid after which recrystallisation from acetone gave ligand **30** as a yellow crystalline solid.

The C_2-symmetry of the ligand results in a simple ^{1}H NMR spectrum. Only one imine proton is observed as a singlet at 8.2 ppm and the aromatic region is very distinctive due to there being only two aromatic protons on each of the phenyl rings which appear as two doublets at 6.9 and 7.2 ppm with coupling constants of 2.4 Hz. This coupling constant is consistent with ^4J coupling in aromatic systems.[109] Mass spectrometry and a melting point

comparable to the literature value also confirmed the formation of the ligand **30**. The optical rotation of ligand **30** was also consistant with literature values. In chloroform, a value of -292 was obtained, compared with the literature value of -314.[7]



Scheme 35: synthesis of Jacobsen's ligand **30**.

Hansen's procedure allows ligand **30** to be synthesised quickly and in high purity. From here it was possible to complex vanadium to the ligand. Two sources of vanadium employed in past research [110] are vanadyl sulphate hydrate and vanadium oxychloride as both are available commercially and give the vanadium(salen) complex although the counterions differ depending on which is used. Vanadyl sulphate hydrate was chosen for this research and was added to ligand **30** in tetrahydrofuran and the reaction was refluxed for three hours. Formation of a dark green solution from the intense yellow salen ligand solution confirmed that complexation of the vanadium had occured. Upon reaction completion, the green residue obtained was passed through a silica column, eluting with dichloromethane. This was required to remove any uncomplexed ligand which eluted first as a yellow band. Any vanadium(IV)(salen) complex **109** also eluted, as a light green band. Vanadium(V)(salen) ethyl sulphonate **110** complex remained on the silica until a more polar solvent, in this case methanol, was added and compound **110** could then be eluted as a dark green band.

Complexation was further confirmed using ^{1}H NMR spectroscopy. The presence of the V=O bond means that the C_2-symmetry is destroyed resulting in the complex becoming C_1 symmetric, evidence of which is seen in the ^{1}H NMR spectrum. Two peaks are observed for the imine protons and four doublets are visible in the aromatic region of the spectrum each having a ^{4}J value of 2.4 Hz. The splitting of the original peaks of the free ligand **30** into two distinguishable peaks in the complexed ligand is consistent with the two imine protons and

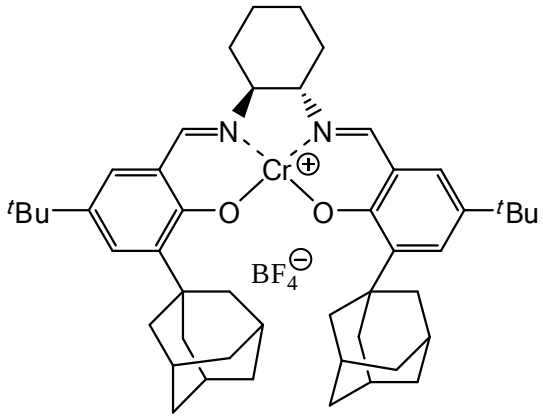
the aromatic protons now being unequivalent. Two peaks at 1.4 ppm correspond to the four *tert*-butyl groups. The counter-ion for the complex is an ethyl sulphonate anion which produces a triplet and a quartet at 0.8 and 3.4 ppm respectively in the ^{1}H NMR spectrum. X-ray crystallography has previously shown that a water molecule is present, coordinated to the vanadium, in the axial position *trans* to the V=O bond making the vanadium atom six coordinate.[112]

An ion-exchange was then carried out by adding concentrated hydrochloric acid to complex **110**, dissolved in dichloromethane. Washing with water and concentrating the solution gave vanadium(V) chloride complex **118** as a dark green crystalline solid. Ion-exchange was confirmed by proton NMR spectroscopy due to the disappearance of the ethyl peaks of the ethyl sulphonate anion. The vanadium(IV)(salen) complex **109**, obtained previously, was oxidised to the vanadium(V) species using ceric ammonium nitrate. Work up by treatment with concentrated hydrochloric acid afforded an additional batch of vanadium(V)(salen) chloride complex **118**. The vanadium(IV) species **109** has been shown to be inactive in the Strecker reaction [112] so it is desirable that all traces of this species are removed from the catalyst. Due to the paramagnetic nature of vanadium(IV) it was possible to assess whether there was any present by running a ^{1}H NMR spectrum, as the presence of vanadium(IV)(salen) complex would result in line broadening and carrying out this analysis showed that all traces of the paramagnetic material had been removed. Complexes **110** and **118** have been synthesised numerous times in the North group with extensive studies been carried out in this field of asymmetric catalysis involving these complexes. Due to this, no further analysis was undertaken of these complexes, as the ^{1}H NMR spectra were deemed sufficient to show the purity of these catalysts was of an acceptable standard.

2.1.2 Synthesis of New Catalysts

Early research carried out on salen complexes has shown that ^{t}Bu groups in the *ortho*-position of the aromatic rings of the ligand are essential for high enantioselectivity in some asymmetric transformations. When these substituents are changed to less sterically demanding substituents, or electronically different species, the selectivity has been shown to decrease in some cases. Larger substituents are yet to be investigated in Strecker reactions or asymmetric cyanohydrin synthesis. Adamantyl containing complexes such as chromium(III) containing complex **215** have been shown to increase the selectivity of glyoxylate-ene reactions (Scheme 36).[111] When compared to the use of the standard Jacobsen's ligand **30** in the reaction shown in Scheme 36, the enantioselectivity increased from 15% to 79%. A variety of other substituents were tested with the adamantyl substituted ligand giving the best

results. Therefore, the synthesis of adamantyl ligand **216** and trityl ligand **217** were carried out using standard protocols reported by Jacobsen.[7]



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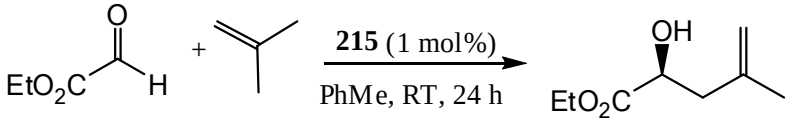
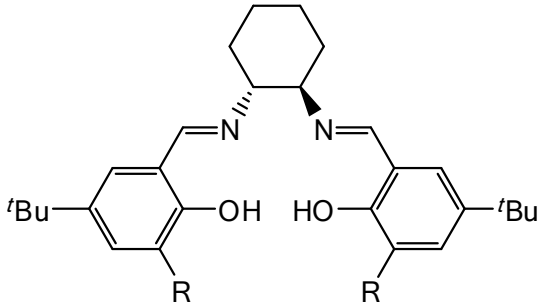


Scheme 36: application of complex **215** in asymmetric synthesis.

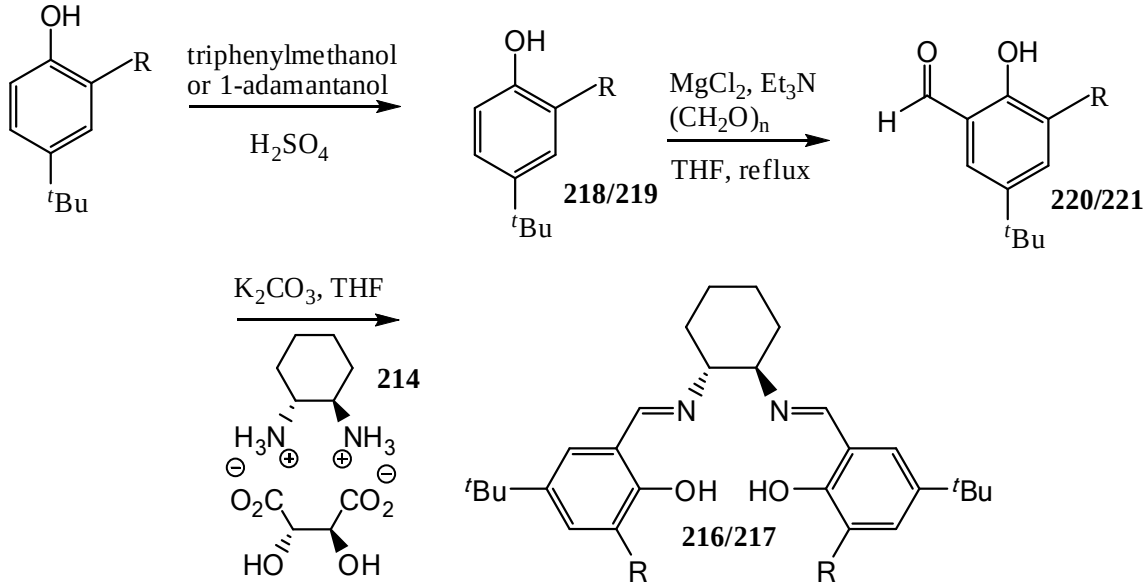


216) R= adamantyl
217) R= trityl

4-*Tert*-butylphenol was dissolved in dichloromethane along with 1-adamantanol. Concentrated sulphuric acid was added dropwise to this solution and the reaction was left to stir for 30 minutes, [112,113] to bring about the formation of the tertiary carbocation and its subsequent electrophilic substitution onto the aromatic ring. The adamantyl group adds in the position *ortho* to the hydroxyl group as this is the electronically most favoured position. Neutralisation of the reaction was carried out using sodium hydroxide, followed by work-up. A thick clear oil was obtained to which methanol was added, the solution was heated to reflux and then kept overnight at 4 ^{o}C. The *ortho*-substituted phenol, compound **218** (Scheme 37), was obtained as a white solid in 65% yield. Once the phenol starting material **218** had been synthesised in a high purity, Hansen's[7] procedure was attempted for the synthesis of ligand **216**. The synthesis was not as clean as for ligand **30** as after the final work-up there was a large amount of unreacted aldehyde **220** still present in the final product. Increasing the size of the substituent at the 2-position appeared to have a

detrimental effect on the one pot synthesis. Since Hansen's procedure was not a viable option in this case, formylation of compound **218** using Duff's procedure[114,115] was attempted. It was found that, even though aldehyde **220** was present in the product, many by-products had been formed and the reaction yields were low. Duff's procedure is sensitive to temperature changes as reported by Jacobsen and is also sensitive to substituent changes on the aromatic ring.[7] Due to the large change in substituent size it was concluded that this was the reason for the diminished reactivity in this case.

Therefore Hansen's procedure was employed for the aldehyde synthesis and it was isolated at that stage; compound **218**, magnesium chloride and paraformaldehyde were dissolved in tetrahydrofuran. Triethylamine was added dropwise to produce a yellow coloured solution. The mixture was refluxed for six hours, followed by work-up. Compound **220** was obtained in 46% yield as a pale yellow powder. ^{1}H NMR spectroscopy showed the distinct aldehyde peak at 9.98 ppm confirming the successful synthesis of compound **220**. Recrystallisation from ethanol was the only purification technique required. Synthesis of compound **216** was carried out in the same way as for the standard Jacobsen's ligand **30**. (*R*,*R*)-1,2-Diaminocyclohexane tartrate salt **214** and potassium carbonate were combined in tetrahydrofuran, along with aldehyde **220** and refluxed for four hours. The adamantyl ligand **216** was prepared in good purity and in 54% yield (Scheme 37) after a simple work-up.



216, 218 and **220)** R= adamantyl
217, 219 and **221)** R= trityl

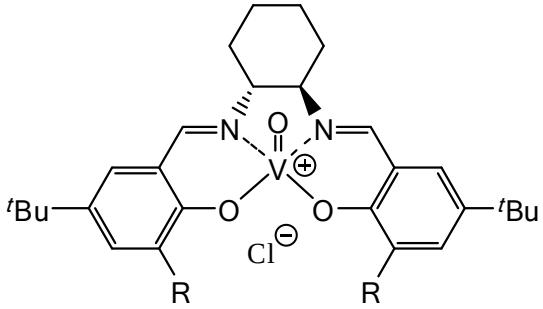
Scheme 37: synthesis of ligands **216/217**.

The trityl containing ligand **217** was prepared using the same route, (Scheme 37) however, longer reaction times were required and different purification procedures were necessary. 4-*Tert*-butylphenol and triphenylmethanol were dissolved in dichloromethane,

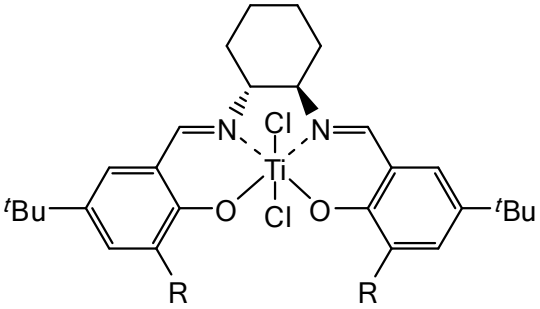
followed by addition of sulphuric acid which resulted in a deep red/brown solution.[116] This was verification of the formation of the trityl carbocation known to possess an intense red colour, due to the high level of conjugation throughout the extensive aromatic system. Purification of the trityl substituted phenol **219** proved more problematic. Firstly, recrystallisation was required using ethanol to remove any unreacted triphenylmethanol. The remaining material was purified by column chromatography, eluting with dichloromethane to remove any unreacted 4-*tert*-butylphenol giving compound **219** in 60% yield. Hansen's formylation was employed for the synthesis of aldehyde **221,** which was isolated and purified to give a 70% yield followed by the synthesis of ligand **217** in a 44% yield.

Complexation of these ligands to vanadium was carried out using vanadium(V) oxychloride as the vanadium source. Vanadium(V) oxychloride was dissolved in dichloromethane and the appropriate ligand was added and the reaction stirred overnight. Removal of the solvent produced a dark green solid in both cases which was purified via column chromatography eluting with dichloromethane followed by methanol. Analysis of these complexes proved to be problematic due to solubility issues though it was possible to obtain a ^{1}H NMR spectrum of complex **222**. Complexation was confirmed by the change in the imine proton peaks. Two distinguishable imine peaks were visible as well as the aromatic region becoming more complex due to the loss of the C_2 symmetry as seen with complex **118**. Complex **223** was found to be much more insoluble, so a ^{1}H NMR spectrum could not be obtained. It was however possible to analyse compound **223** using mass spectrometry. A mass of 983.4357 was predicted with a mass of 983.4341 being detected.

The titanium complexes **224** and **225** were prepared using the procedure previously developed for the synthesis complex **37**.[117] Ligand **216/217** was dissolved in dichloromethane and titanium tetrachloride added to the stirring solution. The complexation of the titanium was indicated by an immediate colour change to red/brown. The solution was stirred at room temperature for one hour and the solvent removed to give compounds **224** and **225** in 70% and 79% yield respectively. These catalysts were to be tested in the synthesis of cyanohydrins and Strecker reactions.

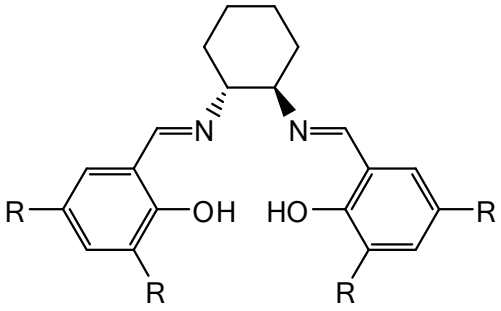


222) R = adamantyl
223) R = trityl

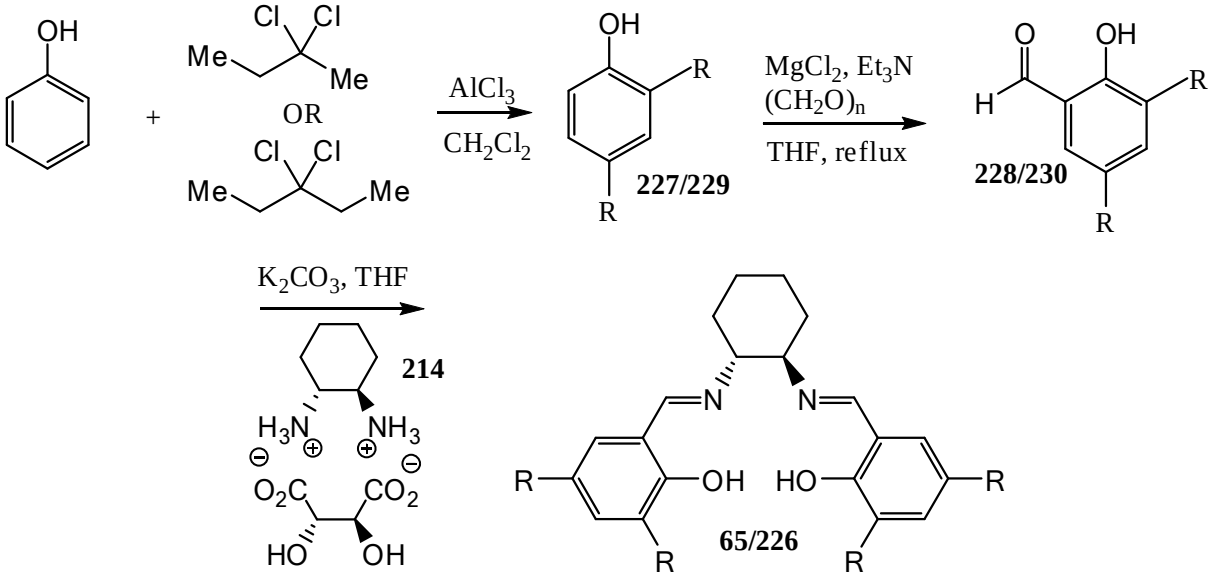


224) R = adamantyl
225) R = trityl

Ligand **65** has been shown to display high activity in cyanohydrin synthesis. Liang *et al* showed that when used in combination with titanium tetraisopropoxide in dichloromethane, the complex formed *in situ* would catalyse the addition of cyanide to benzaldehyde giving cyanohydrin in 97% (*S*) enantiomeric excess at -78 ^{o}C. To achieve this result, 5 mol% of ligand **65**, along with 5 mol% of titanium tetraisopropoxide were required (see section 1.2.3).[47] In light of these findings, this ligand was of interest due to the extensive study that has been carried out in the group, in this area of asymmetric synthesis.



65) R= *tert*-pentyl
226) R= *tert*-hexyl



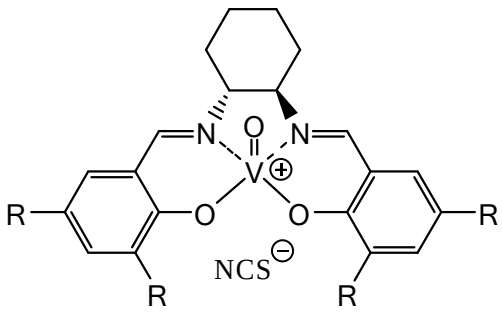
226, 229 and 230) R= *tert* hexyl
65, 227 and 228) R= *tert*-pentyl

Scheme 38: synthesis of ligands **65** and **226**.

This ligand was synthesised using phenol as the starting material. The first step in the synthesis involved the addition of the *tert*-pentyl substituent to the aromatic ring. This was achieved using a Friedel Crafts alkylation reaction.[118] Phenol and 2-chloro-2-methylbutane were added to aluminium chloride and the resulting mixture was stirred at room temperature for five hours followed by further addition of 2-chloro-2-methylbutane and aluminium chloride.[119] After this second addition the reaction temperature was raised to 60-70 ^{o}C and

held at that temperature for 24 hours. The mixture was then poured onto ice, and extracted into diethyl ether and washed with water several times. The organic layer was collected, dried and the solvent removed to leave a pale coloured oil. Purification via column chromatography gave the di-substituted compound **227** in 22% yield. Hansen's one pot procedure [7b] was attempted for the synthesis of ligand **65** but proved to be ineffective. The aldehyde **228** was therefore prepared and isolated using Hansen's formylation giving compound **228** in a yield of 73% after a short reaction procedure. Ligand **65** was subsequently prepared by adding (*R*,*R*)-1,2-diaminocyclohexane tartrate salt **214** and potassium carbonate. No further purification was necessary. The *tert*-hexyl ligand **226** was also prepared using the same route through intermediates **229** and **230** (Scheme 38).

Whilst this work was in progress, results from other researchers in the group showed that vanadium(V) isothiocyanate complex **132** was an even more active catalyst for asymmetric cyanohydrin synthesis than the complex **118**.[120] Therefore, the vanadium(V)(salen) isothiocyanate complexes **231a** and **231b** were synthesised for testing in asymmetric cyanohydrin synthesis. As with the standard salen ligand **30**, vanadylsulphate hydrate was added to a solution of ligand **65** or **226** in dichloromethane and refluxed overnight. The vanadium(IV)(salen) complexes were separated from the vanadium(V) material using column chromatography eluting with dichloromethane followed by methanol. The vanadium(V)(salen) complex eluted as a dark band on addition of methanol after which the complexes were isolated on removal of the solvent and redissolved in ethanol. Potassium thiocyanate was then added and the mixture was stirred at room temperature for two hours, inorganic salts were removed by filtration and the solution concentrated to give complexes **231a** and **231b** in 80% and 88% yield respectively. Distinct changes in the ^{1}H NMR spectrum confirmed that complexation had occured with two imine peaks being observed for both complexes at 8.4-8.7 ppm. These complexes were to be used in the synthesis of cyanohydrins and Strecker reactions.



231a) R= *tert*-pentyl
231b) R= *tert*- hexyl

2.1.3 Testing New Catalysts in the Strecker Reaction and Cyanohydrin Synthesis.

Due to the unexpected solubility problems, it was predicted that complexes **222** and **223** would not perform well in the Strecker reaction (Scheme 39). This was confirmed with catalyst **223** giving aminonitrile **232** with just 11% (*R*) enantioselectivity and catalyst **222** giving compound **232** with an enantioselectivity of 20% (*R*) after three hours at -40 ^{o}C. Additives have been shown to increase the rate of Strecker reactions with methanol giving the best results, therefore methanol was used as the reaction additive in these reactions.[117] The enantioselectivity was determined using ^{1}H NMR spectroscopy by adding (*S*)-camphor sulphonic acid to the NMR sample.[110] Complexation of the camphor sulphonic acid to the aminonitrile forms diastereomeric salts and the enantiomeric CH_{α} protons of the aminonitrile, which cannot usually be distinguished by ^{1}H NMR spectroscopy now become diastereomeric and so the (*R*)- and (*S*)-stereoisomers can now be seen as separate peaks in the NMR spectrum (Figure 7). The CH_{α} of the free aminonitrile can be seen in the NMR spectrum as a sharp single peak at 4.58 ppm. After addition of the chiral acid the peak is split into two peaks now at 4.86 ppm (minor) and 4.91 ppm (major), corresponding to the (*S*)- and (*R*)-enantiomers respectively. Integration of these peaks was then carried out and the enantiomeric excess calculated.

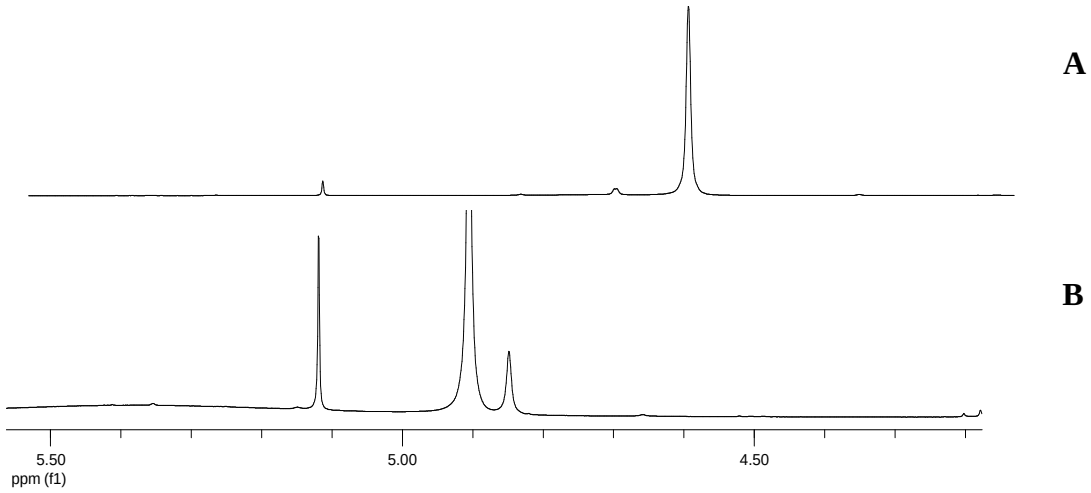
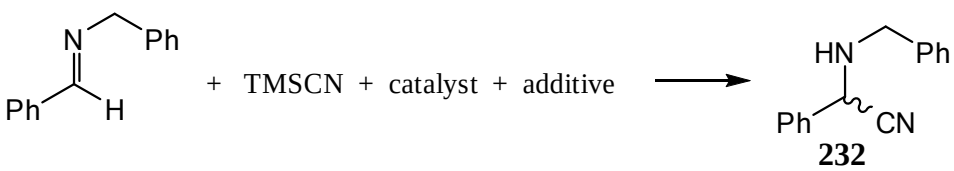
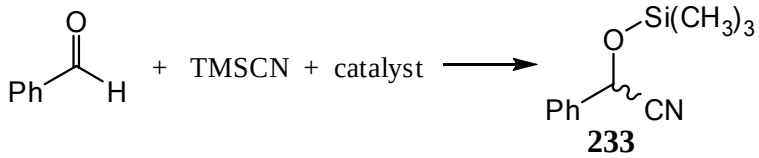


Figure 7: A = CH_{α} of the free aminonitrile; **B** = after addition of (*S*)-camphor sulphonic acid.



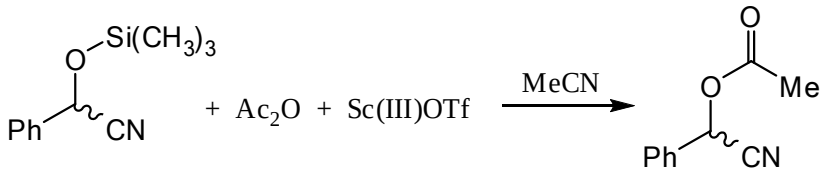
Scheme 39: the asymmetric Strecker reaction.



233

Scheme 40: asymmetric cyanohydrin synthesis.

Catalysts **222** and **223** were also screened in cyanohydrin synthesis using benzaldehyde as the test substrate (Scheme 40). Catalyst **223** gave product **233** with 13% conversion and an enantioselectivity of 10% (*S*) and complex **222** gave product **233** with a conversion of 12% and an enantioselectivity of 15% (*S*). Upon completion of the reaction, the conversion was calculated using ^{1}H NMR spectroscopy integrating the H_{α} peak of the cyanohydrin and the aldehyde peak, at 5.4 ppm and 10.0 ppm respectively. Determination of the enantioselectivity utilised Kagan's procedure which has been shown not to bring about any racemisation with the protected cyanohydrin being converted into the corresponding acetate using acetic anhydride and scandium(III) trifluoromethanesulphonate in acetonitrile as solvent (Scheme 41).[121] The enantioselectivity could then be determined using chiral gas chromatography. For compound **233,** the peaks at 19.10 (*R*) and 19.60 (*S*) minutes were integrated to give the enantiomeric excess. Figure 8 shows the gas chromatogram of a chiral sample of *O*-acetyl-mandelonitrile.



Scheme 41: the formation of *O*-acetyl-mandelonitrile.

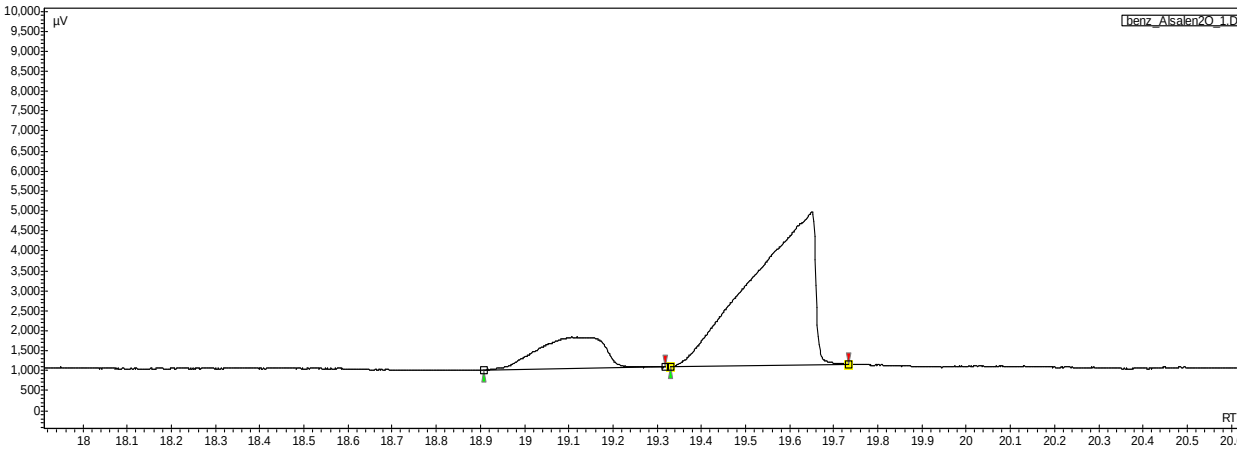


Figure 8: GC conditions: initial temperature: 95 ^{o}C; final temperature: 180 ^{o}C; ramp rate: 5.0 ^{o}C/min; flow rate: 2.0 ml/min; column pressure: 10 psi.

The titanium complexes **224** and **225** showed higher enantioselectivity in cyanohydrin synthesis reactions, with catalyst **224** giving compound **233** with 70% conversion and an enantioselectivity of 30% (*S*) after a one week reaction stirring at room temperature. Shorter reaction times gave compound **233** with decreased conversions, however, the enantioselectivity was found to be consistent throughout. A reaction time of 18 hours using complex **224** gave product with 21% conversion and with an enantiomeric excess of 25% (*S*). Increasing the reaction time to 36 hours gave product with 32% conversion and with 30% (*S*) enantioselectivity. Compound **225** gave cyanohydrin product **233** with 17% conversion and 20% (*S*) enantioselectivity after a reaction time of one week at room temperature. Attempts to synthesise bimetallic titanium complexes from monometallic complexes **224** and **225** were unsuccessful. All the results obtained using catalysts **222-225** in the Strecker reaction and cyanohydrin synthesis are summarised in Table 28.

Table 28; results obtained when using ligands **222-225** with vanadium and titanium in the Strecker reaction and cyanohydrin synthesis.

Catalyst	Metal	Strecker Reaction		Cyanohydrin Synthesis	
		conversion %	ee%[a]	conversion %	ee%[b]
222	V	100	20	12	15
223	V	100	11	13	10
224[c]	Ti	-	-	70	30
225[c]	Ti	-	-	17	20

[a] all aminonitriles were determined to be predominantly the (*R*) enantiomer using ^{1}H NMR.
[b] all cyanohydrins were determined to be predominantly the (*S*) enantiomer using chiral GC.
[c] reaction time of one week using 1 mol% of **224** or **225** at room temperature in dichloromethane.

Large substituents have previously been shown to increase the enantioselectivity of some reactions.[113] In the case of the Strecker reaction and cyanohydrin synthesis however, they are detrimental to the efficiency of the catalyst. Increasing the substituent size from *tert*-butyl to adamantyl and trityl effectively destroys all catalytic activity. Mechanistic studies of cyanohydrin synthesis using complex **118** have shown that the benzaldehyde has to coordinate to the vanadium(V) centre of the catalyst. This simultaneously activates the substrate making the carbonyl more electrophilic, and also brings the substrate into a chiral environment for enantioselective addition of cyanide. Significantly increasing the size of the substituents in the *ortho*-position of the aromatic ring appears to obstruct the benzaldehyde substrate so that this coordination is significantly reduced though some coordination is observed which is reflected in the slight asymmetric induction. The coordination is reduced

even further when using complexes **223** and **225,** as the size of the substituents are increased further to the sterically demanding trityl group. A significant reduction in conversion is also observed along with a decrease in enantioselectivity. This is more apparent in cyanohydrin synthesis as the conversion decreases considerably (70% to 17% for complex **225**) with a slight decrease in enantioselectivity.

The lower reactivity may also be due to the configuration of the salen ligand around the metal centre. Compound **118** has one available coordination site for the benzaldehyde to coordinate to the vanadium(V) centre, which is *trans* to the V=O bond. This *trans* arrangement of the V=O bond and the V-O bond of the benzaldehyde means that the metal(salen) complex has *trans* geometry. This is the preferred geometry of these salen complexes as it reduces the steric interactions between the two ligands as shown in Figure 9.

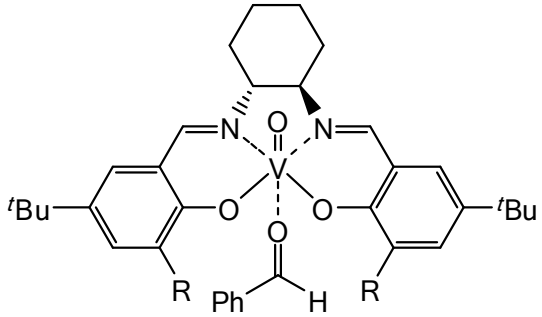
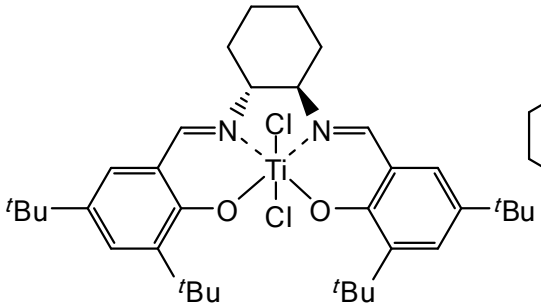
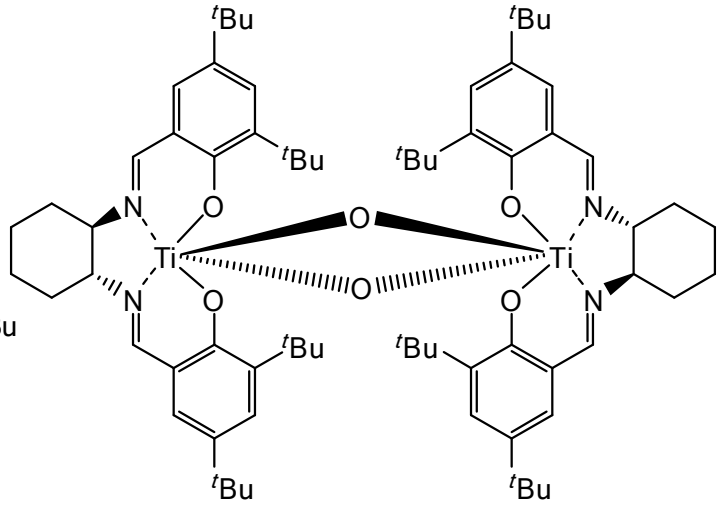


Figure 9: proposed co-ordination of benzaldehyde to the vanadium(salen) catalyst.

Complex **37** is active in cyanohydrin synthesis giving a 100% conversion and an enantioselectivity of 86% (*S*). X-ray crystallography has shown that the chloride ligands in complex **37** occupy the axial coordination sites around the titanium metal, with the salen ligand occupying the equatorial coordination sites.[122,123] An initial study hypothesised that it was complex **37** that was responsible for the catalysis though further work showed that a titanium(salen) dimer **41** was the catalytically active species and was formed *in situ* from complex **37**. X-ray crystallography of the dimeric species showed that the salen ligand takes on a different geometry, known as *cis*-β. In this geometry, the salen ligand occupies one axial coordination site and three equatorial coordination sites with the chloride ligands being *cis* with respect to one another. Complex **41** gives compound **233** with 86% (*S*) enantiomeric excess in less than five minutes at room temperature using 0.1 mol% of the catalyst. This extremely high activity is a consequence of the change in the ligand geometry from *trans* to *cis*-β. Mechanistic studies showed that both titanium metals are involved in the catalytic cycle confirming that the titanium dimer **41** is the active species and not the monometallic complex **37**.[124]



37



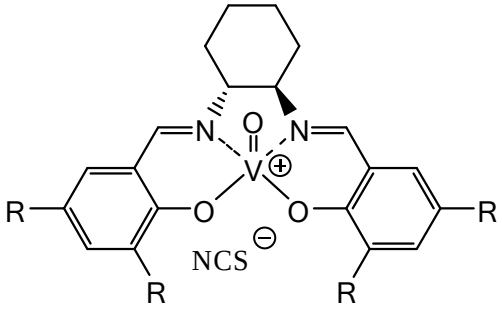
41

Cis-β geometries are preferred when the size of the metal atom is increased or the salen ligand carries large substituents and so by increasing the size of the substituents from *tert*-butyl to adamantly or trityl, enhanced formation of the *cis*-β configuration was predicted.[125,126] C*is*-β configurations reduce the steric interaction between the substituents on the salen ligand that would otherwise occur in the *trans* arrangement. Zirconium[127] and hafnium[128] salen complexes have been shown to display *cis*-β geometry and these compounds have been shown to display high catalytic activity in a variety of reactions. [129] However, using complexes **224** and **225** in cyanohydrin synthesis was not successful and it appears that the larger substituents do not allow the formation of the catalytically active *cis*-β dimeric species. Complexes **224** and **225** are still not as active in the monomeric form as complex **37**, as the substituents are too large to allow efficient coordination of the benzaldehyde substrate to the titanium metal centre. This is reflected in the lower conversions and enantioselectivities when using these complexes as catalysts in cyanohydrin synthesis. Attempts to isolate the dimeric species of complexes **244** and **225** and grow crystals for X-ray crystallography analysis proved unsuccessful.

2.1.4 Testing of Complexes 231a and 231b in Cyanohydrin Synthesis and the Strecker reaction.

Complexes **231a** and **231b** were added to a cyanohydrin forming reaction in a 0.1 mol% catalyst loading with trimethylsilylcyanide as the cyanide source. Complex **231a** was found to give compound **233** with complete conversion and with an enantiomeric excess of 90% (*S*). Complex **231b** gave compound **233** with complete conversion and an enantiomeric excess of 84% (*S*), Table 29. Both of these reactions were carried out at room temperature for a period of three hours. Comparison of this data with the results obtained by Liang

showed that the vanadium(V)(salen) isothiocyanate complexes are more active than the titanium isopropoxide complexes prepared *in situ* from ligand **65**.[47] Liang's system required a reaction temperature of -10 ^{o}C to achieve the same enantiomeric excesses and also 5 mol% of ligand **65**. The vanadium(V) isothiocyanate complexes required a loading of just 0.1 mol% to give product **233** in three hours and so were shown to be more active catalytic systems than Liang's system. Lower enantioselectivity was observed using complex **231b** due to the substituent size increasing from *tert*-pentyl to *tert*-hexyl, therefore making the system more hindered and so more difficult for the benzaldehyde to coordinate to the vanadium atom. This decreases the influence of the chiral environment therefore resulting in a decrease in enantioselectivity. Table 29 shows the results obtained for complexes **231a** and **231b** along with the results obtained for complexes **118** and **132**. It is clear to see that complex **132** is still the more active catalyst in terms of the reaction time required to give an enantiomeric excess of 90% (*S*) under the standard reaction conditions. Complex **132** requires two hours with complexes **231a** and **231b** only requiring a further hour to give the same results, therefore these newly synthesised catalysts show very similar activity complex **132**. The major drawback with complexes **231a** and **231b** is the longer synthesis required to obtain them and therefore their use on an industrial scale to obtain enantiomerically enriched cyanohydrins is unlikely.



231a) R= *tert*-pentyl
231b) R= *tert*-hexyl

Table 29; comparative data for complexes **118, 132, 231a** and **231b** in cyanohydrin synthesis**.**

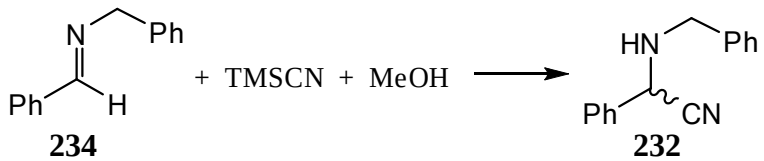
Catalyst	Time, h[a]	Conversion %	ee %[b]
118	18	100	93
132	2	100	91
231a	3	100	90
231b	3	100	84

[a] reactions were carried out using benzaldehyde as the reaction substrate and 0.1 mol% of catalyst at room temperature in dichloromethane as the reaction solvent.
[b] all cyanohydrin products were determined to be predominantly the (*S*) enantiomer.

From these findings, it can be concluded that larger aromatic substituents have a detrimental effect on the enantioselectivity and the general activity of these systems as displayed by complexes **222-225** especially complexes **222** and **223** when used in cyanohydrin synthesis. Both the enantioselectivities and reaction conversions were exceptionally poor with enantioselectivities no greater than 15% being achieved with conversions showing similar values. Complex **224** gave a higher conversion of 70% however, the enantioselectivity was still poor at 30%. Due to these poor results, these catalysts are not viable in either an academic or commercial sense. The solubility issue experienced with regard to the trityl containing catalysts **223** and **225** supports this conclusion. These solubility issues were also problematic when trying to gain characterisation data and so the purity of these less soluble catalysts is not known. Complexes **225** and **223** were particulary insoluble with complex **223** only being characterised using infra-red spectroscopy and mass spectrometry. Complexes **231a** and **231b,** however showed high activity with enantioselectivities of greater than 90% being achieved. These results and full characterisation demonstrated the purity of these catalysts, which were the most active from the screening studies.

3.1 Research into the Strecker Reaction using Metal Salen Complexes.

Catalyst **118** has been shown to asymmetrically catalyse the addition of trimethylsilylcyanide to imines giving moderate to good enantioselectivities.[112] In an attempt to improve on these results, further research was undertaken using catalyst **118**, investigating a range of variables to try and optimise the current reaction conditions. *N*-Benzylidene benzylamine was chosen as the test substrate and was synthesised from benzaldehyde and benzylamine in dichloromethane. Initially, a Strecker reaction was carried out in the absence of catalyst to establish if any background reaction was occurring. Standard reaction conditions were chosen; 1.2 equivalents of trimethylsiylcyanide and 1.2 equivalents of methanol, 1.0 equivalents of imine **234** (Scheme 42) with toluene as the solvent. This control experiment gave the expected result of 0% enantiomeric excess, and 50% conversion to the Strecker product **232**.

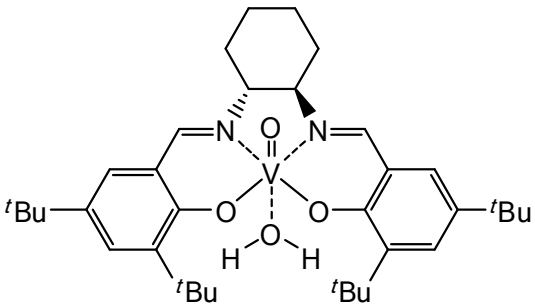


234 **232**

Scheme 42: standard Strecker reaction used in this work.

A Strecker reaction carried out using vanadium(IV)(salen) complex **109** (10 mol%) as the catalyst also gave racemic product, but the conversion was higher at 70%. This shows that complex **109** does catalyse the reaction, but does so racemically due to complex **109** being a neutral species and therefore the imine is not strongly attracted to the vanadium atom of the catalyst. Vanadium(V)(salen) complexes possess a positive charge on the vanadium centre, so the electrophilic nitrogen of the imine bond can strongly coordinate to the vanadium atom bringing the imine into a chiral, catalytically active environment.

The first catalysed Strecker reactions carried out in this project used the conditions as described above along with 10 mol% of catalyst **118**. First attempts at the reaction gave α-aminonitrile product **232** with exceptionally low enantiomeric excess and in lower conversion than those previously reported; 13% (*R*) and 70% respectively. This much lower enantioselectivity was worrying as previous work had shown enantiomeric excesses as high as 75% were possible using complex **118** as catalyst.[112] It is believed that the actual cyanating agent is hydrogen cyanide, generated from the reaction between trimethylsilylcyanide and an appropriate additive in this case methanol. The use of an additive possessing a more acidic proton was suggested, to encourage the generation of greater amounts of hydrogen cyanide in the reaction system. 4-Nitrophenol was selected and added to the reaction in the same quantities previously used for methanol as the additive. This increased the enantiomeric excess to 40% as predicted, however this was still not as enantioselective as previously reported. A number of variables were then investigated with distilled toluene being used along with distilled trimethylsilylcyanide but these changes made no difference to the enantioselectivity of the product.



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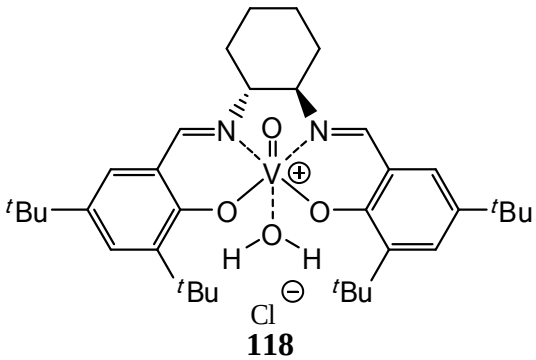


118

Testing of catalyst **118** in asymmetric cyanohydrin synthesis showed that it was of high activity (Scheme 40). Complex **118** was dissolved in dichloromethane and trimethylsiylcyanide and benzaldehyde were added to the reaction. The reaction was stirred at room temperature overnight and the reaction mixture passed through a silica plug eluting with dichloromethane to remove complex **118**. ^{1}H NMR spectroscopy confirmed the conversion to be 51% and chiral gas chromatography showed the enantiomeric excess to be

87% (*S*) using the method of Kagan. Comparison with literature data[119] showed this to be the expected result, verifying that complex **118** was an active catalyst. Taking these findings into account, other variables for the Strecker reaction were investigated, starting with a closer inspection of substrate **234** which showed it to contain trace amounts of unreacted benzylamine and which was calculated to be of 93% purity. Catalytic activity in this system is dependent on the Lewis basicity of the imine substrate and the ability of the nitrogen to complex to the central metal atom of the catalyst. Amines can also behave in a Lewis basic manner as they too possess lone pairs of electrons on the nitrogen, therefore any residual amine present in the reacting substrate will compete with this complexation and hinder the reaction. It was suspected that this was occurring in the reaction due to the lowered enantioselectivities and conversions, therefore *N*-benzyl benzylimine **234** was taken up into dichloromethane and washed repeatedly with acidified water. ^{1}H NMR spectroscopy confirmed that all traces of the amine had been removed and that the imine was now of >99% purity. Using this newly purified imine in a Strecker reaction confirmed the deleterious effect of amines on the activity of the catalytic system as the enantioselectivities and conversions were restored to those obtained in previous studies (75% (*R*) enantiomeric excess and 98% yield respectively) when using 4-nitrophenol as the reaction additive. A lower enantiomeric excess of 65% (*S*) was obtained when using methanol as the additive. Comparision of the optical rotation values the with literature values confirmed that the (*R*)-enantiomer of the aminonitrile was predominant in the product mixture.[130]

To test the effect of amines directly on the reaction, a Strecker reaction was carried out and one equivalent of benzylamine was deliberately added. Work up and ^{1}H NMR analysis showed that the aminonitrile product was present with only 20% (*R*) enantioselectivity, confirming the ability of the amine to inhibit the catalyst. ^{1}H NMR studies were carried out to see if the coordination of the amine could be followed spectroscopically (Figure 10).

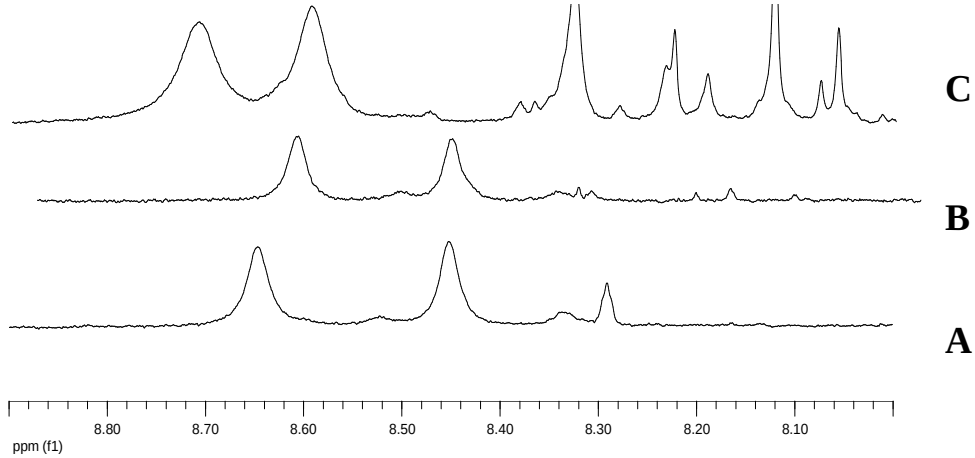
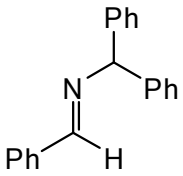


Figure 10: interaction of benzylamine and V(V) salen complex; **A =** 0.5 eq, **B** = 1.0 eq, **C** = 1.5 eq of imine

Increasing amounts of benzylamine were added to a sample of complex **118** and there appeared to be a change in the imine protons of the catalyst. The two peaks observed at 8.55 and 8.76 ppm in the original spectrum of complex **118** can be seen to be merging together and there is a change in their chemical shifts. When 0.5 equivalents of amine (A) are added the peaks shift to 8.47 and 8.65 ppm. On addition of 1.5 equivalents of amine (C) an obvious change in chemical shift is observed with the imine peaks almost fully merged. As was discussed previously, the free ligand displays C_2-symmetry. As a result of this only one imine proton signal is seen in the ^{1}H NMR spectrum as the two imine protons are equivalent. The addition of vananium to the ligand destroys this symmetry and the system then becomes C_1-symmetric due to the V=O bond, This is confirmed in the ^{1}H NMR spectrum, as the single imine signal in the free ligand is now split into two distinguishable signals, each integrating to one proton. If the prediction is correct, then the binding of benzylamine to the vanadium will further alter the spectrum. The effect of the binding benzylamine can be clearly seen in the ^{1}H NMR spectra presented in Figure 10. Spectrum C showed the appearance of additional peaks in the aromatic region of the spectrum. It would appear as though these are a result of the addition of the benzylamine as benzylamine also contains aromatic protons, though a careful inspection of the ^{1}H NMR spectrum showed that these signals were not cauased by free benzylamine and so may be due to the benzylamine binding to the vanandium of the catalyst as was predicted before the study began. This possibility was not explored further due to time constraints.

Having established how easily the activity of the system could be disrupted and how readily imines and amines can coordinate to the metal centre, the steric requirements of the imine substrate were investigated. The following imines were chosen for synthesis: *N*-benzylidene benzhydrylamine[131,132,133] **235**, *N*-benzylidene-2,6-dimethylaniline[134] **236**, and *N*-benzylidenetritylamine[135] **237**. Synthesis of these imines was carried out without difficulty. Thus the appropriate amine was added to benzaldehyde in dichloromethane, adding magnesium sulphate as a dehydrating agent and the reaction allowed to stir at room temperature for 24 hours. Great care was taken to purify the imines to >99% purity and to remove all traces of the starting amine. Each substrate was tested in the Strecker reaction using the same conditions as for the preceding reactions. *N*-Benzylidene benzhydrylamine **235** reacted within three hours to give α-aminonitrile product **238** with 46% enantiomeric excess (*R*), with 88% conversion. *N*-Benzylidene-2,6-dimethylaniline **236** and *N*-benzylidene-tritylamine **237**, gave racemic products however the conversion was 100% after three hours.



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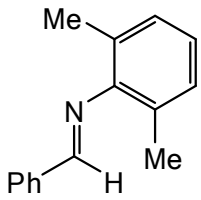

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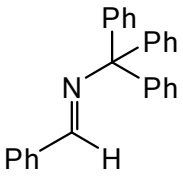

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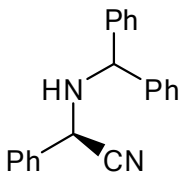


238

As the size of the imines increases the conversion and the enantiomeric excess was shown to decrease. When using *N*-benzylidene benzhydrylamine **235** some selectivity is still observed though the enantiomeric excess is lower than the selectivity obtained using *N*-benzyl benzylimine **234**. Using *N*-benzylidene-2,6-dimethylaniline **236**, and *N*-benzylidenetritylamine **237** as reaction substrates gave totally racemic product however a complete conversion was achieved. This strongly suggested that there is a very prominent background reaction which was bypassing the catalysed reaction as even though imines **236** and **237** appeared to be too sterically hindered to coordinate to the catalyst a reaction was still occurring. If high asymmetric induction is to be observed in any asymmetric synthesis, then any racemic or background reaction has to be totally suppressed or significantly reduced. Another possibility was uncatalysed reaction on work-up when the product was passed through the silica plug to remove the vanadium catalyst. This could be responsible for lowering the enantioselectivities of the reaction whilst also giving a 100% conversion in the majority of cases. In an attempt to prevent any reaction on work-up, triethylamine was added to the eluent used when passing the crude product down the silica plug and the silica was exchanged for alumina. This made no difference to the results obtained with a complete conversion and an enantiomeric excess of 60% (*R*) achieved, when using *N*-benzylidene benzylamine as the reaction substrate, which was slightly lower than previously obtained when using complex **118**. To test the theory of possible reaction on work-up, ^{1}H NMR experiments were carried out by removing samples and analysing them at various timepoints throughout the duration of the reaction. Over a period of three hours, samples were removed and passed through a silica plug to remove the catalyst and the residue was analysed in deuterated chloroform. The results are presented in Table 30.

Table 30; results obtained from sampling the Strecker reaction at different time intervals using complex **118** as a chiral catalyst.

Time Sample was taken (min)	Conversion %	ee %
30	100	50
60	100	59
90	100	63
120	100	70
150	100	77
180	100	78
210	100	77

Two observations in this experiment were the consistent conversions of 100% suggesting that the reaction was going to completion on work-up, and also the increasing enantioselectivity. The lower enantioselectivities obtained with early sampling are consistent with racemic reaction on work-up. At earlier stages in the reaction, there has not been sufficient catalysis to bring about high stereoinduction, therefore when the reaction is worked up, any unreacted imine reacts racemically on the silica and this lowers the apparant enantioselectivity. It was predicted that if the reaction was left for a longer period of time then the selectivity would keep on increasing as the catalyst converted all of the imine into chiral aminonitrile product, leaving no unreacted starting material susceptible to racemic work-up. However when this theory was tested over a two day reaction time, there was no further improvement in the enantioselectivity. Figure 11 shows the increase in enantioselectivity over the first three hours followed by a plateau with a decrease observed after 24 hours which was probably caused by racemisation of the product.

To ensure a thorough study of all possible variables, a number were investigated in an attempt to increase the enantioselectivity of the reaction (Table 31) with the solvent, additive and reaction temperature all being investigated. Temperature can have a direct bearing on the enantioselectivity of a reaction; in the majority of cases, lowering the reaction temperature increases the enantioselectivity, though at the expense of decreasing the rate of the reaction. The reactions discussed thus far were all carried out at -40 ^{o}C and therefore lower temperatures of -60 and -80 ^{o}C were investigated. Performing a reaction at -60 ^{o}C in toluene gave consistent results with an enantioselectivity of 77% (*R*) and a conversion of 100% (Entry 1). Changing the additive from 4-nitrophenol to methanol gave product with 64% (*R*) enantioselectivity with a 90% conversion at a reaction temperature of -60 ^{o}C. Reducing the reaction temperature to -80 ^{o}C using 4-nitrophenol as the reaction additive gave comparable results to when using methanol as the reaction additive (Entry 2).

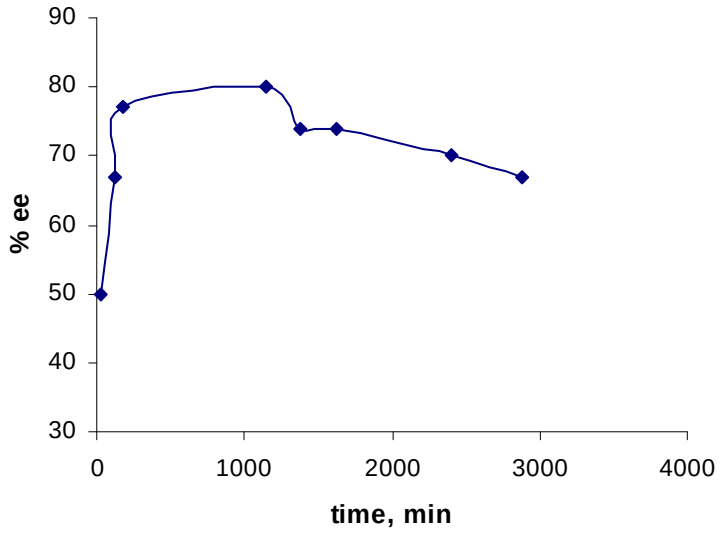


Figure 11: variation of enantiomeric excess with time when using complex **118** in the asymmetric Strecker reaction.

Table 31; data from the optimisation studies using complex **118** in the asymmetric Strecker reaction.

Entry	Additive	Temperature ^{o}C	Conversion %	ee %
1[a]	4-nitrophenol	-60	100	77
2[a]	4-nitrophenol	-80	100	75
3[b]	4-nitrophenol	-40	89	32
4[c]	4-nitrophenol	-40	82	6
5[a]	4-methoxyphenol	- 40	100	65
6[a]	MeOH	-80	90	64
7[d]	MeOH	-40	100	0
8[a]	1-adamantanol	-40	96	57
9[a]	^{t}BuOH	-40	100	80
10[a]	CH_3COOH	-40	100	65
11[e]	MeOH	-40	71	0

[a] Reaction carried out in toluene using 10 mol% cat., 1.2 eq additive, 1.2 eq of TMSCN, 3 h.
[b] Reaction carried out in dichloromethane using 10 mol% cat., 1.2 eq of additive, 1.2 eq of TMSCN, 6 h.
[c] Reaction carried out in EtOH using 10 mol% ca, 1.2 eq of additive, 1.2 eq of TMSCN,10 h.
[d] As (a) except using 1 mol% of catalyst.
[e] Reaction carried out in propylene carbonate using 10 mol% cat, 1.2 eq additive, 1.2 eq TMSCN, 3 h.

Changing the solvent to dichloromethane or ethanol had a detrimental effect on the selectivity. Using dichloromethane at -40 ^{o}C gave α-aminonitrile product **232** with 32% (*R*) enantioselectivity with an 89% conversion (Entry 3). Ethanol at -60 ^{o}C gave an enantioselectivity of only 6% (*R*) with an 82% conversion. At -40 ^{o}C, racemic product was obtained when using ethanol as the reaction solvent (Entry 4). Using a more polar solvent will lower the enantioselectivity of the product as the ability of the solvent molecules to interact with the charged vanadium(V) atom will increase and therefore will make it more difficult for the imine to coordinate to the catalyst. Toluene is the solvent of choice for the Strecker reaction as it is non-polar, therefore giving the highest enantioselectivities. 4-Methoxyphenol was tested as a reaction additive and gave a lowered enantioselectivity of 65% (*R*) due to the lower acidity of the phenolic proton (Entry 5). Changing the additive has a direct bearing on the enantioselectivity of the reaction with *tert*-butanol giving a higher enantioselectivity of 80% at -40 ^{o}C and 1-adamantanol and acetic acid giving lower enantioselectivities (Entries 8, 9 and 10 respectively). A reaction was also carried out using propylene carbonate as the reaction solvent at -40 ^{o}C, giving aminonitrile product with 71% conversion with 0% enantioselectivity (Entry 11).

Changing the rate of addition of the additive also had an effect on the enantioselectivity. Using complex **118** at -40 ^{o}C and methanol as the additive; all reagents except methanol were dissolved into toluene and cooled to the required temperature. The methanol was added to the reaction in ten 1 μl portions every 15 minutes. This gave product **232** with 80% (*R*) enantioselectivity compared to 65% (*R*) enantioselectivity obtained when adding methanol in one portion. Similarly, adding *tert*-butanol slowly to the reaction gave an increased enantioselectivity of 83% (*R*). Slow addition of the additive results in slow release of hydrogen cyanide and so the addition to the imine bond occurs at a slower rate. Adding methanol in one portion results in all of the hydrogen cyanide being generated in one step therefore it may be possible for some to escape into the atmosphere lowering the amount available for reaction. Initial studies have shown that the racemic reaction can occur rapidly, therefore if hydrogen cyanide is produced quickly some will react to give the racemic product also lowering the enantioselectivity of the reaction. Allowing the concentration of hydrogen cyanide to build slowly lessens these possibilities, which is reflected in the subsequently higher enantioselectivities.

3.1.1 Kinetic Study of the Strecker Reaction using Complex 118.

It was decided that a closer analysis of the reaction was required as it was beginning to appear more complex than initially anticipated and therefore attempts were made to study the reaction kinetics of the Strecker system. A reliable method has been developed in our group for studying the kinetics of cyanohydrin reactions. This involves taking samples manually from a reaction at appropriate time intervals and analysing each sample using UV spectroscopy to monitor the disappearance of the carbonyl bond. It was decided to apply this methodology to asymmetric Strecker reactions. All reagents were distilled and a reaction was set up at 0 ^{o}C from which samples were taken manually and the disappearance of the imine bond monitored. However, it quickly became apparent that this method was not going to be a suitable means to carry out a kinetics study. Due to the high amount of catalyst being used and the dark colour of the catalyst, the detector quickly became saturated and it became impossible to detect any imine in the sample. Even lowering the catalyst loading made little improvement to this problem. There were also suspicions that reaction was occurring in the microsyringe when removing the sample as the reaction warmed up to room temperature. Attempts were then made to use stop-flow kinetics techniques, however the same problems were encountered. Due to the problems of reaction on work-up and reaction when sampling, a method was required whereby the reaction could be monitored *in situ* at lowered temperatures without disturbing the sample. ^{1}H NMR spectroscopy was chosen to obtain *in situ* data.

Therefore, a Strecker reaction was set up in an NMR sample tube. All the reagents were dissolved in d_8-toluene except *N*-benzylidene benzylamine and the probe of the 400 MHz NMR spectrometer was cooled to -40 ^{o}C. The imine was then added to the NMR tube and the sample placed in the spectrometer. After two minutes the spectrum showed complete conversion to aminonitrile product **232**. A second attempt was made only this time the sample was cooled to -78 ^{o}C in a dry ice/acetone bath. Once again the imine was added in one portion and the sample placed in the spectrometer for analysis, which again showed complete conversion to the aminonitrile product. It seemed as though the reaction was occurring at a very fast rate, much faster than initially anticipated, or the process of transferring the sample from the dry ice/acetone bath to the spectrometer was allowing the sample to reach higher temperatures and so momentarily increasing the rate of the reaction to bring about complete conversion to the aminonitrile product. To prevent any such reaction occurring in the sample tube before monitoring could begin, both the tube and spectrometer probe were cooled to -78 ^{o}C. Once the sample was in the spectrometer, the probe was warmed to -40 ^{o}C. Complete conversion was observed in the first spectrum taken after two

minutes. Decreasing the monitoring temperature of the probe to -60 ^{o}C resulted in 50% conversion being observed after two minutes. Allowing the probe to warm to -40 ^{o}C proved that the reaction was occurring at an extremely fast rate even at this temperature as after two minutes at this temperature, the reaction had gone to completion. The best temperature to monitor the reaction was chosen as -60 ^{o}C with initial experiments showing that warming the reaction from -78 ^{o}C to -60 ^{o}C brought about a 50% conversion. From this the monitoring of the remaining 50% of reaction could be carried out from which the data could be analysed to give some kinetic information. For a first order reaction; $[A] = [A]_0e^{-kt}$, where A= imine. This equation can be rewritten in the form $\ln[A]/[A]_0 = -kt$ whereby a plot of the natural logarithm of imine concentration against time will give a straight line for which the gradient is equal to the negative rate constant. As shown in Figure 12 the reaction was found to be first order overall with a rate constant of 0.0015 s^{-1} at -60 ^{o}C.

For this Strecker reaction a rate equation can be written as follows;

$$\text{Rate} = k[\text{imine}]^a [\text{TMSCN}]^b [\text{catalyst}]^c.$$

If the concentration of the catalyst remains constant throughout the duration of the reaction then the rate equation can be rewritten as;

$$\text{Rate} = k_{obs}[\text{imine}]^a [\text{TMSCN}]^b \text{ where } k_{obs} = k [\text{catalyst}]^c.$$

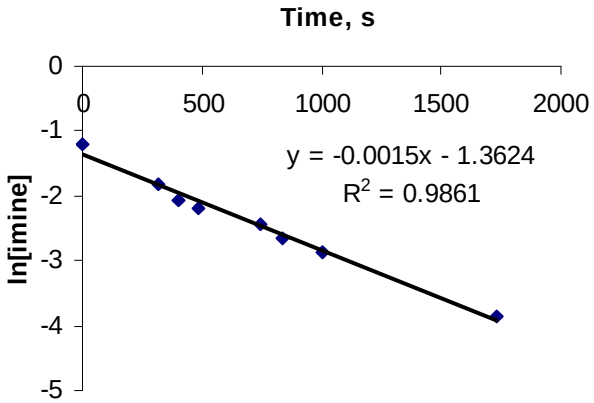


Figure 12; [imine] = 0.301 M; [MeOH] = 0.361 M; [TMSCN] = 0.361 M; [**118**] = 0.0301 M in d_8-toluene at -60 ^{o}C.

Therefore this first order behaviour is either a result of a first order dependence on the imine concentration or a first order dependence on the trimethylsilylcyanide concentration. For first order reactions; the rate of the reaction is directly proportional to the concentration of the reagent in question, i.e. if the concentration of the reagent is doubled then the rate of the reaction will also double. Using this theory it would be possible to determine which

reagent was responsible for the first order kinetics by changing the initial concentrations and observing the effect on the rate of the reaction. The imine concentration was halved and the same experiment was repeated at -60 ^{o}C as shown in Figure 13 with all the other components being kept at the previously used concentrations.

There appeared to be a decrease in the rate constant to 0.0003 s^{-1} strongly suggesting that the rate of reaction depended on the imine concentration. However, analysis of the rate of consumption of trimethylsiylcyanide for these two experiments (Figure 14) showed that the initial rate of both reactions appeared to be the same.

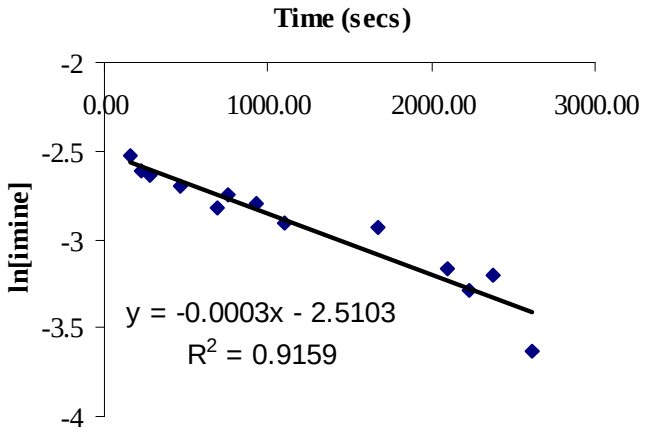


Figure 13; [imine] = 0.150 M; [MeOH] = 0.361 M; [TMSCN] = 0.361 M; [**118**] = 0.0301 M in d_8-toluene at -60 ^{o}C.

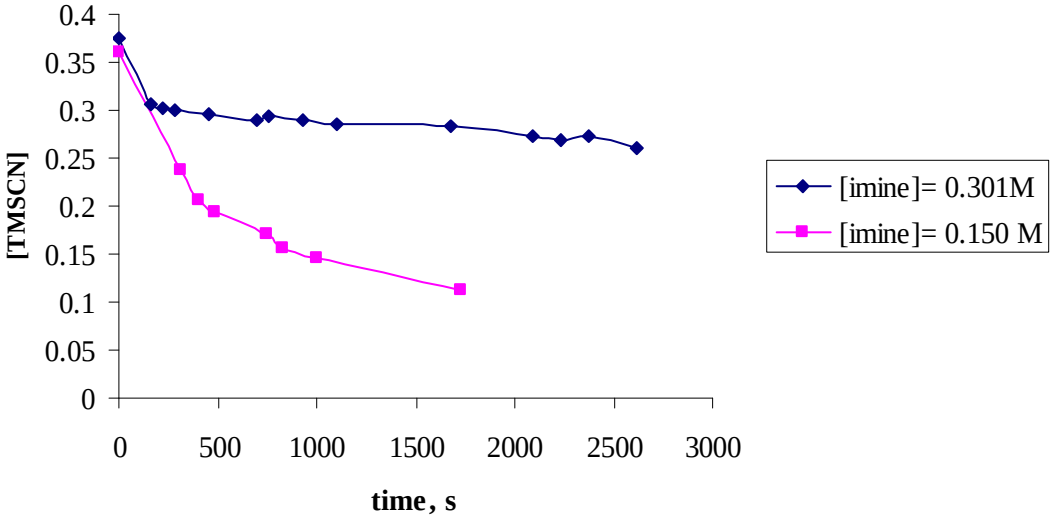


Figure 14: plot of trimethylsilylcyanide concentration against time.

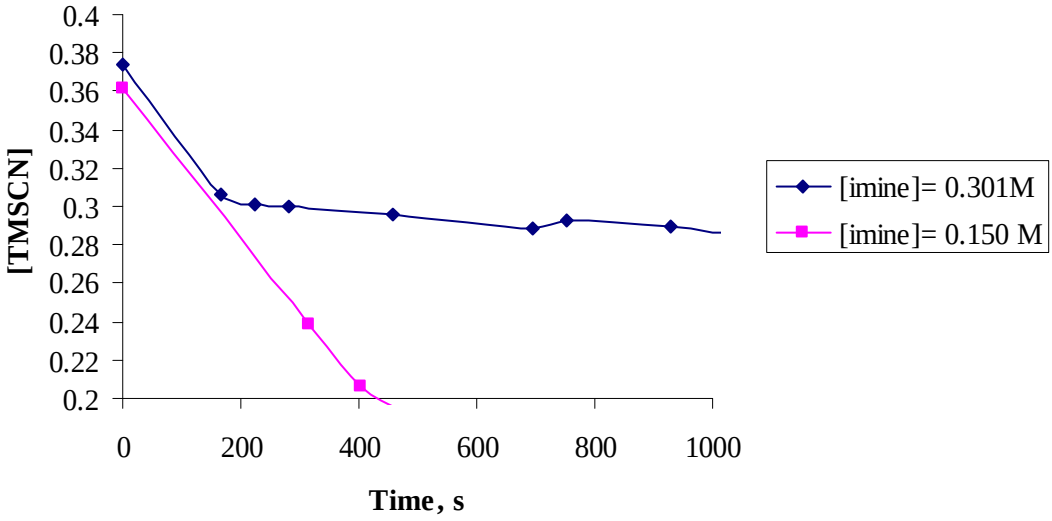


Figure 15: expanded view of Figure 14.

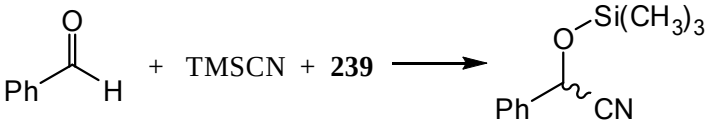
Being unable to prevent any background reaction from occurring before the kinetic analysis could begin proved problematic when it came to analysing the data. Before any data points could be collected, a large portion of the reaction had already occurred. Initial analysis of the graphs in Figure 14 appeared to show a first order dependence on the imine concentration. However, close inspection of the early stages of the reaction seem to show that the reactions are proceeding at the same initial rate; between 0.38 and 0.30 M trimethylsilylcyanide. Figure 15 shows the initial stages of the same reaction as Figure 14. Data collection was only possible for the final stages of reaction giving a potentially false result of first order in the imine substrate in the first 200 seconds of the reaction. Figure 15 appears to show zero order dependence in the imine substrate. Due to the lack of data points in this early stage of the reaction, these results were not sufficient for a full kinetic analysis of the reaction and so it became apparent that ^{1}H NMR spectroscopy was not a convenient method for studying the kinetic profile of the Strecker reaction and the experiment was not continued further as the background reaction was shown to be occur at too fast a rte, and any attempts to prevent or significantly reduce this background reaction failed.

4.1 Aluminium(salen) Complexes in cyanohydrin synthesis.

4.1.1 Cyanation of Aldehydes Using Alumium(salen) Dimer 239.

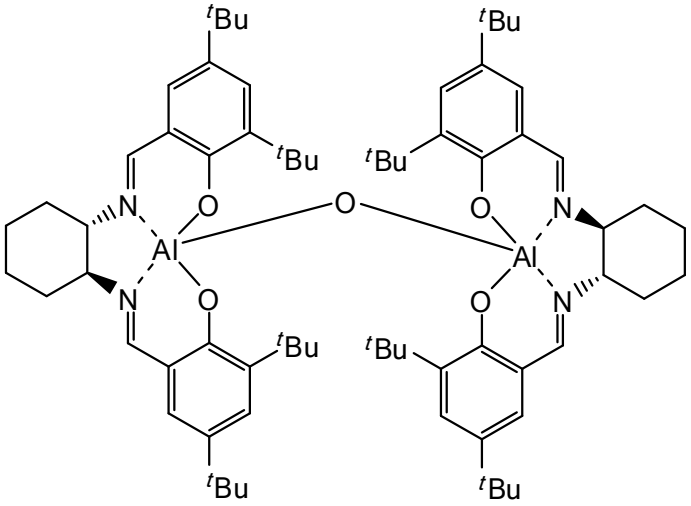
Much research has focused on the use of titanium[136] and vanadium(salen)[61,67] complexes as chiral catalysts for the cyanation of aldehydes and ketones.[137] All these systems have been thoroughly studied and highly optimised giving compound **233** (Scheme 43) with high enantioselectivity under mild reaction conditions. Aluminium salen complexes

have also been shown throughout the literature to be active in cyanohydrin synthesis using aldehydes and ketones as substrates.[79,80,81] Extensive work has been carried out in our group investigating the use of dimeric aluminium(salen) complexes as catalysts for the insertion of CO_2 into epoxides to form cyclic carbonates.[138] These complexes have been shown to be active in this reaction with the dimer **239** derived from ligand **30** displaying the highest activity. Due to this high activity and the known activity of aluminium(salen) complexes in cyanohydrin synthesis, complex **239** was synthesised for testing in asymmetric cyanohydrin synthesis.



233

Scheme 43: standard cyanohydrin synthesis used in this study.



239

To prepare complex **239** the procedure of Melendez *et al* was followed.[140] Initial cyanohydrin reactions were attempted using only complex **239** as the chiral catalyst and benzaldehyde was chosen as the test substrate in combination with trimethylsilylcyanide as the cyanide source. A catalyst loading of 1 mol% of complex **239** was used for preliminary reactions with a reaction time of 16 hours at room temperature. Cyanohydrin product **233** was obtained with 30% conversion and with 30% (*S*) enantioselectivity. These results showed that complex **239** exhibited some catalytic activity in cyanohydrin synthesis, though the selectivity and conversion were low. Increasing the catalyst loading to 10 mol% under the same reaction conditions improved these results with the conversion increasing to 55% and the enantioselectivity increasing to 50% (*S*) after 16 hours at room temperature. A study of the literature showed that aluminium based systems require the use of a Lewis basic additive to enhance the activity of the catalyst and therefore, triphenylphosphine oxide (10 mol%) was

chosen and added to a reaction catalysed by 1 mol% of **239**. Immediately there was a substantial improvement in conversion and enantioselectivity of the product; 100% and 67% (*S*) respectively at room temperature after 16 hours. Lowering the reaction temperature in an attempt to increase enantioselectivity proved successful as at 0 ^{o}C, -20 ^{o}C and -40 ^{o}C enantioselectivities of 68%, 75% and 90% (*S*) were obtained respectively, though the conversion decreased. Reactions carried out at -40 ^{o}C resulted in conversions of 60%. Increasing the amount of phosphine oxide additive (20-30 mol%) restored the conversion, however the enantioselectivity decreased to 54% (*S*). Triphenylphosphine oxide has been shown to catalyse cyanohydrin reactions racemically and so by adding more to the system, this competing achiral reaction increases which is reflected in the lowered enantioselectivity, however, lowering the phosphine oxide loading also decreased the enantioselectivity. The reaction temperature of -40 ^{o}C was chosen as the optimal temperature for this system, however the conversion at this temperature using 1 mol% of **239** was low (60%) and so the catalyst loading was increased to 2 mol% giving cyanohydrin product **233** with 80% conversion and an enantioselectivity of 89% (*S*). These conditions were chosen as the optimal reaction conditions; **239** (2.0 mol%), triphenylphosphine oxide (10 mol%), trimethylsilylcyanide (1.2 eq) in dichloromethane at -40 ^{o}C for 16 hours. Pyridine *N*-oxide and tri-octyl phosphine oxide were also tested as additives in a 10 mol% loading giving **233** with 83% conversion, 80% (*S*) enantioselectivity and 73% conversion, 89% (*S*) enantioselectivity respectively, but longer reaction times were required: 48 hours at -40 ^{o}C. These results were still respectable with conversions higher than those obtained using triphenylphosphine oxide, but the enantioselectivity was lower in both cases, by as much as 10% when using tri-octyl phosphine oxide. Also the rate of the reaction when using both of these phosphine oxides was much lower and so triphenylphosphine oxide was chosen as the best phosphine oxide for use in this reaction, due to the faster rates of reaction, availability, and lower cost of the compound. The optimisation results are tabulated in Table 32.

Corey suggested that in cyanohydrin synthesis reactions, the purpose of the triphenylphosphine oxide is to activate the trimethylsilylcyanide by forming species **141,** which is the true cyanting agent (Scheme 44).[139] Aluminium is a weak Lewis acid so coordination of the aldehyde to the aluminium metal centre will be a weak interaction, the consequence of this being that the aldehyde is not strongly activated towards nucleophilic addition evidence of which is seen when using **239** in the absence of cocatalyst as much lower enantiomeric excesses and conversions are achieved. Addition of triphenylphosphine oxide activates the trimethylsiylcyanide in the form of species **141** which can then react with the aldehyde and can be used to explain the results obtained when using different phosphine

oxides. Pyridine-*N* oxide and tri-octylphosphine oxide are less Lewis basic than triphenylphosphine oxide, therefore the trimethylsilylcyanide is not activated as strongly and so the activity of the system decreases.

Table 32; optimisation results obtained using complex **231** in asymmetric cyanohydrin synthesis with benzaldehyde as the reaction substrate.

Entry[a]	$Ph_3P=O$ mol%	Temperature ^oC	Yield %	ee %
1	-	RT	30	30
2	-	RT	55	50
3	10	RT	100	67
4	10	-10	100	68
5	10	-20	100	75
6	10	-40	60	90
7	1	-20	-	-
8	2	-20	-	-
9	5	-20	100	73
10	7	-20	100	77
11[b]	10	-40	80	89

[a] reactions carried out using 1 mol% of **239.**
[b] reaction carried out using 2 mol% of **239.**

$$Ph_3P=O + TMSCN \rightleftharpoons Ph_3P(OTMS)(N=C^{\cdot\cdot})$$
141

Scheme 44: proposed reaction of triphenylphosphine oxide with trimethylsilylcyanide.

A variety of substituted aromatic and aliphatic aldehydes were screened as substrates to investigate the general applicability of complex **239** using the standardised reaction conditions established in earlier studies. The results are shown in Table 33. All aromatic substrates gave consistent enantioselectivities, with electron-rich substrates (Entries 1-7) giving lower conversions as the carbonyl is less electrophilic than benzaldehyde. This reduces the reaction rate and so the cyanide reacts more slowly with the carbonyl. Attempts to increase the conversion were made by increasing the catalyst loading to 3 mol% using *p*-methylbenzaldehyde as the reaction substrate (entry 2) which gave a conversion of 63% and an enantioselectivity of 81% (*S*). Increasing the reaction time to 24 hours did not improve the result further with a conversion of 60% and 85% (*S*) enantioselectivity being obtained (entry 3). Electron-deficient substrates (Entries 8-12) gave higher conversions and

enantioselectivities ranging from 84-90%. In an attempt to increase the enantioselectivity for these more active substrates, the temperature was lowered to -60 ^{o}C, but *p*-trifluoromethylbenzaldehyde (entry 9) gave just 35% conversion and a lower enantioselectivity of 79% (*S*) under these conditions. The aliphatic substrates (Entries 13-16) were more reactive, all giving complete conversion after 16 hours at -40 ^{o}C, however, the enantioselectivities were lower. Lowering the temperature to -60 ^{o}C for pivaldehyde (entry 16) gave complete conversion but a very low enantioselectivity of 37% (*S*). A solvent screen confirmed that dichloromethane was the most compatible solvent with the system. Changing the solvent to more polar and less polar solvents lowered the enantioselectivity of the reaction. Toluene lowered the conversion to 69% but still gave a good selectivity of 89% (*S*). Tetrahydrofuran gave a poor conversion of 23% and a decreased enantioselectivity of 60% (*S*). Acetonitrile gave a conversion of 38% and depressed the enantioselectivity to 73% (*S*). Propylene carbonate gave a conversion of 70% with 77% (*S*) enantiomeric excess at -40 ^{o}C.

^{1}H NMR spectroscopy was used to calculate the enantiomeric excess of *m*- and *p*-methoxybenzaldehyde (entries 6 and 7) according to the procedure of Moon *et al* using benzaldehyde to initially test this method.[140] The silyl protected cyanohydrin was deprotected using concentrated hydrochloric acid, and to the free cyanohydrin, in chloroform, dimethylaminopyridine and (*R*)-mandelic acid were added. The formation of diastereomeric complexes in solution allowed the enantiomeric excess to be calculated by integrating the peaks at 5.30 (*S*) and 5.65 (*R*) ppm for the two diastereomers resulting from the splitting of the single peak corresponding to the CH_{α} protons of the free cyanohydrin. Figure 16 shows the ^{1}H NMR spectrum of racemic mandelonitrile after the application of Moon's procedure.

Applying the same method to the cyanohydrin obtained from *para*-methoxybenzaldehyde gave the ^{1}H NMR spectrum shown in Figure 17. Integrating the peaks at 5.16 (*S*) and 5.22 (*R*) ppm gave an enantiomeric excess of 75% (*S*) with the same analysis being carried out on *meta*-methoxybenzaldehyde which gave the same result. These enantiomeric excesses were lower than those obtained for other electron-rich substrates. The free cyanohydrin is prone to racemisation and therefore some racemisation may have taken place during the deprotection resulting in a lower enantiomeric excess. The remaining enantiomeric excesses were obtained using chiral gas chromatography using the procedure of Kagan.[76] Table 34 shows the retention times of the substrates and Figures 18 and 19 show gas chromatograms of pivaldehyde and *meta*-methylbenzaldehyde as examples of the chiral gas chromatograms obtained from these chiral cyanohydrins.

Table 33; substrate screen using complex **239.**

Entry	R	Conversion %	ee % [e]
1	p-Me	54	83
2[a]	p-Me	63	81
3[b]	p-Me	60	85
4	m-Me	61	96
5	o-Me	88	93
6 [c]	m-OMe	71	75
7 [c]	p-OMe	36	75
8	p-CF_3	100	87
9[d]	p-CF_3	35	79
10	p-F	83	90
11	p-Cl	83	87
12	m-Cl	90	84
13	$C_8H_{17}CHO$	100	37
14	$(CH_3)_3CHO$	91	63
15	CyCHO	100	53
16[d]	CyCHO	100	37

Optimum reaction conditions; **239** (2.0 mol%), triphenylphosphine oxide (10 mol%), trimethylsilylcyanide (1.2 eq) in dichloromethane at -40 ^{o}C for 16 hours unless otherwise stated.

[a] reaction carried out using 3 mol% of **239.**

[b] reaction carried out using 3 mol% of **239** after a reaction time of 24 hours.

[c] enantioselectivities were calculated using ^{1}H NMR.

[d] reaction carried out at -60 ^{o}C.

[e] all cyanohydrins were determined as being the *S* enantiomer.

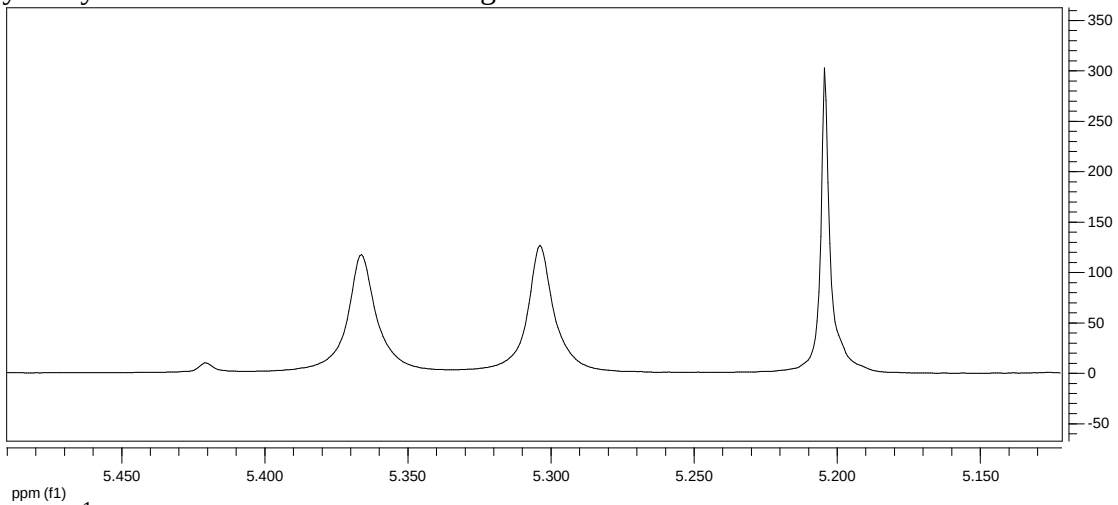


Figure 16: ^{1}H NMR spectrum of racemic mandelonitrile after treatment with dimethylaminopyridine and (*R*)-mandelic acid.

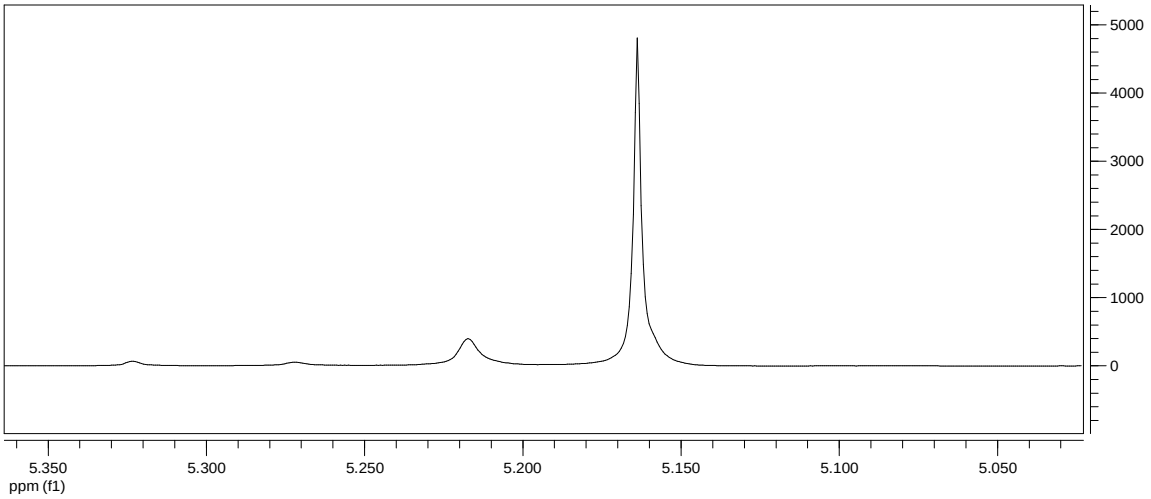


Figure 17: ^{1}H NMR spectrum of the *para*-methoxybenzaldehyde derived cyanohydrin used to obtain the enantiomeric excess.

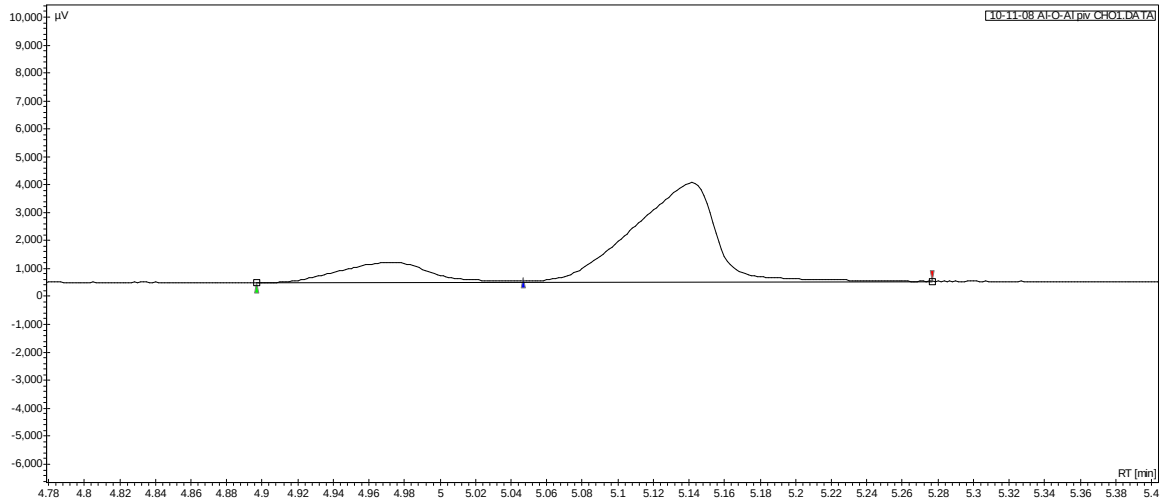


Figure 18: GC trace of the pivaldehyde derived cyanohydrin; GC conditions; initial temperature: 95 ^{o}C; final temperature: 180 ^{o}C; ramp rate: 5.0 ^{o}C/min; flow rate: 2.0 ml/min; column pressure: 10 psi.

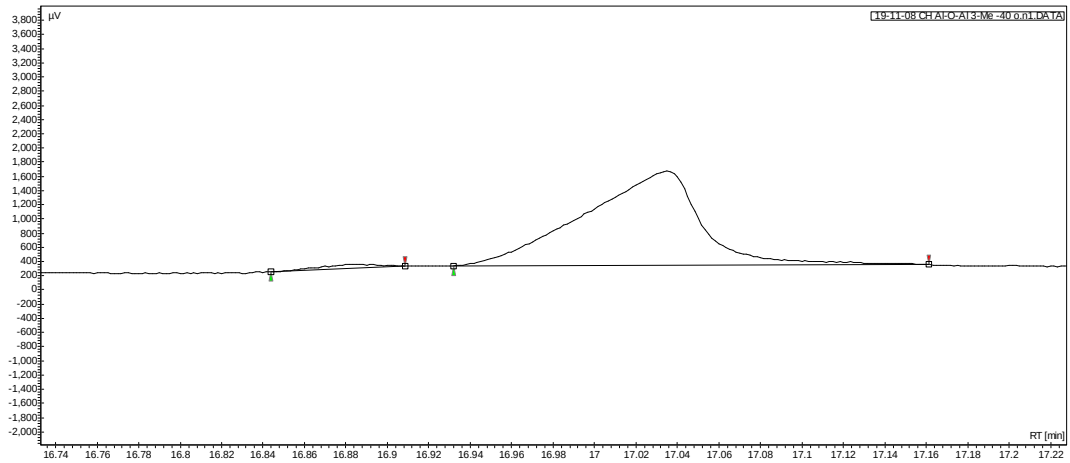


Figure 19: GC trace of *meta*-methylbenzaldehyde derived cyanohydrin. GC conditions: initial temperature: 95 ^{o}C; final temperature: 180 ^{o}C; ramp rate: 5.0 ^{o}C/min; flow rate: 2.0 ml/min; column pressure: 10 psi.

Table 34; retention times for different reaction substrates obtained from chiral gas chromatography.

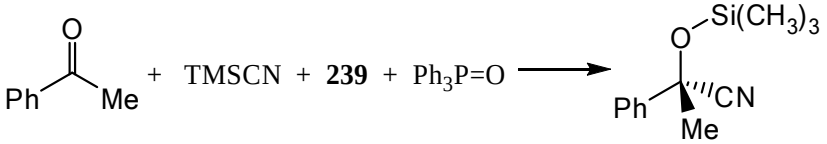
Entry[a]	R	1st peak (min)	2nd peak (min)
1	p-Me	17.38	17.57
2	m-Me	16.96	17.06
3[b]	o-Me	28.72	28.93
4	p-CF_3	14.01	14.33
5	p-F	14.75	14.97
6	p-Cl	19.44	19.63
7	m-Cl	18.97	19.14
8	$C_8H_{17}CHO$	16.17	16.29
9	$(CH_3)_3CHO$	4.95	5.08
10	CyCHO	13.97	14.13

[a] GC conditions; initial temperature: 95 ^oC; final temperature: 180 ^oC; ramp rate: 5.0 ^oC/min; flow: 2.0 ml/min; column pressure: 10 psi.

[b] GC conditions; initial temperature: 95 ^oC; final temperature: 180 ^oC; ramp rate: 2.0 ^oC/min; flow 2.0 ml/min; column pressure: 10 psi.

4.1.2 Cyanation of Ketones Using Alumium(salen) Dimer 239.

Due to the high activity of complex **239** with aromatic and aliphatic aldehyde substrates, ketones were then chosen for study. Ketones are less reactive than aldehydes due to the lower electrophilicity of the carbonyl and are known to be difficult substrates even with the most active catalysts. This is a result of the inductive effect from the groups directly bonded to the carbon of the carbonyl group and these groups can also hinder the approach of any nucleophile such as cyanide so attack becomes more difficult. Acetophenone **240** was chosen as the test substrate and initial reactions used the optimised conditions established for benzaldehyde (Scheme 45).



240 **241**

Scheme 45: reaction scheme for cyanohydrin synthesis using ketones and complex **239**

With a catalyst loading of 2 mol% of complex **239,** compound **241** was obtained with a low conversion of 12% after a reaction time of 16 hours at -40 ^oC. Increasing the temperature to room temperature and increasing the reaction time to 48 hours resulted in an increase of the conversion to 85% and the enantioselectivity was confirmed at 56% (*S*). Figure 20 shows the ^1H NMR spectrum of compound **241,** in the presence of DMAP and (*R*)-mandelic acid,

using the peaks at 2.69 and 2.71 ppm for integration to give the enantiomeric excess. This method was used on all reactions using ketone substrates to obtain the enantiomeric excesses.

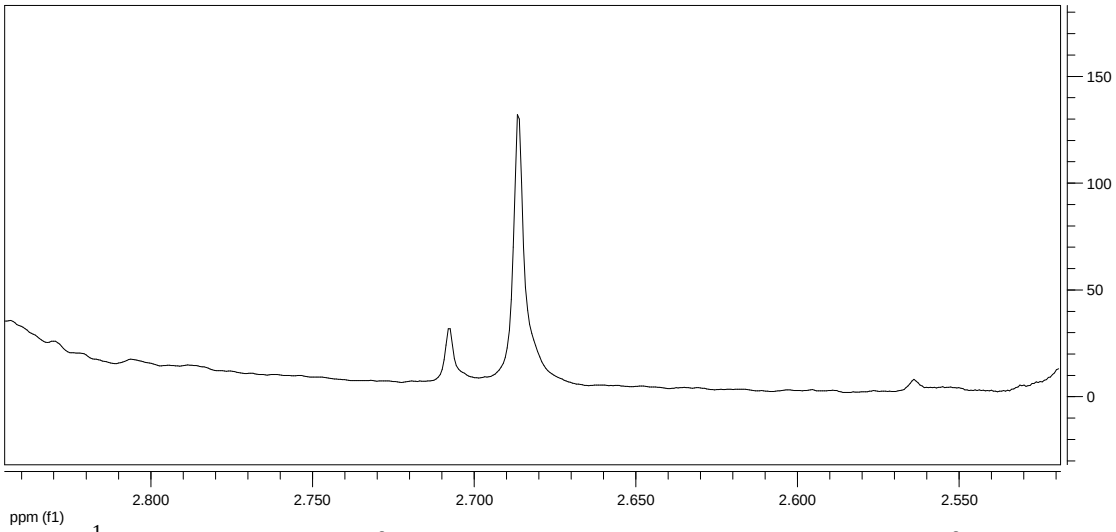


Figure 20: ^{1}H NMR spectrum of acetophenone derived cyanohydrin **241** after treatment with dimethylaminopyridine and (*R*)-mandelic acid.

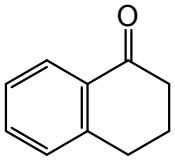
To further improve on these results the catalyst loading was increased to 4 mol% resulting in no further improvement in the conversion (77%) or enantioselectivity (54% (*S*)) As predicted, the cyanide ion cannot attack the carbonyl as easily as with aldehyde substrates which is exemplified by these lower conversions and enantiomeric excesses and so higher catalyst loadings and higher reaction temperatures are needed when using ketones as substrates. Substrate screening showed the same trends as observed with substituted aromatic aldehydes; electron-deficient ketones showed higher reactivity and electron-rich substrates showed lower reactivity, Table 35.

Table 35; substrate screen using ketone substrates with complex **239**.

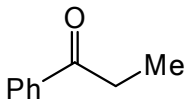
Entry	R	Conversion %	ee %	*R*/*S*
1	p-Cl	86	68	*S*
2	m-Cl	100	65	*S*
3	p-Br	80	62	*S*
4	p-F	83	65	*S*
5	p-Me	47	64	*S*
6	p-OMe	27	59	*S*
7	2-pentanone	100	40	*S*
8	Tetralone	21	-	-
9	Propiophenone	0	-	-

Electron-deficient substrates (Entries 1-4) gave cyanohydrin product with conversions ranging from 80-100% with consistent enantioselectivities of 62-68% (*S*) although these were lower than the enantioselectivities obtained with the equivalent aldehyde substrates. Electron-rich substrates (Entries 5-6) gave lower conversions, with *p*-methoxyacetophenone giving a conversion of just 27%, but still a respectable enantioselectivity of 59% (*S*) and 2-pentanone (Entry 7) gave 100% conversion but a lower enantioselectivity than that obtained using aromatic substrates, 40% (*S*).

The substituted aromatic ketone substrates screened were all methyl ketones, therefore tetralone **242** (Entry 8) and propiophenone **243** (Entry 9) were screened giving conversions of 21% and 0% respectively. Attempts to gain an enantiomeric excess for the tetralone derived cyanohydrin proved unsuccessful using both chiral gas chromatography and ^{1}H NMR spectroscopy. This lowered reactivity when increasing the size of the ketone substituents is commonly seen when using ketone substrates. The consequences of increasing the size of the substituent (in the case of **243**; from a methyl to an ethyl group) are that the cyanide finds it increasingly difficult to approach the carbonyl group due to steric interactions and so the carbonyl becomes blocked by the increasing size of the groups on the carbonyl group. The reactivity of the carbonyl also decreases due to the increased inductive effect from the ethyl group which is reflected in the unsuccessful attempt of reacting **243** with trimethylsilylcyandie using complex **239** as a chiral catalyst. In the case of **242**, the increased size of the substituent is held in a cyclic structure therefore allowing some access of the cyanide to the carbonyl however some significant steric interactions are still experienced as the conversion using this substrate was much lower than those obtained using methyl ketones.



242



243

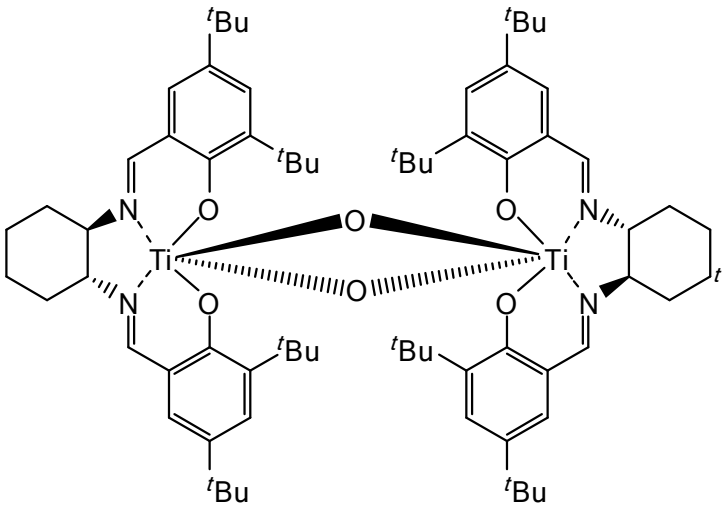
4.1.3 Using complex 239 in the Strecker Reaction.

Complex **239** was also used in a Strecker reaction, using 10 mol% of complex **239** in toluene at -40 ^{o}C in the absence of triphenylphosphine oxide. *N*-Benzylbenzylimine was cyanated using trimethylsilylcyanide as the cyanide source and methanol as the reaction additive for three hours, giving aminonitrile product with complete conversion, however the product was found to be racemic. Due to the absence of phosphine oxide there was no background reaction taking place catalysed by the phosphine oxide and so complex **239** was

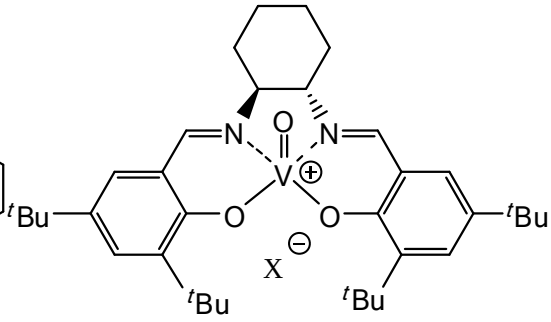
shown to be inactive in the Strecker reaction as indicated by the lack of stereoinduction from the chiral catalyst. Adding phosphine oxides to the reaction did not improve on these findings as triphenylphosphine oxide and diphenylmethylphosphine oxide both gave racemic product with complete conversion, though in these cases catalysis by the phosphine oxide was probably responsible for the complete conversion to racemic aminonitrile product. Another possibility was reaction on work-up when passing the crude material through a silica plug or on warming the reaction to room temperature as shown in previous work.

5.1 Kinetic Studies of the Dimeric Aluminium(Salen) System

Having established that aluminium(salen) dimer **239** was an active catalyst in cyanohydrin synthesis, a thorough study of the reaction kinetics was undertaken. The corresponding vanadium[122] and titanium[141] based systems have all been previously studied and rate equations and reaction mechanisms determined for each system. The reaction mechanisms were more complex than initially anticipated with complex **41** giving a rate equation of the form; rate= k[TMSCN][**41**]$^{1.3}$, displaying zero order kinetics with respect to benzaldehyde. Complex **132** gave a rate equation of the form; rate= k[TMSCN][PhCHO][**132**]$^{1.2}$ and complex **110** gave a rate equation of the form; rate = k[TMSCN][PhCHO][**110**]$^{0.64}$. The non-integer values obtained for the orders with respect to the catalysts suggested that the structure of the active catalysts were not as initially anticipated, with a complex monomer/dimer equilibria existing in the solution throughout the duration of the catalytic cycles. This prompted an indepth study of the kinetics of catalyst **239** using UV analysis.



41

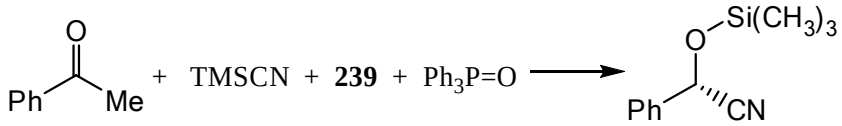


110) X= $EtOSO_3$
132) X= NCS^-

The kinetics of the system were studied using UV spectroscopy monitoring the disappearance of the carbonyl bond of the aldehyde as benzaldehyde absorbs at 246 nm which is a convienient wavelength to follow as there is no overlap with the absorbance from other species in the reaction. Samples were removed at appropriate time intervals during the course of the reaction and scanned at 246 nm. For a first order reaction; $[A] = [A]_0e^{-kt}$ therefore; $\ln[A]/[A]_0 = -kt$. A plot of ln[A] against time will give a straight line where the slope gives the negative rate constant. For a second order reaction; $1/[A] = 1/[A]_0 + kt$. A plot of 1/[A] against time will give a straight line with a slope that corresponds to the positive rate constant. This analysis is only valid when the concentrations of each reactant are equal (rate = $k[A]^2$) so for a more accurate kinetic analysis a different approach should be used. Revising the second order rate equation gives $\ln(([TMSCN]_0[PhCHO])/([PhCHO]_0[TMSCN])) = kt([TMSCN]_0-[PhCHO]_0)$. Therefore plotting $1/([PhCHO]_0).\ln(([TMSCN]_0.[PhCHO])/([TMSCN].[PhCHO]_0))$ against time will give a plot with the gradient being equal to the more accurate second order rate constant. For the reaction shown in Scheme 46, using complex **239** as catalyst, a rate equation can be written as; rate= $k[TMSCN]^a[PhCHO]^b[\mathbf{239}]^c[Ph_3P=O]^d$. Complex **239** and triphenylphosphine oxide act as catalysts and so their concentrations remain constant throughout the duration of the reaction, therefore the rate equation can be simplified to; rate= $k'[TMSCN]^a[PhCHO]^b$, where $k'= k[\mathbf{239}]^c[Ph_3P=O]^d$. Simplifying the rate equation means that the order with respect to trimethylsilylcyanide and benzaldehyde can be determined from initial kinetic experiments. For the reaction shown in Scheme 46; first and second order kinetics plots are shown in Figures 21 and 22 respectively. Figure 21 shows how the data fits overall first order kinetics as a straight line is obtained with a first order rate constant of 0.0016 s^{-1}. Figure 22, derived from the same data as used for Figure 21, demonstrates how the reaction does not fit second order kinetics. Figure 23 shows the more complex second order kinetic analysis, again showing a poor correlation to second order kinetics. To establish which component of the reaction was responsible for this first order behaviour a number of reactions were carried out varying the concentrations of trimethylsilylcyanide and benzaldehyde in the reaction and monitoring the effect on the rate of the reaction. The concentration of trimethylsilylcyanide was halved and doubled and the reaction repeated in each case and the consumption of benzaldehyde was monitored. A clear dependence of the reaction rate on the trimethylsilylcyanide concentration is shown in Figure 24 as the rate varies as the trimethylsilylcyanide concentration is varied. To confirm zero order kinetics with respect to benzaldehyde, the equivalent experiment was carried out; changing the concentration of benzaldehyde and monitoring the consumption of

trimethylsilylcyanide. No change in the rate is observed on changing the concentrations of benzaldehyde, clearly shown in Figure 25.

The order with respect to trimethylsilylcyanide and benzaldehyde were shown to be a = 1 and b = 0 (rate = k'[TMSCN]) respectively. The zero order dependence on benzaldehyde concentration can be interpreted in two ways; the aldehyde is only involved in the reaction after the rate determining step, or a pre-equilibrium between the catalyst and the aldehyde forms an aldehyde-catalyst complex. If this is the case then the concentration of the aldehyde-catalyst complex would be of interest rather than the aldehyde concentration and since the aldehyde is present in large excess compared to the catalyst, the concentration of aldehyde will not change on formation of the complex. To establish if such a complex was being formed, ^{1}H and ^{13}C NMR experiments were undertaken. Coordination of the carbonyl to the metal centre would cause a downfield shift of the original aldehyde peak at 9.99 ppm as the aldehyde proton will become deshielded due to electron movement away from the carbonyl group. Benzaldehyde and **239** were mixed together in equimolor amounts in deuterated chloroform and the ^{1}H and ^{13}C NMR spectra obtained. Free benzaldehyde was shown to appear at 9.99 ppm in the ^{1}H spectrum and at 192 ppm in the ^{13}C spectrum. Adding **239** to the solution had no effect on the chemical shifts in either case offering no evidence for the formation of an aldehyde-catalyst complex in solution.



Scheme 46: asymmetric cyanohydrin synthesis using ketones as the reaction substrate.

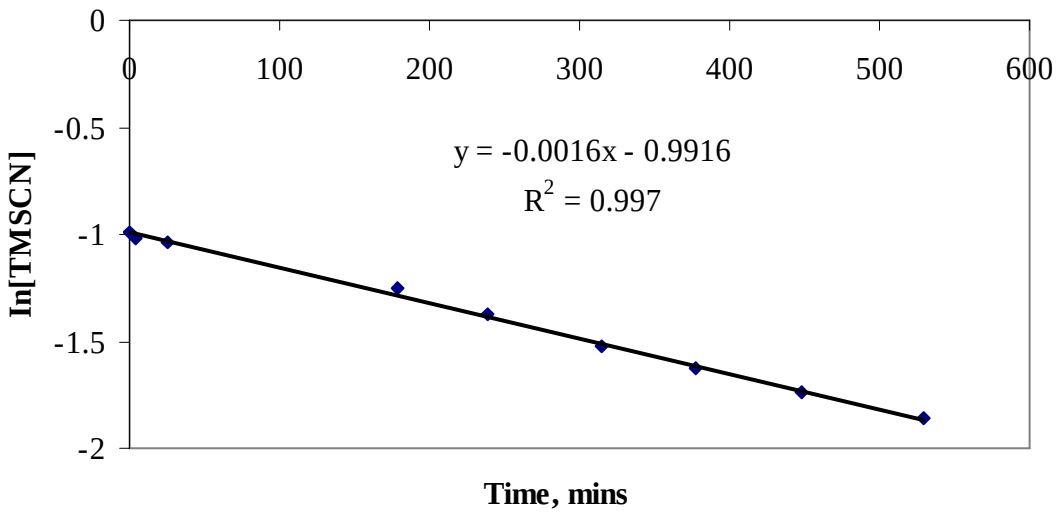


Figure 21; [**239**] = 0.005 M; [$Ph_3P=O$] = 0.025 M; [PhCHO] = 0.25 M; [TMSCN] = 0.40 M, in 1.75 ml of dichloromethane at 0 ^{o}C.

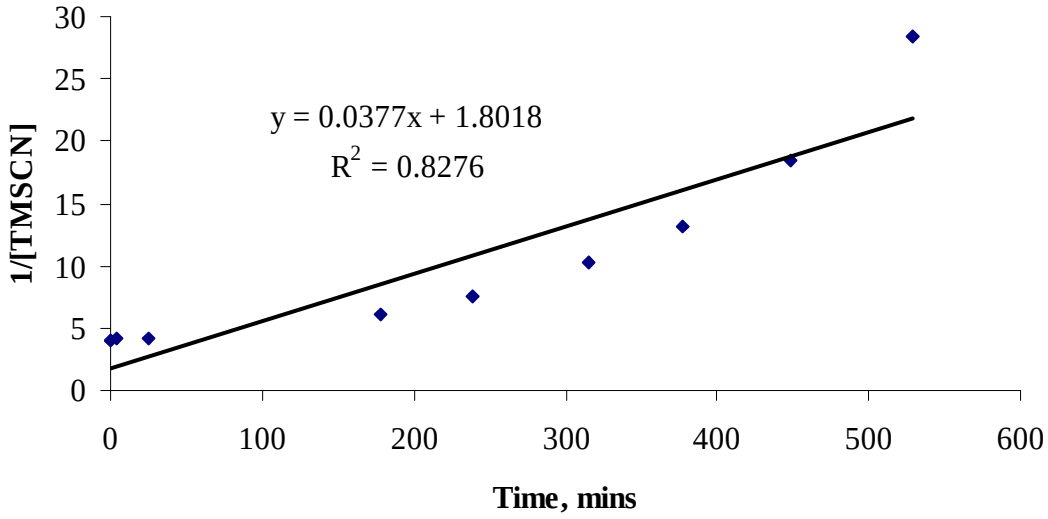


Figure 22: kinetics carried out under the same reaction conditions used for **Figure 21**

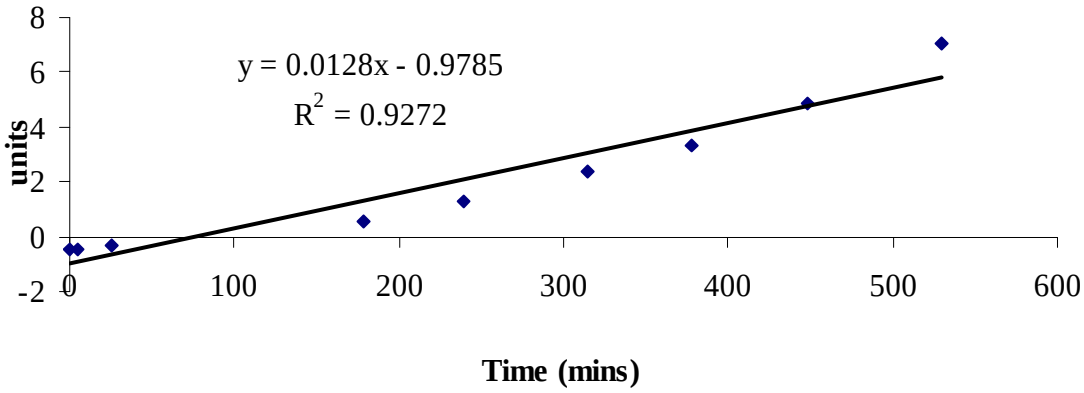


Figure 23: plot of $1/([PhCHO]_0).ln(([TMSCN]_0.[PhCHO])/([TMSCN].[PhCHO]_0))$ against time.

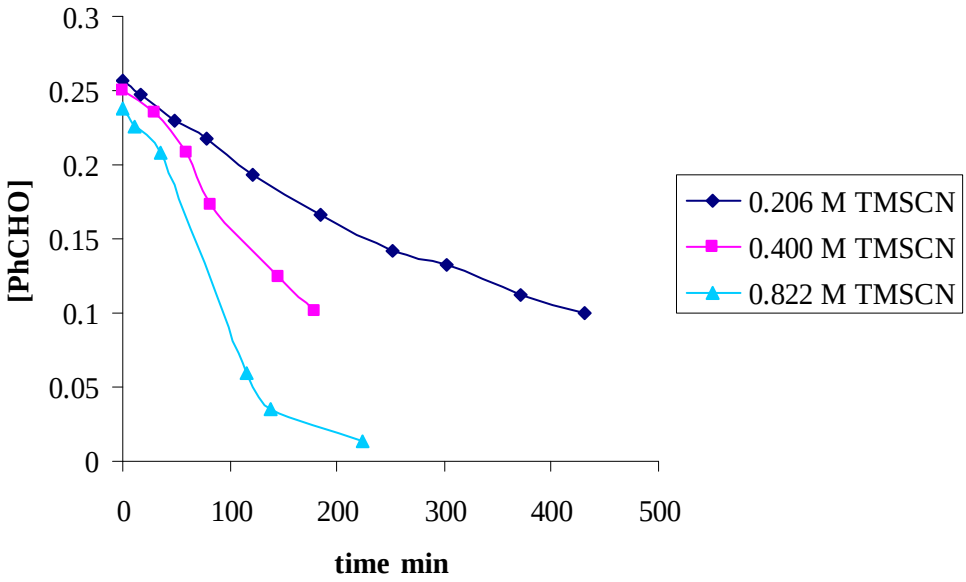


Figure 24; [**239**] = 0.0005 M; [Ph_3P=O] = 0.025 M; [PhCHO] = 0.25 M, in 1.75 ml of dichloromethane at 0 ^oC

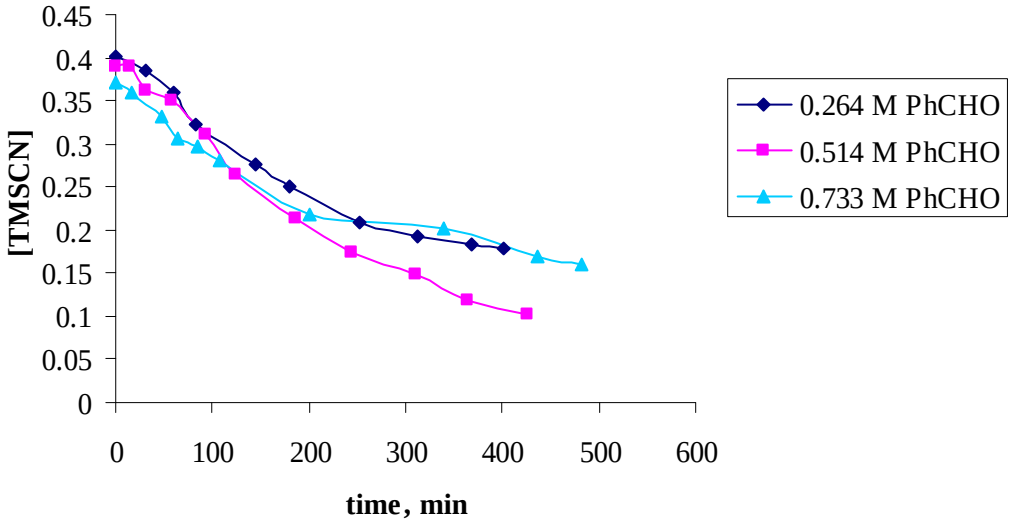


Figure 25; [**239**] = 0.0005 M; [$Ph_3P=O$] = 0.025M; {TMSCN] = 0.40 M, in 1.75 ml of dichloromethane at 0 ^oC.

To study the kinetics of the system further, the orders with respect to **239** and triphenylphosphine oxide were investigated. To determine the order with respect to these components a series of experiments were carried out varying the concentration of the component under investigation and keeping all other reactant concentrations constant. The order with respect to **239** or triphenylphosphine oxide can be determined from the rate equation; rate = k'[TMSCN] where k' = k[**239**]^c[$Ph_3P=O$]^d. Therefore log(k') = log(k) + c.log[**239**] + d.log[$Ph_3P=O$]. A plot of the logarithm of the apparant rate constant against the logarithm of the concentration of **239** or triphenylphosphine oxide will therefore give a straight line with the slope of the straight line being equal to the order with respect to either **239** or triphenylphosphine oxide. Carrying out this analysis for **239** gave the result shown in Figure 26. A plot of the logarithm of **239** concentration against the logarithm of the apparant rate constant gave a plot with a slope equal to 0.80. It was suspected that complex **239** retained its bimetallic structure in the catalytic cycle and if this was the case then the order with respect to **239** should be exactly equal to one. If the order is exactly one, then a plot of **239** concentration against apparent rate constant (k') will produce a straight line since k' = k[**239**][$Ph_3P=O$]^d. Figure 27 shows this analysis with a straight line being obtained, confirming first order kinetics with respect to complex **239** and not an order of 0.80. Non-integer orders for reactions are possible for catalysts if monomeric and dimeric species are present in a reaction mechanism, as seen with the titanium(salen) and vanadium(salen) complexes in cyanohydrin synthesis. A plot of the logarithm of reaction rate against the logarithm of triphenylphosphine oxide concentration also gave a straight line with a slope equal to 0.95 (Figure 28). As with complex **239** the same analysis was conducted by plotting

the concentration of triphenylphosphine oxide against the apparent rate constant (k'). As seen in Figure 29, a straight line was again obtained confirming first order kinetics with respect to triphenylphosphine oxide.

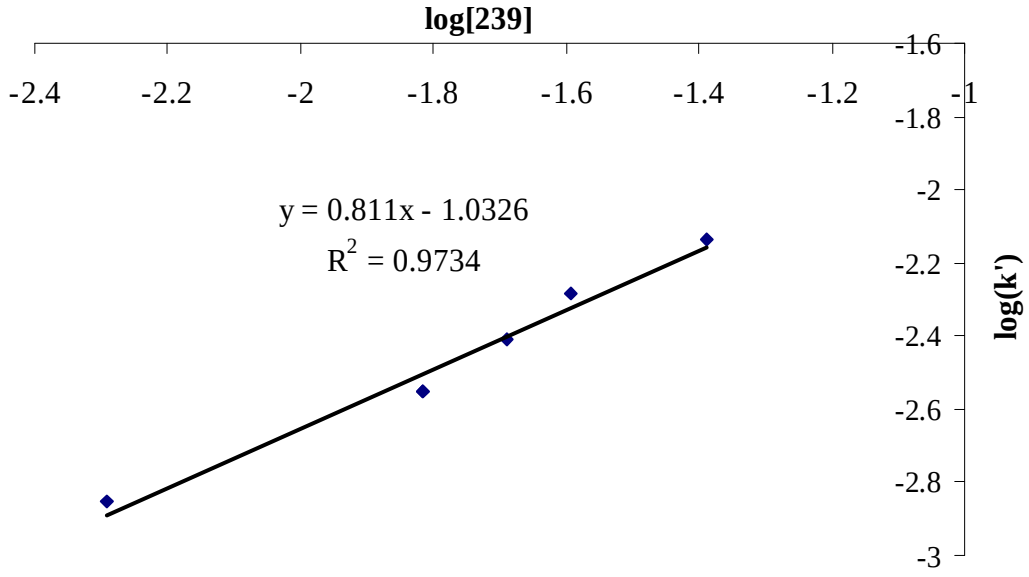


Figure 26; [$Ph_3P=O$] = 0.0025 M; [PhCHO] = 0.25 M; [TMSCN] = 0.40 M, in 1.75 ml of dichloromethane at 0 ^oC.

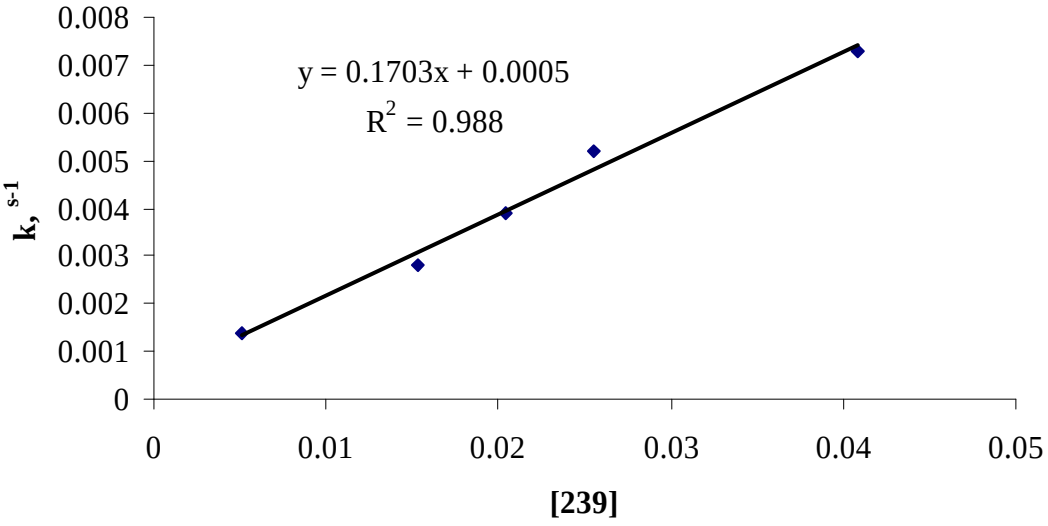


Figure 27; [$Ph_3P=O$] = 0.025 M; [PhCHO] = 0.25 M; [TMSCN] = 0.40 M, in 1.75 ml of dichloromethane at 0 ^oC.

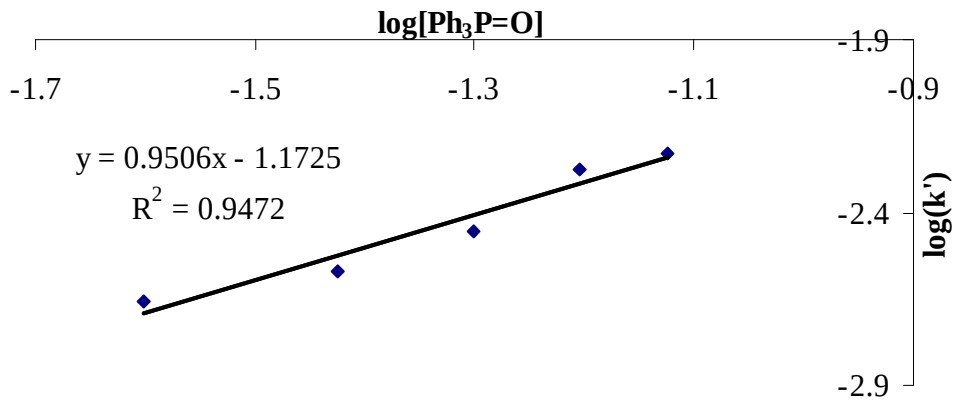


Figure 28; [**239**] = 0.0005 M; [PhCHO] = 0.25 M; [TMSCN] = 0.40 M, in 1.75 ml of dichloromethane at 0 ^{o}C.

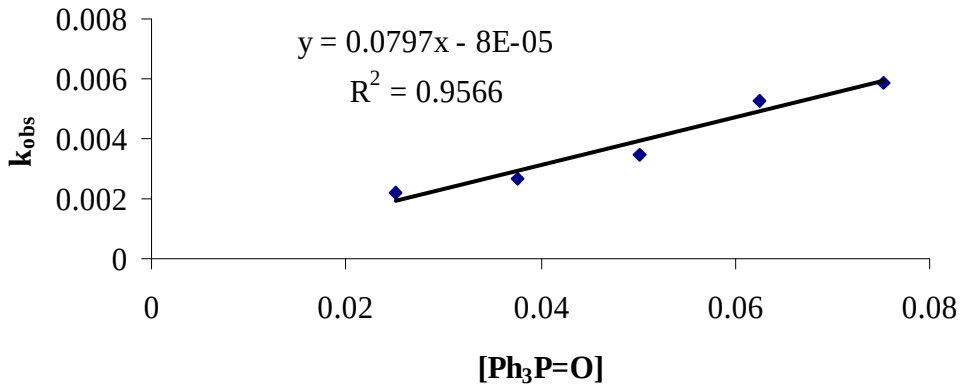
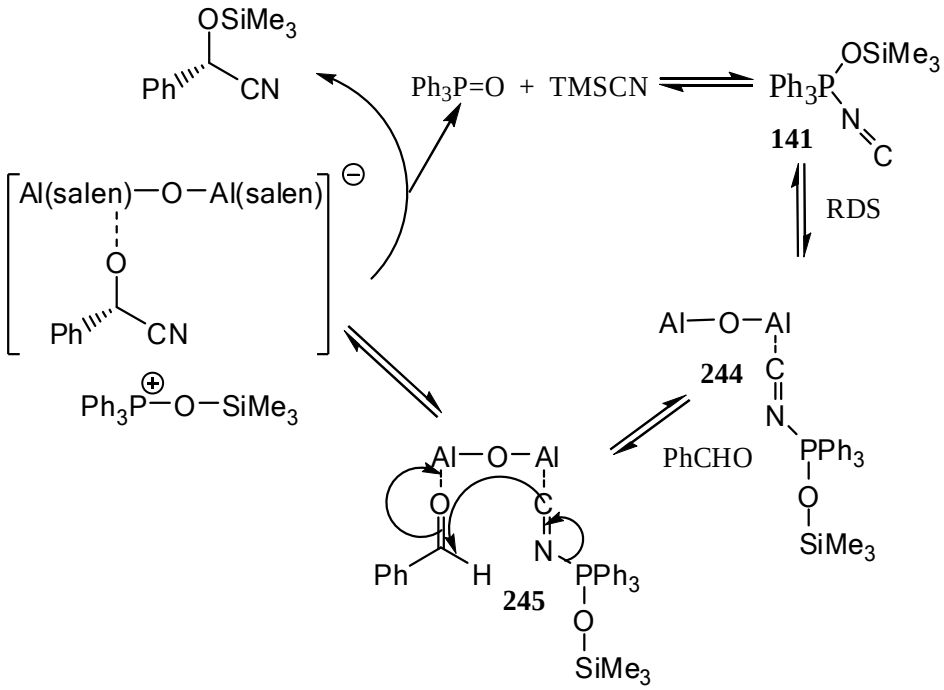


Figure 29; [**239**] = 0.0005 M; [PhCHO] = 0.25 M; [TMSCN] = 0.40 M, in 1.75 ml of dichloromethane at 0 ^{o}C.

A full rate equation can therefore be written for cyanohydrin synthesis catalysed by complex **239**; rate = k[TMSCN][**239**][Ph_3P=O], and zero order in benzaldehyde. Based on this kinetic data and literature precedent, a catalytic cycle for asymmetric cyanohydrin synthesis catalysed by complex **239** was proposed and is shown in Scheme 47. Triphenylphosphine oxide acts as a Lewis base and reacts with the trimethylsilyl cyanide to form species **141** which then coordinates to complex **239** via one of the aluminium atoms to form intermediate **244** in the rate determining step of the reaction. Benzaldehyde can then coordinate to the second aluminium atom to form species **245** which is followed by an intramolecular transfer of cyanide to the carbonyl group. The new stereocentre is established within the chiral environment of the salen ligands with the trimethylsilyl protected cyanohydrin being released, regenerating the aluminium catalyst and triphenylphosphine oxide and so the catalytic cycle can continue.

Other possible reaction mechanisms may involve the direct interaction of the trimethylsilylcyanide with the aluminium catalyst which would also result in a rate equation that is first order in trimethylsilylcyanide concentration. If this is the case, then species **141** would not be involved in the reaction mechanism and the role of the triphenylphosphine oxide would again come into question.[139] Triphenylphosphine oxide may play an alternative role in the transition state of the reaction, albeit the role of the additive has been demonstrated to be crucial as without the Lewis basic additive the rate of the reaction and the enantioselectivity are greatly decreased. Direct binding to one of the aluminium centres of the catalyst may explain the first order kinetics observed with triphenylphosphine oxide, which may then influence the arrangement of the transition state which in turn affects the selectivity of the catalyst. What is clear from these results is that no one single reaction mechanism can be accepted as accurate. Due to the evidence put forward by Corey for the generation of complex **141** it is likely that there is some interaction between the triphenylphosphine oxide and trimethylsilylcyanide.[139] Attempting the same cyanohydrin synthesis using complex **239** under the same reaction conditions, but substituting trimethylsilylcyanide with ethyl cyanoformate or potassium cyanide, rendered the system inactive. Adding triphenylphosphine oxide to these systems gave complete conversion to the cyanohydrin product but this was shown to be racemic. Racemic catalysis via the triphenylphosphine oxide is almost certainly the reason for this. This raised the possibility that the first order kinetics shown for triphenylphosphine oxide could be as a result of the racemic reaction, however this was quickly dismissed based on the enantioselectivities obtained in the substrate screen, (Table 33) as the high enantiomeric excesses show that the reaction was proceeding almost exclusively via the asymmetrically catalysed reaction.

For the purpose of this study, it was concluded that the most likely mechanistic pathway for this system was the mechanism shown in Scheme 47, nevertheless alternative mechanisms should not be ruled out. There may also be the possibility that there are two or more different reaction mechanisms in operation thoughout the duration of the reaction. Current work involving the use of the vanadium(salen) chloride complex **118** and **132** in cyanohydrin synthesis using benzaldehyde as the reaction substrate, appears to show that there may be more than one reaction mechanism involving these catalysts and the same can not be ruled out for the aluminium based catalyst.



Scheme 47: proposed mechanistic cycle for complex **239** in asymmetric cyanohydrin synthesis.

6.1 Hammett Study of Complex 239.

Having carried out an extensive kinetic analysis of asymmetric cyanohydrin synthesis catalysed by complex **239**, a Hammett study was undertaken to investigate the effect that a substituent (X), on the aromatic ring of an aldehyde substrate would have on the rate of reaction. Hammett studies are used to investigate the effect of this substituent on an equilibrium or the rate of a reaction, where the unsubstituted aromatic species (X=H) is used as a reference.[142] The Hammett equation is as follows;

$$\log(k_X/k_H) = \sigma.\rho \quad (\mathbf{1})$$

Equation **1** relates the relative rate of reaction (k_X/k_H) between a substituted aromatic substrate and the unsubstituted substrate to the substituent constant (sigma, σ,) and the reaction constant (rho, ρ). The substituent constant is a predetermined parameter that numerically represents the electronic effect a substituent has on the substrate. Generally, electron-withdrawing substituents have a positive substituent constant and electron-donating substituents have a negative substituent constant and so sigma is a measure of the substituents ability to affect the electronic environment of a reaction system. Values for the substituents used in this project are shown in Table 37. Substituent constant values are determined using the dissociation of benzoic acid in water as a standard (Scheme 48). Electron-withdrawing substituents increase the dissociation constant of benzoic acid by

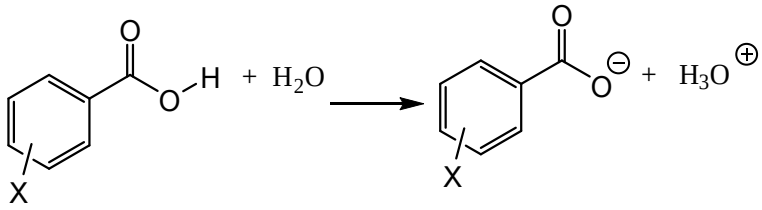
making the proton more acidic and electron-donating substituents decrease the dissociation constant of benzoic acid by making the proton less acidic and so the substituent constant is defined as the logarithm of K_0 (dissociation constant for unsubtituted benzoic acid) divided by K_X (the dissociation constant for substituted benzoic acid). A Hammett study measures the change in the rate of a reaction when the substituent on the aromatic ring is changed. Plotting $\log(k_X/k_H)$ against sigma gives a Hammett plot where the slope of the graph is equal to the reaction constant and the magnitude of the reaction constant depends upon the reaction itself and expresses the amount of charge build up in the transition state of a reaction. There are four conclusions that can be drawn from a Hammett plot each determined by the magnitude of the rho value;

1) $\rho > 1$: the reaction rate is strongly influenced by the substituents of the aromatic ring and a negative charge is generated in the reaction.

2) $\rho > 0 \leq 1$: the reaction rate is less strongly influenced by the substituents of the aromatic ring and a negative charge it generated in the reaction.

3) $\rho = 0$: the reaction rate is not influenced by the substituents on the aromatic ring

4) $\rho < 0$: a positive charge is generated in the reaction.



Scheme 48: dissociation of benzoic acid in water.

A Hammett study of the cyanation of aldehydes using complex **239** as catalyst was conducted using a range of substrates (Table 36). The same method used for previous kinetic studies was employed here with samples being removed manually from a reaction and quenched into dichloromethane. The UV absorbance was measured at relevant time intervals at appropriate wavelengths. Table 36 shows the rate constants obtained for each substrate, along with the sigma values.

Table 36; reaction rates obtained from the Hammett analysis with a variety of *meta* and *para* substituted aromatic substrates.

Substrate[a]	σ	k_x [b]	k_x' [b]	Average k_x [a]
p-H	0.00	-0.00150	-0.00160	-0.00155
m-Cl	0.37	-0.00240	-0.00190	-0.00215
p-Cl	0.23	-0.00210	-0.00200	-0.00205
p-F	0.06	-0.00190	-0.00240	-0.00215
m-F	0.34	-0.00330	-0.00280	-0.00305
p-Br	0.23	-0.00180	-0.00110	-0.00145
p-CF_3	0.53	-0.00240	-0.00210	-0.00215
m,p-diCl	0.60	-0.00170	-0.00190	-0.00180
m,m-diF	0.68	-0.00250	-0.00350	-0.00300
m-Me	-0.06	-0.00150	-0.00170	-0.00160
p-Me	-0.14	-0.00160	-0.00150	-0.00155
m,p-diMe	-0.20	-0.00100	-0.00120	-0.00115
p-$O(CH_3)_3$	-0.27	-0.00080	-0.00100	-0.00090
p-OMe	-0.14	-0.00070	-0.00060	-0.00065
p-SMe	0.00	-0.00110	-0.00130	-0.00120

[a] kinetic reaction conditions; 2 mol% **239**, 10 mol% $Ph_3P=O$, at 0 ^oC in dichloromethane.
[b] all reactions were duplicated and the average was calculated for use in the Hammett plot.

The substituent seemed to be having only a small effect on the reaction rate for cyanohydrin synthesis catalysed by complex **239** as judged by the reaction constant of 0.38 obtained from the slope of the graph shown in Figure 30. This can be interpreted as the aldehyde not strongly interacting with complex **239**. Previous research has shown that the addition of triphenylphosphine oxide leads to an increase in the rate of the reaction and an increase in enantioselectivity but triphenylphosphine oxide also has the ability to react with trimethylsilylcyanide to generate the isocyanide species **141** the formation of which may be responsible for the catalysis in this catalytic system.[80] Only when comparing the data obtained for complex **239** to other metal(salen) catalysts studied in cyanohydrin synthesis do mechanistic differences become more apparent. Table 37 shows the reaction constant values obtained for other metal(salen) catalysts obtained by other group members.

Table 37; reaction constants obtained from Hammett studies using complexes **239 132, 110** and **41**.

Catalyst	$Ph_3P=O$, mol%	Rho, ρ
239	10	0.38
132	-	1.57
110	-	1.87
41	-	2.37

Two processes within the catalytic cycle are crucial for high conversions and high enantioselectivity;

1) The Lewis acidity of the metal centre of the catalyst
2) The nucleophilicity of the oxygen of the carbonyl, influenced by the substituents on the aromatic ring of the substrate. The more electron-rich the aldehyde, in the case of electron-donating substituents, the more electrophilic the oxygen. The opposite argument is true for electron-deficient aldehydes.

In the case of complex **239**, a Hammett plot was obtained with a rho value of 0.38 (Figure 30). If exclusively Lewis basic catalysis was occurring in the reaction mechanism, a reaction constant of zero would be expected as no activation of the aldehyde by the Lewis acidic metal would be taking place and so changing the substituent on the aromatic ring would not have an effect on the rate of the reaction. Aluminium is a weaker Lewis acid than vanadium or titanium, therefore coordination of the aldehyde to the aluminium atom will be weaker with all substrates, however there is evidence in the Hammett plot to suggest that some coordination is taking place albeit only a weak coordination, as the rate is seen to vary as the substituents are varied. Electron-deficient substrates are seen to react with at a greater rate than electron-rich substrates (Table 36). This is consistant with the nucleophilic cyanide anion attacking the electrophilic carbonyl, as electron-deficient substrates will make the carbonyl more electrophilic and so more reactive. The opposite argument is true for electron-rich substrates. Due to the weak coordination of the carbonyl oxygen to the aluminium, the substituents on the aromatic ring can not exert their full electronic influence as there is no pathway for the electron density to move though the transition state so electron movement towards the carbonyl is less pronounced which is suggested by the small rho value.

The main role of complex **239** in this reaction is therefore to provide a chiral environment for the asymmetric transfer of cyanide rather than to solely activate the aldehyde. The catalytic system using complex **239** is governed predominantly by Lewis

basic catalysis. Triphenylphosphine oxide reacts with trimethylsilylcyanide to generate a more reactive species, possibily in the form of species **141** which can then go on to react with the weakly activated substrate and asymmetrically deliver the cyanide to the carbonyl group. These findings are also consistent with the results obtained when screening ketone substrates. Ketones coordinate less strongly than aldehydes to the metal centre of the catalyst. The kinetic and Hammett study have shown this coordination to be less important for complex **239** so the ability of the substrates to coordinate to the metal centre is not as crucial as with other catalysts. The Lewis base catalysis from the triphenylphosphine oxide allows the ketone substrates to be cyanated although these substrates were shown to be even less reactive than aldehydes, as longer reaction times are required along with higher reaction temperatures.

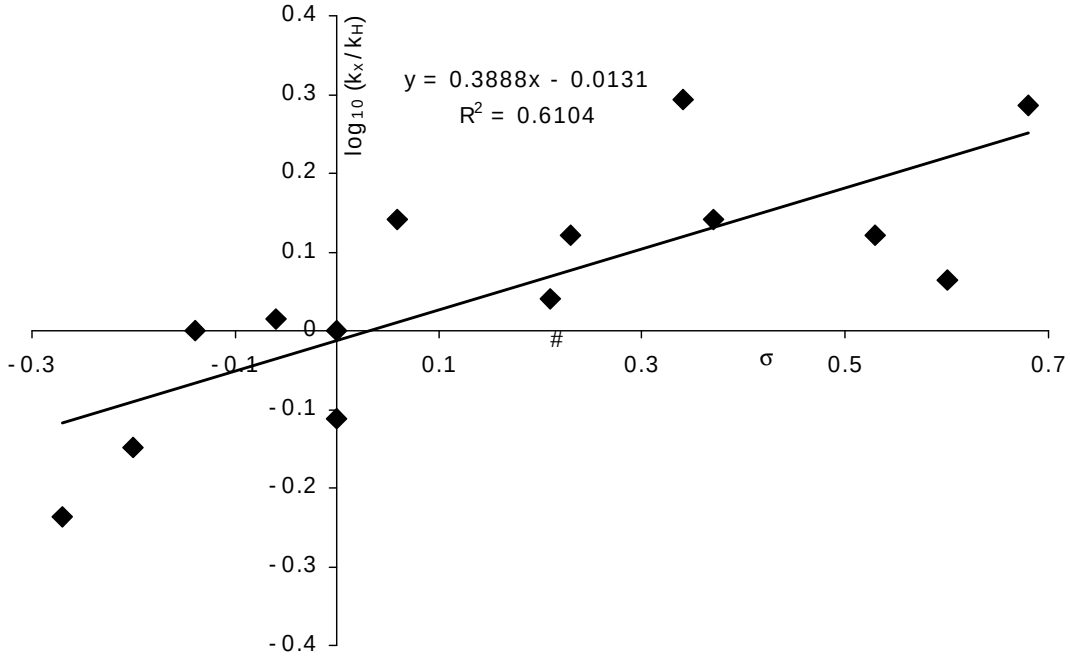


Figure 30; [**239**] = 0.0005 M; [Ph_3P=O] = 0.025 M; [TMSCN] = 0.40 M; [RCHO] = 0.25 M in 1.75 ml of dichloromethane at 0 ^oC.

The data for complex **41** can be fitted to a single straight line with a larger reaction constant of 2.37 (Figure 31) suggesting that the substrates have a large influence on the reaction rate. As titanium is a stronger Lewis acid than aluminium, co-ordination of the aldehyde will be strong for all aldehydes and so the substituents can exert their full electronic influence on reactivity of the carbonyl.[45] As the aldehyde becomes coordinated, electron density is pulled away from the carbonyl towards the metal centre therefore making the aldehyde more electrophilic and more reactive towards the nucleophilic cyanide ion and so this system is governed by Lewis acid catalysis. Electron donating substituents will bind more strongly to the Lewis acid as the substituent increases the nucleophilicity of the

carbonyl oxygen however this increased electron density in the carbonyl will also repel the incoming cyanide anion and so the overall effect is that the reaction reate decreases.

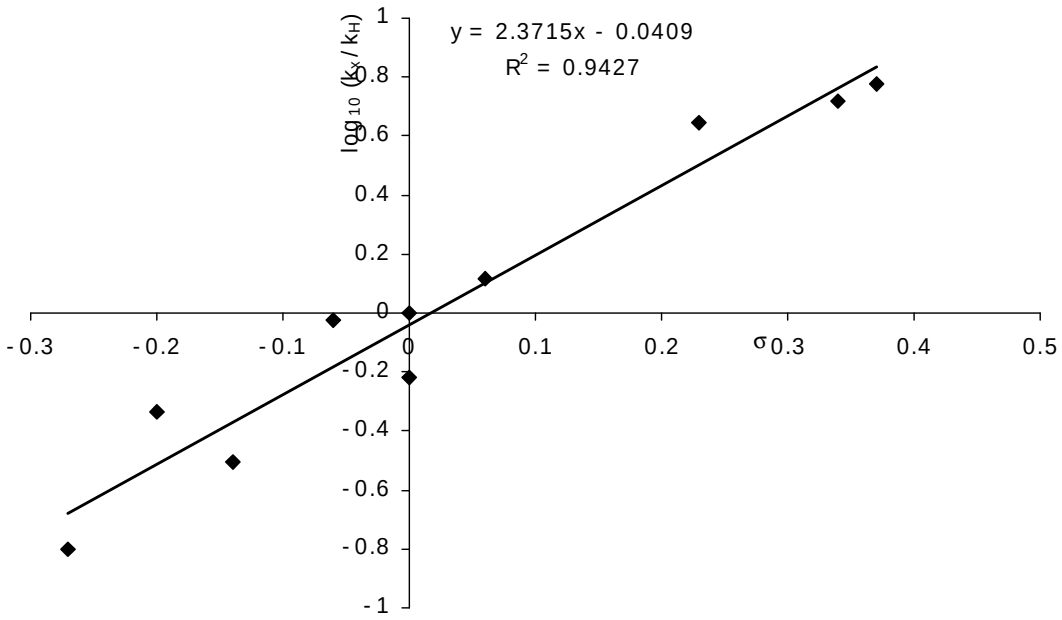


Figure 31; Hammett plot using complex **41**.

Vanadium catalysts seem to fall inbetween these two extremes and the Hammett plots for complexes **132** and **110** are shown in Figures 32 and 33 respectively. Vanadium is also more Lewis acidic than aluminium but not as strong a Lewis acid as titanium, however complexes **132** and **110** also carry counterions which can also have an influence on the activity of the catalyst. A reaction constant of 1.57 and 1.87 was obtained for both complexes **132** and **110** respectively. Complex **132** contains a Lewis basic isothiocyanate counterion which has been shown, via X-ray crystallography to be bound directly to the vanadium metal and therefore, there is no free site for the aldehyde to bind to the metal which makes the activation of the aldehyde more difficult.[73] Also the isothiocyanate anion has been shown to activate the trimethylsilylcyanide in much the same way as seen with triphenylphosphine oxide and so Lewis base catalysis may be responsible for some of the catalysis in the system when using complex **132**. Complex **110** contains an ethyl sulphonate counterion which is not co-ordinated to the vanadium centre and so the aldehyde can co-ordinate more freely. It could be hypothesised that Lewis acidic catalysis would be prevalent in the system using complex **110** as a chiral catalyst, but the similar reaction constants obtained for these two complexes suggests that a common mode of reaction is in operation for both complexes. The V=O double bond also possesses some Lewis basicity which is responsible for the formation of oligomeric vanadium species.[143] Kinetic studies have shown that these oligomeric species are important for the most active vanadium(salen) catalysts.

The Lewis basic V=O bond may be responsible for some of the catalytic activity displayed by these vanadium systems along with the Lewis acidity of the vanadium metal, and so a reaction constant between the two extremes of aluminium and titanium is observed. The mechanism involving vanadium(salen) complexes has been shown to be very complex and is still not fully understood.

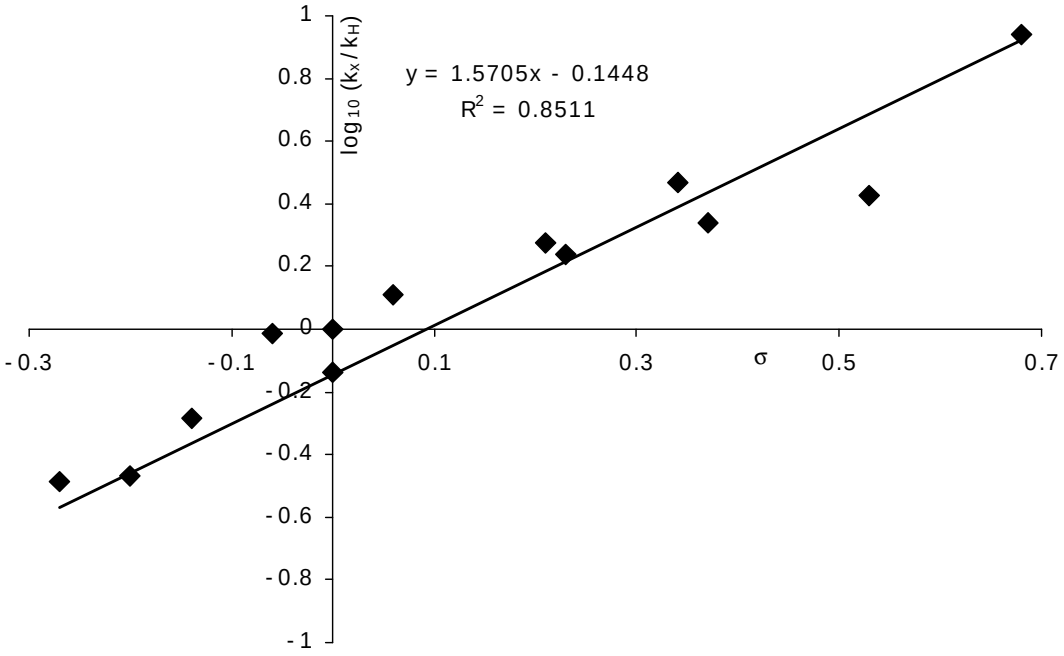


Figure 32: Hammett study for complex **132**.

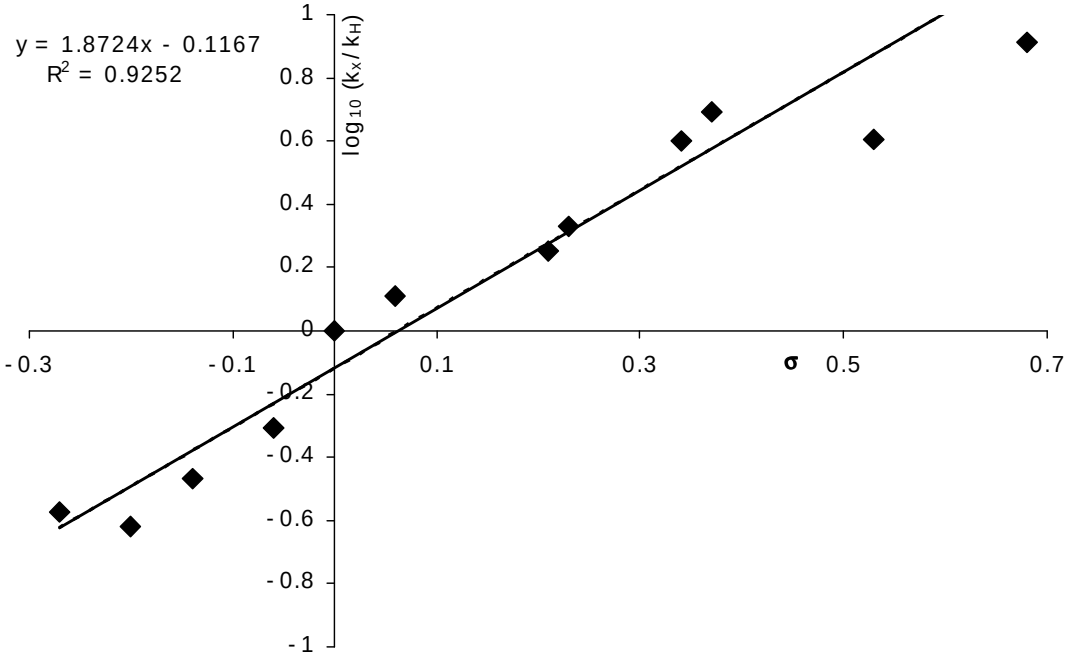


Figure 33; Hammett study for complex **110**.

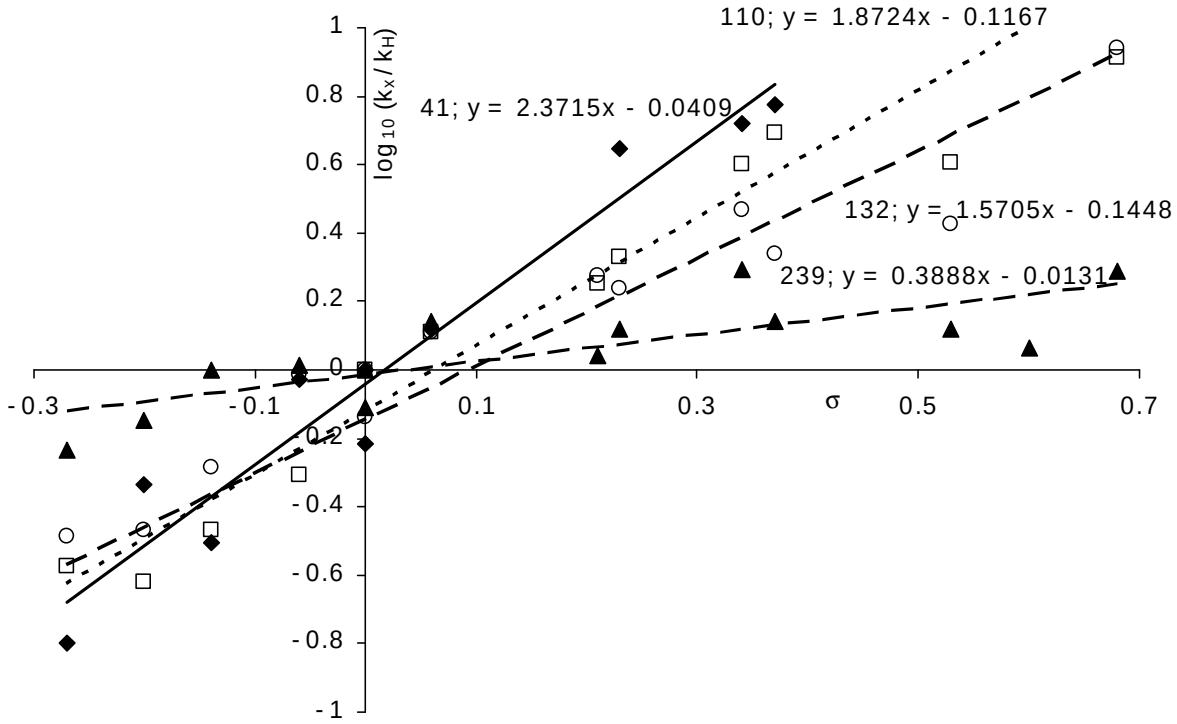


Figure 34; Hammett plot of complexes **41, 132, 110 and 239.** ♦ = **41;** □ = **110;** ▲ = **239;** ○= **132**

Plotting all the Hammett plots obtained for these four metal(salen) complexes onto the same graphical axis demonstrates the mechanistic differences between the catalysts (Figure 34). On the scale used in Figure 34, the Hammett plot for complex **239** can be interpreted as an almost horizontal straight line reinforcing the hypothesis that this system is dominated by Lewis basic catalysis. The Hammett plot for complex **41** shows a steeper gradient, demonstrating a system dominated by Lewis acid catalysis with complexes **132** and **110** lying in between these two extremes.

7.1 Arhenius Study of Cyanohydrin Synthesis using Complex 239

To complete the kinetic study on complex **239**, variable temperature kinetics were carried out on the cyanation of benzaldehyde, using complex **239** as a chiral catalyst, in order to construct an Arhenius plot for the reaction. Figure 35 shows the Arhenius plot and from this the activation parameters can be determined using the Eyring equation. The Eyring equation **1** relates the rate constant for a reaction to the enthalpy ($\Delta H^{\ddagger}$) and entropy ($\Delta S^{\ddagger}$) of activation.[144]

$k = (k_B . T . h^{-1}).\exp(-\Delta H^{\ddagger}/RT).\exp(\Delta S^{\ddagger}/R)$ (**1**); where k_B= Boltzmann's constant, *h*= Plank's constant, R= gas constant.

It is more convenient to use the apparent rate constant (k_{app} = k[catalyst][Ph_3P=O]) so equation **1** can be modified to equation **2**;

$k_{app}/T = (k_B\, h^{-1})$. [catalyst] [$Ph_3P$=O] exp(-$\Delta H^{\ddagger}$/RT). exp($\Delta S^{\ddagger}$/R) **(2)**

Taking the natural logarithm of both sides of the equation gives equation **3**

$\ln(k_{app}/T) = (-\Delta H^{\ddagger}/RT) + (\Delta S^{\ddagger}/R) + \ln(k_B\, h^{-1}) + \ln[\text{catalyst}] + \ln[Ph_3P{=}O]$. **(3)**

Plotting $\ln(k_{app}/T)$ against 1/RT gives the Arhenius plot shown in Figure 35, where the slope is equal to the enthalpy of activation and the entropy of activation can be obtained from the intercept of the y-axis. Carrying out this analysis gives the activation parameters as follows; $\Delta H^{\ddagger}$= 17.7 kJmol^{-1}, $\Delta S^{\ddagger}$= -155 Jmol^{-1}.

The Gibb's free energy of activation can be determined using these values from equation **4;**

$$\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger};\ T = 273\ K \quad \textbf{(4)}$$

From equation **4,** the Gibb's activation parameter is 60.0 kJmol^{-1} at 273 K. Table 38 shows the rate constants obtained when carrying out the reaction at various temperatures

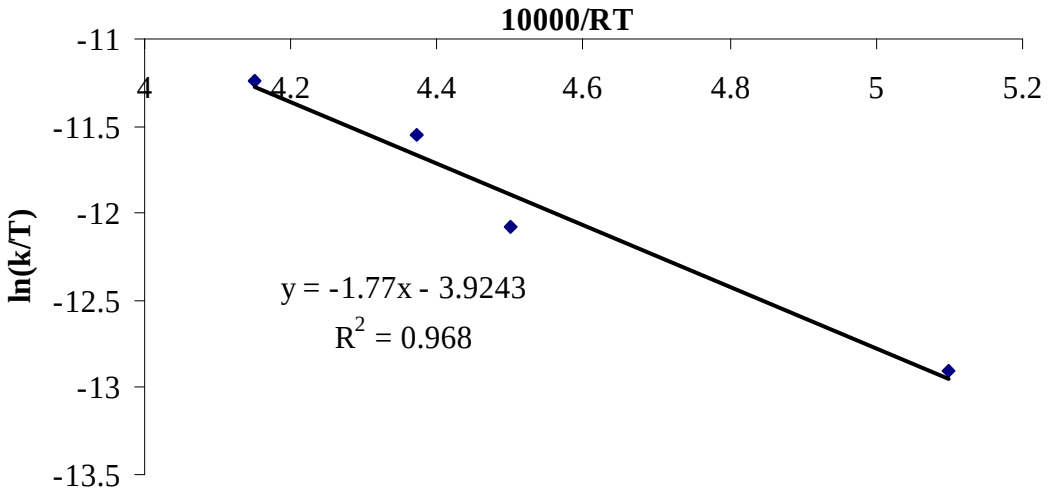
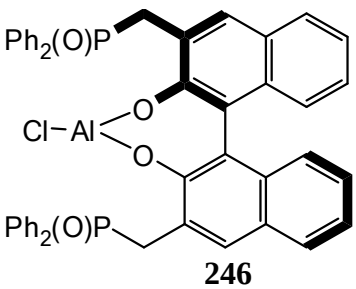


Figure 35; [**239**] = 0.005 M; [Ph_3P=O] = 0.025 M; [PhCHO] = 0.25 M; [TMSCN] = 0.40 M, in 1.75 ml of dichloromethane at 241.15-296.15 K.

Table 38; rate constants obtained at different reaction temperatures using complex **239** with benzaldehyde as the reaction substrate.

Temperature, K	k_{obs} s^{-1}
241.15	0.00060
273.15	0.00155
281.15	0.00270
296.15	0.00390

The data obtained for complex **239** was compared to other catalysts with high activity in asymmetric cyanohydrin synthesis (Table 39). These complexes were the titanium(salen) dimer **41** and two vanadium(salen) catalysts **110** and **132** possessing the ethyl sulphonate and isothiocyanate anions respectively. Catalyst **239** was also compared to two BINOL based catalysts **246** and **247**. Complex **246** was developed by Shibasaki, and possesses internal phosphine oxides, which behave in the same manner as triphenylphosphine oxide, acting as a Lewis base to activate the trimethylsilylcyanide; however, external phosphine oxide was shown to still be an essential component of the reaction.[145,146] Complex **247,** developed by Najera, contains the same BINOL unit, however, the phosphine oxides have been replaced with tertiary amines to behave as Bronsted bases which pre-organise hydrogen cyanide formed *in situ* from trimethylsilylcyanide and water, along with 4 Å molecular sieves to form a highly organised transition state.[147,148] From these variable temperature studies, complex **239** was found to have a Gibb's free energy of activation of +60 $kJmol^{-1}$. This data is consistent with the catalytic activity of the systems studied as the most active catalysts (**41** and **132**) display the lowest Gibb's free energy of +59.4 and +57.5 $kJmol^{-1}$ respectively. Cyanohydrin forming reactions are typically complete within 1-2 hours with catalyst loadings of 1.0 - 0.1 mol% when using complexes **41, 110** and **132**. Catalysts **246** and **247** display the highest Gibb's free energies of +79 and +71 $kJmol^{-1}$ with cyanohydrin forming reactions typically going to completion within 6-36 hours using 2-10 mol% of catalyst. Complex **239** lies inbetween these values, as reactions are complete within 16 hours at -40 ^{o}C using a 2.0 mol% catalyst loading.



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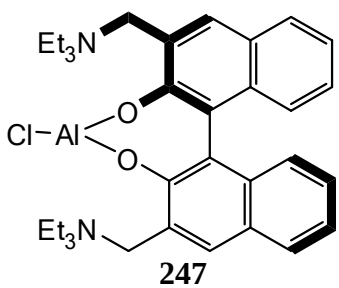

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Table 39; reaction parameters obtained from a variety of catalysts used in asymmetric cyanohydrin synthesis.

Catalyst	ΔH (kJmol^{-1})	ΔS (Jmol^{-1})	ΔG (kJmol^{-1})
41	+35.9	-86	+59.4
132	+20.4	-136	+57.5
110	+27.6	-184	+77.8
239	+17.7	-155	+60.0
246	+34.8	-162	+79.0
247	+54.7	-61	+71.3

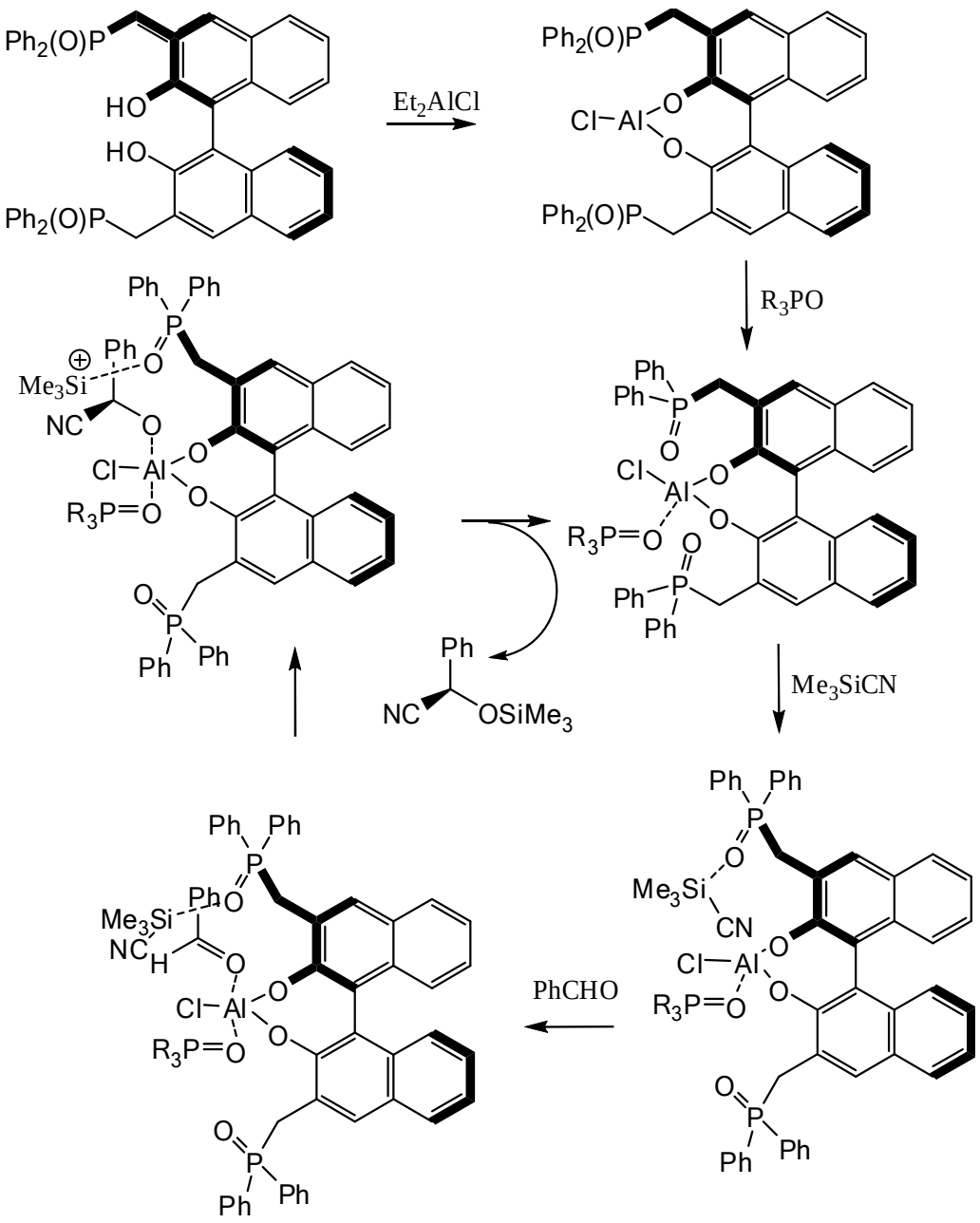
The Gibb's free energy is derived from a contribution from the enthalpy of activation and the entropy of activation ($\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$). From the four salen systems studied complexes **239**, **110** and **132** showed the greatest negative entropies of activation of -155 and -184 and -136 kJmol^{-1}. Unlike the other salen systems, complex **239** requires the addition of a Lewis basic additive for the catalyst to be active in cyanohydrin synthesis. This extra species present in solution results in more components having to assemble in the transition state and this generates a large negative entropy of reaction. With regard to complexes **110** and **132**, mechanistic studies have shown that cyanohydrin synthesis proceeds via a dimeric species generated from the association of two monomeric units in solution resulting in a large negative entropy contribution.

Schemes 49 and 50 show the catalytic cycles for complexes **246** and **247** respectively, to allow a direct comparison with complex **239.** Scheme 50 shows a modified mechanism in the absence of 4 Å molecular sieves, as Najera proposed the use of 4 Å molecular sieves along with trimethylsilylcyanide to generate hydrogen cyanide which would then go on to react with the aluminium bound carbonyl substrate to give the asymmetrically enriched cyanohydrin product. In order to carry out an effective kinetic analysis, a homogeneous reaction had to be developed which also gave the same enantioenriched cyanohydrin product and this negated the use of molecular sieves. Kinetic studies were carried out on complexes **246** and **247** and led to the following rate equations. The rate equation for complex **239** is included for comparison;

246; rate = k[**246**][TMSCN]

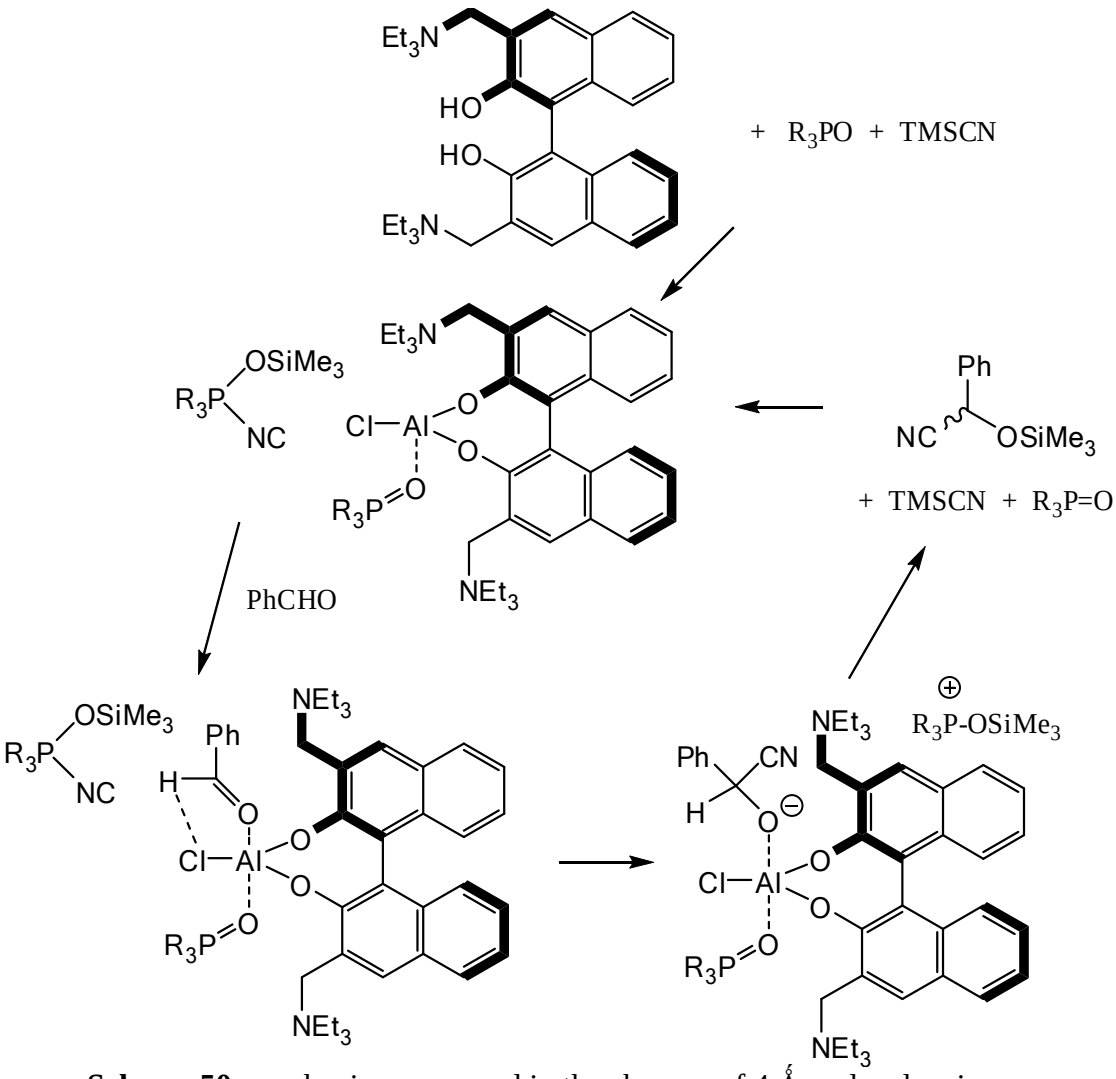
247; rate = k[**247**]$^{0.5}$[TMSCN][$MePh_2PO$]

239; rate = [**239**][TMSCN][$Ph_3P{=}O$]



Scheme 49: mechanism proposed by Shibasaki.

The most noticeable difference between the rate equations for the three aluminium catalysts, is the order with respect to catalyst concentration. Complexes **239** and **246** show a first order dependence of the rate on catalyst concentration while complex **247** exhibited an order of 0.5 with respect to the catalyst. A reaction order of 0.5 has been shown to be consistent with a mechanism in which the precatalyst is organised into dimers or higher oligomers, but where the catalytically active species is monomeric.[25]



Scheme 50; mechanism proposed in the absence of 4 Å molecular sieves.

All the reaction mechanisms proposed for complexes **239, 246** and **247** are very similar with a highly ordered transition state being formed by the coming together of a number of different reaction components; the catalyst, trimethylsilylcyanide and the phosphine oxide. This proposal is supported by the entropy of activation values determined from the Arrhenius study except for complex **247** which showed a less negative value of -61 kJmol^{-1}**.** This can be explained on the basis of the order with respect to the catalyst when using complex **247**, as an order of 0.5 was determined suggesting that the catalytic species is preorganised as a dimer or higher oligomers in solution though the active catalyst is monomeric in nature. If this is the case then dissociation into monomeric form has to occur for the catalyst to become active and so this allows for a positive entropy contribution. However, this favourable entropy is off-set by the highly ordered transition state as seen in Scheme 50 and so an overall value of -61 kJmol^{-1} was observed. All three systems show a zero order dependence of the rate on the benzaldehyde concentration, suggesting that the involvement of the substrate in the mechanistic cycle takes place after the rate determining step of the reaction. Phosphine oxide

is required in all three mechanisms, but for complex **246** a zero order dependence of the rate on phosphine oxide concentration is observed. The role of the external phosphine oxide may be to alter the geometry of the aluminium atom from trigonal planer to trigonal bipyramidal allowing for a more favourable binding of the aldehyde substrate due to reduced steric constraints. The phosphine oxide plays no other role in the mechanistic cycle since the internal phosphine oxide activates the trimethylsilylcyanide, resulting in the observed zero order kinetics. Complexes **239** and **247** show a first order dependence on phosphine oxide concentration as the phosphine oxide directly activates the trimethylsilylcyanide.

The conclusion that can be drawn from these studies is that the most active metal(salen) catalysts are those which contain the highly Lewis acidic vanadium and titanium metal centres as demonstrated by complexes **41, 110** and **132**. Though these catalysts do not necessarily give the highest enantioselectivities, enantioselectivities greater then 90% can be achieved in less than ten minutes at room temperature when using catalyst loadings of 0.1 - 1.0 mol% of complex **41**. Complexes **246** and **247** are highly enantioselective giving enantioselectivities as high as 99%, however, catalysts loadings of 2 – 10 mol% are required along with reaction times of 6-36 hours at reaction temperatures of -20 to -40 ^{o}C. Catalyst **239** was shown to have an activity that lies between that of complexes **41, 110** and **132** and that of complexes **246** and **247**, with complex **239** being more active than the aluminium BINOL complexes developed by Shibasaki and Najera. The catalyst loading for complex **239** was found to be optimal at 2 mol%, however, enantioselectivities as high as 96% were achievable in reaction times of 16 hours at -40 ^{o}C. These catalytic activities were supported by the Arrhenius study where the energy of activation for complex **239** was lower than that seen for complexes **246** and **247**. Complexes **41, 110** and **132** still remain the most active metal(salen) complexes for the addition of cyanide to the carbonyl bond. Mechanisitic studies have shown that the catalytic cycles for the titanium and vanadium(salen) complexes are more complex than the aluminium systems as shown in Scheme 9 for complex **41.** Research is still ongoing into the mechanism involving vanadium(salen) complexes which has been shown to be very complex.

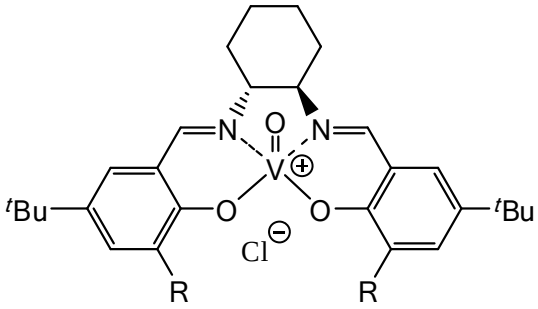
In conclusion, complex **239** was shown to be an active catalyst in cyanohydrin synthesis with reliable and reproducable kinetic data being obtained from a full kinetic analysis, Hammett study and Arrhenius study. There is strong evidence to suggest that the role of the triphenylphosphine oxide is to active the trimethylsilylcyanide and so increase the overall activity of the catalytic system with the role of complex **239** being to provide a chiral environment for the asymmetric reaction to take place in. Reactions in the absence of triphenylphosphine oxide were shown to give inferior results to those obtained in the

presence of a Lewis basic additive, again strongly supporting the role of the additive. Species **141** was proposed by Corey[139] as the product of a reaction between trimethylsilylcyanide and triphenylphosphine oxide and has been incorporated into a possible catalytic cycle, shown in Scheme 47. This study has also given an insight into Kim's cyanohydrin system, which used the monomeric aluminium(salen) complex **140**.[77,78] The addition of triphenylphosphine oxide was also required for the formation of an active system, suggesting that complex **140** may behave in a similar manner to complex **239** in the catalytic cycle.

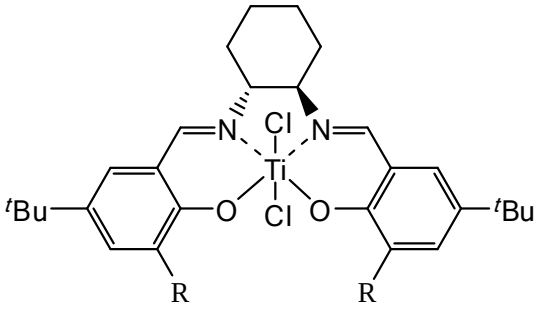
8.1 Summary of Results, Conclusions and Future Work.

8.1.1 Testing of New Catalysts in the Strecker Reaction and Cyanohydrin Synthesis.

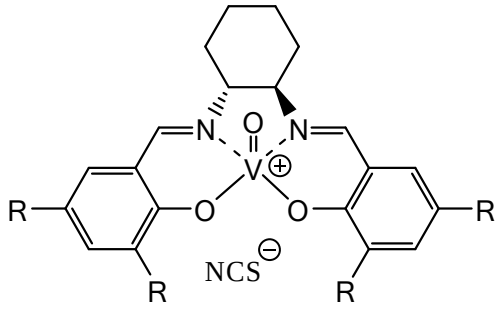
Attempts to improve on the activity of catalysts **118** and **132** proved unsuccessful. Complexes **222-225** were synthesised and screened in the Strecker Reaction and cyanohydrin synthesis, with lower enantiomeric excesses being obtained in both reactions, with the greatest stereocontrol coming from complex **224** when used in cyanohydrin synthesis when using benzaldehyde as the reaction substrate. An enantioselectivity of 30% (*S*) was achieved, however a reaction time of one week at room temperature was required to achieve this result. Shorter reaction times and lower reaction temperatures resulted in lower conversions and lower enantioselectivity. The vanadium(V)(salen) chloride complexes **222** and **223** were screened in the Strecker reaction with both complexes giving much lower enantiomeric excesses than complex **118**. Complex **222** gave the higher enantioselectivity of these two complexes, 20% (*R*). These lowered activities were explained by the dramatic increase in substituent size as complexes **224** and **225,** were synthesised to contain an adamantly and trityl substituent in the *ortho*-positions on the aromatic rings of the salen ligand. The formation of the catalytically active dimeric species, as in the case of complexes **37** and **41**, could not occur *in situ* and therefore these complexes displayed low activity in cyanohydrin synthesis. Attempts to isolate the dimeric species of complexes **224** and **225** were unsuccessful as the steric interaction between the larger substituents prevents two monomer units coming together to form the dimer.



222) R = adamantly
223) R = trityl



224) R = adamantyl
225) R = trityl



231a) R= *tert*-pentyl
231b) R= *tert*- hexyl

Due to the results reported by Liang *et al*, the vanadium(V)(salen) isothiocyanate complexes **231a** and **231b** were synthesised and screened in cyanohydrin synthesis giving high enantiomeric excesses and conversions.[46] The results were comparable to those obtained using complex **132.** Complex **231a** gave cyanohydrin product with 90% (*S*) enantiomeric excess with complete conversion. The enantioselectivity decreased to 84% (*S*) when using complex **231b**, which was accounted for by the increase in the substituent size from *tert*-pentyl to *tert*-hexyl and so the reacting aldehyde, in this case benzaldehyde cannot coordinate to the vanadium atom of complex **231b** as easily as seen with complexes **118**, **132** and **231a** and so is not as activated towards nucleophilic attack by the cyanide nucleophile. The consequence of this being that the activity decreases which is reflected in the lowered enantiomeric excess. Complexes **231a** and **231b** were shown to be more reactive than the corresponding titanium complex developed by Liang.[46] Higher enantioselectivities were obtained using lower catalyst loadings and higher reaction temperatures.

8.1.2 The Strecker Reaction.

Attempts to improve on the results already obtained using complex **118** were undertaken with no improvement in enantioselectivity being achieved. The reaction temperature, reaction solvent, reaction additive and catalyst loading were varied with no improvement being observed. The rate of addition of trimethylsilylcyanide was shown to be a factor in the enantioselective outcome of the reaction as slow addition of trimethylsilylcyanide resulted in α-aminonitrile product being obtained with 80% (*R*) enantiomeric excess when using methanol as the reaction additive as opposed to 65% (*R*) when adding the trimethylsilylcyanide in one portion when using methanol as the reaction additive. Adding the trimethylsilylcyanide slowly to the reaction resulted in a slower production of hydrogen cynanide, and therefore addition to the imine bond can occur via the catalytic cycle rather than the racemic background reaction. Also less of the hydrogen

cyanide gas is lost to the atmosphere and so more is available for the asymmetric Stecker reaction.

These results along with the consistent complete conversions led to the suspicion that some of the reaction was occurring on work-up as the crude reaction mixture was passed down a silica plug, or racemically as the reaction was allowed to warm to room temperature after the removal of the catalyst. Kinetic studies confirmed these suspicions with *in situ* monitoring of the reaction using ^{1}H NMR showing that after two minutes at -40 ^{o}C the reaction had gone to completion with no decrease in enantioselectivity. At -60 ^{o}C, the reaction was slower giving complete conversion in 10 minutes. Further attempts to gain kinetic data was unsuccessful as transferring the ^{1}H NMR sample to the spectrometer resulted in a very fast reaction as the sample momentarily warmed up. Attempts to stop or slow down this background reaction were unsuccessful and no reliable kinetics data was obtained. From these findings it has been shown that both the racemic and catalysed Strecker reactions occur at extremely fast rates even at low temperatures. It was not possible to stop or slow down the racemic reaction or sufficiently slow down the catalysed reaction and so the reaction was giving a significant conversion to α-aminonitrile product before any kinetics could be monitored. No further attempts were made to obtain kinetic data as this extremely fast background reaction could not be suppressed which made studying the reaction kinetics very difficult and so so it can be concluded that no further improvements in enantioselectivity is likely to be made using complex **118**.

8.1.3 Cyanohydrin Synthesis using Complex 239.

Complex **239** was shown to be active in cyanohydrin synthesis giving cyanohydrin product with 89% (*S*) enantiomeric excess with 80% conversion after 18 hours at -40 ^{o}C. Triphenylphosphine oxide (10 mol%) was required along with a catalyst loading of 2 mol%. Screening a variety of aromatic and non-aromatic aldehydes gave cyanohydrin product with 36-96% (*S*) enantiomeric excesses and conversions of 35-100%. Aromatic substrates were the most compatible with this catalytic system with the highest enantiomeric excess being achieved when using *meta*-tolualdehyde (96% (*S*)). Complex **239** was also shown to be active with ketone substrates however longer reaction times were required along with higher reaction temperatures and higher catalyst loadings. Extensive kinetic studies gave a rate equation of the form; rate = k[TMSCN][Ph_3P=O][**239**] and so a catalytic cycle consistent with this rate equation was proposed as shown in Scheme 47. A Hammett study was undertaken using a range of substituted benzaldehydes with the Hammett plot (Figure 30) appearing to show a straight flat line with a very low reaction constant of 0.38, suggesting

that the substituent on the aromatic ring of the aldehyde had very little or no effect on the rate of the reaction and that a negative charge was being generated in the transition state of the reaction. From the Hammett study, conclusions were drawn that this system was dominated by Lewis basic catalysis from the triphenylphosphine oxide, activating the trimethylsilylcyanide via species **141** proposed by Corey[138] or the ion pair proposed along with the mechanism in Scheme 47. The role of catalyst **239** is to therefore provide a chiral environment for the addition of cyanide to the carbonyl bond, rather than to activate the carbonyl bond via coordination to one of the aluminium atoms within the complex. Comparison of this data to that obtained from other metal(salen) complexes confirmed this result, with the titanium(salen) complex **41** giving a rho value of 2.37 and the vanadium(salen) complexes **110** and **132** giving rho values of 1.87 and 1.57 respectively. Large positive rho values suggest that the substituents on the aromatic ring of the reaction substrate have a great effect on the rate of the reaction, with electron-withdrawing substituents stabilising the build up of negative charge at the benzylic position of the aldehyde during the transition state. From these rho values, it can be assumed that these catalysts are dominated by Lewis acidic catalysis.

An Arrhenius study at variable temperatures also produced mechanistically consistent results for the system catalysed by complex **239** (Figure 35). Catalyst **239** was shown to have an intermediate activity in comparison to related catalysts of interest and was shown to be more active than Shibasaki's [146,147] and Najera's [148,149] aluminium BINOL catalysts. However, these systems were more enantioselective, giving enantiomeric excesses of >99% when using benzaldehyde as the reaction substrate. The entropies of activation calculated from the Arrhenius study provided a great deal of information regarding the catalytic cycle and were used to support the theories of how these systems behave in solution. Large negative entropies of activation suggest that the reaction proceeds via a highly organised transition state which has been shown to be a very feasible argument for the aluminium complexes **239**, **246** and **247**. All of work involving the aluminium(salen) catalyst has been reviewed by external referees and has led to the publication of three scientific papers in two academic journals.

8.1.4 Future Work.

Further studies should be carried out on complex **239** in cyanohydrin synthesis with particular attention to the Hammett study. To further confirm the importance of Lewis base catalysis, a Hammett study should be carried out using only Lewis bases in the form of chiral phosphine oxides. If Lewis base catalysis is responsible for the catalysis, as in the case of

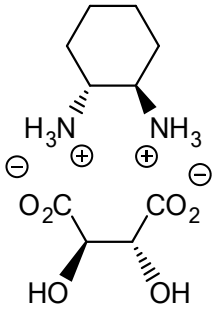
239, then a prediction can be made that the Hammett plot would be very similar to the one obtained in Figure 30. Analysis of the enantiomeric excess would confirm if a Lewis acid catalyst is even required for cyanohydrin synthesis. Chiral phosphine oxides may be sufficient to generate cyanohydrin products with enantiomeric excesses as high as with catalyst **239.** Matched and mis-matched studies should also be carried out using both enantiomers of the Lewis base along with the chiral Lewis acid to give a further insight into the catalytic cycle. As discussed previously, there is still much speculation as to the reaction mechanism using complex **239** in the cyanohydrin system and so further study of this would be advantageous. Also the role of triphenylphosphine oxide should be explored further with further evidence to support the existence of species **141** being provided.[38] The achiral reaction is also of interest using achiral Lewis bases and achiral Lewis acids. This would provide interesting and comparable data to the data obtained using chiral complex **239**. The same analysis could be carried out, obtaining a full kinetic analysis, a Hammett plot and Arrhenius plot and so reaction orders, Hammett parameters and activation parameters could be determined. The achiral system may also be easier to analyse and therefore could give a better insight into the activity of complex **239**.

One-componant catalysts are quickly becoming of more interest especially in the chemical industry. These catalysts tend to show higher activity and so combining the phosphine oxide additive with the catalyst, as seen in complexes **246** and **247**, should be studied further. The possible immobilisation of the catalyst onto a variety of different solid supports also means that the catalyst can be recycled a number of times before a drop in activity is seen. Separation of the catalyst from the crude reaction mixture is also easier. Further research into this area of asymmetric catalysis would be of interest when using complex **239** in cyanohydrin synthesis as the activity of the system may be increased.

9. Experimental

Dichloromethane was dried via distillation from calcium hydride. All deuterated solvents were purchased from GOSS chemicals. Chromatogrpahic separations were performed with silica gel 60 (230-400 mesh) and thin layer chromatography was performed on polyester backed sheets coated with silica gel 60 F254, both supplied by Merck or aluminium-backed flexible silica plates (0.25mm layer, Whatman AL SIL G/UV, containing UV 254) visualised with UV light. Chiral gas chromatography analysis was carried out on a Varian 450 GC using a Supelco Gamaa DEX 120 fused silica capillary column (30 m × 0.25 mm) with hydrogen as a carrier gas (flow rate 2.0 ml / min, column pressure 10 psi). Initial temperature 95 ^{o}C, final temperature 180 ^{o}C, ramp rate 5.0 ^{o}C / min. Optical rotations were recorded using a Polaar 2001 Optical automatic polarimeter and are reported with a concentration value in g/ 100ml. All UV spectra were recorded on a Biochrom Libra S12 spectrometer (100-240 V) at the wavelength specified. ^{1}H and ^{13}C NMR were carried out on a Bruker Avance 300 and Jeol 400 or 500 MHz spectrometers at room temperature unless specified otherwise and the solvent for a particular spectrum is specified in the experimental section. ^{1}H and ^{13}C NMR spectra were referenced to TMS and chemical shift values (δ), expressed in parts per million (ppm), are reported downfield of TMS as: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m) or broad (br). Mass spectrometry was carried out on a Waters LCT Premier Acquity LCMS using positive ion mode. Samples were dissolved into either methanol or acetonitrile and injected manually into the spectrometer via a syringe pump. Samples were also analysed by the EPSRC national service at Swansea. Melting points were obtained using a Barnstead Electrothermal 9100 system. Infra red spectra were recorded on a Varian 800 FT-IR spectrometer. Absorbance intensities were measured as: broad (br), strong (s), medium (m), or weak (w).

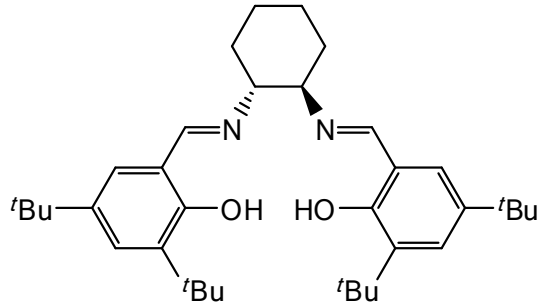
(R,R)-(-)-1,2-diaminocyclohexane-L-tartrate 214.[149]



L-(+)-tartaric acid (100 g, 0.67 mmol) was dissolved in water (270 ml) at room temperature. Racemic *cis* and *trans*-1,2-diaminocyclohexane (144.3 g, 155 ml, 1.26 mmol) was added via a dropping funnel at a rate such that the reaction temperature reached 65 ^{o}C. The reaction was stirred vigorously and a white precipitate formed as the reaction was cooled to room temperature over a period of two hours. The resulting solution was cooled in an ice bath for one hour, and the precipitate collected via suction filtration. This was washed with ice cold water (2 × 100 ml), ice cold methanol (7 × 100 ml) and dried by suction to leave the crude material as a white powder. Glacial acetic acid (70 ml, 1.16 mmol) was added to the mother liquor taking care not to let the temperature rise above 90 ^{o}C. A white precipitate formed immediately upon addition. Again, the slurry was stirred vigorously as it cooled to room temperature over a period of two hours. The mixture was cooled to 5 ^{o}C for one hour and the precipitate was collected by suction filtration. The pale yellow solid was washed with ice cold water (2 × 100 ml), then rinsed with ice cold methanol (10 × 100 ml) and dried via suction giving a second crop as a white powder. The combined crude material was recrystallised from water. Filtration and drying yielded compound **214** as white crystals (64.5 g, 36%).

$[\alpha]_D$= +8.6 (c= 2.9, H_2O) [lit.[130] $[\alpha]_D$= +12.5 (c= 4.0, H_2O)]

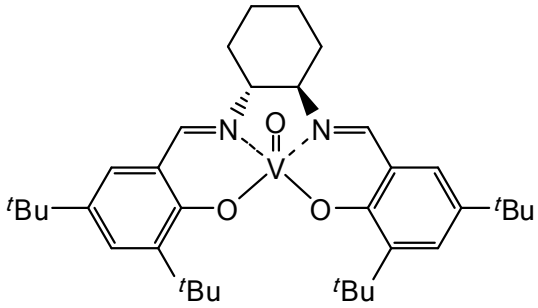
[N,N'-Bis-(3,5-di-tert-butyl-salicylidene)]-(R,R)-1,2-diaminocyclohexane 30. [7]



2,4-Di-*tert*-butylphenol (5.00 g, 24.3 mmol), magnesium chloride (4.60 g, 48.5 mmol) and paraformaldehyde (1.60 g, 53.4 mmol) were added to tetrahydrofuran (50 ml) in a round bottomed flask. Triethylamine (6.45 ml, 48.5 mmol) was added dropwise to the resulting mixture which was then refluxed for ca. two hours. On heating, the reaction turned bright yellow in colour as 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde was formed *in situ*. The aldehyde could be used directly in the next stage of the synthesis without any isolation or purification. To the reaction mixture, potassium carbonate (3.21 g, 27.3 mmol) and (*R,R*)-1,2-diaminocyclohexane tartrate salt **214** (3.77 g, 12.1 mmol) were added at room temperature. The reaction was heated to ca. 80 ^{o}C and allowed to reflux for another two hours. The remaining magnesium chloride was filtered and water added to the solution. The product was taken up into dichloromethane (100 ml) and the organic layer washed with water (3×100ml) and brine (2×50 ml). The organic layer was collected, dried over magnesium sulphate and the solvent removed under vacuum to yield compound **30** as a yellow solid (6.97 g, 53%).

mp = 180-185 ^{o}C [lit.[7]= 200-203 ^{o}C]; $[\alpha]_D$= -292 (c=1, $CHCl_3$) [lit.[7] $[\alpha]_D$= -314.4 (c=1, $CHCl_3$)]; υ_{max} 1630, 2976, 3019 cm^{-1}; δ_H ($CDCl_3$, 300 MHz): 1.25 (s, 18H, C(C**H$_3$**)$_3$), 1.43 (s, 18H, C(C**H$_3$**)$_3$), 1.3-2.0 (m, 8H, Cy**H**), 3.3-3.4 (m, 2H, C**H**N), 6.91 (d, 2H, *J*= 2.4 Hz, Ar**H**), 7.24 (d, 2H, *J*= 2.4 Hz, Ar**H**), 8.23 (s, 2H, C**H**N), 13.64 (br, 2H, O**H**); δ_C ($CDCl_3$, 75 MHz): 24.8, 29.9, 31.8, 33.6, 34.4, 35.4, 72.8, 118.4, 126.4, 127.1, 136.9, 140.3, 158.4, 166.3; Found (ESI) 547.4269 $C_{36}H_{55}N_2O_2$ [MH^+] requires 547.4264.

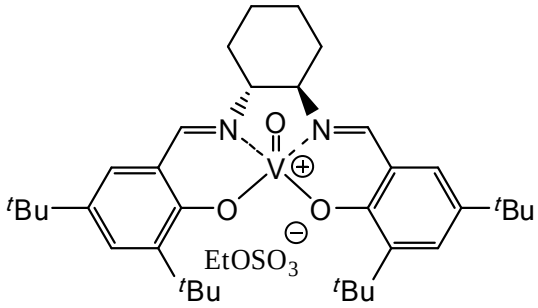
(R,R)-V(IV)O(salen) 109.[107]



Compound **30** (1.0 g, 1.8 mmol) in pyridine (4 ml) and vanadyl sulphate (0.55 g, 2.02 mmol) in warm ethanol (40 ml) were mixed under argon and refluxed for three minutes to form a crystalline solid. The reaction was cooled to room temperature and after ca. three hours, the light green crystals were collected by filtration and washed thoroughly with ethanol (20 ml). The crystals were dried under high vacuum to yield complex **109** as a light green solid (0.98 g, 88 %).

$[\alpha]_D$ -440 (c= 0.01, $CHCl_3$) [lit.[107] $[\alpha]_D$ -442 (c= 0.01, $CHCl_3$)].

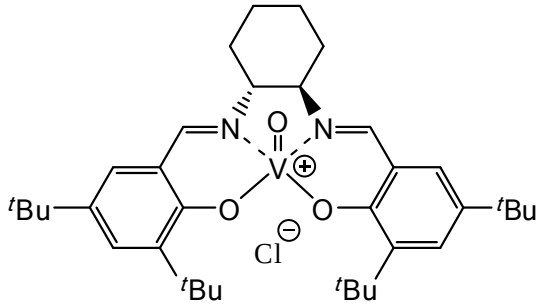
(R,R)-V(V)O(salen) ethylsulphonate 110 [108]



Vanadyl sulphate (4.0 mmol, 650 mg) was added to ethanol (60 ml), and the solution heated to dissolve the vanadyl sulphate. The resulting solution was added to a solution of salen ligand **30** (3.7 mmol, 2.0 g) in ethanol (40 ml). The reaction was allowed to reflux for ca. three hours. The ethanol was removed using reduced pressure and the residue was taken up in dichloromethane (40 ml) and passed through a flash chromatography column, eluting with dichloromethane and methanol. Unreacted salen ligand was removed first as a yellow band with dichloromethane. Further elution with dichloromethane removed vanadium(IV)salen complex which travelled down the column as a green band. Methanol was flushed through the column to remove compound **110** which moved as a dark green/black band. The methanol was removed under reduced pressure to yield compound **110** as a dark green solid (1.60 g, 2.17 mmol, 59%).

mp = >320 ^{o}C [lit.[108] = >320 ^{o}C]; $[\alpha]_D$= -707 (c=0.01, $CHCl_3$) [lit.[109] $[\alpha]_D$= -915 (c=0.01, $CHCl_3$)]; υ_{max} 1630, 2976, 3019, cm^{-1}; δ_H ($CDCl_3$, 300 MHz): 0.80 (t, 3H, C**H$_3$**CH_2SO_3), 1.25 (s, 18H, C(C**H$_3$**)$_3$), 1.43 (s, 18H, C(C**H$_3$**)$_3$), 1.3-2.0 (m, 8H, Cy**H**), 3.4 (q, 2H, CH_3C**H$_2$**SO_3), 3.8-3.9 (m, 1H, C**H**N), 4.1-4.2 (m, 1H, CHN), 7.51 (d, 1H, *J*= 2.4 Hz, Ar**H**), 7.55 (d, 1H, *J*= 2.4 Hz, Ar**H**), 7.71 (d, 1H, *J*= 2.4 Hz, Ar**H**), 7.77 (d, 1H, *J*= 2.4 Hz, Ar**H**), 8.55 (s, 1H, C**H=**N), 8.76 (s, 1H, C**H**=N); δ_C ($CDCl_3$, 75 MHz): 24.9, 29.2, 29.3, 29.5, 30.2, 30.4, 30.9, 31.7, 31.8, 34.8, 34.9, 35.9, 36.1, 50.2, 70.1, 71.0, 121.3, 122.4, 128.7, 129.8, 131.9, 132.4, 135.7, 136.4, 144.5, 160.5, 161.8, 165.2.

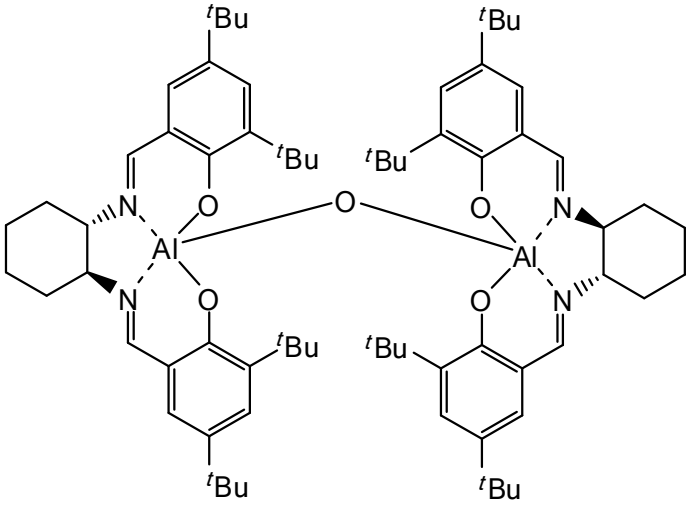
(R,R)-V(V)O(salen)Cl ***118*** [108]



VO(salen)EtOSO$_3$ **110** (0.20 g, 0.27 mmol) was dissolved in acetonitrile (20 ml) and a solution of ceric ammonium nitrate (0.18 g, 0.33 mmol) in acetonitrile (25 ml) was added in one portion. The resulting solution was stirred for five minutes at room temperature. The solution was then concentrated to ca. 1/3 the volume using reduced pressure. Water (150 ml) was added to the mixture. The resulting solution was treated with aqueous hydrochloric acid (1.5 M) and the green product was taken up into dichloromethane (3 × 150 ml). The organic layer was washed with water (100 ml) and brine (100 ml) and dried with sodium sulphate. Upon removal of the sodium sulphate the solvent was removed under vacuum to give compound **118** as a dark green solid (0.15 g, 84%).

mp = >320 ^{o}C [lit.[108]. = >320 ^{o}C]; $[\alpha]_D$= +889 (c=0.01, $CHCl_3$) [lit.[109] $[\alpha]_D$= -1304 (c= 0.01, $CHCl_3$)]; υ_{max} 1630, 2976, 3019, cm^{-1}; δ_H ($CDCl_3$, 300 MHz); 1.33 (s, 18H, C(C**H**$_3$)$_3$), 1.49 (s, 18H, C(C**H**$_3$)$_3$), 1.7-2.8 (m, 8H, Cy**H**), 3.7-3.8 (m, 1H, C**H**N), 4.2-4.3 (m, 1H, C**H**N), 7.49 (d, 1H, *J*= 2.4 Hz, Ar**H**), 7.52 (d, 1H, *J*= 2.4 Hz, Ar**H**), 7.71 (d, 1H, *J*= 2.4 Hz, Ar**H**), 7.77 (d, 1H, *J*= 2.4 Hz, Ar**H**), 8.55 (s, 1H, N=C**H**), 8.76 (s, 1H, N=C**H**); δ_C ($CDCl_3$, 75 MHz): 20.0, 21.7, 25.5, 25.8, 30.5, 31.0, 52.7, 52.8, 56.4, 58.0, 62.5, 63.1, 63.8, 68.2, 127.5, 129.8, 129.9, 130.0, 137.4, 138.0, 138.1, 143.7, 143.8, 144.1, 170.3, 170.4

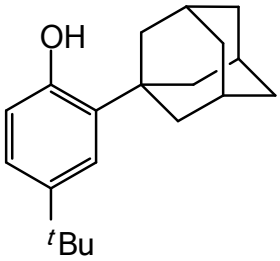
(S,S)-(Al(salen))$_2$O 239. [138]



Jacobsen's ligand **30** (1.0 g, 1.8 mmol) was dissolved into toluene (20 ml) and refluxed for 15 minutes under N_2. $Al(OEt)_3$ (0.60 g, 3.7 mmol) was added in one portion. The reaction was refluxed for a further five hours. After this time, the reaction mixture was allowed to cool and the solvent removed under reduced pressure to yield a yellow oil. The residue was taken up into CH_2Cl_2 and washed with brine (10 × 30 ml), dried over $MgSO_4$ and the solvent removed to leave compound **239** as a yellow solid. (0.77 g, 36%).

m.p= >350 ^oC; $[\alpha]_D$ = -581 (c=1, $CHCl_3$) [lit.[138] $[\alpha]_D$ = -548 (c=0.11, $CHCl_3$)]; υ_{max} 1623, 2951 cm^{-1}; δ_H ($CDCl_3$, 300 MHz): 1.30 (s, 36H, 4 × (C**H$_3$**)$_3$), 1.45 (s, 36H, 4 × (C**H$_3$**)$_3$), 1.8-2.6 (m, 16H, Cy**H**), 3.0-3.1 (m, 4H, C**H**N), 7.00 (d, 4H, *J* = 2.4 Hz, Ar**H**), 7.42 (d, 4H, *J* = 2.4 Hz, Ar**H**) 8.20 (s, 2H, N=C**H**), 8.30 (s, 2H, N=C**H**); Found (ESI) 1231.7716 $C_{78}H_{104}N_4O_5Al_2$ [M^+] requires 1231.7716.

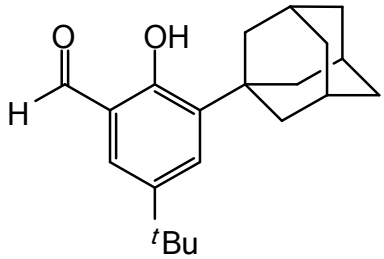
2-Adamantan-2-yl-4-tert-butylphenol 218. [111]



4-*tert*-Butylphenol (3.0 g, 20 mmol) was dissolved in dichloromethane (20 ml). 1-Adamantanol (3.4 g, 22 mmol) was added and the mixture stirred to ensure complete dissolution of the reactants. Concentrated sulphuric acid (2.0 ml) was added to the stirring mixture over 20 minutes. Once the addition was complete the mixture was allowed to stir for a further 20 minutes. Water (30 ml) was added to the reaction vessel at which point a cloudy precipitate was observed. sodium hydroxide (2 M) was added dropwise to achieve pH = 7.0, and the crude product was extracted using ethyl acetate (3 × 30 ml). The combined organic phases were washed with brine (30 ml) and dried over magnesium sulphate. Removal of the solvent yielded a thick clear oil. To this crude product, methanol (30 ml) was added and the mixture was heated to reflux, then allowed to cool to room temperature. The cooled mixture was kept at ca. 4.0 ^{o}C overnight. The mother liquor was concentrated to give compound **218** as a white powder (3.7 g, 65%).

m.p= 202-206 ^{o}C; υ_{max} 3054 cm^{-1}; δ_H ($CDCl_3$, 300 MHz): 1.8-1.9 (m, 6H, Ad**H**), 1.32 (s, 9H, ($C\mathbf{H_3}$)$_3$), 2.11 (m, 3H, Ad**H**), 2.1-2.2 (m, 6H, Ad**H**), 4.62 (s, 1H, O**H**), 6.62 (d, 1H, J = 2.4 Hz, Ar**H**), 7.07 (dd, 1H, J = 2.4 = 8.0 Hz, Ar**H**), 7.27 (d, 1H, J = 2.4 Hz, Ar**H**), δ_C ($CDCl_3$, 75 MHz): 29.7, 31.9, 34.7, 37.4, 37.6, 41.3, 116.7, 123.6, 124.3, 136.0, 143.7, 152.4.

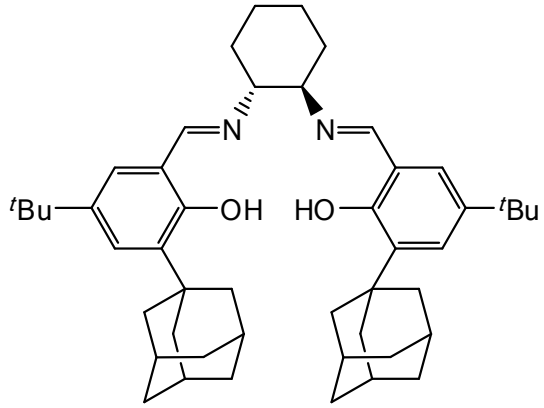
3-(1-Adamantyl)-5-tert-butylsalicylaldehyde 220.[111]



2-Adamantan-2-yl-4-*tert*-butyl-phenol **218** (1.0 g, 3.5 mmol), magnesium chloride (0.69 g, 7.0 mmol), and paraformaldehyde (0.23 g, 7.7 mmol) were added to tetrahydrofuran (90 ml). Triethylamine (0.93 ml, 7.0 mmol) was added dropwise to the stirring mixture at which point a change in colour from white to yellow was observed. The solution was refluxed for ca. six hours. The tetrahydrofuran was removed *in vacuo* to leave a yellow residue. Acidified water (30 ml) was added and the product extracted into ethyl acetate (3 × 30 ml). The combined organic layers were collected, washed with brine (30 ml) and dried using magnesium sulphate. The solvent was removed to give compound **220** as a pale yellow powder (0.50 g, 46%).

mp = 110-111 ^{o}C; υ_{max} 1646 cm^{-1}; δ_H ($CDCl_3$, 300 MHz): 1.35 (s, 9H, (C**H$_3$**)$_3$), 1.8-2.1 (m, 6H, Ad**H**), 2.1-2.2 (m, 9H, Ad**H**), 7.35 (d, 1H, *J* = 2.4 Hz, Ar**H**,), 7.54 (d, 1H, *J* = 2.4 Hz, Ar**H**,), 9.88 (s, 1H, C**H**O), 11.7 (s, 1H, O**H**), δ_C ($CDCl_3$, 75 MHz): 29.5, 31.6, 31.9, 34.6, 37.5, 37.79, 120.6, 128.0, 132.2, 138.2, 142.2, 159.8, 197.5

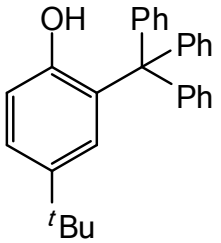
[N,N'-Bis-(3-tert-butyl-5-adamantyl-salicylidene)]-(R,R)-1,2-diaminocyclohexane 216.[111]



3-(1-Adamantyl)-5-*tert*-butylsalicylaldehyde **220** (0.70 g, 0.30 mmol), (*R,R*)-1,2-diaminocyclohexane tartrate salt **214** (0.30 g, 1.1 mmol) and potassium carbonate (0.31 g, 2.2 mmol) were refluxed in tetrahydrofuran (15 ml) for ca. six hours. In this time the reacting mixture turned a bright yellow colour. The solvent was removed to leave a yellow residue and water (15 ml) added. The product was extracted into ethyl acetate (3 × 15 ml), the organic layers combined, washed with brine (15 ml) and dried using magnesium sulphate. Concentration of the solvent left compound **216** as a yellow solid.

mp = 240-246 ^{o}C [lit.[113] = 247-248 ^{o}C]; $[\alpha]_D$ = +224.9 (c=1, $CHCl_3$) [lit.[113] $[\alpha]_D$ = +325 (c=1, $CHCl_3$)]; υ_{max} 1265, 1421, 3054 cm^{-1} ; δ_H ($CDCl_3$, 300 MHz): 1.23 (s, 18H, (C**H**$_3$)$_3$), 1.3-2.0 (m, 8H, Cy**H**), 1.7-1.8 (m, 12H, Ad**H**), 2.0-2.1 (m, 6H, Ad**H**), 2.1-2.2 (m, 12H, Ad**H**), 3.1-3.2 (m, 2H, C**H**N), 6.97 (d, 2H, *J*=2.4 Hz, Ar**H**,), 7.24 (d, 2H, *J*=2.4 Hz, Ar**H**,), 8.29 (s, 2H, C=N**H**); δ_C ($CDCl_3$, 75 MHz): 24.7, 29.7, 31.8, 33.6, 34.4, 37.7, 40.9, 72.8, 118.4, 126.3, 127.1, 137.1, 140.4, 158.7, 166.5; Found (ESI) 703.5207 $C_{48}H_{66}N_2O_2$ [M^+] requires 703.5203.

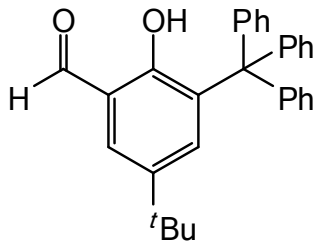
4-tert-Butyl-2-trityl-phenol 219.



4-*Tert*-butylphenol (3.0 g, 20 mmol) was dissolved in dichloromethane (30 ml) to which triphenylmethanol (7.8 g, 30 mmol) was added. The mixture was allowed to stir to ensure complete dissolution of the reactants. The mixture was treated with conc. sulphuric acid (1.07 ml, 20 mmol). This resulted in an immediate colour change from colourless to a deep red/brown. The mixture was refluxed overnight. Water (30 ml) was added and the mixture neutralised to pH = 7.0 (2.0 M NaOH). The solvent was removed to leave a thick clear oil. The crude material was passed through a silica column, eluting with dichloromethane, to remove unreacted 4-*tert*-butylphenol. The appropriate fractions were combined and the solvent removed to leave a white solid. Recrystallisation from methanol removed traces of triphenylmethanol and concentration of the mother liquor gave compound **219** (4.8 g, 60%).

mp= 105-110 ^{o}C; υ_{max} 1266, 2305, 2987 cm^{-1}; δ_H ($CDCl_3$, 300 MHz): 1.98 (s, 9H, ($C\mathbf{H_3}$)$_3$), 6.67 (d, 1H, *J* = 2.4 Hz, Ar**H**,), 7.08 (dd, 1H, *J* = 2.4 = 8.0 Hz, Ar**H**,), 7.2-7.4 (m, 17H, Ar**H** + O**H**); δ_C ($CDCl_3$, 75 MHz): 31.8, 34.6, 63.5, 117.8, 125.7, 128.2, 128.3, 129.1, 131.4, 132.8, 143.1, 145.0, 152.6.

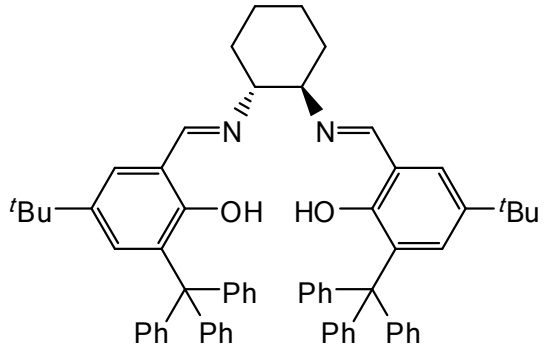
3-(1-Trityl)-5-tert-butylsalicylaldehyde 221.



2-Trityl-4-*tert*-butylphenol **219** (4.5 g, 15 mmol), magnesium chloride (3.0 g, 32 mmol) and paraformaldehyde (1.0 g, 33 mmol) were combined in tetrahydrofuran (120 ml). Triethylamine (4.2 ml, 32 mmol) was added dropwise and the solution heated to reflux. On heating the solution turned yellow. The reaction was left stirring at reflux overnight. Removal of the reaction solvent left a yellow solid. Acidified water (50 ml) was added and the compound extracted into ethyl acetate (3 × 50 ml), washed with brine (50 ml), dried using magnesium sulphate and concentrated to give compound **221** as a pale yellow solid.

mp = 120-123 ^{o}C; υ_{max} 1438 cm^{-1}; δ_H ($CDCl_3$, 300 MHz): 1.31 (s, 9H, (C**H$_3$**)$_3$), 7.0-7.3 (m, 15H, Ar**H**), 7.36 (d, 1H, *J* = 2.4 Hz, Ar**H**,), 7.53 (d, 1H, *J* = 2.4Hz, Ar**H**), 9.76 (s, 1H, C**H**O), 11.11 (s, 1H, O**H**); δ_C ($CDCl_3$, 75 MHz): 31.44, 34.56, 63.76, 126.13, 127.20, 127.54, 127.56, 128.01, 128.21, 128.32, 129.06, 129.18, 131.29, 196.82; Found (ESI) 421.2162 $C_{30}H_{29}O_2$ [MH$^+$] requires 421.2168

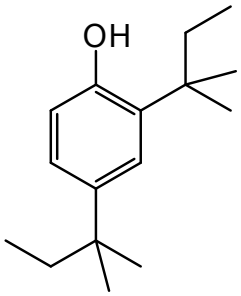
[N,N'-Bis-(3-tert-butyl-5-trityl-salicylidene)]-(R,R)-1,2-diaminocyclohexane 217.



3-Trityl-5-*tert*-butylsalicylaldehyde **221** (1.5 g, 3.5 mmol), (*R,R*)-1,2-diaminocyclohexane tartrate salt **214** (0.47 g, 1.8 mmol) and potassium carbonate (0.49 g, 3.6 mmol) were combined in tetrahydrofuran (30 ml) and refluxed overnight. On heating the reacting solution turned bright yellow. After the reaction was complete, the solvent was removed to leave the yellow crude material. Water (30 ml) was added to the residue and the product extracted into ethyl acetate (3 × 30 ml). The combined organic layers were washed with brine (30 ml) and dried over magnesium sulphate. The solvent was removed to leave a yellow solid. Recrystallisation from methanol yielded compound **217** as a yellow solid (682 mg, 21%).

mp = >350 ^{o}C; $[\alpha]_D$= -148.4 (c=1, $CHCl_3$); υ_{max} 1655, 3035 cm^{-1}; δ_H ($CDCl_3$, 300 MHz): 1.10 (s, 18 H, ($C\mathbf{H_3}$)$_3$), 1.0-1.7 (m, 8H, Cy**H**), 2.98 (m, 2H, C**H**N), 6.97 (d, 2H, *J* = 2.4 Hz, Ar**H**), 7.0-7.3 (m, 30H, $C(Ph)_3$), 7.38 (d, 2H, *J* = 2.4 Hz, Ar**H**), 7.97 (s, 2H, C=N**H**); δ_C ($CDCl_3$, 75 MHz): 24.6, 30.8, 31.7, 33.3, 34.3, 72.9, 125.7, 127.1, 127.5, 128.0, 128.3, 128.6, 129.2, 131.4, 132.2, 134.4, 165.5; Found (ESI) 919.5238 $C_{66}H_{67}N_2O_2$ [MH^+] requires 919.5203.

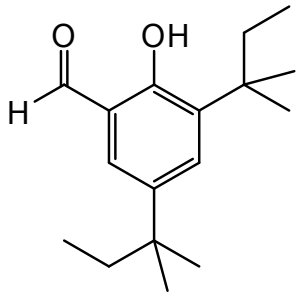
2,4-Bis-(1,1-dimethylpropyl)-phenol 227.[45]



Phenol (1.00 g, 11.2 mmol), 2-chloro-2-methylbutane (1.73 ml, 14.1 mmol) and aluminium chloride (71 mg, 0.532 mmol) were combined into a round bottomed flask and held between 20-30 ^{o}C for ca. five hours. After this time further portions of 2-chloro-2-methylbutane (1.73 ml, 14.1 mmol) and aluminium chloride (71 mg, 0.532 mmol) were added to the reaction mixture and the temperature was increased to 60-70 ^{o}C. The reaction was held at this temperature for a further 24 hours. On completion, the cooled reaction mixture was poured over cracked ice and the product extracted into diethyl ether (20 ml). The organic layer was washed with water (3 × 20 ml) and brine (30 ml). The diethyl ether layer was dried over magnesium sulphate and the solvent removed to leave the crude material as a dark oil (1.8 g). This crude mixture was purified via column chromatography eluting with dichloromethane. Compound **227** was collected and concentrated to a straw coloured oil (0.57 g, 22%).

υ_{max} 2253, 2965, 3589 cm^{-1}; δ_H ($CDCl_3$, 300 MHz): 0.7-0.8 (t, 6H, *J*= 7.5 Hz, 2 × $CH_2C\mathbf{H_3}$), 1.32 (s, 6H, 2 × $C\mathbf{H_3}$), 1.44 (s, 6H, 2 × $C\mathbf{H_3}$), 1.66 (q, 2H, *J*= 7.5 Hz, $C\mathbf{H_2}CH_3$), 1.92 (q, 2H, *J*= 7.5, $C\mathbf{H_2}CH_3$), 6.63 (d, 1H, *J*= 2.4 Hz, Ar**H**), 7.6 (dd, 1H, *J*= 2.4 = 8.1 Hz, Ar**H**), 7.23 (d, 1H, *J*= 2.1 Hz, Ar**H**); δ_C ($CDCl_3$, 75 MHz): 9.7, 28.1, 29.0, 30.2, 34.0, 37.5, 37.8, 38.7, 116 .4, 124.5, 126.4, 134.0, 141.7, 152.2.

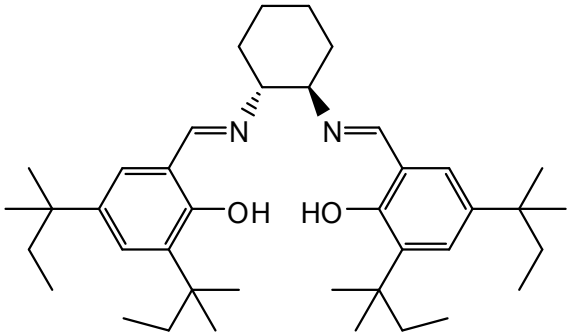
3,5-Bis-(1,1-dimethylpropyl)-2-hydroxybenzaldehyde 228.[45]



2,4-Bis-(1,1-dimethylpropyl)-phenol **227** (1.0 g, 6.1 mmol), magnesium chloride (1.2 g, 12 mmol) and paraformaldehyde (0.40 g, 14 mmol) were combined in tetrahydrofuran (30 ml). Triethylamine (1.6 ml, 12 mmol) was added dropwise and the reaction heated to reflux and kept at reflux for 12 hours. On cooling the magnesium chloride was filtered and the reaction solvent removed *in vacuo*. The crude material was taken up into diethyl ether (20 ml). Water was added to the organic layer and the diethyl ether layer collected. The aqueous layer was further washed with diethyl ether (20 ml). The combined organic layers were washed with brine and dried over magnesium sulphate. Removal of the solvent gave an off white solid which was identified as compound **228** (0.85 g, 73%).

υ_{max} 1650, 2964 cm^{-1}; δ_H ($CDCl_3$, 300 MHz): 0.5-0.6 (m, 6H, 2 × $CH_2C\mathbf{H_3}$); 1.20 (s, 6H, 2 × $C\mathbf{H_3}$); 1.20 (s, 6H, 2 × $C\mathbf{H_3}$); 1.5-1.6 (m, 2H, $C\mathbf{H_2}CH_3$); 1.8-2.0 (m, 2H, $C\mathbf{H_2}CH_3$); 7.20 (d, 1H, *J*= 2.4 Hz, Ar**H**); 7.38 (d, 1H, *J*= 2.4 Hz, Ar**H**); 9.78 (s, 1H, C**H**O); 11.6 (s, 1H, O**H**); δ_C ($CDCl_3$, 75 MHz): 15.5, 27.7, 28.7, 33.2, 37.1, 37.8, 39.0, 66.0, 120.5, 129.0, 134.1, 136.4, 140.2, 159.5, 197.5.

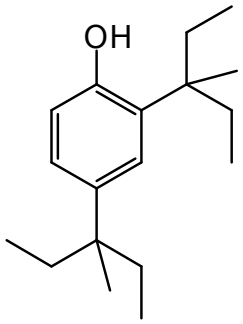
[N,N'-Bis-(3,5-tert-pentyl-salicylidene)]-(R,R)-1,2-diaminocyclohexane 65 [45]



3,5-Bis-(1,1-dimethylpropyl)-2-hydroxybenzaldehyde **228** (0.75 g, 3.92 mmol), (*R*,*R*)-1,2,diaminocyclohexane tartrate salt **214** (1.1 g, 4.31 mmol) and potassium carbonate (0.27 g, 1.96 mmol) were combined in ethanol (20 ml) and heated at reflux for ca. 12 hours. On heating the reaction mixture turned a bright yellow in colour. Diethyl ether (20 ml) and water (20 ml) were added to the cooled reaction mixture and the product was extracted into the organic layer. The aqueous layer was washed with further portions of diethyl ether (3× 20 ml). The combined organic fractions were washed with brine and dried over magnesium sulphate. Removal of the solvent yielded compound **65** a bright yellow solid (0.62 g, 53%).

m.p = 209-211 ^{o}C; $[\alpha]_D$ = -254.6 (c= 1, $CHCl_3$); υ_{max} 1632 cm^{-1}; δ_H ($CDCl_3$, 300 MHz); 0.5-0.6 (m, 12H, 4 × $CH_2C\mathbf{H_3}$), 1.17 (s, 12H, 4 × C$\mathbf{H_3}$), 1.34 (s, 12H, 4 × C$\mathbf{H_3}$), 1.5-1.56 (m, 8H, 4 × C$\mathbf{H_2}CH_3$), 1.7-1.8 (m, 6H, Cy**H**), 1.8-2.0 (m, 2H, Cy**H**), 3.2-3.3 (m, 2H, **H**CN), 6.88 (d, 2H, *J* = 2.4 Hz, Ar**H**,), 7.1-7.2 (d, 2H, *J* = 2.4 Hz, Ar**H**,), 8.26 (s, 2H, C**H**=N); δ_C ($CDCl_3$, 75 MHz): 27.7, 27.8, 28.6, 28.7, 29.9, 31.7, 33.2, 33.5, 37.2, 37.5, 38.9, 118.2, 127.1, 129.0, 135.1, 138.4, 158.4, 166.4.

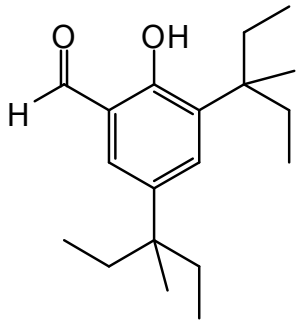
2,4-Bis-(1-ethyl-1-methylpropyl)-phenol 229.



Phenol (1.00 g, 10.6 mmol), 3-chloro-3-methylpentane (3.83 ml, 28.1 mmol) and aluminium chloride (141 mg, 1.06 mmol) were combined in a round bottomed flask and held between 20-30 ^{o}C for ca. five hours. After this time further portions of 3-chloro-3-methylpentane (3.83 ml, 28.1 mmol) and aluminium chloride (141 mg, 1.06 ml) were added to the reaction mixture and the temperature was increased to 60-70 ^{o}C. The reaction was held at this temperature for a further 24 hours. Then the cooled reaction mixture was poured over cracked ice and the product extracted into diethyl ether (20 ml). The organic layer was washed with water (3 × 20 ml) and brine (30 ml). The diethyl ether layer was dried over magnesium sulphate and the solvent removed to yield the crude material as a dark oil (1.8 g). This crude mixture was purified via column chromatography eluting with dichloromethane. Compound **229** was collected and concentrated to give the title compound as a pale coloured oil (0.60 g, 35%).

υ_{max} 2253, 2876, 2966 cm^{-1}; δ_H ($CDCl_3$, 300 MHz): 0.5-0.6 (m, 12H, 4 × $CH_2C\mathbf{H_3}$), 1.21 (s, 3H, $C\mathbf{H_3}$), 1.22 (s, 3H, $C\mathbf{H_3}$), 1.4-2.1 (m, 8H, 4 × $C\mathbf{H_2}CH_3$), 4.63 (s, br, 1H, O**H**), 6.60 (d, 1H, *J* = 2.4 Hz, Ar**H**), 6.99 (dd, 1H, *J* = 2.4, 8.0 Hz, Ar**H**), 7.07 (d, 1H, *J* = 2.4 Hz, Ar**H**); δ_C ($CDCl_3$, 75 MHz): 8.8, 9.2, 9.3, 23.5, 24.0, 29.0, 33.0, 33.9, 35.6, 36.7, 41.1, 42.5, 116.2, 125.2, 128.4, 131.8, 139.4, 152.0; Found (ESI) 262.2294 $C_{18}H_{30}O$ [M^+] requires 262.2291.

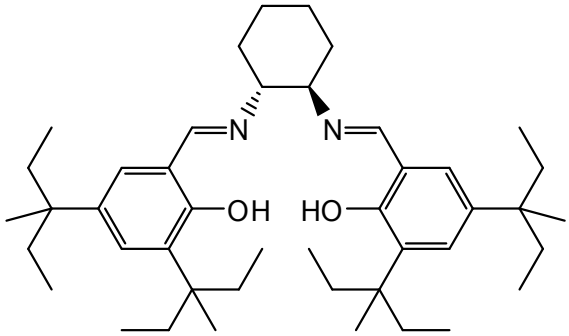
3,5-Bis-(1-ethyl-1-methylpropyl)-2-hydroxybenzaldehyde 230.



Compound **229** (1.50 g, 5.80 mmol), magnesium chloride (1.10 g, 11.6 mmol) and paraformaldehyde (0.38 g, 12.8 mmol) were combined in tetrahydrofuran (50 ml). Triethylamine (1.50 ml, 11.6 mmol) was added dropwise to the reaction mixture which was left to reflux over a 48 hours hour period. The cooled reaction mixture was filtered to remove magnesium sulphate and the solvent removed under reduced pressure. The residue was taken up into diethyl ether (30 ml) and water (50 ml) added to the organic layer. The organic layer was removed and the aqueous layer washed further with diethyl ether (3 × 20 ml). The combined organic layers were washed with brine and dried over magnesium sulphate. Removal of the solvent afforded a dirty white solid which was shown to contain some unreacted starting material. The solid was purified further using column chromatography eluting with methanol:hexane (1:99). Compound **230** was obtained as a white solid (1.20 g, 71%).

υ_{max} 1646, 3019 cm^{-1}; δ_H ($CDCl_3$, 300 MHz): 0.5-0.6 (m, 12H, 4 × $CH_2C\mathbf{H_3}$), 1.15 (s, 3H, $C\mathbf{H_3}$), 1.20 (s, 3H, $C\mathbf{H_3}$), 1.4-1.5 (m, 4H, 2 × $C\mathbf{H_2}CH_3$), 1.59-1.6 (m, 2H, $C\mathbf{H_2}CH_3$), 2.1-2.2 (m, 2H, $C\mathbf{H_2}CH_3$), 7.15 (d, 1H, *J*= 2.4 Hz, Ar**H**), 7.25 (d, 1H, *J*= 2.4 Hz, Ar**H**), 9.76 (s, 1H C**H**O), 11.58 (s, 1H, O**H**); δ_C ($CDCl_3$, 75 MHz): 8.8, 9.2, 23.3, 23.9, 28.3, 32.2, 35.3, 41.2, 42.9, 120.4, 130.0, 134.5, 136.0, 138.1, 159.5, 198.0; Found (ESI) 291.2317 $C_{19}H_{30}O_2$ [M^+] requires 291.2319

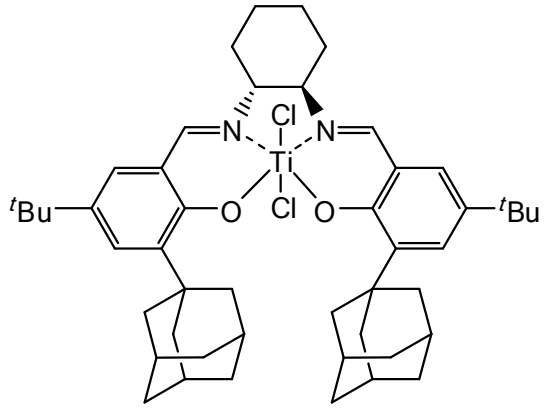
[N,N'-Bis-(3,5-di-tert-hexyl-salicylidene)]-(R,R)-1,2-diaminocyclohexane 226



3,5-Bis-(1-ethyl-1-methylpropyl)-2-hydroxybenzaldehyde **228** (0.25 g, 0.86 mmol), tartrate salt **214** (0.11 g, 0.43 mmol) and potassium carbonate (0.13 g, 0.95 mmol) were combined in tetrahydrofuran (5.0 ml) and refluxed overnight. The solvent was evaporated to leave a yellow residue. The product was extracted into diethyl ether (3 × 20 ml) and the combined organic layers washed with water (20 ml) and brine (20 ml). The ethereal layers were dried over magnesium sulphate and the solvent removed *in vacuo* to gave compound **228** as a bright yellow solid (0.26 g, 46%).

m.p. = 221-223 ^{o}C; $[\alpha]_D$ -272.6 (c=1, $CHCl_3$); υ_{max} 1265, 1420, 3056 cm^{-1}; δ_H ($CDCl_3$, 300 MHz): 0.5-0.6 (m, 24H, 8 × $CH_2C\mathbf{H_3}$), 1.04 (s, 6H, 2 × C**H$_3$**), 1.18 (s, 6H, 2 × C**H$_3$**), 1.3-1.6 (m, 16H, 8 × C**H$_2$**CH_3), 1.6-1.7 (m, 2H, cy**H**), 1.7-1.8 (m, 2H, cy**H**), 1.8-1.9 (m, 2H, cy**H**), 2.0-2.1 (m, 2H, cy**H**), 3.2-3.2 (m, 2H, C**H**N), 6.74 (d, 2H, *J*=2.4, Ar**H**), 7.02 (d, 2H, *J*=2.4, Ar**H**) 8.23 (s, 2H, C**H**=N), 13.7 (s, br, 2H, O**H**); δ_C ($CDCl_3$, 75 MHz): 8.8, 9.3, 15.1, 18.6, 23.4, 24.7, 28.3, 32.1, 32.2, 33.4, 35.1, 35.2, 38.7, 40.8, 42.6, 72.7, 118.2, 127.9, 129.4, 131.0, 133.1, 136.3, 158.4; found (ESI) 659.5518 [M^+] $C_{44}H_{70}N_2O_2$ requires 659.5510.

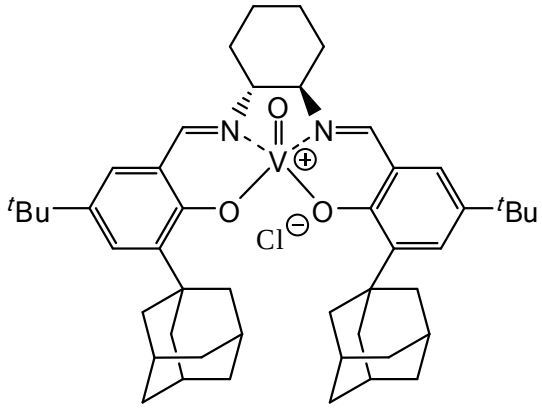
(R,R)-$TiCl_2$(salen) 224.



Titanium tetrachloride (0.1 M in CH_2Cl_2, 0.3 ml, 0.3 mmol) was diluted in dichloromethane (4.0 ml) and added dropwise to a solution of compound **216** (0.2 g, 0.3 mmol) in dichloromethane (4.0 ml) at room temperature. On addition the solution turned a red/brown colour. After ca. one hour the solvent was removed to give a red/brown residue which was washed with diethyl ether (4.0 ml). The supernatant was decanted and the residue washed again with diethyl ether:hexane (1:1, 8.0 ml). Removal of the solvent gave compound **224** as a red powder (0.15 g, 70%).

mp >350 ^oC; υ_{max} 1644 cm^{-1}; δ_H ($CDCl_3$, 300 MHz): 1.31 (s, 18H, 2 × (C**H**$_3$)$_3$), 1.7-1.8 (m, 12H, Ad**H**), 1.7-2.8 (m, 8H, Cy**H**), 2.0-2.1 (m, 6H, Ad**H**), 2.1-2.2 (m, 12H, Ad**H**), 3.8-3.9 (m, 2H, 2 × C**H**N), 7.2 (d, 2H, *J* = 2.4 Hz, 2 × Ar**H**), 7.5 (d, 2H, *J* = 2.4 Hz × Ar-**H**,), 8.28 (s, 2H, 2 × C**H**=N): Found (ESI) 779.3639 $C_{48}H_{64}O_2N_2TiOCH_3$ [(M-Cl_2+OMe)$^+$] requires 779.3637.

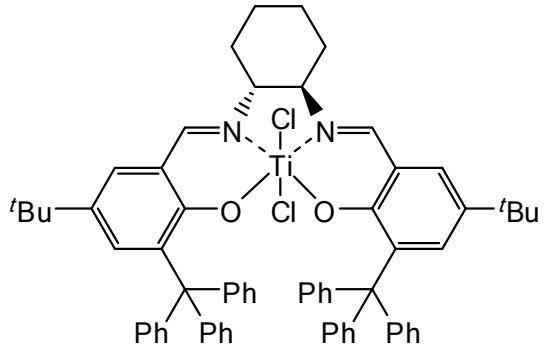
(R,R)-V(V)O(salen) 222.



Vanadium oxychloride (0.78 mmol, 0.07 ml) was added to a solution of compound **216** (0.5 g, 0.7 mmol). The solution was allowed to stir overnight at room temperature. After this time, the reaction mixture was loaded onto a silica column and eluted with dichloromethane followed by methanol. Compound **222** eluted as a green band which was collected and the solvent removed to give compound **222** a green powder (0.45 g, 79%).

mp >350 ^{o}C; $[\alpha]_D$= -1765 (c= 0.01, $CHCl_3$); υ_{max} 1645 cm^{-1}; δ_H ($CDCl_3$, 300 MHz): 1.26 (s, 9H, ($C\mathbf{H}_3)_3$), 1.31 (s, 9H, ($C\mathbf{H}_3)_3$), 1.6-1.7 (m, 8H, Cy**H**), 1.7-1.8 (m, 10H, Ad**H**), 1.9-2.4 (m, 6H, Ad**H**), 2.6-2.8 (m, 6H, Ad**H**), 2.9-3.1 (m, 1H, C**H**N), 3.5-3.6 (m, 1H, C**H**N), 7.52 (d, 1H, *J*= 2.4 Hz, Ar**H**), 7.55 (d, 1H, *J*= 2.4 Hz, Ar**H**), 7.74 (d, 1H, *J*= 2.4 Hz, Ar**H**), 7.79 (d, 1H, *J*= 2.4 Hz, Ar**H**), 8.52 (s, 1H, N=C**H**), 8.75 (s, 1H, N=C**H**).

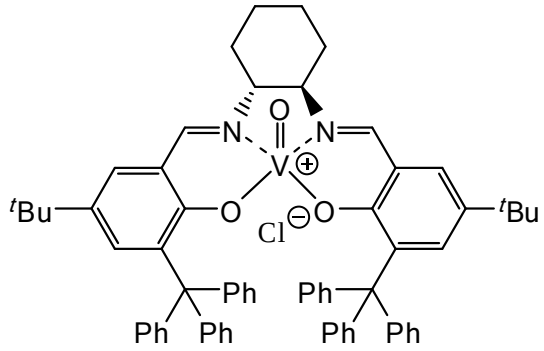
(R,R)-V(V)O(salen) 225.



Titanium tetrachloride (0.1 M in CH_2Cl_2, 0.2 ml, 0.2 mmol) was diluted in dichloromethane (4.0 ml) and added dropwise to ligand **217** (0.2 g, 2.2 ml) in dichloromethane (4.0 ml). On addition, the solution turned a red/brown colour. The solution was then left stirring at room temperature for ca. one hour. The solvent was removed under reduced pressure to give a red/brown residue which was washed with diethyl ether (2×30 ml). The solvent was decanted and the remaining residue washed with diethyl ether:hexane (1:1, 60 ml). The solvent was decanted and the solid dried under high vacuum. Compound **225** was obtained as an orange/red solid (0.18 g, 79%).

mp >350 ^{o}C; υ_{max} 1634 cm^{-1}; δ_H ($CDCl_3$, 300 MHz): 1.11 (s, 18H, 2 × (C**H**$_3$)$_3$), 0.9-2.0 (m, 8H, Cy**H**), 4.9-5.1 (m, 2H, C**H**N), 7.0-7.1 (m, 30H, 2 × C(Ph)$_3$), 7.5 (d, 2H, *J* = 2.4, Ar**H**,), 8.5 (d, 2H, *J* = 2.4, Ar**H**,), 9.14 (s, 2H, 2 × C**H**=N): Found (ESI) 995.4637 $C_{66}H_{63}N_2O_2TiOCH_3$ [(M-Cl_2+OMe)$^+$] requires 995.4639.

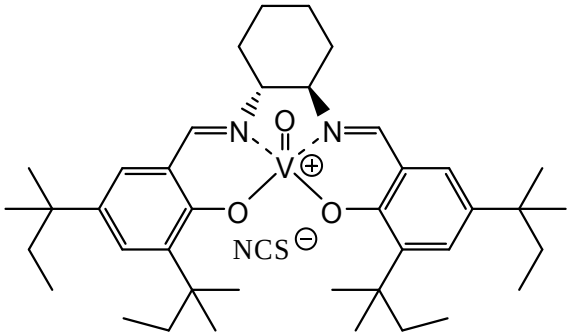
(R,R)-V(V)O(salen) 223.



Vanadium oxychloride (0.02 ml, 0.2 mmol) was added to a solution of compound **217** (0.20 g, 2.2 mmol) in dichloromethane (20 ml). The reaction was stirred overnight at room temperature at which point the reaction mixture was loaded straight onto a silica column and eluted with dichloromethane followed by methanol. Compound **223** eluted as a dark green band with methanol and was collected. Concentration of the solvent left a dark green solid which was washed with dichloromethane. The solvent was decanted and evaporated to leave compound **223** as a green powder (51 mg, 23%).

mp >350 ^{o}C; $[\alpha]_D$ -1335 (c= 0.01, $CHCl_3$); υ_{max} 1625 cm^{-1}; Found (ESI) 983.4341 $C_{66}H_{64}O_3N_2V$ $(M\text{-}Cl)^+$ requires 983.4357.

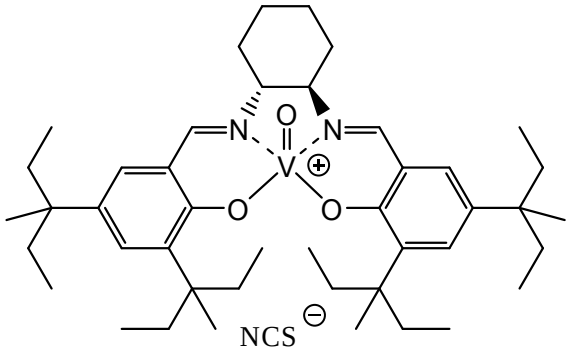
(R,R)-V(V)O(salen) 231a.



Ligand **65** (0.50 g, 0.83 mmol) and vanadyl sulphate (0.15 g, 0.91 mmol) were dissolved in ethanol (60 ml) and refluxed overnight. The solvent was removed to leave a dark green solid which was purified via column chromatography eluting with dichloromethane followed by methanol. The ethyl sulphonate complex moved as a dark band which was collected. Removal of the solvent gave the ethyl sulphonate complex as a dark green solid (0.40 g, 61%). Vanadium(V) ethyl sulphonate complex (0.40 g, 0.54 mmol) was dissolved in ethanol (50 ml) and potassium thiocyanate (1.4 g, 15 mmol) added. This reaction mixture was stirred at room temperature for ca. two hours. After this time the solvent was removed and the residue taken up into diethyl ether (30 ml). The organic layer was filtered though a cotton plug to remove any inorganic salts and the ethereal layer washed with water (5 × 40 ml), followed by brine (40 ml). The ethereal layer was collected and dried over magnesium sulphate. Removal of the solvent gave product **231a** as a green solid (0.32 g, 80%).

m.p = >350 ^{o}C; $[\alpha]_D$ = -1580 (c=0.01, CH_2Cl_2); υ_{max} 1635 cm^{-1}; δ_H ($CDCl_3$, 300 MHz): 0.7-0.8 (m, 12H, 4 × $CH_2C\mathbf{H_3}$), 1.3-1.4 (m, 12H, 4 × C**H$_3$**), 1.4-1.5 (m, 12H, 4 × C**H$_3$**), 1.6-1.7 (m, 8H, 4 × C**H$_2$**CH_3), 1.8-1.9 (m, 4H, cy**H**), 2.0-2.2 (m, 4H, cy**H**), 2.5-2.6 (m, 1H, NC**H**), 2.7-2.8 (m, 1H, NC**H**), 7.39 (d, 1H, *J*= 2.4 Hz, Ar**H**), 7.49 (d, 1H, *J* = 2.4 Hz, Ar**H**), 7.58 (d, 1H, *J* = 2.4 Hz, Ar**H**), 7.62 (d, 1H, *J* = 2.4 Hz, Ar**H**) 8.46 (s, 1H, N=C**H**), 8.71 (s, 1H, N=C**H**); δ_C ($CDCl_3$, 75 MHz): 24.6, 24.8, 28.0, 28.1, 28.2, 28.6, 28.8, 29.7, 30.8, 31.7, 33.8, 33.8, 37.2, 37.3, 37.3, 38.0, 38.0, 38.1, 39.6, 39.7, 129.4, 129.4, 130.3, 133.8, 133.9, 134.1, 134.2, 134.4, 134.5, 135.0, 142.4, 142.5, 162.1, 165.6; Found (ESI) 667.4028 $C_{40}H_{60}N_2O_3V$ [M^+] requires 667.4044.

(R,R)-V(V)O(salen) 231b.



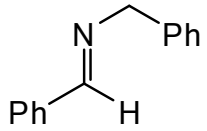
Ligand **226** (0.32 g, 0.44 mmol) and vanadyl sulphate (0.08 g, 0.48 mmol) were dissolved in ethanol (30 ml) and refluxed overnight. The solvent was removed to yield a dark green solid. The solid was purified via column chromatography eluting with dichloromethane followed by methanol. The ethyl sulphonate complex moved as a dark band on addition of methanol. The fraction was collected and the solvent removed to give the vanadium(V) ethylsulphonate complex (0.30 g, 74%). Vanadium(V) ethylsulphonate complex (0.30 g, 0.32 mmol) was dissolved into ethanol (50 ml) and potassium thiocyanate (0.84 g, 8.64 mmol) added. The reaction mixture was stirred at room temperature for ca. two hours. After this time the solvent was removed and the residue taken up into diethyl ether (30 ml). The organic layer was filtered though a cotton plug to remove any inorganic salts and the ethereal layer washed with water (5 × 40 ml), followed by brine (40 ml). The ethereal layer was collected and dried over magnesium sulphate. Removal of the solvent gave product **231b** as a green solid (0.23 g, 88%).

mp; >350 ^{o}C; $[\alpha]_D$ = -1535 (c=0.01, $CHCl_3$); υ_{max} 1647 cm^{-1}; δ_H ($CDCl_3$, 300 MHz): 0.6-0.7 (m, 12H, 4 × $CH_2C\mathbf{H_3}$), 1.2-1.3 (m, 12H, 4 × C$\mathbf{H_3}$), 1.4-1.6 (m, 8H, 4 × C$\mathbf{H_2}CH_3$), 1.4-1.5 (m, 12H, 4 × $CH_2C\mathbf{H_3}$), 1.5-1.6 (m, 8H, 4 × C$\mathbf{H_2}CH_3$), 2.1-2.2 (m, 4H, Cy**H**), 2.2-2.3 (m, 2H, Cy**H**), 2.7-2.8 (m, 2H, Cy**H**), 3.66 (m, 1H, C**H**N), 3.72 (m, 1H, C**H**N), 7.36 (d, 1H, *J* = 2.4 Hz, Ar**H**), 7.44 (d, 1H, *J* = 2.4 Hz, Ar**H**), 7.48 (d, 1H, *J* = 2.4 Hz, Ar**H**), 7.51 (d, 1H, *J* = 2.4 Hz), 8.48 (s, 1H, N=C**H**), 8.68 (s, 1H, N=C**H**); δ_C ($CDCl_3$, 75 MHz): 7.7, 7.9, 8.0, 8.1, 8.2, 16.5, 21.7, 22.1, 22.2, 22.3, 22.7, 22.7, 23.4, 23.6, 23.6, 28.5, 28.5, 28.5, 28.6, 28.7, 31.0, 31.7, 31.8, 34.0, 34.1, 34.2, 34.3, 40.1, 120.7, 120.8, 120.9, 123.7, 129.1, 129.9, 130.0, 131.9, 134.3, 134.4, 135.1, 139.1, 159.2; Found (ESI) 723.4616 $C_{44}H_{68}N_2O_3V$ [M^+] requires 723.4670.

General Procedure for Imine Synthesis

The appropriate amine (1.2 eq) and benzaldehyde (1.0 eq) were combined in dichloromethane along with magnesium sulphate and allowed to stir at room temperature for ca. 24 hours, then the solvent was removed under vacuum to leave the crude material which was purified as specified for each product.

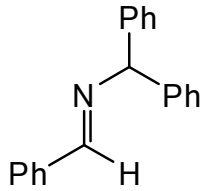
Synthesis of N-Benzylidine benzylamine 234



The crude material was taken up into dichloromethane and washed with acidified water (pH= 5-6, 3×100 ml) and brine (100 ml). The organic layer was collected and dried using sodium sulphate and the solvent removed to leave compound **234** as a yellow oil (20 g, 98%).

υ_{max} 1644, 2986, 3053 cm^{-1}; δ_H ($CDCl_3$, 300 MHz); 4.92 (2H, s, NC**H**$_2$Ph), 7.3-7.6 (8H, m, Ar**H**), 7.8-7.9 (2H, m, Ar**H**), 8.48 (1H, s, N=C**H**).

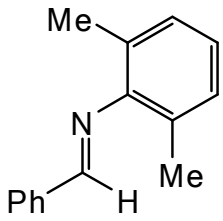
Synthesis of N- Benzylidine benzhydrylamine 235 [131,132,133]



The crude material was recrystallised from ethanol to leave compound **235** as white crystals (1.3 g, 51%).

mp = 96-103 ^oC [lit.[132] = 101-102 ^oC]; υ_{max} 1654, 2986, 3053 cm^{-1}; δ_H ($CDCl_3$, 300 MHz); 5.53 (s, 1H, NC**H**$(Ph)_2$), 7.3-7.7 (m, 13H, Ar**H**), 7.8-7.8 (m, 2H, Ar**H**), 8.36 (1H, s, N=C**H**)

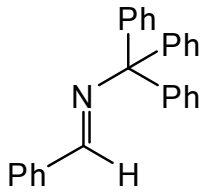
Synthesis of N-Benzylidine-2,6-dimethylaniline 236 [134]



The crude material was taken up in dichloromethane and washed with acidified water (pH= 5-6, 3×100ml) and brine (100 ml). The organic layer was collected and dried using sodium sulphate and the solvent removed to compound **236** as a yellow oil (1.5 g, 67%).

υ_{max} 1640, 2919, 3063 cm^{-1}; δ_H ($CDCl_3$, 300 MHz); 2.23 (s, 3H, C**H**$_3$), 2.24 (s, 3H, **CH$_3$)**, 7.03 (t, 1H, *J*= 8.0 Hz, Ar**H**), 7.15 (d, 2H, *J*= 7.5 Hz, Ar**H**) 7.5-7.6 (m, 3H, Ar**H**), 7.9-8.0 (m, 2H, Ar**H**), 8.29 (s, 1H, N=C**H**).

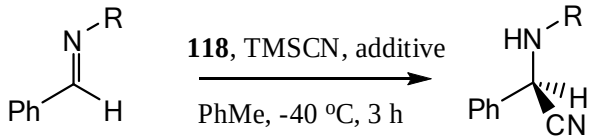
Synthesis of N-Benzylidine-tritylamine 237 [135]



The crude material was recrystallised from hexane to give compound **237** as a white solid (88 mg, 27%).

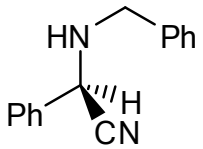
mp = 143-150 ^oC [lit.[135] = 153-159 ^oC]; υ_{max} 1635, 2919, 3054, cm^{-1}; δ_H ($CDCl_3$, 300 MHz); 7.1-7.2 (m, 15H, Ar**H**), 7.3-7.4 (m, 3H, Ar**H**), 7.75 (s, 1H, N=C**H**), 7.7-7.8 (m, 2H, Ar**H**); δ_C ($CDCl_3$, 75 MHz); 58.7, 128.2, 128.4, 128.5, 129.3, 129.4, 131.1, 144.5, 161.2.

General Procedure for Aminonitrile Synthesis



Compound **118** (0.10 eq, 10 mol%) was dissolved in toluene (2.0 ml) and transferred to a round bottomed flask. Methanol or 4-nitrophenol (1.2 eq) was added to the reaction vessel which was flushed with argon for ca. five minutes. Trimethylsilylcyanide (1.2 eq) was then added to the reaction mixture in one portion and the reaction cooled to -40 ^{o}C. The required imine was added to the reaction mixture after ca. one hour and the reaction left to stir at -40 ^{o}C for three hours. The reaction was worked up as specified for each product. The conversion was obtained using ^{1}H NMR spectroscopy. To the sample was added (*R*)-camphor sulphonic acid (15 eq) and the enantiomeric excess determined by integrating the peaks specified in each product.

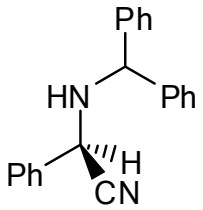
Synthesis of N-Benzyl-(R)-2-amino-2-phenylacetonitrile 232.[150]



Compound **232** was purified using column chromatography eluting with dichloromethane. Upon removal of the solvent, a yellow oil was isolated (46 mg, 80%, 75% ee (*R*)). The enantiomeric excess was determined by proton NMR spectroscopy using the peaks at 5.36 and 5.24 ppm.

$[\alpha]_D$= +80.0 (c= 1, $CHCl_3$) [lit.[150] $[\alpha]_D$= +64.0 (c= 1, $CHCl_3$)]; δ_H ($CDCl_3$, 300 MHz); 1.79 (s, 1H, N**H**), 3.85 (d, 1H, *J*= 13 Hz, NC**H**$_2$Ph), 3.96 (d, 1H, *J*= 13 Hz, NC**H**$_2$Ph), 4.65 (s, 1H, NC**H**), 7.2-7.9 (m, 10H, Ar**H**).

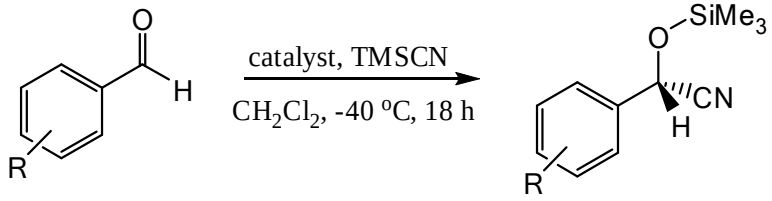
Synthesis of N-Benzhydryl-(R)-2-amino-2-phenylacetonitrile 238.[150]



The reaction mixture was purified via column chromatography eluting with dichloromethane to give compound **238** as a yellow oil (17 mg, 31%, 46% ee (*R*)). The enantiomeric excess was determined by proton NMR spectroscopy using the peaks at 5.13 and 5.16 ppm.

$[\alpha]_D$= -10.4 (c= 1, $CHCl_3$) [lit.[150] $[\alpha]_D$= -1.2 (c= 1, $CHCl_3$)]; δ_H ($CDCl_3$, 300 MHz) 2.00 (s, 1H, N**H**), 4.44 (s, 1H, NC**H**Ph_2), 5.07 (s, 1H, NC**H**), 7.2-7.6 (m, 15H, Ar**H**).

General Procedure for Cyanide Addition to Aldehydes;



Catalyst **239** (2.0 mol%) and triphenylphosphine oxide (10 mol%) were dissolved in dichloromethane (1.0 ml). Aldehyde (1.0 eq) was added to the solution, then trimethylsilylcyanide (1.6 eq) was added in one portion. The reaction mixture was stirred at room temperature for 16 hours. After this time the solution was passed through a silica plug eluting with dichloromethane. The solvent was removed under reduced pressure to leave the crude material which was analysed by ^{1}H NMR spectroscopy to obtain the conversion. The crude material was then purified using column chromatography eluting with ethyl acetate/hexane to obtain the pure silyl protected cyanohydrin product.

Procedures for the Determination of Enantiomeric Excess;

General Procedure for acetylation of cyanohydrin trimethylsilyl ether.

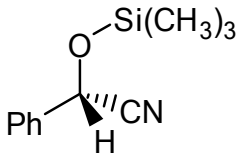
The appropriate cyanohydrin trimethylsilyl ether (1.0 eq) was dissolved in acetonitrile (2.0 ml) and scandium(III) trifluoromethanesulphonate (0.01 eq) was added along with acetic anhydride (2.0 eq). The reaction was allowed to stir at room temperature for ca. 20 minutes and then filtered through a silica plug to remove any solid residues. The sample was then analysed by chiral gas chromatography to determine the enantiomeric excess. GC conditions: initial temperature 95 ^{o}C, final temperature 180 ^{o}C, ramp rate 5.0 ^{o}C/min, flow rate 2.0

ml/min, except for the *o*-Me substrate. GC conditions: initial temperature 95 ^{o}C, final temperature 180 ^{o}C, ramp rate 2.0 ^{o}C/min, flow rate 2.0 ml/min.

General Procedure for the deprotection of the cyanohydrin trimethylsilyl ether to the free cyanohydrin

Cyanohydrin trimethylsilyl ether (1.0 eq) was dissolved in dichloromethane (2.0 ml) and several drops of hydrochloric acid (1.0 M) added. The solution was left to stir at room temperature for ca. four hours. The solution was transferred to a separating funnel and the organic layer separated. The aqueous layer was washed with dichloromethane (2 × 5 ml) and dried over magnesium sulphate. Removal of the solvent left the free cyanohydrin to which dimethylaminopyridine (1.0 eq) and (*R*)-mandelic acid (1.0 eq) were added. The enantiomeric excess was determined by ^{1}H NMR spectroscopy.

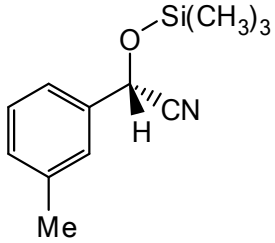
(S)-Phenyl-trimethylsilyloxy-acetonitrile 233 [118]



After conversion to the acetate, the enantiomeric excess was determined using chiral GC using the peaks at T_R 18.30 minutes (minor, *R*) and 18.50 minutes (major, *S*); (77 mg, 80%, 89% ee, (*S*)).

δ_H ($CDCl_3$, 300 MHz): 0.26 (s, 9H, (C**H**$_3$)$_3$), 5.53 (s, 1H, C**H**CN), 7.4-7.5 (m, 5H, Ar**H**).

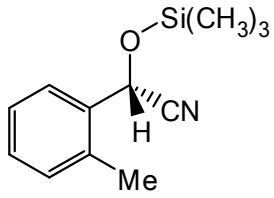
(S)-m-Tolyl-trimethylsilyloxy-acetonitrile.



After conversion to the acetate, the enantiomeric excess was determined using chiral GC using the peaks at T_R 16.96 minutes (minor, *R*) and 17.06 minutes (major, *S*); (50 mg, 55%, 61% ee, (*S*)).

δ_H ($CDCl_3$, 300 MHz): 0.21 (s, 9H, (C**H**$_3$)$_3$), 2.38 (s, 3H, ArC**H**$_3$), 5.44 (s, 1H, C**H**CN), 7.2-7.4 (m, 4H, Ar-**H**).

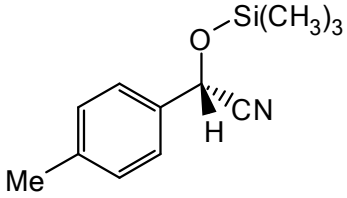
(S)-o-Tolyl-trimethylsilyloxy-acetonitrile.



After conversion to the acetate, the enantiomeric excess was determined using chiral GC using the peaks at T_R 28.72 minutes (minor, *R*) and 28.93 minutes (major, *S*); (73 mg, 79%, 93% ee (*S*)).

δ_H ($CDCl_3$, 300 MHz,): 0.20 (s, 9H, $(C\mathbf{H_3})_3$), 2.42 (s, 3H, Ar$C\mathbf{H_3}$), 5.55 (s, 1H, C**H**CN), 7.2-7.3 (m, 3H, Ar**H**), 7.4-7.5 (m, 1H, Ar**H**).

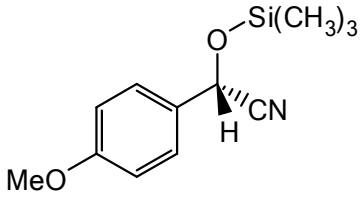
(S)-p-Tolyl-trimethylsilyloxy-acetonitrile.



After conversion to the acetate, the enantiomeric excess was determined using chiral GC using the peaks at T_R 17.38 minutes (minor, *R*) and 17.57 minutes (major, *S*); (52 mg, 56%, 81% ee (*S*))

δ_H ($CDCl_3$, 300 MHz): 0.14 (s, 9H, $(C\mathbf{H_3})_3$), 2.29 (s, 3H, Ar$C\mathbf{H_3}$), 5.38 (s, 1H, C**H**CN), 7.1-7.2 (m, 4H Ar**H**).

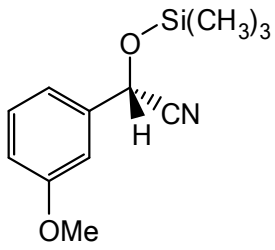
(S)-(4-Methoxyphenyl)-trimethylsilyloxy-acetonitrile.



After deprotection to the free cyanohydrin, the enantiomeric excess was determined using proton NMR spectroscopy using the peaks at 5.41 ppm (major, *S*) and 5.47 ppm (minor, *R*); (36%, 75% ee (*S*)).

δ_H ($CDCl_3$, 300 MHz): 0.34 (s, 9H, $(C\mathbf{H_3})_3$), 3.75 (s, 3H, O$C\mathbf{H_3}$), 5.23 (s, 1H, C**H**CN), 7.1-7.5 (m, 4H, Ar**H**).

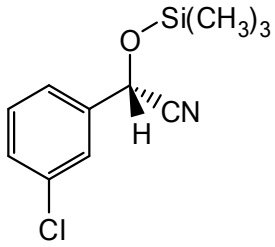
(S)-(3-Methoxyphenyl)-trimethylsilyloxy-acetonitrile.



After deprotection to the free cyanohydrin, the enantiomeric excess was determined using proton NMR spectroscopy using the peaks at 5.53 ppm (major, *S*) and 5.59 ppm (minor, *R*); (45 mg, 49%, 75% ee (*S*)).

δ_H ($CDCl_3$, 300 MHz); 0.25 (s, 9H, $(C\mathbf{H_3})_3$), 3.72 (s, 3H, $OC\mathbf{H_3}$), 5.59 (s, 1H, C**H**CN), 7.2-7.3 (m, 3H, Ar**H**), 7.4-7.5 (m, 1H, Ar**H**).

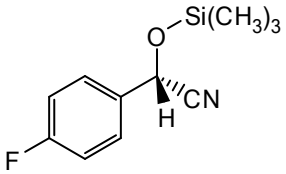
(S)-(3-Chlorophenyl)-trimethylsilyloxy-acetonitrile.



After conversion to the acetate, the enantiomeric excess was determined using chiral GC using the peaks at T_R 18.97 minutes (minor, *R*) and 19.14 minutes (major, *S*); (71 mg, 78%, 84% ee (*S*))

δ_H ($CDCl_3$, 300 MHz): 0.16 (s, 9H, $(C\mathbf{H_3})_3$), 5.37 (s, 1H, C**H**CN), 7.2-7.3 (m, 3H, Ar**H**), 7.37 (s, 1H, Ar**H**).

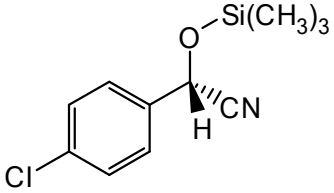
(S)-(4-Fluorophenyl)-trimethylsilyloxy-acetonitrile.



After conversion to the acetate, the enantiomeric excess was determined using chiral GC using the peaks at T_R 14.75 minutes (minor, *R*) and 14.97 minutes (major, *S*); (71 mg, 74%, 90% ee (*S*)).

δ_H ($CDCl_3$, 300MHz): 0.39 (s, 9H, (C**H**$_3$)$_3$), 5.63 (s, 1H, C**H**CN), 7.2-7.3 (m, 2H, Ar**H**), 7.5-7.6 (m, 2H, Ar**H**)

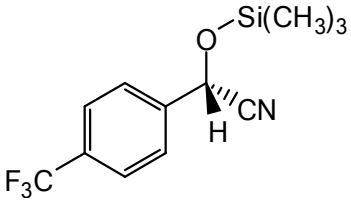
(S)-(4-Chlorophenyl)-trimethylsilyloxy-acetonitrile.



After conversion to the acetate, the enantiomeric excess was determined using chiral GC using the peaks at T_R 19.44 minutes (minor, *R*) and 19.63 minutes (major, *S*); (67 mg, 74%, 87% ee (*S*)).

δ_H ($CDCl_3$, 300 MHz): 0.24 (s, 9H, (C**H**$_3$)$_3$), 5.47 (s, 1H, C**H**CN), 7.3-7.4 (m, 4H, Ar**H**).

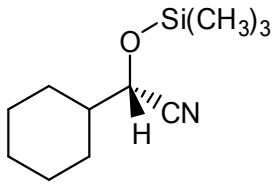
(S)-(4-Trifluoromethylphenyl)-trimethylsilyloxy-acetonitrile.



After conversion to the acetate, the enantiomeric excess was determined using chiral GC using the peaks at T_R 14.01 minutes (minor, *R*) and 14.33 minutes (major, *S*); (73 mg, 93%, 87% ee (*S*)).

δ_H ($CDCl_3$, 300 MHz,): 0.11 (s, 9H, (C**H**$_3$)$_3$), 5.22 (s, 1H, C**H**CN), 7.1-7.2 (m, 4H Ar**H**).

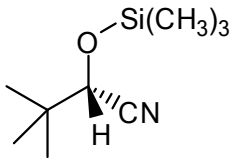
(S)-Cyclohexyl-trimethylsilyloxy-acetonitrile.



After conversion to the acetate, the enantiomeric excess was determined using chiral GC using the peaks at T_R 13.97 minutes (minor, *R*) and 14.13 minutes (major, *S*); (85 mg, 90%, 53% ee (*S*)).

δ_H ($CDCl_3$, 300 MHz): 0.12 (s, 9H, (C**H**$_3$)$_3$), 1.0-1.3 (m, 5H, Cy**H**), 1.6-1.7 (m, 6H, Cy**H**), 4.15 (s, 1H, C**H**CN).

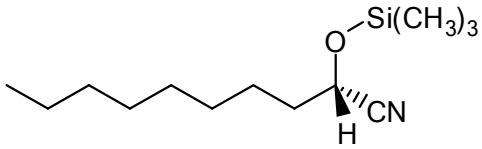
(S)-3,3-Dimethyl-2-trimethylsilyloxy-butyronitrile.



After conversion to the acetate, the enantiomeric excess was determined using chiral GC using the peaks at T_R 4.95 minutes (minor, *R*) and 5.08 minutes (major, *S*); (89 mg, 83%, 63% ee (*S*)).

δ_H ($CDCl_3$, 300 MHz); 0.17 (s, 9H, (C**H₃**)₃), 1.84 (9H, s, C**H₃**), 5.06 (s, 1H, C**H**CN)

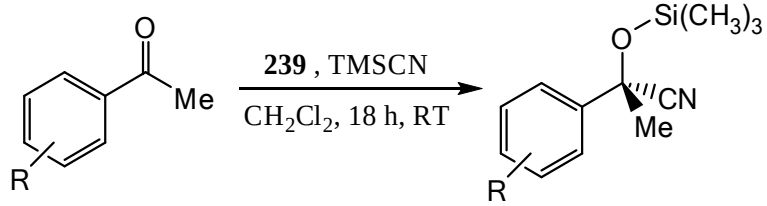
(S)-2-Trimethylsilyloxy-decanenitrile.



After conversion to the acetate, the enantiomeric excess was determined using chiral GC using the peaks at T_R 16.17 minutes (minor, *R*) and 16.29 minutes (major, *S*); (80 mg, 94%, 68% ee (*S*)).

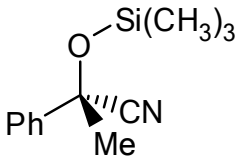
δ_H ($CDCl_3$, 300 MHz); 0.25 (s, 9H, (C**H₃**)₃), 0.5-1.9 (m, 17H, 1 × C**H₃** + 7 × C**H₂**), 5.13 (s, 1H, C**H**CN).

General procedure for cyanide addition to ketones;



Triphenylphosphine oxide (10.0 mol%) and catalyst **239** (2.0 mol%) were dissolved in dichloromethane (1.0 ml) and ketone (50 mg, 1.0 eq) was added in one portion. Trimethylsilylcyanide (1.6 eq) was then added and the resulting solution stirred at room temperature for 48 hours. After this time, the reaction mixture was passed through a silica plug eluting with dichloromethane. The solvent was removed under reduced pressure and the residue purified via column chromatography eluting with diethyl ether/petrol to give the pure silyl protected cyanohydrin product.

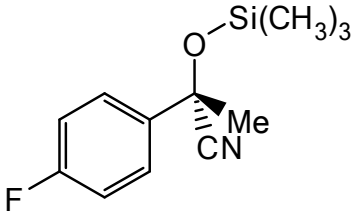
(S)-2-Trimethylsilyloxy-2-phenylpropanenitrile 241.[150]



The enantiomeric excess was determined using ^{1}H NMR spectroscopy integrating the peaks at 1.73 (major, *S*) and 1.77 (minor, *R*) ppm; (78 mg, 80%, 56% ee, (*S*)).

$[\alpha]_D$ = -7.9 (c=1, CH_2Cl_2, 56% ee (*S*)) [lit.[150] $[\alpha]_D$ = +16.9 (c=2.58, CH_2Cl_2, 94% ee (*R*))]; δ_H ($CDCl_3$, 300 MHz); 0.25 (s, 9H, OSi(C**H$_3$**)$_3$), 1.68 (s, 3H, C**H$_3$**), 7.2-7.4 (m, 5H, Ar**H**)

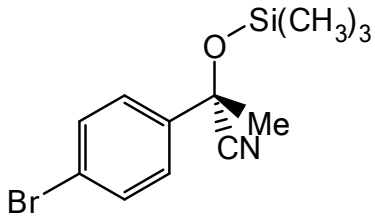
(S)-2-Trimethylsilyloxy-2-(4-fluorophenyl)propanenitrile.[150]



The enantiomeric excess was determined using proton NMR spectroscopy integrating the peaks at 1.56 (major, *S*) and 1.59 (minor, *R*) ppm; (68 mg, 79%, 64% ee (*S*)).

$[\alpha]_D$ = -16.9 (c=1, CH_2Cl_2, 90% ee (*S*)) [lit.[150] $[\alpha]_D$ = +17.6 (c= 2.7, CH_2Cl_2, 92% ee (*R*)]; δ_H ($CDCl_3$, 300 MHz): 0.18 (s, 9H, OSi(C**H$_3$**)$_3$), 1.84 (s, 3H, C**H$_3$**), 7.0-7.1 (m, 2H, Ar**H**), 7.5-7.6 (m, 2H, Ar**H**).

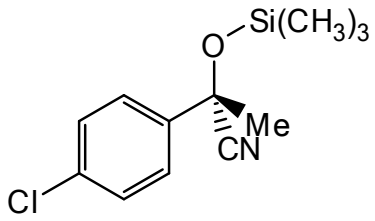
(S)-2-Trimethylsilyloxy-2-(4-bromophenyl)propanenitrile.



The enantiomeric excess was determined by proton NMR spectroscopy integrating the peaks at 1.65 (major, *S*) and 1.69 (minor, *R*) ppm; (50 mg, 67%, 62% ee (*S*)).

δ_H ($CDCl_3$, 300 MHz); 0.19 (s, 9H, OSi(C**H$_3$**)$_3$), 1.83 (s, 3H, C**H$_3$**), 7.3-7.4 (m, 2H, Ar**H**), 7.5-7.6 (m, 2H, Ar**H**).

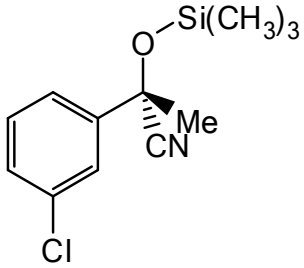
(S)-2-Trimethylsilyloxy-2-(4-chlorophenyl)propanenitrile [150]



The enantiomeric excess was determined by proton NMR spectroscopy integrating the peaks at 1.53 (major, *S*) and 1.56 (minor, *R*) ppm; (68 mg, 82%, 68% ee (*S*))

$[\alpha]_D$ = -8.6 (c=1, CH_2Cl_2, 68% ee (*S*)) [lit.[150] $[\alpha]_D$ = +18.2 (c=2.06, CH_2Cl_2, 90% ee (*R*)]; δ_H ($CDCl_3$, 300 MHz); 0.19 (s, 9H, OSi(C**H**$_3$)$_3$), 1.83 (s, 3H, C**H**$_3$), 7.3-7.4 (m, 2H, Ar**H**), 7.4-7.5 (m, 2H, Ar**H**).

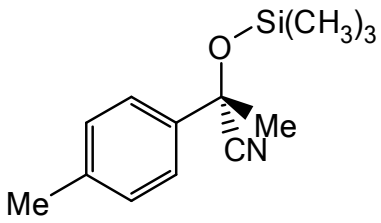
(S)-2-Trimethylsilyloxy-2-(3-chlorophenyl)propanenitrile. [150]



The enantiomeric excess was determined using proton NMR spectroscopy integrating the peaks at 1.79 (major, *S*) and 1.82 (minor, *R*) ppm; (68 mg, 83%, 65% ee (*S*)).

$[\alpha]_D$ = -10.5 (c=1, CH_2Cl_2, 65% ee (*S*)) [lit.[150] $[\alpha]_D$ = +19.6 (c=2.88, CH_2Cl_2, 90% ee (*R*)]; δ_H ($CDCl_3$, 300 MHz): 0.21 (s, 9H, OSi(C**H**$_3$)$_3$), 1.84 (s, 3H, C**H**$_3$), 7.3-7.5 (m, 4H, Ar**H**).

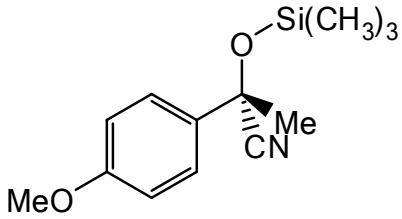
(S)-2-Trimethylsilyloxy-2-(4-methylphenyl)propanenitrile.[150]



The enantiomeric excess was determined using proton NMR spectroscopy integrating the peaks at 1.49 (major, *S*) and 1.52 (minor, *R*) ppm; (300 mg, 86%, 64% ee (*S*)).

$[\alpha]_D$ = -15.8 (c=1, CH_2Cl_2, 64% ee (*S*)) [lit.[150] $[\alpha]_D$ = +22.1 (c=2.44, CH_2Cl_2, 92% ee (*R*)]; δ_H ($CDCl_3$, 300 MHz); 0.15 (s, 9H, OSi(C**H₃**)$_3$), 1.83 (s, 3H, C**H₃**), 2.38 (s, 3H, ArC**H₃**), 7.2-7.3 (m, 2H, Ar**H**), 7.4-7.5 (m, 2H, Ar**H**).

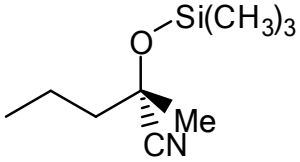
(S)-2-Trimethylsilyloxy-2-(4-methoxyphenyl)propanenitrile.



The enantiomeric excess was determined using proton NMR spectroscopy integrating the peaks at 1.76 (major, *S*) and 1.79 (minor, *R*) ppm; (278 mg, 82%, 59% ee (*S*)).

δ_H ($CDCl_3$, 300 MHz); 0.16 (s, 9H, OSi(C**H₃**)$_3$), 1.84 (3, 3H, C**H₃**), 3.82 (s, 3H, OC**H₃**), 6.8-7.0 (m, 4H, Ar**H**)

(S)-2-Trimethylsilyloxy-2-methyl-3-methylpentanenitrile.[150]



The enantiomeric excess was determined by proton NMR spectroscopy integrating the peaks at 1.45 (minor, *R*) and 1.56 (major, *S*) ppm; (84 mg, 78%, 40% ee (*S*)).

$[\alpha]_D$= -5.9 (c=1, CH_2Cl_2, 40% ee (*S*)) [lit.[150] $[\alpha]_D$ = -0.9 (c=1.6, CH_2Cl_2), 80% ee (*R*)]; υ_{max}: 1253, 2159, 2963 cm^{-1}; δ_H ($CDCl_3$, 300 MHz); 0.23 (s, 9H, OSi(C**H₃**)$_3$), 0.97 (t, 3H, *J* = 6.0 Hz, CH_2C**H₃**), 1.56 (s, 3H, C**H₃**), 1.6-1.7 (m, 4H, CH_2C**H₂**CH_3 + C**H₂**CH_2CH_3); δ_C ($CDCl_3$, 75 MHz): 12.5, 16.4, 26.6, 27.7, 44.4, 68.5, 120.9

10. References

1. Zhang W., Loebach J. L., Wilson S. R., Jacbosen E. N., *J. Am. Chem. Soc.*, **1990**, *112*, 2801.
2. (a) Achard T. J. R., Belokon Y. N., Llyin M., Moskalenco M. North. M., Pizzato F., *Tetrahedron Lett.*, **2007**, *48*, 2965; (b) Achard T J R., Belokon Y N., Hunt J., North M., Pizzato F., *Tetrahedron Lett*, **2007**, *48*, 2961.
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